RBGO Gynecology & Obstetrics

ISSN 0100-7203
eISSN 1806-9339

Revista Brasileira de Ginecologia e Obstetrícia
Number 5 • Volume 44 • Pages 449–556 • May 2022

febrasgo
Federação Brasileira das Associações de Ginecologia e Obstetrícia

OPEN ACCESS

Thieme

ISSN 0100-7203

RBGO Gynecology and Obstetrics
Revista Brasileira de Ginecologia e Obstetrícia

Editorial Office

Bruno Henrique Sena Ferreira

Editorial Production

Thieme Medical Publishers

ISSN 0100-7203

Federação Brasileira das Associações de Ginecologia e Obstetrícia

Brazilian Federation of Gynecology and Obstetrics Associations

Presidency and Executive Staff

Av. Brigadeiro Luís Antônio, 3421 - Sala 903 -
Jardim Paulista, São Paulo, SP, Brazil
CEP: 01401-001
Phone.: (+55 11) 5573-4919
www.febrasgo.org.br
presidencia@febrasgo.org.br

RBGO Editorial Office

editorial.office@febrasgo.org.br

Volume 44, Number 5/2022

RBGO Gynecology and Obstetrics
Revista Brasileira de Ginecologia e Obstetrícia

Thieme Revinter Publicações Ltda

online www.thieme-connect.com/products

Review

Review

Febrasgo Statement Position

Complementary material is available online at www.rbgo.org.br.

Cover design: © Thieme
Cover image source: © Thieme

 RBGO Gynecology and Obstetrics/Revista Brasileiro de Ginecologia e Obstetrícia is published monthly by Thieme-Revinter Publicações Ltda., Rua do Matoso, 170, Rio de Janeiro 20270-135, Brazil.

Editorial comments should be sent to **journals@thieme.com**. Articles may be submitted to this journal on an open-access basis. For further information, please send an e-mail to openaccess@thieme.com. The content of this journal is available online at **www.thieme-connect.com/products**. Visit our Web site at **www.thieme.com** and the direct link to this journal at **www.thieme.com/rbgo.**

Revista Brasileiro de Ginecologia e Obstetrícia is an official publication of the Federação Brasileira das Associações de Ginecologia e Obstetrícia (Brazilian Federation of Association of Gynecology and Obstetrics, Febrasgo), It is listed in Isi - Web of Science, Web of Knowledge (*Emerging*), MEDLINE / PubMed, Index Medicus, Scopus (Sci Verse), SCImago, SciELO (Scientific Electronic Library Online), LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde, Index Medicus Latino Americano), and Portal de Periódicos Capes (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior). Thieme Medical Publishers is a member of the CrossRef initiative.

ISSN 0100-7203

Editorial

Is it the Ideal Time to Start Prescribing *Cannabis* Derivatives to Treat Endometriosis-associated Pain?

Omero Benedicto Poli-Neto[1] Jaime Eduardo Cecílio Hallak[2] Julio Cesar Rosa-e-Silva[1] José Alexandre de Souza Crippa[2]

[1] Gynecological and Obstetrics Department, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, SP, Brazil
[2] Neurosciences and Behavioral Sciences Department, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, SP, Brazil

Rev Bras Ginecol Obstet 2022;44(5):449–451.

Endometriosis affects ~5%-10% of women of reproductive age and is often associated with painful symptoms like dysmenorrhea, dyschezia, dyspareunia, and even non cyclical pain.[1] The disease is diagnosed in at least 20% of women with dysmenorrhea and/or non-menstrual pelvic pain, reaching a prevalence of 50% among adolescents.[2] There is an alignment among international societies[3,4] that the presumed diagnosis of this disease is enough to start clinical treatment. Moreover, there seems to be a consensus that first-line treatment should be hormonal contraceptives since the efficacy is similar to that of surgery but with lower complication rates and costs.[5] However, these drugs are effective in only approximately two-thirds of patients,[6] have limited long-term efficacy,[7] and may occasionally lead to undesirable side effects. Additionally, there are serious limitations in the interpretation of clinical trials.[8] Accordingly, evidence on the best therapeutic regimens has not yet been established.[9] Other clinical options exist, but the cost, side effects, and similarity of results compared with hormonal contraceptives give them limited utility.[10] Thus, due to the persistence of pain, a significant portion of women undergo surgery, which is obviously capable of eliminating visible endometriotic lesions, but not curing the disease.[11] Despite short-term clinical improvement, postoperative recurrence is common, especially if hormone therapy was not initiated.[12]

Thus, the clear clinical demand for more effective or lasting options for symptomatic relief, together with an increasing recognition of the participation of the central nervous system in the genesis and/or modulation of chronic endometriosis-associated pain,[13] has aroused growing interest in novel therapeutic modalities.[14] Among these treatments, drugs derived from the *Cannabis sativa* plant, which we will call cannabinoids in the following text, currently seem to be the main topic. In fact, increasing attention has been directed to the potential beneficial effects of these medicines in controlling the symptoms of patients with chronic pain.[15] *Cannabis* contains over a hundred chemical compounds that act on the endocannabinoid system, yet two are rather distinct, delta-9-tetrahydrocannabinol (THC), which is responsible for the psychoactive effects associated with the use of this plant, and cannabidiol (CBD), which does not produce psychomimetic symptoms.[16] Overall, unlike THC, CBD is not addictive or tolerant and has a very favorable safety and adverse effect profiles. At first, it was believed that cannabinoids produced their analgesic effects by the direct activation of specific receptors (CB1 and CB2). However, it is now known that they can reduce pain by interacting with a wide range of cannabinoid, opioid, vanilloid, serotonergic, and anti-inflammatory receptors.[17] Furthermore, preclinical studies have shown that CBD can interfere with the levels of cytokines potentially involved in the pathophysiology of endometriosis-associated pain[18]; CBD has been shown to decrease the secretion of pro-inflammatory cytokines, including IL-6 and TNF-α, and increase levels of anti-inflammatory cytokines, including IL-10.[19] In addition to these broad potential pain-related mechanisms of action, there is a vast evidence on its anxiolytic, antidepressant, neuroprotective, mood-stabilizing, sleep-modulating effects of cannabinoids, along with many other benefits,[20] which may be useful in the concomitant treatment of non-painful symptoms as the aforementioned comorbidities are also frequent among patients with endometriosis. This makes cannabinoids potentially useful in treating patients with pelvic pain secondary to endometriosis.

Address for correspondence Omero Benedicto Poli-Neto, MD, PhD, Bandeirantes Avenue, 3900, 8th Floor, 14049-900, Ribeirão Preto, SP, Brazil (e-mail: polineto@usp.br).

DOI https://doi.org/10.1055/s-0042-1749430.
ISSN 0100-7203.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

A recent Australian national survey found that 13% of women with surgically confirmed endometriosis reported significant positive effects of using *cannabis in natura* both on relieving pain and reducing the use of pharmaceutical drugs as a form of self-medication. However, as the study was not controlled and the investigational products did not have a pharmaceutical grade as a standardized formulation, the conclusions and the reproducibility of findings are limited.[21] Nevertheless, similar findings have been reported in other longitudinal studies.[22] However, at least two meta-analyses focusing on different types of pain[23,24] clarified the limitation of the methodological designs available thus far. Furthermore, they raised a legitimate concern about the significantly higher prevalence of the adverse effects on the nervous system and psychiatric disorders associated with THC use,[24] particularly including psychosis, depressive episodes, and cognitive alterations commonly. More specifically, regarding the treatment of endometriosis-associated pain, two clinical trials registered on the clinicaltrials.gov platform (NCT03875261 and NCT04527003) were retrospectively proposed by researchers from Barcelona and Pennsylvania to assess the effect of cannabinoids on hyperalgesia in women with deep endometriosis, yet both are currently "not yet recruiting." To the best of our knowledge, in Brazil, we already have a clinical trial in progress and another that will soon start recruiting and is under our responsibility.

Considering the popular saying that "not everything that glitters is gold" there has been a growing concern in the specialized scientific community regarding the increasingly frequent use of *cannabis* or its derivatives for pain relief, despite the potential adverse effects, the lack of robust evidence on benefits and, consequently, the absence of clear recommendations on doses and/or composition to be used. In 2021 the International Association for the Study of Pain (IASP) published a statement position[25] recognizing the legitimacy of the life experience of people who report an improvement in pain following the use of *cannabis* and cannabinoids. Nevertheless, the association made it explicit that it does not endorse the use of cannabinoids until rigorous investigations and robust results clearly show the benefits and harms of its use in humans. The PAIN journal has even allocated an entire collection of 13 scientific articles representing the IASP's Presidential Task Force on *Cannabis* and Cannabinoid Analgesia and calling for high-quality clinical trials to be initiated. Some of the concerns regarding the use of cannabinoids are potential reductions in neurocognitive performance, macrostructural and microstructural brain development, and alterations in brain function secondary to heavy use by adolescents,[26] who have a higher risk of early onset psychosis,[27] and addiction.[28]

In Brazil, cannabinoid-based medications are officially approved for use only in patients with refractory epilepsy with a THC concentration $<0.2\%$. These drugs have a very high cost and any use outside the approved indication is off-label. In any case, we have seen a growing supply of *cannabis*-derived products on the market linked to the promise of pain relief. Many serious groups and companies have devoted efforts to drug development, but international quality standards are not followed by all, which poses a health risk as it is impossible to guarantee a high level of quality, adequate pharmacovigilance, and extensive monitoring of adverse reactions. This can also lead to abusive and illegal use.

Nevertheless, the prospect of good results is an encouragement to women with persistent symptoms and professionals who assist them to use cannabinoids, but it is necessary to be aware of the temptation of the premature clinical use of medication. Unfortunately, from a strictly medical and scientific point of view, it is currently impossible to guarantee the efficacy, safety and tolerability of *cannabis* or its derivatives in the treatment of pain symptoms in women with endometriosis. Incentives have been made to disseminate the need for large clinical trials in this domain. To finish, I will restate a part of a text written by Michael Eisenstein[29] which seems to me to be very lucid, sensible and relevant for the situation that we are currently living in: "Unfortunately, if studies such as these are not done—or not done properly—then consumers will be left to fend for themselves in a poorly monitored marketplace. In that scenario, the signal of true clinical benefit would almost certainly be drowned out by the noise from personal anecdotes and the placebo effect, which could jeopardize the future of a potentially valuable medicine."[29]

Conflicts to Interest
None to declare.

Acknowledgments
We acknowledge the Coordination for the Improvement of Higher Education Personnel (CAPES) for supporting our post-graduate program. We would like to thank Editage (www.editage.com) for English language editing.

References

1 Eisenberg VH, Weil C, Chodick G, Shalev V. Epidemiology of endometriosis: a large population-based database study from a healthcare provider with 2 million members. BJOG. 2018;125 (01):55–62. Doi: 10.1111/1471-0528.14711
2 Janssen EB, Rijkers AC, Hoppenbrouwers K, Meuleman C, D'Hooghe TM. Prevalence of endometriosis diagnosed by laparoscopy in adolescents with dysmenorrhea or chronic pelvic pain: a systematic review. Hum Reprod Update. 2013;19(05):570–582. Doi: 10.1093/humupd/dmt016
3 Dunselman GA, Vermeulen N, Becker C, et al; European Society of Human Reproduction and Embryology. ESHRE guideline: management of women with endometriosis. Hum Reprod. 2014;29 (03):400–412. Doi: 10.1093/humrep/det457
4 Kuznetsov L, Dworzynski K, Davies M, Overton CGuideline Committee. Diagnosis and management of endometriosis: summary of NICE guidance. BMJ. 2017;358:j3935. Doi: 10.1136/bmj.j3935
5 Chaichian S, Kabir A, Mehdizadehkashi A, Rahmani K, Moghimi M, Moazzami B. Comparing the efficacy of surgery and medical therapy for pain management in endometriosis: a systematic review and meta-analysis. Pain Physician. 2017;20(03):185–195
6 Vercellini P, Buggio L, Frattaruolo MP, Borghi A, Dridi D, Somigliana E. Medical treatment of endometriosis-related pain. Best Pract Res Clin Obstet Gynaecol. 2018;51:68–91. Doi: 10.1016/j.bpobgyn.2018.01.015
7 Surrey ES, Soliman AM, Johns B, Vora JB, Taylor HS, Agarwal SK. Real-world characterization of women with diagnosed endometriosis initiating therapy with elagolix using a US Claims Database.

Clinicoecon Outcomes Res. 2020;12:473–479. Doi: 10.2147/CEOR.S264905
8 Capraş RD, Urda-Cîmpean AE, Bolboacă SD. Is scientific medical literature related to endometriosis treatment evidence-based? A systematic review on methodological quality of randomized clinical trials. Medicina (Kaunas). 2019;55(07):E372. Doi: 10.3390/medicina55070372
9 Brown J, Crawford TJ, Datta S, Prentice A. Oral contraceptives for pain associated with endometriosis. Cochrane Database Syst Rev. 2018;5(05):CD001019. Doi: 10.1002/14651858.cd001019.pub3
10 Donnez J, Dolmans MM. endometriosis and medical therapy: from progestogens to progesterone resistance to GnRH antagonists: a review. J Clin Med. 2021;10(05):1085. Doi: 10.3390/jcm10051085
11 Keckstein J, Becker CM, Canis M, et al; Working group of ESGE, ESHRE, and WES. Recommendations for the surgical treatment of endometriosis. Part 2: deep endometriosis. Hum Reprod Open. 2020;2020(01):a002
12 As-Sanie S, Till SR, Schrepf AD, et al. Incidence and predictors of persistent pelvic pain following hysterectomy in women with chronic pelvic pain. Am J Obstet Gynecol. 2021;225(05):568.e1–568.e11. Doi: 10.1016/j.ajog.2021.08.038
13 Coxon L, Horne AW, Vincent K. Pathophysiology of endometriosis-associated pain: A review of pelvic and central nervous system mechanisms. Best Pract Res Clin Obstet Gynaecol. 2018;51:53–67. Doi: 10.1016/j.bpobgyn.2018.01.014
14 Carey ET, Till SR, As-Sanie S. Pharmacological management of chronic pelvic pain in women. Drugs. 2017;77(03):285–301. Doi: 10.1007/s40265-016-0687-8
15 Romero-Sandoval EA, Fincham JE, Kolano AL, Sharpe BN, Alvarado-Vázquez PA. Cannabis for chronic pain: challenges and considerations. Pharmacotherapy. 2018;38(06):651–662. Doi: 10.1002/phar.2115
16 Mackie K. Cannabinoid receptors: where they are and what they do. J Neuroendocrinol. 2008;20(Suppl 1):10–14. Doi: 10.1111/j.1365-2826.2008.01671.x
17 Vučković S, Srebro D, Vujović KS, Vučetić Č, Prostran M. Cannabinoids and pain: new insights from old molecules. Front Pharmacol. 2018;9:1259. Doi: 10.3389/fphar.2018.01259
18 Malvezzi H, Hernandes C, Piccinato CA, Podgaec S. Interleukin in endometriosis-associated infertility-pelvic pain: systematic review and meta-analysis. Reproduction. 2019;158(01):1–12. Doi: 10.1530/REP-18-0618
19 Nichols JM, Kaplan BLF. Immune responses regulated by cannabidiol. Cannabis Cannabinoid Res. 2020;5(01):12–31. Doi: 10.1089/can.2018.0073
20 Crippa JA, Guimarães FS, Campos AC, Zuardi AW. Translational investigation of the therapeutic potential of cannabidiol (CBD): toward a new age. Front Immunol. 2018;9:2009. Doi: 10.3389/fimmu.2018.02009
21 Sinclair J, Smith CA, Abbott J, Chalmers KJ, Pate DW, Armour M. Cannabis use, a self-management strategy among australian women with endometriosis: results from a National Online Survey. J Obstet Gynaecol Can. 2020;42(03):256–261. Doi: 10.1016/j.jogc.2019.08.033
22 Liang AL, Gingher EL, Coleman JS. Medical cannabis for gynecologic pain conditions: a systematic review. Obstet Gynecol. 2022;139(02):287–296. Doi: 10.1097/AOG.0000000000004656
23 Chang Y, Zhu M, Vannabouathong C, Mundi R, Chou RS, Bhandari M. Medical cannabis for chronic noncancer pain: a systematic review of health care recommendations. Pain Res Manag. 2021;2021:8857948. Doi: 10.1155/2021/8857948
24 Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2018;3:CD012182. Doi: 10.1002/14651858.CD012182.pub2
25 IASP Presidential Task Force on Cannabis and Cannabinoid Analgesia. International Association for the Study of Pain Presidential Task Force on Cannabis and Cannabinoid Analgesia position statement. Pain. 2021;162(Suppl 1):S1–S2. Doi: 10.1097/j.pain.0000000000002265
26 Jacobus J, Tapert SF. Effects of cannabis on the adolescent brain. Curr Pharm Des. 2014;20(13):2186–2193. Doi: 10.2174/13816128113199990426
27 Pardo M, Matalí JL, Sivoli J, et al. Early onset psychosis and cannabis use: Prevalence, clinical presentation and influence of daily use. Asian J Psychiatr. 2021;62:102714. Doi: 10.1016/j.ajp.2021.102714
28 Rup J, Freeman TP, Perlman C, Hammond D. Cannabis and mental health: Prevalence of use and modes of cannabis administration by mental health status. Addict Behav. 2021;121:106991. Doi: 10.1016/j.addbeh.2021.106991
29 Eisenstein M. The reality behind cannabidiol's medical hype. Nature. 2019;572(7771):S2–S4. Doi: 10.1038/d41586-019-02524-5

Screening of Perinatal Depression Using the Edinburgh Postpartum Depression Scale

Rastreamento da depressão perinatal através da escala de depressão pós-parto de Edinburgh

Tenilson Amaral Oliveira[1,2] Guilherme Guarany Cardoso Magalhães Luzetti[2]
Márcia Maria Auxiliadora Rosalém[1,2] Corintio Mariani Neto[1,2]

[1] Hospital Maternidade Leonor Mendes de Barros, São Paulo, SP, Brazil
[2] Universidade Cidade de São Paulo, Faculdade de Medicina, São Paulo, SP, Brazil

Address for correspondence Tenilson Amaral Oliveira, PhD, Av. Celso Garcia, 2477, 03015-000, São Paulo, SP, Brazil (e-mail: tenilson@uol.com.br).

Rev Bras Ginecol Obstet 2022;44(5):452–457.

Abstract

Objective To detect depression during pregnancy and in the immediate postpartum period using the Edinburgh postpartum depression scale (EPDS).

Methods Cross sectional study of 315 women, aged between 14 and 44 years, who received perinatal care at the Leonor Mendes de Barros Hospital, in São Paulo, between July 1st, 2019 and October 30th, 2020. The cutoff point suggesting depression was $\geq$ 12.

Results The screening indicated 62 (19.7%) patients experiencing depression. Low family income, multiparity, fewer prenatal appointments, antecedents of emotional disorders, dissatisfaction with the pregnancy, poor relationship with the partner, and psychological aggression were all risk factors associated with depression in pregnancy or in the immediate postpartum period. Antecedents of depression and psychology aggression during pregnancy were significant variables for predicting perinatal depression in the multivariate analysis.

Conclusion There is a significant association between the occurrence of perinatal depression and the aforementioned psychosocial factors. Screening patients with the EPDS during perinatal and postpartum care could facilitate establishing a line of care to improve the wellbeing of mother and infant.

Keywords
- depression
- pregnancy
- risk factors
- prenatal care
- postpartum period

Resumo

Objetivo Identificar as pacientes com quadro de depressão na gravidez e puerpério imediato através da escala de depressão pós-parto de Edimburgo (EPDS).

Métodos Estudo observacional transversal que incluiu 315 mulheres no ciclo grávido-puerperal com idades entre 14 e 44 anos, que foram atendidas no Hospital Maternidade Leonor Mendes de Barros entre 1° de Julho de 2019 e 30 de Outubro de 2020. O ponto de corte utilizado foi $\geq$ 12 da EPDS para definir se a paciente apresentava depressão.

received
June 5, 2021
accepted
October 19, 2021
published online
March 4, 2022

DOI https://doi.org/10.1055/s-0042-1743095.
ISSN 0100-7203.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resultados Encontramos 62 (19,7%) com depressão. Baixa renda familiar, multiparidade, menor número de consultas pré-natal, antecedentes de transtornos emocionais, insatisfação com a gravidez, mau relacionamento com o parceiro, e agressão psicológica foram fatores de risco associados à depressão na gravidez ou no período pós-parto imediato. Antecedentes de depressão e agressão psicológica durante a gravidez foram preditores significativos de depressão perinatal na análise multivariada.
Conclusão O estudo mostrou uma associação significativa entre a ocorrência de depressão e os fatores psicossociais acima mencionados. O pré-natal e o puerpério imediato permitem identificar através da EPDS tais pacientes e estabelecer uma linha de cuidados para melhorar o bem-estar materno e do recém-nascido.

Palavras-chave
- depressão
- gravidez
- fatores de risco
- pré-natal
- perído pós-parto

Introduction

The pregnancy-puerperal cycle, either due to psychosocial factors or hormonal changes, is a time of high risk for the development of depression.[1] A study of 1,558 women revealed that 17% of the pregnant women and 18% of women in the immediate puerperium period screened had significant depressive symptoms in late pregnancy.[2] Perinatal depression can lead to a range of consequences, such as the deterioration of maternal care and the distress of the mother-infant relationship. It may also cause adverse outcomes for the child's growth and development if it occurs during the puerperium period.[3] It is vital, therefore, to pay special attention to the diagnosis and early treatment of perinatal depression.

According to Martins,[4] the psychiatric disorders that predominantly affect women in the perinatal period are divided into three categories: deep sadness syndrome, postpartum depression, and postpartum psychosis. The deep sadness syndrome, also known as "baby blues," begins within the first 2 weeks postpartum, and symptoms may include crying, sadness, increased anxiety, irritability, instability, mood swings, fatigue, and sleep disorders. Postpartum psychosis develops within the first 3 weeks after delivery, a period in which the symptoms are intense and severe, and may include delusions, conferring risk to both mother and child.[5]

Perinatal psychiatric disorders usually occur within the first months postpartum, but can happen earlier,[6] with the gradual development of depressive symptoms, which may be mistaken with the deep sadness syndrome after childbirth.[7] Postpartum depression is a psychiatric disorder that causes emotional, behavioral, and physical changes associated with the puerperium. It is estimated that 25 to 35% of women develop depressive symptoms and $\sim$ 20% may experience depression, with an intensification of symptoms in the 3rd trimester of pregnancy.[8]

Perinatal depression is multifactorial, involving psychosocial and sociodemographic variables, physiological and biological factors, hereditary predispositions, and hormonal changes. It relates to the body, mind, and lifestyle of the puerperal woman, and is deemed difficult to prevent, as no single strategy has so far been capable of preventing the disorder effectively.[9] Increased stress during pregnancy and delivery has been associated with the etiology of postpartum depression. Consequently, both gestation and postpartum periods require careful analysis to facilitate an early identification of the psychosocial, hormonal, and physiological factors causing depression.[10]

As suggested by Salum e Morais et al.,[11] the major risk factors for postpartum depression include the lack of support from the partner, family, and friends; low level of education; being a single mother with a high parity; pregnancy at a young age; stress; and low family income. Other factors, such as unwanted pregnancies, primiparous women, preterm births, marital conflicts, and the death of family members or the last infant, also contribute to the adversity.[12]

We highlight, thus, the importance of the health professional for the early awareness of the aforementioned factors in the effort to prevent depressive disorders and their consequences in the perinatal period. Difficulties, however, such as lack of time, the stigma related to mental illnesses during pregnancy and in the postpartum, and insufficient or inadequate training in graduate school hinder the early detection by obstetricians.[13] On that account, to reduce the impact of depression in pregnancy and the puerperium on the mother, child, family, and community, it is necessary to discuss the different aspects of the complication in the context of public health.

Developed by Cox et al.[14] in 1987 to assist primary care health professionals to detect postpartum depression disorders, the Edinburgh postpartum depression scale (EPDS) is a screening questionnaire that has been widely used to evaluate symptoms of depression during pregnancy and the puerperium. The test can be completed by the patient in 5 minutes and consists of a scale with 10 items, assessing symptoms related to depression over the preceding 7 days, with scores ranging from 0 to 3 for each item. The final result, therefore, varies from 0 to 30.

The authors evaluated its psychometric properties in the United Kingdom, obtaining a sensitivity of 86% and a specificity of 78%. Different scores (between 9–13 points) were compared in the EPDS, with a good correlation.[14] The scores often used for diagnosis were $\geq$ 10 or $\geq$ 12 points. Decreasing the score, the sensitivity increases, but the specificity decreases, causing the occurrence of an elevated false-positive rate.[14] In Brazil, the scale was validated by Santos et al. in 1999.[15] The authors suggest a cutoff point of 11 to 12, with a sensitivity of 72% and a specificity of 88%. The main objective of the present research was to identify patients experiencing depression during pregnancy and the immediate postpartum period using

a score ≥ 12 in the EPDS as a cutoff point indicating depression, so as to establish a line of care for the vulnerable group.

Methods

The cross sectional study included 315 women, aged between 14 and 44 years, who received perinatal care at the Maternity Hospital Leonor Mendes de Barros (HMLMB), in São Paulo, between July 1, 2019 and October 30, 2020. The interview was conducted with 136 pregnant women with more than 28 weeks of gestation, and 176 postpartum women within the first postpartum week. The research protocol was approved by the local research ethics committee before the study began, and all of the women provided written informed consent prior to participating in the interview. After signing the consent form, the patient was enrolled in the study and replied to the interview conducted by one of the authors of study (T. A. O./G. G. C. M. L.). In the interview, the women first answered a questionnaire to identify the major risk factors associated with depression. Afterward, the patient herself filled out the EPDS. The scale was completed in $\sim$ 5 minutes. The interviewers had been trained in the use of the EPDS, and any doubts that eventually came up were jointly discussed. All such interviews took place in ambulatory or maternity ward settings. The interviewer remained blind to the score or the answers because after EPDS to be completed by the mother then it was placed together with the questionnaire in an envelope.

The cutoff was ≥ 12 to indicate whether the patient had depression. The exclusion criteria were: absence of prenatal care, women pregnant with fetuses with congenital malformations and/or diseases incompatible with life, assisted fertilization, stillbirth, and neo-mortality. The collected data was assessed on Microsoft Office Excel 10 spreadsheets (Microsoft Corp., Redmond, WA, USA), the Epi Info 7 program was used to analyze the frequency distribution of categorical variables, and the Mann-Whitney test was used to analyze the continuous variables. The independent variables were categorized to analyze the association between each independent and outcome variable using a bivariate analysis to calculate the crude odds ratio with 95% confidence interval. Those variables that were associated with a p-value < 0.1 in the bivariate analysis were entered into a multivariate logistic regression model to calculate the adjusted Odds Ratio and to eliminate the effects of confounding. Analyses by means of logistic regression were performed using the BioStat version 5.3 software.The statistical significance level was set to $p < 0.05$ for all analyses.

Results

Among 315 patients, 62 (19.7%) patients scored ≥ 12 in the EPDS screening, experiencing probable perinatal depression. The demographic characteristics of the patients are shown in ►**Table 1**. The age ranged from 14 to 44 years, with the average age of 28.3 ± 6.1 in the group signaling perinatal depression (group 1) and 28.9 ± 6.8 years in the group of women without depression (group 2). There were no significant differences in relation to skin color, marital status, use of contraceptive methods by the couple, occupation of the partner or the pregnant woman, and level of education. There were significant differences related to the average family income, which was lower in the group with depression (group 1).

As seen in ►**Table 2**, depressive symptoms were more frequent in multiparous than in nulliparous women, and the average of prenatal appointments was lower. Group 1 also

Table 2 Clinical and obstetric variables of the group screened with the Edinburgh postpartum depression scale

Variables	Group 1 ($n = 62$)	Group 2 ($n = 253$)	*P*-value
Nulliparous (%)	8 (12.9)	76 (30)	0.01
Average perinatal appointments	7.8 ± 3.2	9.2 ± 3.6	0.01
Pregnancy adversities	26 (43)	78 (30.8)	0.09
Antecedents of depression or psychiatric disorders	26 (41.9)	33 (13)	< 0.01
Vaginal birth	18/27 (66.7)	92/149 (61.7)	0.62

Table 1 Sociodemographic characteristics of the group screened with the Edinburgh postpartum depression scale

Variables	Group 1 ($n = 62$)	Group 2 ($n = 253$)	*P*-value
Age average (years)	28.3 ± 6.1	28.9 ± 6.8	0.65
White (%)	26 (41.9)	125 (49.4)	0.29
Married/cohabitation	50 (80.6)	220 (86.9)	0.20
Do not use contraceptives	15 (24.2)	60 (23.7)	0.93
Partner with occupation	48 (77.4)	202 (79.8)	0.67
Mothers with occupation	28 (45.2)	138 (54.5)	0.18
Monthly income average	$1{,}954 \pm 1{,}320$	$2{,}393 \pm 1{,}488$	0.02
Education ≤ 8 years	10 (16.1)	41 (16.2)	0.98

Table 3 Behavioral variables of the group screened with the Edinburgh postpartum depression scale

Behavioral variables	Group 1 ($n = 62$)	Group 2 ($n = 253$)	*P*-value
Satisfaction with pregnancy	55 (88.7)	244 (96.4)	0.03
Desire to abort in the beginning of the pregnancy	10 (16.1)	13 (5.1)	< 0.01
Bad relationship with the partner	18 (29)	18 (7.1)	< 0.01
Partner's support during pregnancy	52 (83.9)	227 (89.7)	0.19
Partner's support after childbirth	24/27 (88.9)	138/149 (92.6)	0.45
Physical aggression	3 (4.8)	2 (0.8)	0.05
Psychological aggression	14 (22.6)	14 (5.5)	< 0.01
Negative experience during delivery	5/27 (18.5)	13/149 (8.7)	0.16

had a higher incidence of previous depression or emotional disorders. Contrarily, complications associated with the pregnancy and the type of delivery did not present significant differences between the two groups (►**Table 2**).

The behavioral aspects of the couple during the third trimester and the first postpartum week were analyzed in ►**Table 3**. Dissatisfaction with the pregnancy was more evident in group 1, in which some patients even acknowledged the wish for abortion in early pregnancy. The lack of a good relationship with the partner was another aspect more frequent in group 1. Contrarily, the support of the partner, both during pregnancy and after childbirth, was not contrasting statistically. Psychological aggression (mistreatment) was also more frequent in group 1, while physical aggression was situated on the threshold of statistical significance. The delivery experience, however, was considered positive for most patients in both groups.

Standard multiple regressions were performed to differentiate the independent effects of predictor variables on the occurrence of perinatal depression (►**Table 4**). Antecedents of depression or psychiatric disorders and psychology aggression during pregnancy showed to be predictive of perinatal depression development on a multivariable analysis.

Discussion

The lower income in group 1 demonstrates the lack of social support for the exercise of motherhood, as concerns, doubts, and domestic conflicts can be triggered due to the lack of economic resources to support the newborn or even the family, also considering that multiparous women are associated with an increased risk of depression. Our study shows that psychosocial risk factors are strongly related with the onset of depression in the sample group, whether due to dissatisfaction with the pregnancy or poor relationship with the partner, even when the experience of childbirth was positive.

The study did not relate physical or hormonal factors as some authors have done,[9,16] searching for a biological cause for depression. It was considered that the antecedent of depression or emotional disorders, more frequent in group 1, makes it unlikely that hormonal changes, typical of pregnancy, will have a preponderant role in depression during the period since all pregnant women had similar hormonal changes, yet only 20% developed depression.

Gauthreaux et al.[17] examined the relationship between the desire to be pregnant and postpartum depression by assessing depressive symptoms. The authors concluded that

Table 4 Multivariable analysis showing the risk factors associated with the perinatal depression of the pregnant women ($n = 315$) screened with the Edinburgh postpartum depression scale

Variables	Coefficient	OR	IC95%	*P*-value
Nuliparous	-0.2312	0.7936	0.33 a 1.93	0.6103
Montly income $\leq$ R$ 1,800**	0.5200	1.6820	0.91 a 3.11	0.0972
Satisfaction with pregnancy	0.0482	1.0504	0.25 a 4.43	0.9459
Desire to abort in the beginning of the pregnancy	0.8886	2.4316	0.87 a 6.77	0.0890
Bad relationship with the partner	0.0954	1.1001	0.14 a 8.92	0.9288
Physical aggression	-0.3464	0.7020	0.08 a 6.65	0.7619
Psychological aggression	1.2900	3.6329	1.49 a 8.88	0.0047*
< 10 appointments **	-0.0204	0.9798	0.53 a 1.82	0.9486
Antecedents of depression or psychiatric disorders	1.1362	3.1149	1.52 a 6.39	0.0019*

*Statistically significant
**Best cutoff point for analysis

women who did not wish to become pregnant had a higher risk of developing postpartum depression than women who desired pregnancy. Turkcapar et al.[18] noticed the same correlation, detecting a percentage of women with postpartum depression who were dissatisfied with their pregnancies. Similar to our case study, the authors also concluded that episodes of domestic violence were associated with the group experiencing depression. Among the main risk factors, antecedents of depression and psychological aggression were highlighted. In fact, women who experienced previous history of depression have strong association with depressive symptoms in pregnancy, regardless of ethnicity.[19] In the present study, antecedents of depression or psychiatric disorders along with psychological aggression were found to be independently associated with perinatal depression.

The occurrence of perinatal depression may lead to the discontinuation of breastfeeding, family conflicts, and the neglect of the infant's physical and psychological needs. By compromising the ability to create healthy and stable bonds, the disorder can negatively influence the relationship between mother and child, in addition to cause damage to the psychomotor and language development and, as a result, lead to relevant cognitive and social impairments.[20] Adolescents and children whose mothers had postpartum depression showed an elevated risk of multiple adverse outcomes.[21]

This study emphasizes the importance of identifying risk factors based on an individual's subjective experience. The scales for diagnosing depression are tools that facilitate tracking and diagnosing the disorder during prenatal care and the immediate puerperium. The use of validated scales can contribute to the production of new evidence concerning the correlation of risk factors and protective measures during pregnancy. Evidence is necessary to support health professionals in the preventive implementation of an adequate approach to coping with the problem.

Antecedents of depression, physical and emotional stress, either caused by socioeconomic factors such as income or by the lack of support from the partner, are risk factors for perinatal depression. The creation of prenatal programs based on a psychological approach, as stated by some authors,[22–24] can contribute to the definition of a preventive line of care focused on perinatal depression. During prenatal care, it is necessary to verify the need for support by assessing the quality of the pregnant women's relationships, contributing to the establishment of positive social relations during the period. Since depression is the most common complication of the perinatal period currently, health professionals, particularly doctors and nurses, play a fundamental role in its early detection as well as intervention. Thus, avoiding the occurrence or worsening of the depressive process and its consequences.

This study suggests that all pregnant women should undergo screening in the third trimester of pregnancy or the postpartum period. The EPDS is a simple and useful instrument for screening, as it presents an easy method for diagnosis. To treat the vulnerable group, alongside screenings, professional references and therapeutic resources are also needed.

Conclusion

In conclusion, there is a significant association between the occurrence of depression and certain psychosocial factors, notably antecedents of depression and psychological abuse, which were predictive factors in a multivariate analysis. To face this challenge, prenatal care must provide a comprehensive psychological approach to identify and treat the disorder. Offering an appropriate line of care to the vulnerable group will contribute to the improvement of the wellbeing of the mother and the future of the infant.

Contributions

Authors T. A. O. and G. G. C. M. L. conducted all aspects of data collection and analysis, and T. A. O. wrote the manuscript with input from all other authors. Authors M. M. A. R. and C. M. N. collaborated with the critical revision of the article.

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgments

The authors would like to thank Clarissa Aidar Oliveira for the formatting and translation support and Júlio Cesar Barbour Oliveira for the statistical analysis.

References

1 Learman LA. Screening for depression in pregnancy and the postpartum period. Clin Obstet Gynecol. 2018;61(03):525–532. Doi: 10.1097/GRF.0000000000000359
2 Josefsson A, Berg G, Nordin C, Sydsjö G Prevalence of depressive symptoms in late pregnancy and postpartum. Acta Obstet Gynecol Scand. 2001;80(03):251–255. Doi: 10.1034/j.1600-0412.2001.080003251.x
3 Field T. Postpartum depression effects on early interactions, parenting, and safety practices: a review. Infant Behav Dev. 2010;33(01):1–6. Doi: 10.1016/j.infbeh.2009.10.005
4 Martins RA. A depressão materna do pós-parto: algumas compreensões e outros nevoeiros [dissertação]. São Paulo: Pontifícia Universidade Católica de São Paulo; 2006
5 Costa R, Pacheco A, Figueiredo B. Prevalência e preditores de sintomatologia depressiva após o parto. Rev Psiquiatr Clin (Santiago). 2007;34(04):157–165. Doi: 10.1590/S0101-6083200 7000400001
6 Cantilino A, Zambaldi CF, Sougey EB, Rennó J Jr. Transtornos psiquiátricos no pós-parto. Rev Psiquiatr Clin (Santiago). 2010;37(06):278–284. Doi: 10.1590/S0101-60832010000600006
7 Schmidt EB, Piccoloto NM, Miller MC. Depressão pós-parto: fatores de risco e repercussões no desenvolvimento infantil. Psico-USF. 2005;10(01):61–68. Doi: 10.1590/S1413-82712005000100008
8 Hildebrandt FM. Depressão pós-parto: aspectos epidemiológicos e tratamento cognitivo-comportamental [tese]. Rio de Janeiro: Universidade Federal do Rio de Janeiro; 2013
9 Zinga D, Phillips SD, Born L. Depressão pós-parto: sabemos os riscos, mas podemos preveni-la? Br J Psychiatry. 2005;27(Suppl 2):S56–S64. Doi: 10.1590/S1516-44462005000600005
10 Arrais AR, Araujo TC. Depressão pós-parto: uma revisão sobre fatores de risco e proteção. Psicol Saude Doencas. 2017;18(03):828–845. Doi: 10.15309/17psd180316
11 Salum e Morais ML, Fonseca LA, David VF, Viegas LM. Fatores psicossociais e sócio-demográficos associados à depressão pós-parto: um estudo em hospitais público e privado da cidade de São

Paulo, Brasil. Estud Psicol (Natal). 2015;20(01):40–49. Doi: 10.5935/1678-4669.20150006

12 Nishimura A, Fujita Y, Katsuta M, Ishihara A, Ohashi K. Paternal postnatal depression in Japan: an investigation of correlated factors including relationship with a partner. BMC Pregnancy Childbirth. 2015;15:128. Doi: 10.1186/s12884-015-0552-x

13 Rennó Júnior J, Rocha R. Gravidez e depressão [Internet]. São PauloFEBRASGO2018 [cited 2020 Apr 20]. (Protocolo FEBRASGO – Obstetrícia; no. 92/ Comissão Nacional Especializada em Gestação de Alto Risco). Available from: https://sogirgs.org.br/area-do-associado/gravidez-e-depressao.pdf

14 Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987;150(06):782–786. Doi: 10.1192/bjp.150.6.782

15 Santos MF, Martins FC, Pasquali L. Escala de auto-avaliação de depressão pós-parto: estudo no Brasil. Rev Psiquiatr Clin (Santiago). 1999;26(02):90–95

16 Aliane PP, Mamede MV, Furtado EF. Revisão sistemática sobre fatores de risco associados à depressão pós-parto. Psicol Pesqui. 2011;5(02):146–155

17 Gauthreaux C, Negron J, Castellanos D, Ward-Peterson M, Castro G, Rodríguez de la Vega P, et al. The association between pregnancy intendedness and experiencing symptoms of postpartum depression among new mothers in the United States, 2009 to 2011: A secondary analysis of PRAMS data. Medicine (Baltimore). 2017;96(06):e5851. Doi: 10.1097/MD.0000000000005851

18 Turkcapar AF, Kadıoğlu N, Aslan E, Tunc S, Zayıfoğlu M, Mollamahmutoğlu L. Sociodemographic and clinical features of postpartum depression among Turkish women: a prospective study. BMC Pregnancy Childbirth. 2015;15:108. Doi: 10.1186/s12884-015-0532-1

19 Shakeel N, Eberhard-Gran M, Sletner L, Slinning K, Martinsen EW, Holme I, et al. A prospective cohort study of depression in pregnancy, prevalence and risk factors in a multi-ethnic population. BMC Pregnancy Childbirth. 2015;15:5. Doi: 10.1186/s12884-014-0420-0

20 Schaffir J. Consequences of antepartum depression. Clin Obstet Gynecol. 2018;61(03):533–543. Doi: 10.1097/GRF.0000000000000374

21 Netsi E, Pearson RM, Murray L, Cooper P, Craske MG, Stein A. Association of persistent and severe postnatal depression with child outcomes. JAMA Psychiatry. 2018;75(03):247–253. Doi: 10.1001/jamapsychiatry.2017.4363

22 Arrais AR, Mourão MA, Fragalle B. O pré-natal psicológico como programa de prevenção à depressão pós-parto. Saude Soc. 2014;23(01):251–264. Doi: 10.1590/S0104-12902014000100020

23 Almeida NM, Arrais AR. O pré-natal psicológico como programa de prevenção à depressão pós-parto. Psicologia (Cons Fed Psicol). 2016;36(04):847–863. Doi: 10.1590/1982-3703001382014

24 Bortoletti FF. Psicoprofilaxia no ciclo gravídico puerperal. In: Bortoletti FF, Moron AF, Bortoletti Filho J, Nakamura MU, Santana RM, Mattar R. Psicologia na prática obstétrica: abordagem interdisciplinar. Barueri: Manole; 2007:37–46

Hematological Parameters to Predict the Severity of Hyperemesis Gravidarum and Ketonuria

Parâmetros hematológicos para prever a gravidade da hiperêmese gravídica e da cetonúria

Mehmet Musa Aslan[1] Mustafa Taner Yeler[2] İsmail Bıyık[3] Hilal Uslu Yuvacı[4] Arif Serhan Cevrioğlu[4] Selcuk Özden[4]

[1] Department of Obstetrics and Gynecology, Sakarya Training and Research Hospital, School of Medicine, Sakarya University, Sakarya, Turkey
[2] Department of Biochemistry, Muş State Hospital, Muş, Turkey
[3] Department of Obstetrics and Gynecology, Kütahya Health Sciences University, Kütahya, Turkey
[4] Sakarya University, School of Medicine, Sakarya Training and Research Hospital, Department of Obstetrics and Gynecology, Sakarya, Turkey

Address for correspondence Mehmet Musa Aslan, MD, Department of Obstetrics and Gynecology, Sakarya Training and Research Hospital, Adnan Menderes Avenue Sağlık Street No: 195 Adapazarı/Sakarya, Turkey (e-mail: Jinopdrmma@gmail.com).

Rev Bras Ginecol Obstet 2022;44(5):458–466.

Abstract

Objective Hyperemesis gravidarum (HG) is a pregnancy complication that can progress with persistent nausea and vomiting. The aim of the present study is to evaluate the relationship between hematological parameters and HG.

Method A total of 532 pregnant women with HG who were admitted to the Department of Obstetrics and Gynecology between March 2019 and February 2021, and 534 healthy pregnant women with characteristics similar to those of the case group were included in the study. The hematological parameters of both groups were compared. In addition, the hematological parametersof patients with HG according to the severity of ketonuria were compared.

Results The mean age of the HG group ($n = 532$) was 26.3 ± 4.1 years, and that of the control group ($n = 534$) was 25.9 ± 4.8 years. Among patients with HG, 46% ($n = 249$) had ketone(+), 33% ($n = 174$), ketone(++), and 21% ($n = 109$), ketone(+++). The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were higher in the HG group than in the control group: 3.8 (2.8–5.8)/3.2 (2.6–4.0); $p < 0.001$; and $135.2 \pm 30.4/108.9 \pm 62.2$; $p < 0.001$ respectively. The neutrophil count, NLR, and PLR were higher in the group with ketone(+++) than in the groups with ketone(+) or ketone(++): $7.6 \pm 1.9/5.5 \pm 2.4$; $p < 0.001$; 3.8(2.8–4.6)/2.9(2.3–3.6); $p < 0.001$; and $149.9 \pm 48.0/135.9 \pm 65.7$; $p < 0.001$ respectively. The mean corpuscular hemoglobin (MCH) level, the NLR, and the PLR were identified as independent predictors of the presence of HG and the level of ketone positivity in HG patients.

Keywords
- hyperemesis gravidarum
- ketonuria
- hematological parameters

received
July 22, 2021
accepted
October 19, 2021
published online
April 11, 2022

DOI https://doi.org/10.1055/s-0042-1743101.
ISSN 0100-7203.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Conclusion The NLR and PLR were high in patients with HG, suggesting the its inflammatory activity. They may be important markers associated with the presence and severity of HG.

Resumo

Objetivo A hiperêmese gravídica (HG) é uma complicação da gravidez que pode evoluir com náuseas e vômitos persistentes. O objetivo deste estudo é avaliar a relação entre os parâmetros hematológicos e a HG.

Método Foram incluídas neste estudo 532 gestantes com HG internadas no Departamento de Obstetrícia e Ginecologia entre março de 2019 e fevereiro de 2021, e 534 gestantes saudáveis com características semelhantes às do grupo de caso. Os parâmetros hematológicos foram comparados entre gestantes com e sem HG. Além disso, os parâmetros hematológicos foram comparados entre as pacientes com HG de acordo com a gravidade da cetonúria.

Resultados A média de idade do grupo GH ($n = 532$) foi de $26,3 \pm 4,1$ anos, e a do grupo de controle ($n = 534$) foi de $25,9 \pm 4,8$ anos. Entre as pacientes com HG, 46% ($n = 249$) tinham cetona(+), 33% ($n = 174$), cetona(++), e 21% ($n = 109$), cetona (+++). A razão de neutrófilos para linfócitos (RNL) e a razão de plaquetas para linfócitos (RPL) foram maiores no grupo HG do que no grupo de controle: 3,8 (2,8–5,8)/ 3,2 (2,6–4,0); $p < 0,001$; e $135,2 \pm 30,4/108,9 \pm 62,2$; $p < 0,001$, respectivamente). A contagem de neutrófilos, a RNL e a RPL foram maiores no grupo com cetona(+++) do que nos grupos com cetona(+) e cetona(++): $7,6 \pm 1,9/5,5 \pm 2,4$; $p < 0,001$; 3,8 (2,8–4,6)/2,9 (2,3–3,6); $p < 0,001$; e $149,9 \pm 48,0/135,9 \pm 65,7$; $p < 0,001$, respectivamente. O nível médio de hemoglobina corpuscular (MHC), a RNL e a RPL foram identificados como preditores independentes da presença de HG e do nível de positividade de cetona em pacientes com HG.

Conclusão A RNL e RPL estavam elevadas em pacientes com HG, o que sugere a sua atividade inflamatória. Elas podem ser marcadores importantes associados à presença e à gravidade da HG.

Palavras-chave
- hiperêmese gravídica
- cetonúria
- parâmetros hematológicos

Introduction

Nausea and/or vomiting occur in ~ 50% to 80% of pregnant women in the first trimester, and have various negative effects.[1] Hyperemesis gravidarum (HG) is the medical term for severe nausea and vomiting during pregnancy. It may progress with excessive nausea, vomiting, dehydration, ketosis, electrolyte and acid-base imbalance, and sometimes hepatic and renal failure, leading to weight loss (> 5% of body weight).[2] It is is a serious complication of pregnancy, with a frequency of 0.3% to 3%.[3] It typically starts at 4 and 8 weeks of gestation and lasts until weeks 14 to 16.[1,4]

Although the underlying cause are not precisely known, it is thought that factors such as high serum levels of steroid hormones, high serum concentrations of human chorionic gonadotropin (hCG), allergens, genetic predisposition, metabolic disorders, hepatic dysfunction, gastrointestinal dysfunction, and neurotic and psychosomatic disorders contribute to the etiology.[3,5] In addition, studies[6,7] have shown that *Helicobacter pylori* could increase the risk of developing HG. In particular, the cytotoxin-associated gene A (CagA) toxin is an important *H. pylori* virulence factor associated with a greater inflammatory response.[8] The role of inflammation in the pathogenesis of HG cannot be adequately explained with current data. Proinflammatory cytokines and inflammatory markers such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) have been found to be elevated in HG patients.[9] As metabolic disorders may cause HG, abnormalities in hematological and biochemical parameters may be associated with nausea and vomiting during pregnancy.

In recent studies,[27,28] various hematological parameters have been used to evaluate the inflammatory status of different diseases. The platelet-to-lymphocyte ratio (PLR) and the neutrophil-to-lymphocyte ratio (NLR) are valuable markers that can be obtained from the complete blood count (CBC) at a low cost, with ease and efficiency. Hematological parameters such as the NLR and PLR have been shown to reflect the inflammatory burden and disease activity in several diseases, including ulcerative colitis, spontaneous bacterial peritonitis, malignancies, and cardiovascular diseases.[10–12] Hyperemesis gravidarum is a disease that requires hospitalization and affects the psychological and physical health of patients,[13] Its diagnosis is still primarily clinical, and any marker that can be used to predict disease

severity may be important. It remains unclear whether hematological parameters are independent markers of the presence and severity of HG.

In the present study, we aimed to investigate the diagnostic value of hematological parameters such as the NLR and PLR in HG patients and their relationship with disease severity.

Methods

The present is a single-center retrospective study in which the data of 532 pregnant women with HG admitted to our Gynecology and Obstetrics Clinic between March 2019 and February 2021 were analyzed. A total of 534 pregnant women who had no complaints and were age-matched were included as the control group. Both the case and control groups consisted of pregnant women between the ages of 18 and 35 years who were between the 6th and 13th weeks of pregnancy, with positive fetal heartbeat, and gravida 1. All abdominal ultrasonography findings of the study sample were normal. Pregnant women with persistent vomiting with more than 4 episodes a day, ketone positivity in the urine, and 5% weight loss since the beginning of pregnancy were diagnosed as having HG. Patients with any other metabolic or infectious diseases causing nausea, multiple pregnancies, trophoblastic diseases, history of any systematic disease (such as diabetes mellitus, hypertension, and thyroid diseases), psychiatric disorders, any inflammatory disease, use of antiemetics, smoking habits, or alcohol consumption were excluded from the study. All data were retrieved from an electronic medical system, using a specific diagnostic code for HG of the International Classification of Diseases (ICD). The age, height, and weight of the patients were recorded. The body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters. The study was approved by the Sakarya University Ethics Committee (under number 329), and was conducted in accordance with the guidelines of the Helsinki Declaration.

All blood samples were collected by drawing 5 mL of blood from the antecubital vein without the use of anticoagulants on the day of admission. The CBC values were recorded for each patient. All CBC analyses were performed in our hospital's hematology laboratory using the same Beckman Coulter Gen-S automated analyzer (Brea, CA, United States) for all samples. All CBC parameters, including basophil, eosinophil, hematocrit, hemoglobin (Hb), lymphocyte, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean cell volume (MCV), monocyte, mean platelet volume (MPV), neutrophil, plateletcrit (PCT), platelet distribution width (PDW), platelet (PLT), red blood cell (RBC), red cell distribution width (RDW), and white blood cell (WBC) values were obtained from the medical records. The NLR was calculated from the differential count by dividing the absolute neutrophil count by the absolute lymphocyte count, and the PLR was calculated by dividing the platelet count by the number of lymphocytes. Ketone levels were analyzed in spot urine samples and classified as (+), (++), or (+++). The CBC parameters were compared between both groups. Then, the HG group was separated according to their ketone positivity, and their CBC parameters were compared.

All statistical tests were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, United States). The Kolmogorov-Smirnov test was used to analyze the normality of the data. The continuous data were expressed as means ± standard deviations (SDs), and the categorical data, as percentages. The Chi-squared test was used to assess the differences regarding the categorical variables between groups. The Student *t*-test or the Mann-Whitney U test was used to compare unpaired samples, as needed. The relationship among parameters was assessed by the Pearson or Spearman correlation analysis, according to the normality of the data. Univariate and multivariate logistic regression analyses were used to identify independent variables for HG and ketone severity. The independent variables in the univariate analysis were age, Hb level, RDW, MCH level, MPV, WBC level, neutrophil level, lymphocyte level, NLR, and PLR. After the univariate analysis, significant variables were selected for the multivariate logistic regression analysis using the stepwise method. The results of the univariate and multivariate regression analyses are presented as odds ratios (ORs) with 95% confidence intervals (95%CIs). All independent variables in the logistic regression were tested for multicollinearity. If the variance inflation factor (VIF) exceeded 3.0, the variable was considered collinear. Statistical significance was set at two-sided $p < 0.05$.

Results

►**Table 1** shows the clinical and demographic characteristics of the 532 patients with HG and the 534 age-matched controls in the study. There was no statistically significant difference between the groups in terms of age and BMI. The CBC parameters of the groups were compared, and RBC, hematocrit, Hb, and PLT levels were found to be significantly higher in the HG group than in the control group ($4.5 \pm 0.5/4.3 \pm 0.4$; $p < 0.001$; $38.6 \pm 4.2/36.0 \pm 3.8$; $p < 0.001$; $12.9 \pm 1.5/12.1 \pm 1.4$; $p < 0.001$; and $284.2 \pm 63.7/207.3 \pm 56.4$; $p = 0.033$ respectively). Likewise, the MCH, MCV, and MPV values were significantly higher in the HG group than in the control group ($28.6 \pm 2.6/27.9 \pm 2.7$; $p < 0.001$; $85.5 \pm 5.9/83.0 \pm 6.2$; $p < 0.001$; and $8.3 \pm 1.5/8.0 \pm 1.5$; $p = 0.005$, respectively). The MCHC was significantly lower in the HG group than in the control group ($33.4 \pm 1.6/33.6 \pm 1.3$; $p = 0.039$). There was no difference in the PCT level between the groups. The PDW was significantly higher in the HG group than in the control group: 20.1 ± 1.2 and 19.5 ± 1.4; $p < 0.001$ respectively. The WBC and neutrophil levels were significantly higher in the HG group than in the control group: $12.3 \pm 4.2/11.4 \pm 4.2$; $p = 0.001$; and $9.6 \pm 4.5/6.6 \pm 2.3$; $p < 0.001$ respectively). There was no difference between the groups in terms of basophil and eosinophil levels. The lymphocyte level was higher in the HG group than in the control group: 2.1 ± 0.7 and 1.9 ± 0.6; $p < 0.001$

Table 1 Demographic and clinical data of the study sample

Clinical characteristics	Control group ($n = 534$)	HG group ($n = 532$)	p-value
Age (years)	25.9 ± 4.8	26.3 ± 4.1	0.212
BMI (kg/m^2)	24.79 ± 3.17	23.12 ± 3.48	0.488
Ketone positivity	–	1.7 ± 0.7	< 0.001
RBC	4.3 ± 0.4	4.5 ± 0.5	< 0.001
Hb (g/dL)	12.1 ± 1.4	12.9 ± 1.5	< 0.001
Hematocrit (%)	36.0 ± 3.8	38.6 ± 4.2	< 0.001
RDW (%)	13.2 ± 1.9	13.1 ± 2.0	0.213
MCH (pg)	27.9 ± 2.7	28.6 ± 2.6	< 0.001
MCHC (g/dL)	33.6 ± 1.3	33.4 ± 1.6	0.039
MCV (fL)	83.0 ± 6.2	85.5 ± 5.9	< 0.001
MPV (fL)	8.0 ± 1.5	8.3 ± 1.5	0.005
PLT (/mm^3 $\times 10^3$)	207.3 ± 56.4	284.2 ± 63.7	0.033
PCT (%)	0.1 ± 0.04	0.1 ± 0.05	0.714
PDW (%)	19.5 ± 1.4	20.1 ± 1.2	< 0.001
WBC (/mm^3 $\times 10^3$)	11.4 ± 4.2	12.3 ± 4.2	0.001
Neutrophil (/mm^3 $\times 10^3$)	6.6 ± 2.3	9.6 ± 4.5	< 0.001
Basophil (/mm^3 $\times 10^3$)	0.1(0.0–0.1)	0.1(0.0–0.1)	0.489
Eosinophil (/mm^3 $\times 10^3$)	0.1(0.0–0.1)	0.1(0.0–0.1)	0.646
Lymphocyte (/mm^3 $\times 10^3$)	1.9 ± 0.6	2.1 ± 0.7	< 0.001
Monocyte (/mm^3 $\times 10^3$)	0.6 ± 0.2	0.5 ± 0.2	< 0.001
Neutrophil-to-lymphocyte ratio	3.2(2.6–4.0)	3.8(2.8–5.8)	< 0.001
Platelet-to-lymphocyte ratio	108.9 ± 62.2	135.2 ± 30.4	< 0.001
Ketone positivity, n(%)			
0	534(100)	0(0)	
+	0(0)	249(46)	
++	0(0)	174(33)	
+++	0(0)	109(21)	

Abbreviations: BMI, Body mass index; Hb, hemoglobin; HG, hyperemesis gravidarum; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean cell volume; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; PLT, platelet; RBC, red blood cell; RDW, red cell distribution width; WBC, white blood cell.
Note: Values expressed as means ± standard deviations, or as medians(ranges), unless otherwise specified.

respectively). The NLR and PLR were also higher in the HG group than in the control group: 3.8(2.8–5.8)/3.2(2.6–4.0); $p < 0.001$; and $135.2 \pm 30.4/108.9 \pm 62.2$; $p < 0.001$ respectively) (►**Fig. 1**). The HG patients were categorized according to their ketone levels; there were 249 (46%) patients with ketone (+), 174 (33%) with ketone (++) was, and 109 (21%) with ketone (+++). Patients with ketone (+++) were compared with patients with ketone (+) and ketone (++); the neutrophil count, NLR, and PLR were found higher in the ketone (+++) group than ketone(+) and ketone(++); groups (3.8(2.8–4.6) vs 2.9 (2.3–3.6), $p < 0.001$ for NLR; and 149.9 ± 48.0 vs 135.9 ± 65.7, $p < 0.001$ for PLR rescpectively) (►**Table 2**).

Parameters affecting the presence of HG were identified by univariate and multivariate analyses with logistic regression. The age, Hb, RDW, MCH, MPV, WBC, neutrophil, lymphocyte, NLR, and PLR were first evaluated in the univariate analysis. The Hb, MCH, MPV, WBC, neutrophil, lymphocyte, NLR, and PLR were statistically significant in univariate analysis, and they were reevaluated in the multivariate analysis. The Hb, MCH, MPV, WBC, NLR, and PLR were found to be significant independent predictors of the presence of HG (Hb – OR: 1.409; $p < 0.001$; MCH – OR: 0.785; $p < 0.001$; MPV – OR: 1.161; $p < 0.001$; WBC – OR: 0.952; $p = 0.002$; NLR – OR: 0.817; $p < 0.001$; and PLR – OR: 1.291. $p < 0.001$). However, parameters that were thought not to affect the development of HG or did not reach statistical significance between the groups were not included in the regression model (►**Table 3**).

Parameters affecting the level of ketone positivity were identified through univariate and multivariate analyses with logistic regression. The MCH, NLR, and PLR were found to be significant independent predictors of the level of ketone positivity in HG patients (MCH – OR: 0.889; $p = 0.003$; NLR – OR: 1.111; $p = 0.033$; PLR – OR: 0.995; $p = 0.035$) (►**Table 4**).

The Pearson or Spearman correlation analysis was used to evaluate the relationship between ketone positivity and CBC

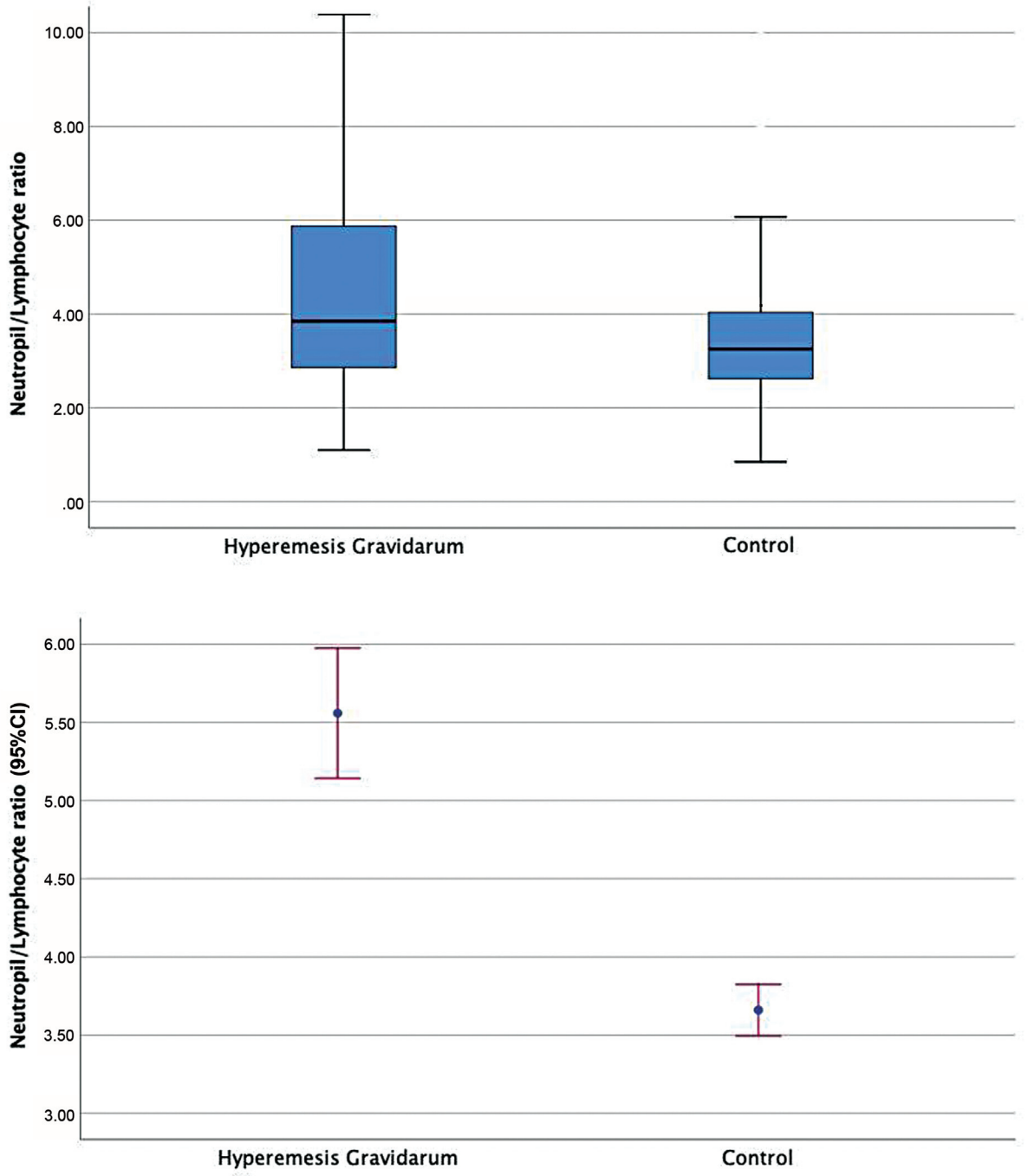


Fig. 1 Comparison of the neutrophil-to-lymphocyte ratio (NLR) of patients with hyperemesis gravidarum and the control group.

parameters. A statistically significant positive correlation was found between the level of ketone positivity and Hb, neutrophil, NLR, and PLR ($r = 0.290$; $p < 0.001$; $r = 0.276$; $p < 0.001$; $r = 0.664$; $p < 0.001$; and $r = 0.590$; $p < 0.00$ respectively) (►**Table 5**).

Discussion

In the present study, we aimed to investigate the diagnostic value of hematological parameters in HG patients and their relationship with disease severity. Our main findings were as follows: 1) the NLR and PLR were higher in the HG group than in the control group; 2) the NLR and PLR were higher in HG patients with ketone(+++), indicating greater disease severity compared with that of patients with ketone(+) or ketone(++); 3) the MCH, NLR, and PLR were independent predictors of the presence of HG and of the level of ketone positivity in HG patients; and 4) a statistically significant positive correlation was found between the ketone positivity level and the Hb, neutrophil, NLR, and PLR.

Table 2 Comparison of patients with hypermesis gravidarum according to ketone positivity

Clinical characteristics	Ketone +/++ ($n = 423$)	Ketone +++ ($n = 109$)	*p*-value
Age (years)	26.1 ± 4.0	26.9 ± 4.3	0.111
RBC	4.5 ± 0.4	4.4 ± 0.6	0.339
Hb (g/dL)	13.0 ± 1.3	12.5 ± 1.8	0.014
Hematocrit (%)	38.7 ± 3.9	37.9 ± 5.1	0.106
RDW (%)	13.1 ± 2.0	12.9 ± 1.8	0.228
MCH (pg)	28.8 ± 2.5	28.0 ± 2.8	0.004
MCHC (g/dL)	33.5 ± 1.6	33.0 ± 1.7	0.003
MCV (fL)	85.7 ± 5.8	84.7 ± 6.3	0.116
MPV (fL)	8.3 ± 1.5	8.4 ± 1.5	0.699
PLT (/mm^3 $\times 10^3$)	270.0 ± 57.2	298.5 ± 53.3	0.404
PCT (%)	0.1 ± 0.05	0.1 ± 0.04	0.637
PDW (%)	19.4 ± 1.3	19.7 ± 1.8	0.153
WBC (/mm^3 $\times 10^3$)	11.4 ± 4.2	11.7 ± 3.9	0.499
Neutrophil (/mm^3 $\times 10^3$)	5.5 ± 2.4	7.6 ± 1.9	< 0.001
Basophil (/mm^3 $\times 10^3$)	0.1(0.0–0.1)	0.0(0.0–0.1)	0.127
Eosinophil (/mm^3 $\times 10^3$)	0.1(0.0–0.1)	0.1(0.0–0.1)	0.609
Lymphocyte (/mm^3 $\times 10^3$)	1.9 ± 0.6	2.0 ± 0.5	0.062
Monocyte (/mm^3 $\times 10^3$)	0.5 ± 0.2	0.5 ± 0.2	0.774
Neutrophil-to-lymphocyte ratio	2.9(2.3–3.6)	3.8(2.8–4.6)	< 0.001
Platelet-to-lymphocyte ratio	135.9 ± 65.7	149.9 ± 48.0	< 0.001

Abbreviations: Hb, hemoglobin; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean cell volume; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; PLT, platelet; RBC, red blood cell; RDW, red cell distribution width; WBC, white blood cell.
Note: Values expressed as means ± standard deviations, or as medians(ranges).

Severe vomiting and nausea are characteristic in HG, leading to malnutrition, electrolyte imbalance, and disruption in biochemical parameters, and generally requiring hospitalization.[14,15] Although the etiology of HG is not fully known, psychological factors, hormonal changes, abnormal gastrointestinal motility, *H. pylori*, vitamin/mineral deficiencies, changes in the autonomic nervous system, changes in the lipid profile, genetic factors, and immunological regulation disorders have been implicated in HG.[3,15,16] However, the net effect of any factor could not be determined. Nevertheless, active or chronic *H. pylori* infection is observed more frequently in HG patients compared with asymptomatic pregnant women, and certain parameters such as inflammation-related CRP and IL-6 are higher in HG patients, suggesting that inflammation may play a role in the pathogenesis of this disease.[6,9]

In addition to the classic markers of inflammation, the NLR and PLR have been investigated[10–12,17,18] as inflammatory markers in recent years. The basis of these studies is the physiological response of leukocytes to stimuli, the increase in the number of neutrophils, and the decrease in the lymphocyte count accompanying neutrophilia.[17] The NLR has been shown to play a prognostic role in various disease groups, such as infectious diseases, metabolic syndrome, chronic obstructive pulmonary disease, end-stage renal disease, subdural hemorrhage, Behcet disease, malignancy, and diseases of the cardiovascular system.[10–12] The PLR has been reported to be an independent predictor of reduced survival, with a negative prognostic value in gynecological and hepatobiliary system malignancies.[18]

Various studies have been conducted to investigate the diagnostic importance of hematological system markers in HG patients. In a prospective study by Kurt et al.,[19] the NLR and high-sensitivity CRP level were found to be significantly higher in the HG group. In a retrospective study by Tayfur et al.[20] including 433 pregnant women, the authors found that inflammatory markers such as the NLR, PLR, and PCT level were significantly higher in HG patients. In a prospective study by Beyazit et al.[21] with 112 patients, the PLR and NLR were found to be higher in patients with HG, and the NLR was found to be correlated with the CRP level.[21] In a prospective study including 355 pregnant women, the WBC, NLR, PLR, and RDW were found to be higher in the HG group, and even in the late second trimester of pregnancy, they remained high in patients with HG.[22] A study by Çintesun et al.[23] demonstrated that the NLR and PLR were effective markers in HG. In agreement with the literature, the NLR and PLR were high in patients with HG in the present study. In addition, we found that the NLR and PLR were independent predictors of the presence and severity of HG. In

Table 3 Univariate and multivariate logistic regression analyses of the risk factors associated with the presence of hyperemesis gravidarum

Variable	Univariate			Multivariate		
	OR	95%CI	*p*-value	OR	95%CI	*p*-value
Age	1.011	0.986–1.037	0.392			
Hemoglobin	1.440	1.321–1.570	< 0.001	1.409	1.280–1.552	< 0.001
RDW	0.973	0.917–1.033	0.365			
MCH	1.098	1.051–1.147	< 0.001	0.785	0.701–0.881	< 0.001
MPV	1.068	1.046–1.090	< 0.001	1.161	1.104–1.221	< 0.001
WBC	0.953	0.927–0.979	0.001	0.952	0.923–0.982	0.002
Neutrophil	0.952	0.939–0.965	< 0.001	0.991	0.971–1.011	0.370
Lymphocyte	1.063	1.046–1.081	< 0.001	0.995	0.964–1.026	0.733
NLR	0.819	0.777–0.862	< 0.001	0.817	0.772–0.864	< 0.001
PLR	1.081	1.003–1.165	0.042	1.291	1.173–1.420	< 0.001

Abbreviations: 95%CI, 95% confidence interval; MCH, mean corpuscular hemoglobin; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PLR, platelet-to-lymphocyte ratio; RDW, red cell distribution width; WBC, white blood cell.

Table 4 Univariate and Multivariate logistic regression analyses of the risk factors associated according to ketone positivity levels

Variable	Univariate			Multivariate		
	OR	95%CI	*p*-value	OR	95%CI	*p*-value
Age	1.044	0.992–1.099	0.096	1.042	0.989–1.099	0.124
Hemoglobin	0.821	0.718–0.938	0.004	0.905	0.772–1.059	0.213
RDW	0.934	0.836–1.044	0.228			
MCH	0.898	0.833–0.968	0.005	0.889	0.824–0.960	0.003
MCV	0.973	0.940–1.007	0.117			
MPV	1.026	0.900–1.171	0.699			
WBC	1.017	0.968–1.068	0.498			
Neutrophil	0.992	0.968–1.017	0.522			
Lymphocyte	0.990	0.962–1.020	0.511			
NLR	1.100	0.998–1.211	0.054	1.111	1.007–1.226	0.033
PLR	0.996	0.992–1.000	0.074	0.995	0.991–0.999	0.035

Abbreviations: 95%CI, 95% confidence interval; MCH, mean corpuscular hemoglobin; MCV, mean cell volume; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PLR, platelet-to-lymphocyte ratio; RDW, red cell distribution width; WBC, white blood cell.

Table 5 Pearson/Spearman correlation coefficients regarding complete blood count parameters and ketone positivity levels in all patients

	Pearson/Spearman	Hb	MCV	Neutrophil	PDW	WBC	NLR	PLR
Ketone	*r*	0.250	0.163	0.276	-0.171	-0.102	0.664	0.590
	p	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	<0.001

Abbreviations: Hb, hemoglobin; MCV, mean cell volume; NLR, neutrophil-to-lymphocyte ratio; PDW, platelet distribution width; PLR, platelet-to-lymphocyte ratio; WBC, white blood cell.

comparison with other studies, the present involved a larger sample.

In patients with HG, increased hemoconcentration can be expected due to vomiting. However, Sari et al.[24] found that the Hb and hematocrit levels did not change in HG patients. In the present study, the Hb and hematocrit levels were high in patients with HG. In addition, we identified the level of Hb as an independent predictor of the presence of HG. The lymphocyte count tends to be higher in pregnant women with HG.[9] However, some studies[20,24] have reported no changes in the lymphocyte count in HG patients. In the present study, the lymphocyte count was higher in the HG group.

The PDW, PCT level, and MPV reflect changes in the PLT volume, and are thought to indicate PLT activation.[25] Beyazit

et al.[21] found that the PDW and MPV did not differ significantly between HG patients and controls.[21] Tayfur et al.[20] found that the PCT level was significantly higher in HG patients than in healthy pregnant controls. In the present study, although there was no difference in the PCT level, the PDW and MPV were high in HG patients. In addition, the MPV was identified as an independent marker in the diagnosis of the disease.

Ketonuria is a parameter used in the diagnosis of severe HG. Hypokalemia, hypochloremic metabolic alkalosis, and ketosis due to low calorie intake can occur in pregnant women. In a study[26] comparing patients with and without HG, higher ketonuria was observed in the HG group, and prolonged hospital stay was associated with higher ketonuria. In a study[23] investigating the relationship between ketonuria and hematological parameters, no marker other than the RDW was correlated with the degree of ketonuria.

In the present study, the patients were grouped according to their ketone positivity level, and hematological parameters were compared. We found that, as the severity of HG increased, the neutrophil count, NLR, and PLR were significantly higher in patients with ketone(+++) than in patients with ketone(++) or ketone(+) in the urine. In contrast to other studies, we showed that the MCH level, NLR, and PLR were independent predictors of the presence and severity of HG. In addition, there was a positive correlation between the ketone positivity level and the Hb, neutrophil, NLR, and PLR parameters.

The present study has several limitations. First, it was a single-center and retrospective study. Second, the Pregnancy Unique-Quantification of Emesis (PUQE) scoring system and the Rhodes index, which enable a more objective evaluation of HG, were not calculated. Third, other inflammatory markers such as the CRP, sedimentation, and IL-6 were not included in the analysis, as they were not measured in all patients.

Conclusion

In conclusion, the results of the present study have demonstrated the association of hematological inflammatory parameters with HG, which may be used to determine disease severity. The NLR and PLR were high in patients with HG, which indicated the inflammatory nature of pregnancy nausea and vomiting. The present study has shown that the NLR and PLR may be used as markers of the inflammatory burden in HG patients. The addition of hematological markers, especially the NLR and PLR, to scoring systems could enable a more objective evaluation of the disease. Further studies on the relationship between HG and inflammation with larger prospective samples are needed.

Contributors

All authors contributed to the writing of the article, relevant revision of the intellectual content, and approved the final version submitted for publication.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Lacroix R, Eason E, Melzack R. Nausea and vomiting during pregnancy: A prospective study of its frequency, intensity, and patterns of change. Am J Obstet Gynecol. 2000;182(04):931–937. Doi: 10.1016/s0002-9378(00)70349-8

2 Godsey RK, Newman RB. Hyperemesis gravidarum. A comparison of single and multiple admissions. J Reprod Med. 1991;36(04): 287–290

3 Eliakim R, Abulafia O, Sherer DM. Hyperemesis gravidarum: a current review. Am J Perinatol. 2000;17(04):207–218. Doi: 10.1055/s-2000-9424

4 Verberg MF, Gillott DJ, Al-Fardan N, Grudzinskas JG. Hyperemesis gravidarum, a literature review. Hum Reprod Update. 2005;11 (05):527–539. Doi: 10.1093/humupd/dmi021

5 Ismail SK, Kenny L. Review on hyperemesis gravidarum. Best Pract Res Clin Gastroenterol. 2007;21(05):755–769. Doi: 10.1016/j.bpg.2007.05.008

6 Golberg D, Szilagyi A, Graves L. Hyperemesis gravidarum and Helicobacter pylori infection: a systematic review. Obstet Gynecol. 2007;110(03):695–703. Doi: 10.1097/01.AOG.0000278571.93861.26

7 Ng QX, Venkatanarayanan N, De Deyn MLZQ, Ho CYX, Mo Y, Yeo WS. A meta-analysis of the association between Helicobacter pylori (H. pylori) infection and hyperemesis gravidarum. Helicobacter. 2018;23(01):e12455. Doi: 10.1111/hel.12455

8 Jafarzadeh A, Hassanshahi GH, Nemati M. Serum levels of high-sensitivity C-reactive protein (hs-CRP)in Helicobacter pylori-infected peptic ulcer patients and its association with bacterial CagA virulence factor. Dig Dis Sci. 2009;54(12):2612–2616. Doi: 10.1007/s10620-008-0686-z

9 Niemeijer MN, Grooten IJ, Vos N, Bais JM, van der Post JA, Mol BW, et al. Diagnostic markers for hyperemesis gravidarum: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014;211(02): 150.e1–150.e15. Doi: 10.1016/j.ajog.2014.02.012

10 Bhat T, Teli S, Rijal J, Bhat H, Raza M, Khoueiry G, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther. 2013;11(01):55–59. Doi: 10.1586/erc.12.159

11 Yildirim M, Turkyilmaz E, Avsar AF. Preoperative neutrophil-to-lymphocyte ratio has a better predictive capacity in diagnosing tubo-ovarian abscess. Gynecol Obstet Invest. 2015;80(04): 234–239. Doi: 10.1159/000371762

12 Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst. 2014;106(06):dju124. Doi: 10.1093/jnci/dju124

13 Ioannidou P, Papanikolaou D, Mikos T, Mastorakos G, Goulis DG. Predictive factors of Hyperemesis Gravidarum: A systematic review. Eur J Obstet Gynecol Reprod Biol. 2019;238:178–187. Doi: 10.1016/j.ejogrb.2019.04.043

14 Austin K, Wilson K, Saha S. Hyperemesis Gravidarum. Nutr Clin Pract. 2019;34(02):226–241. Doi: 10.1002/ncp.10205

15 London V, Grube S, Sherer DM, Abulafia O. Hyperemesis gravidarum: a review of recent literature. Pharmacology. 2017;100(3-4):161–171. Doi: 10.1159/000477853

16 McCarthy FP, Lutomski JE, Greene RA. Hyperemesis gravidarum: current perspectives. Int J Womens Health. 2014;6:719–725. Doi: 10.2147/IJWH.S37685

17 Zahorec R. Ratio of neutrophil to lymphocyte counts–rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy. 2001;102(01):5–14

18 Wang D, Yang JX, Cao DY, Wan XR, Feng FZ, Huang HF, et al. Preoperative neutrophil-lymphocyte and platelet-lymphocyte ratios as independent predictors of cervical stromal involvement in surgically treated endometrioid adenocarcinoma. OncoTargets Ther. 2013;6:211–216. Doi: 10.2147/OTT.S41711

19 Kurt RK, Güler A, Silfeler DB, Ozçil MD, Karateke A, Hakverdi AU. Relation of inflammatory markers with both presence and severity of hyperemesis gravidarum. Ginekol Pol. 2014;85(08): 589–593. Doi: 10.17772/gp/1776
20 Tayfur C, Burcu DC, Gulten O, Betul D, Tugberk G, Onur O, et al. Association between platelet to lymphocyte ratio, plateletcrit and the presence and severity of hyperemesis gravidarum. J Obstet Gynaecol Res. 2017;43(03):498–504. Doi: 10.1111/jog.13228
21 Beyazit F, Öztürk FH, Pek E, Ünsal MA. Evaluation of the hematologic system as a marker of subclinical inflammation in hyperemesis gravidarum: a case control study. Ginekol Pol. 2017;88 (06):315–319. Doi: 10.5603/GP.a2017.0059
22 Yildirim M, Cendek BD, Desdicioglu R, Avşar AF. The existence of continuous systemic inflammation in pregnant women with hyperemesis gravidarum. Cyprus J Med Sci.. 2016;1:46–50. Doi: 10.5152/cjms.2016.167
23 Çintesun E, Akar S, Gul A, Çintesun FN, Sahin G, Ezveci H, et al. Subclinical inflammation markers in hyperemesis gravidarum and ketonuria: A case-control study. J Lab Physicians. 2019;11 (02):149–153. Doi: 10.4103/JLP.JLP_151_18
24 Sari N, Ede H, Engin-Ustun Y, Göçmen AY, Çağlayan EK. Hyperemesis gravidarum is associated with increased maternal serum ischemia-modified albumin. J Perinat Med. 2017;45(04): 421–425. Doi: 10.1515/jpm-2015-0421
25 Bath PM, Butterworth RJ. Platelet size: measurement, physiology and vascular disease. Blood Coagul Fibrinolysis. 1996;7(02):157–161
26 Derbent AU, Yanik FF, Simavli S, Atasoy L, Urün E, Kuşçu UE, et al. First trimester maternal serum PAPP-A and free β-HCG levels in hyperemesis gravidarum. Prenat Diagn. 2011;31(05):450–453. Doi: 10.1002/pd.2715
27 Zahorec R. Neutrophil-to-lymphocyte ratio, past, present and future perspectives. Bratisl Lek Listy. 2021;122(7):474-488. doi:10.4149/BLL_2021_078
28 Jiang S, He F, Gao R, et al. Neutrophil and Neutrophil-to-Lymphocyte Ratio as Clinically Predictive Risk Markers for Recurrent Pregnancy Loss. Reprod Sci. 2021;28(4):1101-1111. doi:10.1007/s43032-020-00388-z

Difficulties in the Management of Placenta Accreta Spectrum in Hospitals with Limited Resources

Dificuldades na gestão do espectro da placenta acreta em hospitais com recursos limitados

Lorgio Rudy Aguilera[1] Luz Mariana Mojica-Palacios[1] Federico Urquizu[1] Mirko Gorena[1] Freddy Tinajeros Guzmán[2] Lina María Vergara Galliadi[3] Alejandra Hidalgo[3] Albaro José Nieto-Calvache[4]

[1] Hospital de la Mujer Percy Boland Rodríguez, Santa Cruz de la Sierra, Bolivia
[2] Johns Hopkins University, Baltimore, MD, United States of America
[3] Centro de Investigaciones Clínicas, Fundación Valle de Lili, Cali, Colombia
[4] Clínica de Espectro de Acretismo Placentario, Fundación Valle de Lili, Cali, Colombia

Address for correspondence Albaro José Nieto Calvache, Fundación Valle Del Lili, Cali, Colombia Carrera 98# 18-49, Cali 760032 (e-mail: albaro.nieto@fvl.org.co).

Rev Bras Ginecol Obstet 2022;44(5):467–474.

Abstract

Objective Placenta accreta spectrum (PAS) is a serious diseases, and the recommendation is that the treatment is conducted in centers of excellence. Such hospitals are not easy to find in low- and middle-income countries. We seek to describe the process of prenatal diagnosis, surgical management, and postnatal histological analysis in a low-income country referral hospital with limited resources.

Methods A descriptive, retrospective study was carried out including patients with a pre- or intraoperative diagnosis of PAS. The clinical results of the patients were studied as well as the results of the prenatal ultrasound and the correlation with the postnatal pathological diagnosis.

Results In total, 129 patients were included. Forty-eight of them had a prenatal PAS ultrasound diagnosis (37.2%). In the remaining 81 (62.8%), the diagnosis was intraoperative. Although hysterectomy was performed in all cases, one-third of the patients (31%) did not have a histological study of the uterus. In 40% of the patients who had a histological study, PAS was not reported by the pathologist.

Conclusion The frequency of prenatal diagnosis and the availability of postnatal histological studies were very low in the studied population. Surgical skill, favored by a high flow of patients, is an important factor to avoid complications in settings with limited resources.

Keywords
- placenta accreta
- developing countries
- Latin America

received
October 5, 2021
accepted after revision
December 13, 2021
published online
April 26, 2022

DOI https://doi.org/10.1055/s-0042-1742408.
ISSN 0100-7203.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resumo

Objetivo O espectro da placenta accreta é uma patologia grave, cujo tratamento é recomendado em centros de excelência. Esses hospitais não são fáceis de encontrar em países de baixa e média renda. Procuramos descrever o processo de diagnóstico pré-natal, tratamento cirúrgico, e análise histológica pós-natal em um hospital de referência de baixa renda com recursos limitados.

Métodos Foi realizado um estudo descritivo, retrospectivo, incluindo pacientes com diagnóstico pré ou intraoperatório de espectro da placenta accreta. Foram estudados os resultados clínicos das pacientes, bem como os resultados da ultrassonografia pré-natal e a correlação com o diagnóstico patológico pós-natal.

Resultados No total, 129 pacientes foram incluídas. Quarenta e oito delas tiveram um diagnóstico de ultrassom do espectro da placenta accreta pré-natal (37,2%). Nos 81 (62,8%) restantes, o diagnóstico foi intraoperatório.

Embora a histerectomia tenha sido realizada em todos os casos, um terço deles (31%) não tinha estudo histológico do útero. Em 40% dos pacientes que tiveram estudo histológico, o espectro da placenta accreta não foi relatado pelo patologista.

Conclusão A frequência do diagnóstico pré-natal e a disponibilidade de estudos histológicos pós-natais foram muito baixas na população estudada. A habilidade cirúrgica, favorecida por um alto fluxo de pacientes, é um fator importante para evitar complicações em ambientes com recursos limitados.

Palavras-chave

- placenta accreta
- países em desenvolvimento
- América Latina

Introduction

Placenta accreta spectrum (PAS) is a serious disease that demands the use of many health resources, since interdisciplinary groups to complex supplies and hospital infrastructure.[1] Although it is recommended that its treatment takes place in centers of excellence,[2] such hospitals are not easy to find in low- and middle-income countries (LMICs).[3,4]

The analysis of PAS fatal cases shows that, in most cases, the determining factor of death was not the lack of technological resources but the inexperience of the treating surgeons, and the use of an inappropriate surgical technique.[5] The training of the surgeon and the interdisciplinary team is probably more important than the unlimited availability of resources.

Few publications describe the clinical results of PAS management in settings with limited resources or highlight the management problems in regional referral hospitals for severe obstetric diseases in LMICs.

We seek to describe the process of prenatal diagnosis, surgical management, and postnatal histological analysis in a referral hospital for severe obstetric diseases with limited resources in a LMIC. Additionally, we aim to describe the problems identified and propose some options to overcome them.

Methods

A descriptive and retrospective study was carried out including patients with a preoperative (by ultrasound signs) or intraoperative (applying clinical FIGO staging criteria)[6] diagnosis of PAS between January 2019 and December 2020 who were treated at Santa Cruz de la Sierra, Bolivia.

Taking into account that our hospital does not have a pathology service, and the resources available in our region require that family members be in charge of processing the histological analysis of the uterus posthysterectomy in another hospital (it is not uncommon for the report of the histological analysis to take more than 1 month or not be available to the surgical team), in all cases, a macroscopic evaluation of the surgical specimen was performed in the operating room at the end of the surgery to confirm or rule out the diagnosis of PAS. The diagnostic criteria for PAS endorsed by the International Federation of Gynecology and Obstetrics (FIGO)[6] were considered, so the patients with the following were included:

1. Histological diagnosis confirming PAS, or
2. Presence of evident clinical signs during laparotomy when observing the external surface of the uterus (purple coloring, placental bulge, and others).

The clinical results of the patients as well as the results of the prenatal ultrasound and the correlation with the postnatal pathological diagnosis were studied. Two groups of patients were established according to whether they had (group 1) or did not have (group 2) a prenatal PAS ultrasonographic diagnosis. All the patients included had placenta previa and underwent cesarean hysterectomy, applying the same operative technique (►**Supplementary material 1**). Considering that a significant percentage of patients did not benefit from the histological study of the uterus, we performed an additional analysis including only patients with histological confirmation of PAS. This retrospective study had the approval of the institutional biomedical research ethics committee - IRB/EC (N° 430-2019). A

descriptive statistical analysis was carried out. Continuous variables are expressed as medians and interquartile ranges and were analyzed with the Mann-Whitney U test. The qualitative variables are summarized with absolute and relative frequencies, and the comparison between them was made with the chi-squared test or Fisher exact test, according to the case. Statistical significance was defined as $p < 0.05$. Analyses were performed using STATA version 14 software (StataCorp LP, College Station, TX, USA).

Results

One hundred and twenty-nine patients with pre or intraoperative diagnosis of PAS were included. ►**Table 1** describes the characteristics of the included sample. Forty-eight of them had a prenatal ultrasound diagnosis (Group 1: 37.2%), and in the remaining 81 (Group 2: 62.8%), the diagnosis of PAS was intraoperative (the prenatal ultrasound did not indicate PAS). The median maternal age was 31 years (interquartile range [IQR] 27.5–34), the median number of previous cesarean sections was two (IQR 1–3), attendance at prenatal check-ups was 63.6%, and the median gestational age at the time of surgery was 37 weeks (IQR 36–38). Although all patients had at least one prenatal ultrasound, only 41 women (31.8%) had a placental Doppler evaluation by a maternal-fetal medicine specialist. Only nine patients underwent planned surgery, and the rest underwent surgery with uterine activity or vaginal bleeding. The median volume of blood loss reported was 700 mL (IQR 500–1,000), and 8 patients (6.2% of the included cases) had bleeding equal to or greater than 2,000 mL, 7 of them in group 1.

One hundred and two patients (79.1%) received red blood cell transfusion, with a median of two red blood cell units (RBCUs) (IQR 1–2). Nine patients (7%) received four or more RBCUs. The median preoperative hemoglobin was 11 g/L, and the last hemoglobin before discharge was 10 g/L (median).

Neuraxial anesthesia was used in 96.9% of the patients (125 women), and 47.1% of the surgeries were performed at night (between 7:00 p.m. and 7:00 a.m.). Although all the patients were managed with a hysterectomy and had intraoperative confirmation of PAS when a cut of the operative piece was performed by the main surgeon, a third of them (31%) did not have a histological study of the uterus. In 40% of the patients who had a histological study (27% of the population), PAS was not reported by the pathologist. The intraoperative clinical diagnosis was accreta in 106 patients (82.2%) and increta/percreta in 22 patients (17.1%). The frequencies of admission to the intensive care unit, ureteral injury, bladder injury, and surgical reintervention were 13.2%, 1.6%, 6.2%, and 3.1%, respectively. The median length of postoperative hospitalization was 4 days (IQR 3-4). Group 1 had a higher frequency of previous risk factors for PAS (previous cesarean section plus placenta previa), placental Doppler evaluation, and planned surgery. Group 1 also had a higher frequency of placenta increta/percreta in the histological study, bleeding greater than 2,000 mL, and transfusion of more than four RBCUs. When analyzing only the patients with histological PAS confirmation (n = 54, 41.9%), a higher frequency of more than two liters of bleeding and more than 4 RBCU transfusions persisted in the group with prenatal diagnosis (►**Table 2**), with no other differences from what was observed in the general population. No maternal deaths were observed.

Discussion

The reality of PAS management in the studied sample is different from the model described in centers of excellence in PAS. The performance of the prenatal diagnosis for PAS and the efficacy of the postnatal pathological study in one of the hospitals with the highest number of births per year in an LMIC are very low.

Despite limitations in prenatal diagnosis, the frequency of complications and the need for transfusion of more than four RBCUs were low.

Multiple publications recommend the treatment of patients with PAS in specialized hospitals with trained interdisciplinary groups.[1,2] However, the characteristics of these "centers of excellence for PAS" are fulfilled by very few hospitals in LMICs[3,4] and even in developed countries.[7] Although the establishment of demanding quality standards favors the improvement of processes in hospitals, it is essential to measure the real baseline situation in each center. Most Latin American hospitals treat a patient with PAS every 2 months, as only 11 centers were identified in the region with more than 2 cases per month attended by a "PAS team".[4] Our observations regarding the low performance of prenatal ultrasonographic diagnosis for detecting PAS and the frequent absence of postoperative histological studies are likely shared by other hospitals in LMICs.[8,9]

Some results of this study differ from observations in other populations and allow one to suspect inaccuracy in medical records. Such low blood loss volumes may be due to an underestimation of bleeding because no objective methods were used to quantify blood loss in our hospital; only visual estimation was employed. The inclusion of patients with placenta previa and without accreta was not ruled out. However, if we limited ourselves to analyzing only the 54 patients with histological confirmation of PAS (►**Table 2**), our center would report 2.2 cases per month. This high frequency of patients managed by the same medical group leads us to believe that the surgical experience of the treating group is the reason for the low frequency of complications observed, despite the limited resources available (►**Tables 1** and **2**). The frequency of bladder injuries of 11% (►**Table 2**) is much lower than the 27% reported in other Latin American countries[10] or some centers of excellence for PAS.[11] Something similar happened with the observed frequency of transfusions of more than 4 RBCUs (7%), which is low when compared with other series, where up to 25% of the population required that number of RBCUs.[11]

Some results observed are due to the surgical protocol used and not necessarily the severity of the pathology. The high frequency of transfusions (79.1%) with hemoglobin at a discharge of 10 g/L may suggest that some of these transfusions were not necessary and were due to the "excessive"

Table 1 Clinical results of patients with an intraoperative placenta accreta spectrum diagnosis

		All patients (n = 129)	Group 1 patients with a presurgical diagnosis (n = 48)	Group 2 patients with intraoperative diagnosis (n = 81)	*p*-value
Maternal age (years)*		31 (27.5–34)	30 (28–34)	31 (27–35)	0.502
GA at the time of surgery (weeks) *		37 (36–38)	37 (36–37.5)	37 (36–38)	0.1794
Gravity *		3 (2–4)	3 (2–4)	3 (2–4)	0.9314
History of previous cesarean section plus placenta previa, n (%)		112 (86.8)	47 (97.9)	65 (80.2)	0.02
Number of previous cesarean sections *		2 (1–3)	2 (2–3)	2 (1–3)	0.364
Attendance at prenatal check-ups, n (%)		82 (63.6)	30 (62.5)	52 (64.2)	0.846
Performing prenatal doppler**, n (%)		41 (31.8)	40 (83.3)	1 (1.2)	0
Planned surgery, n (%)		9 (7)	7 (14.6)	2 (2.5)	0.013
Intraoperative bleeding volume *		700 (500–1,000)	700 (500–1,000)	700 (500–900)	0.3282
Bleeding volume ≥ 2,000 ml, n (%)		8 (6.2)	7 (14.6)	1 (1.2)	0.004
RBCU transfusion frequency, n (%)		102 (79.1)	41 (85.4)	61 (75.3)	0.173
RBCUs transfused *		2 (1–2)	2 (1–2)	2 (1–2)	0.4795
Transfusion ≥ 4 RBCUs, n (%)		9 (7)	5 (10.4)	4 (4.9)	0.048
Presurgical Hb (gr/dL) *		11 (9.6–11.6)	11 (9.8–12.1)	10.6 (9.4–11.4)	0.0516
Postsurgical Hb (gr/dL) *		10 (8.9–11.3)	10.65 (8.9–11.4)	10 (8.8–11)	0.2932
Conductive anesthesia (spinal or epidural), n (%)		125 (96.9)	47 (97.9)	78 (96.3)	0.893
Surgery between 7 pm and 7 am, n (%)***		48 (47.1)	17 (43.6)	31 (49.2)	0.723
Accreta (clinical diagnosis), n (%)		106 (82.2)	34 (70.8)	72 (88.9)	0.005
Increta-Percreta (clinical diagnosis), n (%)		22 (17.1)	14 (29.2)	8 (9.9)	0.005
Result of the histological study, n (%)	No histological study	40 (31)	15 (31.5)	25 (30.9)	0.23
	Normal	35 (27.1)	8 (16.7)	27 (33.3)	0.012
	Accreta	40 (31)	17 (35.4)	23 (28.4)	0.32
	Increta and Percreta	14 (10.8)	8 (16.7)	6 (7.4)	0.03
Admission to ICU, n (%)		17 (13.2)	9 (18.8)	8 (9.9)	0.15
Days of postoperative hospitalization *		4 (3–4)	4 (3–4.5)	4 (3–4)	0.4818
Ureteral injury, n (%)		2 (1.6)	1 (2.1)	1 (1.2)	1
Bladder injury, n (%)		8 (6.2)	4 (8.3)	4 (4.9)	0.469
Surgical reintervention, n (%)		4 (3.1)	2 (4.2)	2 (2.5)	0.628

Abbreviations: GA, Gestational age; ICU, intensive care unit; PAS, placenta accreta spectrum; RBCU, red blood cell unit
*Median (Interquartile range -IQR-)
**By a maternal fetal medicine (MFM) specialist
***Calculations among 102 cases with information (39 with prenatal diagnosis, 63 without prenatal diagnosis)

caution of the treating team. The management protocol in our center considers the nonavailability of additional strategies to control bleeding (interventional radiology, cell saver, support from specialists in vascular surgery) and allows a low threshold for transfusion (►**Supplementary material 1**).

This study is the first formal analysis of our results and allows us to observe several opportunities for improvement involving an intervention plan that must be coupled with the "mother-child" nature of our hospital (►**Chart 1**).

Although the model of centers of excellence for PAS requires the permanent availability of a large number of specialists,[12] our hospital attends the majority of births in the largest state of Bolivia,[13] and there is no other nearby public hospital with better resources to attend PAS patients. It is clear that patients with PAS will continue to be cared for in our center. It is, therefore, necessary to plan medium- and long-term interventions to improve the quality of care in our center (►**Chart 1**).

Table 2 Clinical results of patients with a histological confirmation of placenta accreta spectrum

	All patients (n = 54)	**Group 1 patients with a presurgical diagnosis (n = 25)**	**Group 2 patients with intraoperative diagnosis (n = 29)**	***p*-value (comparing groups 1 and 2)**
Maternal age (years)*	31 (28–34)	31 (28–34)	32 (28–37)	0.2202
GA at the time of surgery (weeks) *	37 (35–38)	37 (35–37)	37 (35–38)	0.4695
Gravity *	3 (3–4)	3 (3–4)	3 (3–4)	0.6942
History of previous cesarean section plus placenta previa, n (%)	50 (92.6)	25 (100)	25 (86.2)	0.115
Number of previous cesarean sections *	2 (2–3)	2 (2–3)	2 (1–3)	0.5255
Attendance at prenatal check-ups, n (%)	29 (53.7)	12 (48)	17 (58.6)	0.435
Performing prenatal doppler**, n (%)	22 (40.7)	22 (88)	0 (0)	0
Planned surgery, n (%)	5 (9.3)	3 (12)	2 (6.9)	0.653
Intraoperative bleeding volume *	700 (500–1,750)	700 (550–1,750)	800 (500–1,000)	0.559
Bleeding volume $\geq$ 2,000 ml, n (%)	7 (13)	6 (24)	1 (3.4)	0.038
RBCU transfusion frequency, n (%)	44 (81.5)	23 (92)	21 (72.4)	0.086
RBCUs transfused *	2 (1–3)	2 (1–3)	2 (1–3)	0.4972
Transfusion $\geq$ 4 RBCUs, n (%)	4 (7.4)	3 (12)	1 (3.4)	0.034
Presurgical Hb (gr/dL) *	11 (9.6–12)	11.6 (10.5–12.5)	10.7 (9.5–11.5)	0.0396
Postsurgical Hb (gr/dL) *	9.95 (8.4–11)	10.8 (8.9–11.4)	9.35 (8.35–10.7)	0.1318
Conductive anesthesia (spinal or epidural), n (%)	43 (98.1)	25 (100)	28 (96.6)	1
Surgery between 7 pm and 7 am, n (%)***	13 (24.1)	5 (20)	8 (27.6)	0.745
Accreta (clinical diagnosis), n (%)	40 (71.1)	17 (68)	23 (79.3)	0.017
Increta-Percreta (clinical diagnosis), n (%)	14 (25.9)	8 (32)	6 (20.68)	0.042
Admission to ICU, n (%)	12 (22.2)	8 (32)	4 (13.8)	0.109
Days of postoperative hospitalization *	4 (3–6)	4 (3–7)	4 (3–5)	0.3751
Ureteral injury, n (%)	2 (3.7)	1 (4)	1 (3.4)	1
Bladder injury, n (%)	6 (11.1)	4 (16)	2 (6.9)	0.399
Surgical reintervention, n (%)	3 (5.6)	2 (8)	1 (3.4)	0.591

Abbreviations: GA, gestational age; ICU, intensive care unit; PAS, placenta accreta spectrum; RBCU, red blood cell unit
*Median (Interquartile range -IQR-)
**By a maternal fetal medicine (MFM) specialist
***Calculations among 102 cases with information (39 with prenatal diagnosis, 63 without prenatal diagnosis)

This study has several limitations that must be taken into account to analyze the results. Its retrospective nature allows bias to occur, and there is a possibility that some data collected in hospital records may not be accurate.

The absence of histological analysis in 31% of the cases, and normal histology results in another 27.1% of the included patients represent a problem for the analysis of our results, as it is likely that some of the patients did not have PAS.

Also, the high frecuency of PAS clinical diagnosis without histological correlation, reflects the importance of including pathologist among the PAS interdisciplinary groups and the dificulties for carrying out high quality research in LIMCs. We performed an additional analysis including only patients with histological confirmation of the PAS clinical diagnosis (►**Table 2**), and the results are very similar to those observed in **table 1**.

This paper intends to show the reality of PAS management in one of the largest maternal hospitals in an LMIC. Although the majority of publications in indexed journals show successful experiences, and it is difficult for hospitals with limited resources to develop quality research activities, the reality in our center is the same as that of a significant percentage of institutions that attend PAS patients, at least in LMICs. Commonly, surgery for PAS and histological study of the uterus are carried out in different hospitals, and surgeons do not know the opinion of the pathologist (and vice versa).

In our center, the surgeon always performs a macroscopic analysis of the surgical specimen (videos 1 and 2). It is likely that detachment of the placenta from the uterus in the operating room (after surgery) limits the histological observation of superficial degrees of invasion, and that this explains at least in part the low correlation between the

Chart 1 Improvement opportunities for the care of placenta accreta spectrum patients in a low- and middle-income country maternal and child hospital

Identified improvement option		Possible solutions
Low prenatal diagnostic performance of PAS	Insufficient knowledge of the disease by prenatal control personnel. Nonreferral of women with RF.	Screening for PAS in high-risk populations
	Insufficient knowledge of the disease by obstetricians who perform basic ultrasonography. No active search in population with RF.	Periodic webinars about PAS Virtual continuous support to sonographers by MFM specialists
	Insufficient availability of MFM specialists. Not timely access to specialized evaluation of patients with RF.	Periodic education for professionals Patients with PAS RF prioritization for access to MFM specialist
End of pregnancy with more than 36 weeks of gestation	Insufficient availability of neonatal ICU	Administrative and economic efforts to expand the number of neonatal ICU beds Schedule in advance the birth of these babies to have on notice to the neonatal ICU Visibility of PAS and search for private companies or government support, seeking greater availability of ICU beds (economic support)
	Insufficient opportunity for an operating room due to the high number of daily cesarean section births	Recognition of the risk of severe maternal and neonatal morbidity in late emergent surgery Schedule in advance these surgeries to have "on notice" to the operation room
	Late catchment of the patients	PAS RF patients active search by a specialized center Early identification of the disease
Lack of an interdisciplinary group	The “mother-child” nature of the hospital	Assessment of the adequacy of this hospital model Support from nearby hospitals in scheduled surgeries Remote support of interdisciplinary groups to adapt the protocol to the available personnel
	Difficulties for agile hiring of additional personnel for specific procedures	Administrative effort focused on facilitating the necessary hiring
	Lack of collaborative work with neighboring private hospitals	Creation of regional groups for academic discussion and assistance support around PAS
	Absence of a “PAS team”	Identification of leaders interested in PAS in each specialty (anesthesiology, pediatrics, obstetrics, intensive care, nursing, surgical instrumentation, etc.)
	Lack of contact with groups in other cities or countries	Use of telemedicine and participation in regional (LatAm PAS study group) and international (IS-PAS, PAS2) academic groups
Absence of feedback on histological study results	Insufficient availability of pathology services in the region linked to the public health system	Administrative effort focused on facilitating the necessary hiring
	Absence of pathology service within the hospital	Administrative effort focused on facilitating the necessary hiring
	Lack of institutional messaging system to transfer surgical piece to pathology service	Administrative effort focused on facilitating the safe remission of surgical pieces
	Lack of communication with pathologists from another institution	Inclusion of local or regional pathologists in interdisciplinary groups

Chart 1 (*Continued*)

Identified improvement option		Possible solutions
	High frequency of normal reports of cases with apparent PAS in the macroscopic examination during surgery. It may be related to the fact that surgeons always detach the placenta after surgery to confirm the presence of PAS in the face of the low frequency of histological studies.	Avoid placental delivery in the operating room by surgical group, provided that histological processing is ensured to clarify the diagnosis.
Limited capacity for massive transfusion	Absence of a blood bank inside the hospital	Administrative effort focused on facilitating the necessary hiring
	Variable response to the emerging request for blood components other than RBCU	Administrative effort focused on facilitating the agile and sufficient supply of blood components from external blood banks
	Absence of intraoperative cell recovery system ("cell saver")	Hospital economic investment for the acquisition of the equipment Request to nongovernmental organizations to donate this equipment (for example Jehovah's witnesses)
High frequency of "emergent" surgeries (with vaginal bleeding or uterine activity) or at night	Surgeries scheduling between 34–36 weeks	Construction, disclosure, and supervision of compliance with institutional protocol for PAS
	Lack of prioritization of patients with PAS RF (previous cesarean section and placenta previa) in surgical programs	Recognition of the risk for severe maternal and neonatal morbidity in late emergent surgery

Abbreviations: ICU, intensive care unit; MFM, maternal-fetal medicine; PAS, placenta accreta spectrum; RBCU, red blood cell unit; RF, risk factors

intraoperative diagnosis and the histological diagnosis. Additionally, there was no communication between the surgical group and the pathologists, which has been shown to deteriorate the performance of histological diagnosis.[14]

When we compare our practice to the recommendations of the centers of excellence, most of the opportunities for improvement identified in our management protocol (►**Chart 1**) make it clear that the management of PAS is not optimal in our center. However, it is important to recognize the difficulties of PAS management in LMICs. In some regions, there is simply no other better-equipped hospital to refer PAS patients to.

Most likely, our observations are not exact, but we do not doubt that our results are at least an approximation of the reality in our country.

Among the options to bring the two realities closer (that of the centers of excellence for PAS and that of the Latin American "maternal and child" hospitals) are interinstitutional collaboration by telemedicine, and the incorporation of research into healthcare practice.[3,15] These two activities require the specific training of the participants, incorporation of the best available scientific evidence, greater vigilance of care processes, and fluid contact with other groups dedicated to the management of PAS. Although an economic investment and a great administrative effort are necessary, the availability of obstetricians with extensive exposure to PAS is a favorable factor. In addition, bringing public interest to the problems of managing this disease through scientific publications facilitates investment from public health entities.

Many countries have a reality that is similar to ours in the management of PAS, with few or no hospitals with all the characteristics described for a PAS center of excellence. The first step on the path of change is to expose this situation. Multicenter prospective studies are necessary for Latin America to evaluate the real situation of care for women with PAS, as well as the formation of international academic networks that support the management of this disease in our region.

Conclusion

The frequency of prenatal diagnosis and the availability of postnatal histological studies were very low in the studied sample. Surgical skill, favored by a high flow of patients, is an important factor to avoid complications in settings with limited resources.

Contributors
All authors contributed with the project and data interpretation, the writing of the article, the critical review of the intellectual content, and with the final approval of the version to be published.

Conflict of Interests
The authors have no conflict of interests to declare

References

1 Allen L, Jauniaux E, Hobson S, Papillon-Smith J, Belfort MAFIGO Placenta Accreta Diagnosis and Management Expert Consensus Panel. FIGO consensus guidelines on placenta accreta spectrum

disorders: Nonconservative surgical management. Int J Gynaecol Obstet. 2018;140(03):281–290. Doi: 10.1002/ijgo.12409
2 Silver RM, Fox KA, Barton JR, Abuhamad AZ, Simhan H, Huls CK, et al. Center of excellence for placenta accreta. Am J Obstet Gynecol. 2015; 212(05):561–568. Doi: 10.1016/j.ajog.2014.11.018
3 Nieto-Calvache AJ, López-Girón MC, Nieto-Calvache A, Messa-Bryon A, Benavides-Calvache JP, Burgos-Luna JM. A nationwide survey of centers with multidisciplinary teams for placenta accreta patient care in Colombia, observational study. J Matern Fetal Neonatal Med. 2020;•••:1–7. Doi: 10.1080/14767058.2020. 1786052 [ahead of print]
4 Nieto-Calvache AJ, Palacios-Jaraquemada JM, Hidalgo A, Vergara-Galliadi LM, Cortés Charry R, Aguilera Daga LR, et al. Management practices for placenta accreta spectrum patients: a Latin American hospital survey. J Matern Fetal Neonatal Med. 2021;•••:1–8. Doi: 10.1080/14767058.2021.1906858 [ahead of print]
5 Nieto-Calvache AJ, Palacios-Jaraquemada JM, Osanan G, Cortes-Charry R, Aryananda RA, Bangal VB, et al; Latin American group for the study of placenta accreta spectrum. Lack of experience is a main cause of maternal death in placenta accreta spectrum patients. Acta Obstet Gynecol Scand. 2021;100(08):1445–1453. Doi: 10.1111/aogs.14163
6 Jauniaux E, Ayres-de-Campos D, Langhoff-Roos J, Fox KA, Collins SFIGO Placenta Accreta Diagnosis and Management Expert Consensus Panel. FIGO classification for the clinical diagnosis of placenta accreta spectrum disorders. Int J Gynaecol Obstet. 2019;146(01):20–24. Doi: 10.1002/ijgo.12761
7 Sargent W, Collins SL. Are women antenatally diagnosed with abnormally invasive placenta receiving optimal management in England? An observational study of planned place of delivery. Acta Obstet Gynecol Scand. 2019;98(03):337–341. Doi: 10.1111/ aogs.13487
8 Matsubara S. Re: Moving from intrapartum to prenatal diagnosis of placenta accreta: a quarter of a century in the making but still a long way to go: Obstetricians' intra-surgical 'eyes' keep on shining. BJOG. 2017;124(08):1287–1288. Doi: 10.1111/1471-0528.14568
9 Dannheim K, Shainker SA, Hecht JL. Hysterectomy for placenta accreta; methods for gross and microscopic pathology examination. Arch Gynecol Obstet. 2016;293(05):951–958. Doi: 10.1007/ s00404-015-4006-5
10 Nieto-Calvache AJ, López-Girón MC, Messa-Bryon A, Ceballos-Posada ML, Duque-Galán M, Ríos-Posada JG, et al. Urinary tract injuries during treatment of patients with morbidly adherent placenta. J Matern Fetal Neonatal Med. 2021;34(19):3140–3146. Doi: 10.1080/14767058.2019.1678135
11 Shamshirsaz AA, Fox KA, Erfani H, Clark SL, Salmanian B, Baker BW, et al. Multidisciplinary team learning in the management of the morbidly adherent placenta: outcome improvements over time. Am J Obstet Gynecol. 2017;216(06):612.e1–612.e5. Doi: 10.1016/j.ajog.2017.02.016
12 Shamshirsaz AA, Fox KA, Erfani H, Belfort MA. The role of centers of excellence with multidisciplinary teams in the management of abnormal invasive placenta. Clin Obstet Gynecol. 2018;61(04): 841–850. Doi: 10.1097/GRF.0000000000000393
13 Instituto Nacional de Estadística. Bolivia: población estimada y proyectada por departamento, según años calendario, 2012-2022 [Internet]. 2020 [cited 2021 Jan 19]. Available from: https://www.ine.gob.bo/index.php/censos-y-proyecciones-de-poblacion-sociales
14 Jauniaux E, Hussein AM, Zosmer N, Elbarmelgy RM, Elbarmelgy RA, Shaikh H, et al. A new methodologic approach for clinicopathologic correlations in invasive placenta previa accreta. Am J Obstet Gynecol. 2020;222(04):379.e1–379.e11. Doi: 10.1016/j. ajog.2019.11.1246
15 Nieto-Calvache AJ, Zambrano MA, Herrera NA, Usma A, Bryon AM, Benavides Calvache JP, et al. Resective-reconstructive treatment of abnormally invasive placenta: Inter Institutional Collaboration by telemedicine (eHealth). J Matern Fetal Neonatal Med. 2021;34 (05):765–773. Doi: 10.1080/14767058.2019.1615877

Quality of Life of Pregnant Women with Systemic Lupus Erythematosus

Qualidade de vida de mulheres grávidas com lúpus eritematoso sistêmico

Larissa Rodrigues[1] Maria Laura Costa[1] Francisco Carlos Specian[1]
Maria Margarida Fialho Sim-Sim[2] Fernanda Garanhani Surita[1]

[1] Departamento de Tocoginecologia, Universidade Estadual de Campinas, Campinas, SP, Brazil
[2] Departamento de Enfermagem, Universidade de Évora, Évora, Portugal

Address for correspondence Fernanda Garanhani Surita, Associate Professor, Cidade Universitária Zeferino Vaz, Barão Geraldo, Campinas, 13083-970, SP, Brazil (e-mail: surita@unicamp.br).

Rev Bras Ginecol Obstet 2022;44(5):475–482.

Abstract

Objective To assess the quality of life (QoL) of pregnant women with systemic lupus erythematosus (SLE) treated at a high-risk prenatal outpatient clinic during the third trimester of gestation.

Methods An observational descriptive study was performed in a high-risk prenatal outpatient clinic. Women in the third trimester of pregnancy and undergoing antenatal care between July 2017 and July 2019 answered the abbreviated World Health Organization Quality of Life (WHOQOL-BREF) questionnaire, consisting of 26 questions divided into 4 domains (physical, psychological, social and environmental).

Results We interviewed 50 pregnant women with a mean gestational age of 30 weeks (standard deviation [SD]: 10 weeks) who were diagnosed with SLE. The average age of the participants was 30 years (SD: 14.85), and the average time since the diagnosis of SLE was of 9.06 years (SD: 6.8 years). Most participants had a partner, did not plan their pregnancy (76%), and did not use contraception prior to pregnancy (80%). The score of each domain ranges from 0 (the worst score) to 100 (the best score). The means $\pm$ SDs of the scores of the participants on each domain were: physical – 52.21 $\pm$ 18.44); psychological – 64.17 $\pm$ 18.56); social – 66.33 $\pm$ 27.09); and environmental – 64.56 (18.53). The means $\pm$ SDs of the general QoL, and health-related QoL items were of 70.50 $\pm$ 24.06 and 70.00 $\pm$ 30.72 respectively.

Conclusion The physical domain presented the lowest scores compared with the other three domains. Pregnant women with SLE had high overall QoL scores, and their health-related QoL scores were also relatively high.

Keywords
- pregnancy
- systemic lupus erythematosus
- quality of life

received
January 20, 2021
accepted
November 18, 2021
published online
February 17, 2022

DOI https://doi.org/10.1055/s-0042-1743092.
ISSN 0100-7203.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resumo

Objetivo Investigar a qualidade de vida (QV) de gestantes com lúpus eritematoso sistêmico (LES), em acompanhamento ambulatorial pré-natal de alto risco, durante o terceiro trimestre de gestação.

Métodos Foi realizado um estudo observacional descritivo em ambulatório de pré-natal de alto risco. As mulheres em acompanhamento pré-natal no terceiro trimestre de gravidez entre julho de 2017 e julho de 2019 responderam ao questionário abreviado de Qualidade de Vida da Organização Mundial de Saúde (abbreviated World Health Organization Quality of Life, WHOQOL-BREF, em inglês), composto por 26 questões divididas em 4 domínios (físico, psicológico, social e ambiental).

Resultados Foram entrevistadas 50 gestantes com diagnóstico de LES e média de 30 semanas de idade gestacional (desvio padrão [DP]: 10 semanas). A idade média das participantes foi de 30 anos (DP: 14,85), e o tempo médio desde o diagnóstico de lúpus foi de 9,06 anos (DP = 15,55 anos). A maioria das participantes tinha companheiro, não havia planejado a gravidez (76%), e não fazia uso de anticoncepcional antes da gravidez (80%). A pontuação em cada domínios varia de 0 (pior pontuação) a 100 (melhor pontuação). As médias ± DPs das pontuações das participantes em cada domínios foram: físico – 52,21 ± 18,44; psicológico – 64,17 ± 18,56; social – 66,33 ± 27,09; e ambiental –64,56 ± 18,53). As médias ± DPs dos itens relativos à QV geral e à QV relacionada à saude foram de 70,50 ± 24,06) e 70,00 ± 30,72, respectivamente.

Conclusão O domínio físico apresentou as menores pontuações em comparação com os outros três domínios. Mulheres grávidas com LES tiveram pontuação alta no item de QV geral, e a pontuação no item de QV relacionada à saúde também foi relativamente alta.

Palavras-chave

- gravidez
- lúpus eritematoso sistêmico
- qualidade de vida

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune, multisystem disease that can cause damage to the skin, kidneys, heart, lungs, and other organs. It is more prevalent among women of reproductive age, and has been associated with a high risk of adverse maternal and perinatal outcomes.[1,2]

The most common conditions observed during pregnancy include hypertension, nephropathy, and the presence of autoantibodies, which can affect the materno-fetal binomial.[3,4] The management of SLE during pregnancy can become challenging, due to difficulties distinguishing disease manifestations from the physiological changes associated with pregnancy, and due to the increased need for therapeutic control and surveillance.[5] Therefore, pregnancy may affect the quality of life (QoL) of women with SLE.

The World Health Organization[6] (WHO) defines QoL as how people perceive their position in life, how they view their goals, their expectations, and their concerns, and how they relate to the culture and values of the place where they live. It can be measured with validated instruments, such as the abbreviated World Health Organization Quality of Life (WHOQOL-BREF) questionnaire.[7]

The WHOQOL-BREF has been used to measure general QoL, and it has been validated in Portuguese,[7] making this an appropriate tool for use in Brazil. The questionnaire is not specific to the functional aspects associated with health during pregnancy or with women with SLE. Although the WHOQOL-BREF has been used in Brazil for the assessment of other pregnant women undergoing usual-risk[8–10] and high-risk prenatal care,[8,11,12] the present study is the first to use this instrument in women with two health conditions: pregnancy and SLE.

The QoL of pregnant women with SLE has already been discussed, and their perceptions of pregnancy in the context of the disease appear to be ambiguous. Some reports[13] have described a sense of well-being and satisfaction accompanying pregnancy, in addition to fears and uncertainties regarding the limitations that the disease may impose on materno-fetal health. Women with SLE desire the experience of maternity; however, to fulfill this desire, they require adequate support.[13]

Considering the need for good health practices during pregnancy, childbirth and the postpartum period,[14,15] as well as the recommendation that prenatal care is a good experience for women,[16,17] the present study aimed to assess the QoL of women with SLE during the third trimester of pregnancy while being treated at a specialized prenatal care unit.

Methods

An observational descriptive study was conducted at Woman's Hospital Professor José Aristodemo Pinotti, State University of Campinas, Brazil, a reference in terms of health assistance to ~ 100 municipalities in the region. The hospital has three prenatal outpatient clinics: High-Risk Prenatal Care

(Pré-natal de Alto Risco, PNAR, in Portuguese), which provides care for pregannt woman with clinical and obstetric diseases; Adolescent Prenatal Care (Pré-natal de adolescentes, PNA, in Portuguese), which assists pregnant women up to 18 years of age; and the Specialized Prenatal Care (Pré-natal Especializado, PNE, in Portuguese), which assists women with more complex pregnancies, after the initial screening of the PNAR. Our research scenario was focused specifically on the PNE. Approximately 40 pregnant women are treated at this site on Wednesdays, including a yearly average of 25 SLE patients.

Pregnant women with a diagnosis of SLE (with any degree of severity)[18] were eligible if they were in the third trimester and undergoing prenatal care. The exclusion criteria were: illiterate patients and those without cognitive conditions to understand and talk about QoL. The sampling was intentional: all women who were treated at the aforementioned outpatient clinic between July 2017 and July 2019 were invited to participate in the study, and there were no cases of refusal.

The participants received an explanation about the topic and objectives of the study, and about the rights of the parties involved. The interviewer read and explained the Informed Consent Form to the participants, and the interviews were only conducted after the patients indicated their understanding and signed the form. Then, their sociodemographic data were collected (age, time since SLE diagnosis, parity, miscarriage or fetal death, planned pregnancy, previous contraception, level of schooling, occupational status, and marital status). The questionnaire was applied as an interview, and took an average of 15 minutes to administer. The participants were approached on the same day of their medical consultation for prenatal care. The interviewees were guaranteed confidentiality. Permission was requested to use a recording device.

The instrument used to analyze the QoL measurements was the WHOQOL-BREF,[7] a questionnaire with 26 items regarding QoL divided into 4 domains: physical, psychological, social, and environmental. These 26 items are presented in the format of a Likert scale, with scores from 1 to 5. Lower scores represent worse perceptions of QoL. For the proper interpretation of the results, questions Q3, Q4 (physical domain – sleep and rest and mobility), and Q26 (global QoL – satisfaction with health) have reversed scores, with 5 representing the worst score and 1 representing the best score.[19]

The total score on the WHOQOL-BREF ranges from 0 to 100; therefore, the closer to 0, the worse the score, whereas the best scores are closer to 100. Research defining cutoff points for women and pregnant women has not yet been reported. We found only one study[20] that discussed cutoff points for the perception of QoL among the elderly population.

The sample size was calculated as 50 participants, based on previous studies[11,18] performed with similar groups and instruments. The procedure used was the calculation of a sample size[21] to estimate a mean, using the mathematical equation $n = (\Sigma\sigma/d)^2$, in which n is the estimated sample size, z is the percentile of the normal distribution for a significance level of 5% ($z = 1.96$), σ is the standard deviation (SD) extracted from the studies used as references,[11,18] and d is the maximum absolute error allowed = 5 and 6.

To describe the profile of the sample according to the studied variables, frequency tables were developed for the categorical variables (the four domains of the WHOQOL-BREF, as well as the items pertaining to general QoL and health-related QoL), with values expressed as absolute frequencies (n) and percentages (%), and the descriptive statistics were used to report all numerical variables (WHOQOL-BREF scores for each of the 26 questions), with the values expressed asmeans ± SDs, minimum and maximum, medians, and quartiles. The normality of distribution was tested by histogram, normal-plot, and the Kolmogorv-Smirnov test. The Statistical Analysis System (SAS System for Windows, SAS Institute Inc., Cary, NC, United States) software, version 9.2, was used to perform the statistical analyses.

The present study was performed in accordance with Resolution no. 466 of the Brazilian National Health Council[22] on health research with human beings, and received authorization from the local Ethics Committee under the number #68143817.0.0000.5404.

Results

A total of 50 pregnant women (gestational age: 30 ± 10 weeks) with SLE participated in the present study. They had an average age of 30 ± 14.85 years and an average time since SLE diagnosis of 9.06 ± 6.8 years. Most participants had a partner, did not plan their pregnancies, and did not use contraception. The sample had a normal distribution. The sociodemographic characteristics are show in ►**Table 1**.

On each domain of the WHOQOL-BREF, our participants obtained the following mean ± SD) scores: physical – 52.21 ± 18.44); psychological – 64.17 ± 18.56); social – 66.33 ± 27.09); environmental –64.56 ± 18.53); general QoL – 70.50 ± 24.06); and health-related QoL – 70.00 ± 30.72. ►**Table 2** shows the scores on each domain.

When we examined each question of the WHOQOL-BREF, the lowest average score (2.68 ± 1.24) was found for question 3 (physical domain), which is on sleep and rest, whereas the highest average score was of 4.42 ± 0.73 for question 6 (psychological domain): "To what extent do you feel your life to be meaningful?". ►**Fig. 1** shows the scores on each of the 26 questions.

Discussion

In the present study, when using the WHOQOL-BREF to asses the QoL of women with high-risk pregnancies complicated by SLE, the lowest scores were on the physical domain, with the lowest mean score reported for a question referring to activities of daily life. The scores of the participants of the present study were similar to those reported by other studies on pregnant women undergoing high-risk prenatal care.[8,23]

Table 1 Characteristics of the study sample

Participants ($n = 50$)		n(%)
Variable	Categories	
Age (years)	≤ 30	27(54)
	> 30	23(46)
Time since the diagnosis of systemic lupus erythematosus (years)	≤ 5	23(46)
	> 5	27(54)
Parity	Primiparous	18(36)
	Multiparous	32(64)
Abortion or fetal death	Yes	11(22)
	No	39(78)
Planned pregnancy	Yes	12(24)
	No	38(76)
Previous contraception	Yes	10(20)
	No	40(80)
Level of schooling	High school	30(60)
	Elementary school	8(16)
	Higher education	8(16)
	No schooling	3(6)
	Technical education	1(2)
Employed	Yes	30(60)
	No	20(40)
With partner	Yes	35(70)
	No	15(30)

In the present study, the physical domain of the WHOQOL-BREF was the one in which the participants scored the lowest: 52.21 ± 18.44. In another Brazilian study[8] which also evaluated pregnant women undergoing high-risk prenatal care, the physical domain was also the one with the lowest reported score (47.8 ± 15.9), and a similar finding was reported by a study conducted in Greece;[23] however, a different result was reported by a study conducted in Poland: the lowest score was on the social domain.[24]

Within the physical domain, the question regarding pain and discomfort among the participants yielded an average score of 3.82, which may be associated with the control of pain issues related to SLE, either through medication or alternative therapies, which is consistent with the literature.[25,26]

For the question on energy and fatigue, the participants scored an average of 3.80, which indicates that there were symptoms of fatigue that may be related to the control of the disease and its symptoms, and is similar to studies performed with non-pregnant women with SLE.[25,26]

The participants scored on average 2.68 on the question regarding sleep and rest. Poor sleep quality among women with SLE, whether objective or subjective, has also been reported in a previous study.[27] Similarly, pregnant women, even without SLE, are known to have difficulties achieving good quality in terms of sleep and rest, and report symptoms of sleep disorders at significant rates.[28] Sleep disorders have also been shown to be associated with depressive symptoms.[29,30]

With regard to mobility (walking, driving, climbing stairs), the participants had an average score of 3.48, which indicates a decrease in their ability to move, which may impact their autonomy, their safety, and their abilities to participate in activities, as described in a recent study[31] on the importance of mobility when caring for individuals with SLE.

Regarding the question on activities of daily living, the women had an average score of 2.62, the lowest on this domain. This suggests that women with SLE feel less capable of performing ordinary activities, which may represent the synthesis of the discomfort indicated by the other items.

With regard to dependence on medication or treatment, our subjects had an average score of 3.54, possibly due to a sense of dependence on treatments for the illness and the need to monitor the pregnancy. However, from a more subjective perspective, these women have indicated that the use of some medications makes them feel bad, and that they would prefer to focus on the pregnancy instead of the disease.[13]

The analysis of the ambiguity among these reports has resulted in increasing attention being paid to the possibility that women may wish to discontinue the treatment, or are more inclined toward improved self-care while pregnant.[13]

As for the question on the ability to work, the participants had an average score of 3.0, indicating that they feel less able

Table 2 Descriptive analysis according to the domains of the WHOQOL-bref ($n = 50$)

Domains	n	Mean ± standard deviation	Minimum	Quartile 1	Median	Quartile 3	Maximum
Physical	50	52.21 ± 18.44	14.29	39.29	53.57	67.86	85.71
Psychological	50	64.17 ± 18.56	20.83	54.17	66.67	75.00	100.00
Social	50	66.33 ± 27.09	8.33	50.00	66.67	91.67	100.00
Environmental	50	64.56 ± 18.53	12.50	50.00	65.63	81.25	100.00
General QoL	50	70.50 ± 24.06	0.00	50.00	75.00	75.00	100.00
Health-related QoL	50	70.00 ± 30.72	0.00	50.00	75.00	100.00	100.00

Abbreviations: QoL, quality of life; WHOQOL-BREF, abbreviated World Health Organization Quality of Life questionnaire.

Variable	N	Mean (SD)	Minimum	Quartile 1	Median	Quartile 3	Maximum
Q1	50	3.82 (0.96)	1.00	3.00	4.00	4.00	5.00
Q2	50	3.80 (1.23)	1.00	3.00	4.00	5.00	5.00
Q3	50	2.68 (1.24)	1.00	1.00	3.00	4.00	5.00
Q4	50	3.94 (0.98)	1.00	3.00	4.00	5.00	5.00
Q5	50	3.38 (1.25)	1.00	3.00	4.00	5.00	5.00
Q6	50	4.42 (0.73)	2.00	4.00	3.00	5.00	5.00
Q7	50	3.26 (1.05)	1.00	3.00	3.00	4.00	5.00
Q8	50	3.56 (1.11)	1.00	3.00	4.00	4.00	5.00
Q9	50	3.48 (1.15)	1.00	3.00	4.00	3.00	5.00
Q10	50	2.62 (1.03)	1.00	2.00	3.00	3.00	5.00
Q11	50	3.54 (1.28)	1.00	3.00	4.00	4.00	5.00
Q12	50	3.00 (1.31)	1.00	2.00	3.00	5.00	5.00
Q13	50	3.70 (1.02)	2.00	3.00	4.00	4.00	5.00
Q14	50	3.02 (1.30)	1.00	2.00	3.00	5.00	5.00
Q15	50	3.80 (1.09)	1.00	3.00	4.00	4.00	5.00
Q16	50	3.20 (1.25)	1.00	2.00	3.00	4.00	5.00
Q17	50	3.38 (1.01)	1.00	3.00	3.00	4.00	5.00
Q18	50	3.24 (1.200	1.00	2.00	3.50	4.00	5.00
Q19	50	3.78 (0.91)	1.00	3.00	4.00	4.00	5.00
Q20	50	3.86 (1.18)	1.00	3.00	4.00	5.00	5.00
Q21	50	3.50 (1.39)	1.00	3.00	4.00	5.00	5.00
Q22	50	3.60 (1.39)	1.00	3.00	4.00	5.00	5.00
Q23	50	4.12 (1.06)	1.00	4.00	4.00	5.00	5.00
Q24	50	3.96 (1.28)	1.00	4.00	4.00	5.00	5.00
Q25	50	3.82 (1.08)	1.00	3.00	4.00	5.00	5.00
Q26	50	3.18 (1.32)	1.00	2.00	3.00	5.00	5.00

Physical domain; Psychological domain; Social domain; Environmental domain; General QoL; Health-related QoL

Fig. 1 Descriptive analysis of the numerical variables ($n = 50$).

to perform their professional activities or engage in work at home. A similar finding was reported by another study[32] regarding the difficulties encountered in relation to work after being diagnosed with SLE and the need to maintain a different routine due to the monitoring required and the limitations imposed by the disease.

The psychological score of 64.17 ± 18.56) and the environmental score of 64.56 ± 18.53 were higher than those on

the other domains. In the psychological domain, a connection appears to exist between feeling healthy and being pregnant, despite the underlying presence of the disease.[13] A desire for pregnancy may also be associated with a sense of fulfillment, resulting in the sensation of psychological satisfaction.

The scores on the environmental domain are associated with the fact that the study setting coincided with the most economically- and culturally-developed region of Brazil, which is similar to the findings of other studies that have indicated that qualified insertion and good remuneration in the labor market, transportation, leisure options, and security are aspects that affect the social capital of people.[33,34]

The social domain score of 66.33 ± 27.09) was the highest among the other domains in the present study; however, there are reports in the literature[32] that SLE tends to interfere with the social aspects of the affected individuals.

General QoL is assessed by a specific question, separated from the other domains, and the participants of the present study had a mean score of 70.50 ± 24.06), which is higher than the average score reported among women with SLE in other locations in Brazil, and a study[8] has reported that women with different high-risk pregnancies had an average score of 62.8 ± 13.8.

As for the assessment of health-related QoL, which is also separate from the other domains, the score of the participants of the present study was high (70 ± 30.72), but we did not find comparative values reported in other studies. This discrepancy may be associated with the access to specialized health services for the monitoring of pregnancy and childbirth among our population, as access to health services has been previously indicated and discussed as a factor that is associated with a better QoL perception.[33,34]

The manifestations of SLE during pregnancy[1,3] may bother women more than usual and stand out more strongly when they refer to QoL, even when the disease is under control. Pregnancy involves major physical changes,[35] which may also be associated with the lower scores of our patients on the physical domain.

In Thessaloniki, Greece,[23] and Lublin, Poland,[24] the QoL of pregnant women diagnosed with diabetes and undergoing high-risk prenatal care has been assessed using the same instrument. The WHOQOL-BREF has also been used to assess QoL before and after the implementation of a physical exercise intervention in Brazil (in a hospital environment), and in Szczecin and Warsaw, Poland[36] (in an exercise club environment). It has also been used to assess changes in QoL among women with SLE during pregnancy and puerperium in Providence, United States.[37]

In general, the QoL of pregnant women has been poorly analyzed in the literature, which has hindered the accurate assessment and establishment of adequate parameters for this population.[38]

Some characteristics of our participants may be related to their perceptions of QoL. For example, 38 of the 50 women in the present study had graduated from high school or college, which means they have has more than 10 years of schooling. The literature[39] has indicated that higher levels of schooling may be associated with better perceptions of QoL. Similarly, 35 of the participants of the present study had a partner, which may be associated with the perception of social satisfaction, which is also in line with the reports in the literature.[39]

Another characteristic observed among our participants is the counterpoint between the 38 women who did not plan the pregnancy and the 40 women who did not use any contraceptive method, a practically inverse relationship with the 12 who planned the pregnancy and the 10 who used a contraceptive method, which may be associated with a veiled desire for pregnancy.[13]

The QoL of women diagnosed with SLE during the third trimester of pregnancy has been poorly investigated, and we have not identified any other studies on this issue. Therefore, assessing the QoL of 50 women with SLE in this scenario is unprecedented, and will contribute to future correlations regarding QoL, not only in pregnant women with lupus, but with other comorbidities during pregnancy, as many issues can be similar. The present study is limited to the assessment of QoL perceptions among women in a specific area of one country, and cannot be generalized. Future studies can contribute to the assessment of associations regarding QoL perceptions and sociodemographic characteristics of women in this area or associations with other characteristics of pregnant women with SLE in other locations. In the women herein evaluated, the main clinical complication was SLE; thus, no secondary diseases or other problems related to pregnancy were described. Another limitation is that a group of women without the disease was not recruited for comparison. This is due to the characteristics of the study site, which only assists high-risk pregnancies, and any other group would add biases to the comparison of the data.

Conclusion

Among women with SLE treated at a specialized, high-risk prenatal care center, the physical domain of the WHOQOL-BREF had the lowest score compared with the psychological, social, and environmental domains. The pregnant women with SLE interviewed in the present study had high general QoL scores, and their health-related QoL scores were also relatively high. Certain aspects affect the QoL of these women: access to care in health services may influence the perception of health-related QoL, and the context of the region where these women live (Southeastern Brazil, the most economically-developed region of the country) may influence the social domain of the QoL.

Contributors
All authors contributed to the concept and design of the present study; to the analysis and interpretation of data; to the draft or revision of the manuscript, and they have approved the manuscript as submitted. All authors are responsible for the reported research.

Conflict of Interests
The authors have no conflict of interests to declare.

Acknowledgments
Validation of search: SARHAS Laboratory, Universidade de Évora. Illustration: Elsevier Woman's Hospital Statistic Service, Universidade Estadual de Campinas. The first author disclosed the receipt of the following financial support for the research, authorship and/or publication of the present article: the present work was funded by the Coordination for the Improvement of Higher Education Personnel (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, CAPES, in Portuguese), Brazil, under no. [88881.188510 / 2018- 01].

References

1 Borella E, Lojacono A, Gatto M, Andreoli L, Taglietti M, Iaccarino L, et al. Predictors of maternal and fetal complications in SLE patients: a prospective study. Immunol Res. 2014;60(2-3):170–176. Doi: 10.1007/s12026-014-8572-6
2 Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64(08):2677–2686. Doi: 10.1002/art.34473
3 Lateef A, Petri M. Systemic lupus erythematosus and pregnancy. Rheum Dis Clin North Am. 2017;43(02):215–226. Doi: 10.1016/j.rdc.2016.12.009
4 Pastore DEA, Costa ML, Parpinelli MA, Surita FG. A critical review on obstetric follow-up of women affected by systemic lupus erythematosus. Rev Bras Ginecol Obstet. 2018;40(04):209–224. Doi: 10.1055/s-0038-1625951
5 Pastore DEA, Costa ML, Surita FG. Systemic lupus erythematosus and pregnancy: the challenge of improving antenatal care and outcomes. Lupus. 2019;28(12):1417–1426. Doi: 10.1177/0961203319877247
6 The WHOQOL Group. Development of the World Health Organization WHOQOL-BREF quality of life assessment. Psychol Med. 1998;28(03):551–558. Doi: 10.1017/s0033291798006667
7 Fleck MP, Louzada S, Xavier M, Chachamovich E, Vieira G, Santos L, et al. Aplicação da versão em português do instrumento abreviado de avaliação da qualidade de vida "WHOQOL-bref". Rev Saude Publica. 2000;34(02):178–183. Doi: 10.1590/s0034-89102000000200012
8 Castro GG, Ferreira FF, Camargos AS, Leite MA, Mattos JG. Diferenças da qualidade de vida entre mulheres com alto e habitual risco gestacional. Aletheia. 2019;52(01):102–115
9 Oliveira SX, Oliveira MB, Silva RA, Davim RM. Características dos domínios da qualidade de vida em gestantes da estratégia saúde da família. Rev Enferm UFPE On Line. 2013;7(esp):7007–716. Doi: 10.5205/reuol.4767-42136-1-ED.0712esp201307
10 Santos AB, Santos KE, Monteiro GT, Prado PR, Amaral TL. Autoestima e qualidade de vida e uma série de gestantes atendidas em rede pública de saúde. Cogitare Enferm.. 2015;20(02):392–400. Doi: 10.5380/ce.v20i2.38166
11 Nascimento SL, Surita FG, Parpinelli MA, Siani S, Pinto e Silva JL. The effect of an antenatal physical exercise programme on maternal/perinatal outcomes and quality of life in overweight and obese pregnant women: a randomised clinical trial. BJOG. 2011;118(12):1455–1463. Doi: 10.1111/j.1471-0528.2011.03084.x
12 Vallim AL, Osis MJ, Cecatti JG, Baciuk EP, Silveira C, Cavalcante SR. Water exercises and quality of life during pregnancy. Reprod Health. 2011;8:14. Doi: 10.1186/1742-4755-8-14
13 Rodrigues L, Alves VLP, Sim-Simc MMF, Surita FG. Perceptions of women with systemic lupus erythematosus undergoing high-risk prenatal care: A qualitative study. Midwifery. 2020;87:102715. Doi: 10.1016/j.midw.2020.102715
14 Ministério da Saúde Secretaria de Atenção à Saúde. Departamento de Ações Programáticas Estratégicas. Gestação de alto risco: manual técnico 5a ed. Brasília (DF): Editora do Ministério da Saúde; 2012. (Série A. Normas e Manuais Técnicos).
15 Ministério da Saúde Secretaria de Atenção à Saúde. Manual de acolhimento e classificação de risco em obstetrícia. Brasília (DF): Ministério da Saúde; 2017
16 World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience. Geneva: WHO; 2016
17 Committee on Obstetric Practice. ACOG Committee Opinion No. 731: Group Prenatal Care. Obstet Gynecol. 2018;131(03):e104–e108. Doi: 10.1097/AOG.0000000000002529
18 American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. Guidelines for referral and management of systemic lupus erythematosus in adults. Arthritis Rheum. 1999;42(09):1785–1796. Doi: 10.1002/1529-0131(199909)42:93.0.CO;2-#
19 Pedroso B, Pilatti LA, Gutierrez GL, Picinin CT. Calculation of scores and descriptive statistics of WHOQOL-bref through Microsoft Excel. Rev Bras Qual Vida.. 2010;02(01):31–6. Doi: 10.3895/S2175-08582010000100004
20 Silva PA, Soares SM, Santos JF, Silva LB. Cut-off point for WHOQOL-bref as a measure of quality of life of older adults. Rev Saude Publica. 2014;48(03):390–397. Doi: 10.1590/S0034-8910.2014048004912
21 Siqueira AL, Tibúrcio JD. Estatística na área da saúde: conceitos, metodologia, aplicações e prática computacional. Belo Horizonte: Coopmed; 2011
22 Ministério da Saúde Conselho Nacional de Saúde [Resolution No. 466, 2012 December 12 Approves regulated guidelines and standards for research involving human beings]. Diário Oficial da União. . 2013 Jun 13;Sec. 1:59. Portuguese.
23 Pantzartzis KA, Manolopoulos PP, Paschou SA, Kazakos K, Kotsa K, Goulis DG. Gestational diabetes mellitus and quality of life during the third trimester of pregnancy. Qual Life Res. 2019;28(05):1349–1354. Doi: 10.1007/s11136-018-2090-2
24 Iwanowicz-Palus G, Zarajczyk M, Pięta B, Bień A Quality of life, social support, acceptance of illness, and self-efficacy among pregnant women with hyperglycemia. Int J Environ Res Public Health. 2019;16(20):3941. Doi: 10.3390/ijerph16203941
25 Fangtham M, Kasturi S, Bannuru RR, Nash JL, Wang C. Non-pharmacologic therapies for systemic lupus erythematosus. Lupus. 2019;28(06):703–712. Doi: 10.1177/0961203319841435
26 Toloza SM, Sequeira W, Jolly M. Treatment of lupus: impact on quality of life. Curr Rheumatol Rep. 2011;13(04):324–337. Doi: 10.1007/s11926-011-0189-3
27 Moraleda V, Prados G, Martínez MP, Sánchez AI, Sabio JM, Miró E Sleep quality, clinical and psychological manifestations in women with systemic lupus erythematosus. Int J Rheum Dis. 2017;20(10):1541–1550. Doi: 10.1111/1756-185X.13081
28 Mindell JA, Cook RA, Nikolovski J. Sleep patterns and sleep disturbances across pregnancy. Sleep Med. 2015;16(04):483–488. Doi: 10.1016/j.sleep.2014.12.006
29 Nacar G, Taşhan ST. Relationship between sleep characteristics and depressive symptoms in last trimester of pregnancy. Afr Health Sci. 2019;19(04):2934–2944. Doi: 10.4314/ahs.v19i4.14
30 Kalmbach DA, Cheng P, Ong JC, et al. Depression and suicidal ideation in pregnancy: exploring relationships with insomnia, short sleep, and nocturnal rumination. Sleep Med. 2020;65:62–73. Doi: 10.1016/j.sleep.2019.07.010
31 Stevens MJ, Walker-Bone K, Culliford DJ, Ciesla JA, Kingsberg SA, Sangha R, et al. Work participation, mobility and foot symptoms in people with systemic lupus erythematosus: findings of a UK national survey. J Foot Ankle Res. 2019;12:26. Doi: 10.1186/s13047-019-0335-0

32 Kent T, Davidson A, Newman D, Buck G, D'Cruz D. Burden of illness in systemic lupus erythematosus: results from a UK patient and carer online survey. Lupus. 2017;26(10):1095–1100. Doi: 10.1177/0961203317698594
33 Chen Y, Sun G, Guo X, Chen S, Chang Y, Li Y, et al. Factors affecting the quality of life among Chinese rural general residents: a cross-sectional study. Public Health. 2017;146:140–147. Doi: 10.1016/j.puhe.2017.01.023
34 Tay KC, Seow CC, Xiao C, Lee HM, Chiu HF, Chan SW. Structured interviews examining the burden, coping, self-efficacy, and quality of life among family caregivers of persons with dementia in Singapore. Dementia. 2016;15(02):204–220. Doi: 10.1177/1471301214522047
35 Byerley BM, Haas DM. A systematic overview of the literature regarding group prenatal care for high-risk pregnant women. BMC Pregnancy Childbirth. 2017;17(01):329. Doi: 10.1186/s12884-017-1522-2
36 Krzepota J, Sadowska D, Biernat E. Relationships between physical activity and quality of life in pregnant women in the second and third trimester. Int J Environ Res Public Health. 2018;15(12):2745. Doi: 10.3390/ijerph15122745
37 Kang AW, Pearlstein TB, Sharkey KM. Changes in quality of life and sleep across the perinatal period in women with mood disorders. Qual Life Res. 2020;29(07):1767–1774. Doi: 10.1007/s11136-020-02437-1
38 Morin M, Vayssiere C, Claris O, Irague F, Mallah S, Molinier L, et al. Evaluation of the quality of life of pregnant women from 2005 to 2015. Eur J Obstet Gynecol Reprod Biol. 2017;214:115–130. Doi: 10.1016/j.ejogrb.2017.04.045
39 Cazella LG, Almeida LY, Oliveira JL, Zanetti AC, Souza J. Qualidade de vida de mulheres e as características sociodemográficas associadas. Enferm Foco.. 2019;10(03):34–9. Doi: 10.21675/2357-707X.2019.v10.n3.2448

Preventing Uterine Cervix Cancer: The Clinical Meaning of Atypical Glandular Cells

Prevenção do câncer do colo uterino: Significado clínico das células glandulares atípicas

Gutemberg Almeida[1] Jorge Eduardo Sainz[1] Renata Fonseca[1] Neil Chaves[1] Katia Silveira Silva[2] Julio Nunes[3] Yara Furtado[1,4]

[1] Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil
[2] Instituto Fernandes Figueira, Rio de Janeiro, RJ, Brazil
[3] Department of Psychiatry and Behavior Sciences, Stanford University, Stanford, CA, United States
[4] Universidade Federal do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil

Address for correspondence Yara Furtado, Gynecology Institute, Moncorvo Filho Street, 90, 20211-340, Rio de Janeiro, RJ, Brazil (e-mail: yarafurtadorj@gmail.com).

Rev Bras Ginecol Obstet 2022;44(5):483–488.

Abstract

Objective To determine the prevalence of the atypical glandular cells (AGCs) cytology and to analyze its clinical significance in different age ranges.

Methods Retrospective observational study using computerized data from the Brazilian National Cancer Institute, including women screened between January 2002 and December 2008. The women included were those with an AGC result who were properly followed-up with colposcopy and a second cytology.

Results A total of 132,147 cytopathological exams were performed during the study period. Five-hundred and thirty-three (0.4%) women with AGC cytology were identified and, of these, 69.41% (370/533) were properly referred for colposcopy and a new cytology. Most of the women (79.2%) with a 1st or 2nd AGC cytology were between the ages of 25 and 54 years. The 2nd cytology demonstrated 67.6% (250/370) of normality, 24.5% (91/370) of squamous atypia, and 6.2% (23/370) of AGC, 0.8% (3/370) adenocarcinoma in situ and 0.8% (3/370) adenocarcinoma invasor. On biopsy of the women with a second AGC cytology, 43.4% (10/23) had normal histology, 43.4% (10/23) had squamous lesions, 8.7% (2/23) had invasive adenocarcinoma, and 1.2% (1/23) had an inconclusive report. All of the women with high-grade squamous intraepithelial lesion (HSIL) or invasive adenocarcinoma (respectively 5 and 2 patients), after a 2nd AGC cytology were 25 years old or older.

Conclusion The prevalence of the AGC cytology was low in the studied population. Most of the AGC cytology cases occurred in adult women between the ages of 25 and 54. Although most of the patients had normal histology after follow-up, several of them presented with squamous intraepithelial lesions or invasive adenocarcinoma.

Keywords
- AGC
- atypical glandular cells
- glandular cervical neoplasia
- Bethesda system
- cervical cancer screening
- cytology

received
June 11, 2021
accepted
November 11, 2021
published online
February 9, 2022

DOI https://doi.org/10.1055/s-0042-1742318.
ISSN 0100-7203.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resumo

Objetivo Determinar a prevalência de citologia com laudo de células glandulares atípicas (AGCs, na sigla em inglês) e analisar a significância clínica nas diferentes faixas etárias

Métodos Estudo observacional retrospectivo, usando os dados arquivados no sistema do Instituto Nacional de Câncer no Brasil, que incluiu mulheres rastreadas entre janeiro de 2002 a dezembro de 2008. As mulheres incluídas tinham citologia com resultado de AGCs, que foram acompanhadas com colposcopia e nova citologia

Resultados Um total de132,147 exames citopatológicos foram incluídos durante o período de estudo. Quinhentas e trinta e três mulheres com citologia de AGC foram identificadas e destas, 69.41% (370) foram encaminhadas para colposcopia e nova citologia. A prevalência de citologia de AGC na população estudada foi 0.4%. A maioria das mulheres (79.22%) com resultado citológico de AGC tinham idade entre 25 e 54 anos. A segunda citologia demonstrou 67.56% (250/370) de normalidade, 24.5% (91/370) de atipias escamosas, e 6.2% (23/370) de AGC. Na biopsia das mulheres com a 2ª citologia de AGC, 43.4% (10/23) tinham histologia normal, 43.4% (10/23) tinha lesões escamosas, 8.7% (2/23) tinha adenocarcinoma invasor e 1.2% (1/23) tinha laudo inconclusivo. Todas as mulheres com lesões intraepiteliais escamosas de alto grau (HSIL, na sigla em inglês) ou adenocarcinoma invasor (respectivamente 5 e 2 pacientes), após a 2ª citologia com AGC, tinham 25 anos de idade ou mais.

Conclusão A prevalência de citologia com AGC foi baixa na população estudada. Muitos casos de citologia com AGC apareceram em mulheres adultas, entre 25 e 54 anos de idade. Embora a maioria das pacientes tiveram histologia normal após seguimento, várias apresentaram lesões intraepiteliais escamosas ou glandulares invasoras.

Palavras-chave

- AGC
- células glandulares atípicas
- neoplasia glandular cervical
- sistema Bethesda
- rastreio do câncer do colo uterino
- citologia

Introduction

Several cervical-vaginal cytological classification systems have been suggested since the Papanicolaou and Traut,[1] but, currently, the most used one in the world is the Bethesda system.[2–4] Developed in December 1988, it suggested including lesions related to the human papillomavirus (HPV) and grade I cervical intraepithelial neoplasia (CIN I) in the same category, called low-grade squamous intraepithelial lesions (LSILs). Also, CIN II/III should be categorized as high-grade squamous intraepithelial lesions (HSILs).[3]

Bethesda also introduced undetermined categories: atypical squamous cells of undetermined significance (ASCUS) and atypical glandular cells of undetermined significance (AGUS).[3] These were lesions with microscopic reactive changes unusual for benign processes, but not notable enough for the accurate diagnosis of adenocarcinoma.[3]

In 2001, in a revision, the Bethesda system renamed AGUS as atypical glandular cells (AGCs) cytology.[4] It recommended characterizing AGC according to its anatomical origin: endocervical, endometrial, or of unspecified origin (AGC not otherwise specified—NOS). A new subcategory for AGC suspicious for neoplasia (AGC *favor* neoplasia) was included.[4] All these changes were maintained in the last review of the Bethesda system, in 2015.[5]

In the literature, AGC is present in less than 1% of cytological samples, with an incidence varying from 0.1 to 2.1%.[6–11] In the United States, its prevalence was 0.4% in 2003.[10,11] In Brazil, it corresponded to 4.6% of the altered cytologic exams performed in 2009.[12]

Despite the low prevalence of AGC, this diagnosis holds high importance due to its high frequency of association with neoplastic changes (e.g., squamous intraepithelial neoplasia, adenocarcinoma in situ, invasive adenocarcinomas of the cervix and endometrium, and, more rarely, extrauterine neoplasms). Other benign findings, such as vaginal adenosis, endometrial and endocervical polyps, inflammatory conditions, and reactive changes, may also be related to this cytological change.[13]

A systematic review by Marques et al. (2011)[14] assessed the association between the diagnosis of AGC and the occurrence of benign and/or premalignant or invasive lesions of the cervix. They observed a significant relation between AGC and benign disease. Nevertheless, the frequency of invasive squamous carcinoma (in patients previously diagnosed with AGC) ranged from 0.89 to 4.44%, and that of invasive adenocarcinoma ranged from 1.4 to 18%.[14]

International protocols do not yet establish a consensus regarding the referral of patients with a cytopathological diagnosis of AGC. In the Brazilian Guidelines for Cervical Cancer Screening (2016), used in our population, patients with AGC should be immediately referred to a second

cytology test (including material from the endocervical canal) and colposcopy.[15]

If the endocervical cytology result is adenocarcinoma in situ (AIS) or HSIL, prompt excisional treatment should follow. During colposcopy, if changes of any nature appear, a biopsy is necessary for therapeutic planning.[16] Physicians should employ an excision technique that produces an intact specimen for adequate evaluation of its margins.[17]

In women, those with AGC, older than 35 years or AGC with abnormal uterine or AGC of endometrial origin, endometrial evaluation must be considered (with ultrasound and/or biopsy).[15]

The present study aimed to determine the prevalence and frequency of the AGC cytology and to evaluate its clinical significance in various age ranges.

Methods

Retrospective observational study, using computerized data from the Integrated System of Technology and Cytopathology (SITEC, in the Portuguese acronym), Division of Pathology, from the Brazilian National Cancer Institute (INCA, in the Portuguese acronym). The SITEC is responsible for processing cytological examinations performed in a major part of Rio de Janeiro, Brazil. Therefore, it produces a comprehensive database of medical records. Files dated from January 2002 to December 2008 were evaluated in search of women diagnosed with AGC cytology. The women included were those with an AGC result and then referred to colposcopy and a second cytologic study (including material from the endocervical canal), as recommended by the Brazilian Guidelines for Cervical Cancer Screening (2016).[15] All of the follow-up procedures (colposcopy, second cytology and, possibly, biopsy) were performed at the same reference facility (Posto de Assistência Médica Manoel Guilherme da Silveira Filho, in Rio de Janeiro). When a colposcopy evidenced abnormal findings, a biopsy was the next step in management. Reports were standardized according to the nomenclature guidelines established by the Brazilian Ministry of Health and the Brazilian Society of Cytopathology.[6] Statistically, the prevalence of the AGC cytology was determined, the histological frequency of atypical glandular and squamous cervical lesions was calculated, and the frequency of disagreement between the cytological and histological exams was ascertained. The age ranges were organized (14–24, 25–34, 35–44, 45–54, 55–64, >64). This project was approved by Ethics Committee of Maternidade Escola da Univerisdade Federal do Rio de Janeiro (Ethics Committee Regulation Number 10/2011).

Results

A total of 132,147 cytopathological exams were collected and analyzed. Of these, 533 had AGC results. The prevalence of AGC cytology in the studied population was 0.4%. The average age of women with AGC was 40.7 years (range from 14 to 95 years). A total of 69.4% (370/533) women were submitted to a 2nd cytologic exam and colposcopy. After to the 2nd cytology exam and colposcopy, the following results were obtained: 67.6% (250/370) of normality, 24.5% (91/370) of atypia in squamous cells, 6.2% (23/370) of AGC. 1.6% (6/370) of the patients had a suspected adenocarcinoma (3 in situ, 3 invasive). 30.6% (163/533) of the women did not attend colposcopy/second cytology and were lost to follow-up. A total of 20.8% (77/370) of the women presented colposcopy changes and underwent biopsy and histological studies. Of these, 71.4% (55/77) demonstrated squamous cervical intraepithelial lesion, 9.1% (7/77) invasive adenocarcinoma, 18.2% (14/77) were negative to intraepithelial or invasive lesion, and 4.3% (1/77) had inconclusive results. Of the 23 women with a 2nd AGC cytology, 43.4% (10/23) had normal histology, 43.4% (10/23) had a squamous lesion (LSIL or HSIL), 8.7% (2/23) received the diagnosis of invasive adenocarcinoma (INV A), and in 4.3% (1/23) the histological report was inconclusive. The results of the second cytologic examination and biopsy are exposed in ►**Fig. 1**.

Regarding age ranges, 79.22% (417/533) of them were between 25 and 54 years old. Likewise, 82.61% (19/23) of the women who retested positive for AGC were in the same age group. All the women with HSILs or invasive adenocarcinoma confirmed on biopsy also were between 25 and 54 years old. Lastly, among the 49 patients younger than 25 years with a 1st AGC result, only 1 retested positive for it with LSIL histology. All the associations regarding age range and test results are exposed in ►**Tables 1** and **2**.

Discussion

There are not many publications in the literature investigating the clinical significance of a cytopathological diagnosis of AGC. Perhaps this is due to the low frequency in which this finding occurs. Besides, the interpretation of the cytology exam holds a low inter-observer agreement rate, leading to difficulty in reporting AGC.[18]

The AGC cytology is a diagnostic challenge due to several reasons: (1) the large variability in cytological criteria; (2) the poverty or absence of colposcopic imaging, inhibiting the teaching and learning of its interpretation; and (3) the array of histological findings that AGC may relate with, from benign diseases to squamous or glandular invasive lesions.[19]

Studies that have tried to demonstrate the clinical-histological implications of AGC had mixed outcomes.[19,20] Zhao et al. (2009)[20] showed that despite the low frequency of AGC (0.8%), its clinical importance lies in its high-risk relation to invasive endometrial lesions. These authors showed that the majority of AGC patients who had cancer on biopsy had severe lesions of endometrial origin. However, in the same year, they published a new study demonstrating that even though women with AGC cytology more commonly present with an endometrial disease, this is most likely related to the patient's age (>50 years) than to AGC itself.[21] In our study, none of the women first diagnosed with AGC had an endometrial disease. Similar to our findings, the study by Zhao et al.[20] found a low prevalence of AGC (0.4%).

Lai et al. (2007)[22] performed a 4-year study, which included 103,073 cytologic studies, 0.1% of which were

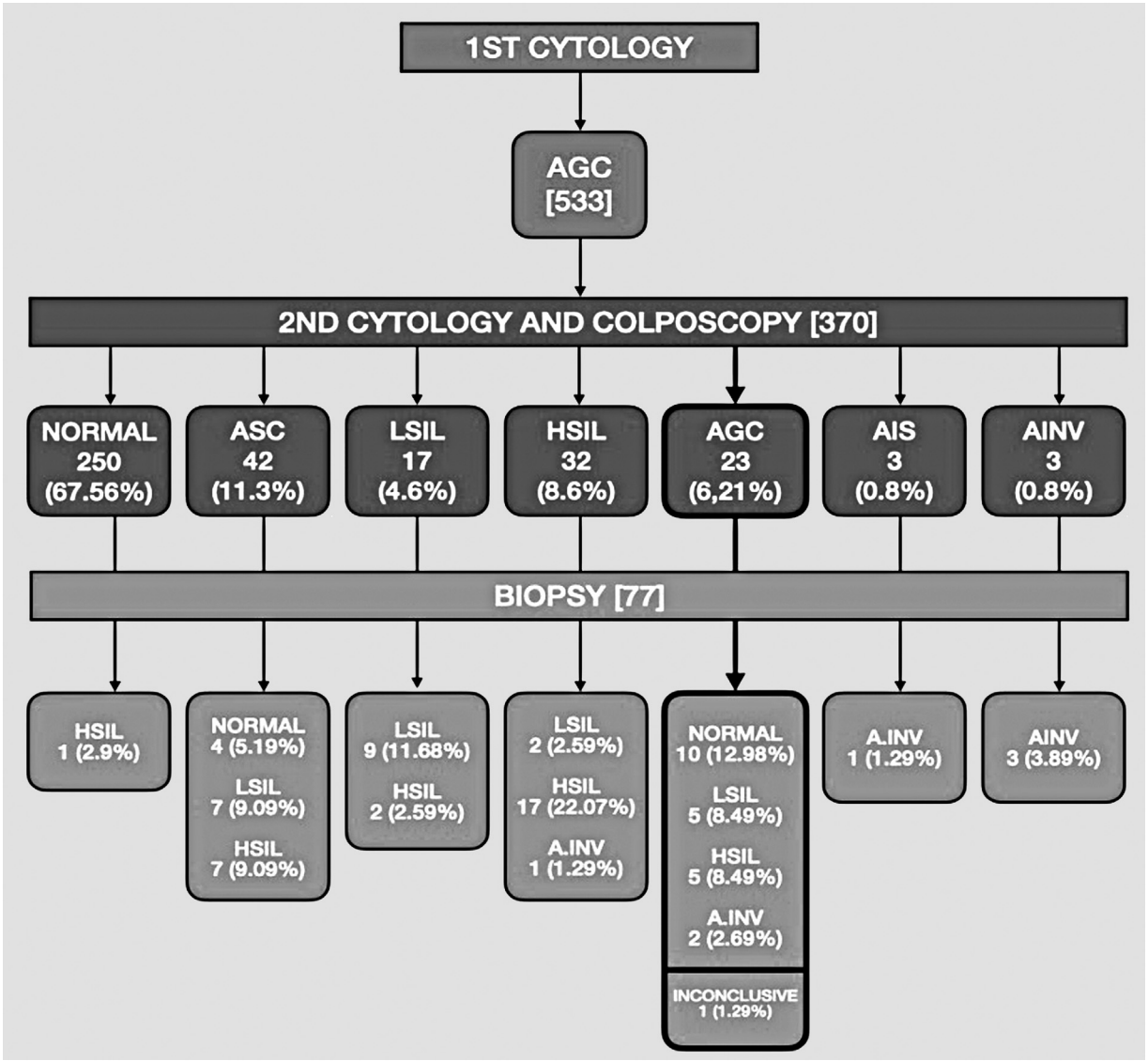


Fig. 1 Second cytologic results in 370 women with a previous atypical glandular cell report, followed by histologic results of 77 cases that required biopsy.

AGC results. In more than 50% of the cases, the histological diagnosis was negative for intraepithelial or invasive lesions, matching our results (43.47%). Our research, similar to Lai et al.[22] study, showed that AGC can correlate with both squamous and glandular diseases on histology.

Table 1 Distribution of patients with atypical glandular cell results according to age, for the first and second cytologic tests

AGE	1st cytology (AGC) n (%)	2nd cytology (AGC) n (%)
14–24	49 (9.2)	1 (4.3)
25–34	125 (24.4)	5 (21.7)
35–44	152 (28.5)	6 (26.1)
45–54	140 (26.3)	8 (34.7)
55–64	36 (6.7)	0 (0)
> 64	31 (5.8)	3 (13.0)
Total	533 (100)	23 (100)

Norman et al. (2017)[23] performed a cross-sectional study evaluating the prevalence of AGC in cytologic exams collected in Sweden. They showed a higher association between AGC and normal (46.3%) or HSIL (25.4%) biopsies. Cases of HSIL were only seen in women older than 40 years. This study agrees with those results, as the majority (43.5%) of our AGC patients were biopsy-proven disease-free, and the ones with HSIL or invasive carcinoma were never younger than 25 years.

At this point, there seems to be no consensus regarding the management and outcomes of an AGC finding on screening cytologic examinations. However, since a part of the patients presenting with it may have advanced diseases, it must be considered the active investigation of this diagnosis (by repeating the exam with sampling the endocervical canal and colposcopy) of utmost importance. Nevertheless, our experience demonstrates that this approach is probably

Table 2 Distribution of histologic results according to age range, among women submitted to biopsy after a second cytologic test indicative of atypical glandular cells

Age	Second cytology (AGC)	Histology				
		Normal n (%)	LSIL n (%)	HSIL n (%)	INVA n (%)	Inconclusive n (%)
14–24	1	0	1(4.3)	0	0	0
25–34	5	2 (8.7)	0	1(4.3)	1(4.3)	1(4.3)
35–44	6	2 (8.7)	3 (13.0)	1(4.3)	0	0
45–54	8	3 (13.0)	1 (4.3)	3 (13.0)	1(4.3)	0
55–64	0	0	0	0	0	0
> 64	3	3 (13.0)	0	0	0	0
TOTAL	23	10 (43.5)	5 (21.7)	5 (21.7)	2 (8.7)	1(4.3)

Abbreviations: INVA, invasive; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

most beneficial for those patients older than 25 years. This is because: (1) the majority of younger women will not repeatedly test positive for AGC; (2) they will only rarely have any histologic alteration; if present, (3) it will most likely be of low-grade; and, in this study, we found HSIL in women under 40 years.

In our study, we observed a great number of normal cytology when these were repeated. This was probably due to misinterpretation in cases of AGC in the first cytology. On the other hand, invasive lesions were not present in the older women. This probably due to the age of the population that go to health service for screening in the studied region.

The Brazilian Guidelines for Cervical Cancer Screening (2016)[15] recommend that screening should be performed in women between 25 and 64 years old. Despite this, several younger women were tested in the studied population. Among them, only one had persistency of AGC on the second cytologic test, and its biopsy resulted in an LSIL. Therefore, we question if these younger patients should also be actively followed-up after their first AGC result. In this study, the discomfort of a colposcopy, the risks of a biopsy, and the costs of all the procedures involved seem to weight against the highly unlikely chance of detecting cancer.

In conclusion, the finding of AGC cytology in the uterine cervix is rare. It will most commonly be found in women of reproductive age, between 25 and 54 years old. Most women with AGC will not have correlating alterations on biopsy. Nevertheless, they should be actively investigated (colposcopy, directed biopsy, endocervical cytology), particularly if they are 25 years old or older, due to the important, albeit rare, malignant diseases that they might present with.

Contributors

Gutemberg Almeida - conceptualization, methodology, investigation, writing (Original Draft). Jorge Wduardo Sainz - supervision, tesources, data surveys. Renata Fonseca - writing (ooriginal draft), writing (review and editing). Neil Chaves—investigation, data curation. Katia Silva - statistical calculation, tables making. Julio C Nunes - writing (review and editing), visualization. Yara Furtado - conceptualization, investigation, writing (Original Draft).

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Papanicolaou GN, Traut HF. The diagnostic value of vaginal smears in carcinoma of the uterus. Am J Obstet Gynecol. 1941;42(02): 193–206. Doi: 10.1016/S0002-9378(16)40621-6

2 Cytryn A, Russomano FB, Camargo MJ, Zardo LM, Horta NM, Fonseca RC, et al. Prevalence of cervical intraepithelial neoplasia grades II/III and cervical cancer in patients with cytological diagnosis of atypical squamous cells when high-grade intraepithelial lesions (ASC-H) cannot be ruled out. Sao Paulo Med J. 2009; 127(05):283–287. Doi: 10.1590/s1516-31802009000500007

3 National Cancer Institute Workshop. The 1988 Bethesda System for reporting cervical/vaginal cytological diagnoses. JAMA. 1989; 262(07):931–934. Doi: 10.1001/jama.1989.03430070079034

4 Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJASCCP-Sponsored Consensus Conference. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. JAMA. 2002;287(16):2120–2129. Doi: 10.1001/jama.287.16.2120

5 Nayar R, Wilbur DC. The Pap test and Bethesda 2014. Cancer Cytopathol. 2015;123(05):271–281. Doi: 10.1002/cncy.21521

6 Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. Coordenação-Geral de Prevenção e Vigilância. Divisão de Detecção Precoce e Apoio à Organização de Rede. Nomenclatura brasileira para laudos citopatológicos cervicais [Internet]. 3a ed. Rio de Janeiro: INCA; 2012 [cited 2020 May 24]. Available from: https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//nomenclatura-brasileira-para-laudos-citopatologicos-cervicais-2012.pdf

7 Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. Am J Obstet Gynecol. 2007;197(04): 346–355. Doi: 10.1016/j.ajog.2007.07.047

8 Boyraz G, Basaran D, Salman MC, Ibrahimov A, Onder S, Akman O, et al. Histological follow-up in patients with atypical glandular cells on Pap smears. J Cytol. 2017;34(04):203–207. Doi: 10.4103/JOC.JOC_209_16

9 Kim TJ, Kim HS, Park CT, Park IS, Hong SR, Park JS, et al. Clinical evaluation of follow-up methods and results of atypical glandular

cells of undetermined significance (AGUS) detected on cervicovaginal Pap smears. Gynecol Oncol. 1999;73(02):292–298. Doi: 10.1006/gyno.1999.5360
10 Chin AB, Bristow RE, Korst LM, Walts A, Lagasse LD. The significance of atypical glandular cells on routine cervical cytologic testing in a community-based population. Am J Obstet Gynecol. 2000;182(06):1278–1282. Doi: 10.1067/mob.2000.106537
11 Eltabbakh GH, Lipman JN, Mount SL, Morgan A. Significance of atypical glandular cells of undetermined significance on ThinPrep Papanicolaou smears. Gynecol Oncol. 2000;78(02):245–250. Doi: 10.1006/gyno.2000.5884
12 Ministério da Saúde. SISCOLO/SISMAMA: Sistema de Informação do câncer do colo do útero e Sistema de Informação do câncer de mama [Internet]. 2020 [cited 2020 Dec 21]. Available from: http://w3.datasus.gov.br/siscam/index.php?area=0401
13 Kumar N, Bongiovanni M, Molliet MJ, Pelte MF, Egger JF, Pache JC. Diverse glandular pathologies coexist with high-grade squamous intraepithelial lesion in cyto-histological review of atypical glandular cells on ThinPrep specimens. Cytopathology. 2009;20(06):351–358. Doi: 10.1111/j.1365-2303.2008.00568.x
14 Marques JP, Costa LB, Pinto AP, Lima AF, Duarte ME, Barbosa AP, et al. Células glandulares atípicas e câncer de colo uterino: revisão sistemática. Rev Assoc Med Bras. 2011;57(02):234–238. Doi: 10.1590/S0104-42302011000200024
15 Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. Coordenação de Prevenção e Vigilância. Divisão de Detecção Precoce e Apoio à Organização de Rede. Diretrizes brasileiras para o rastreamento do câncer do colo do útero. 2nd ed. Rio de Janeiro: INCA; 2016
16 Bornstein J, Bentley J, Bösze P, Girardi F, Haefner H, Menton M, et al. 2011 colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy. Obstet Gynecol. 2012;120(01):166–172. Doi: 10.1097/AOG.0b013e318254f90c
17 Raab SS, Geisinger KR, Silverman JF, Thomas PA, Stanley MW. Interobserver variability of a Papanicolaou smear diagnosis of atypical glandular cells of undetermined significance. Am J Clin Pathol. 1998;110(05):653–659. Doi: 10.1093/ajcp/110.5.653
18 Barreth D, Faught W, Schepansky A, Johnson G. The relationship between atypical glandular cells of undetermined significance on Pap smear and a clinically significant histologic diagnosis. J Obstet Gynaecol Can. 2004;26(10):867–870. Doi: 10.1016/s1701-2163(16)30136-0
19 Torres JC, Derchain SF, Gontijo RC, do Amaral Westin MC, Zeferino LC, Angelo-Andrade LA, et al. Atypical glandular cells: criteria to discriminate benign from neoplastic lesions and squamous from glandular neoplasia. Cytopathology. 2005;16(06):295–302. Doi: 10.1111/j.1365-2303.2005.00300.x
20 Zhao C, Austin RM, Pan J, Barr N, Martin SE, Raza A, et al. Clinical significance of atypical glandular cells in conventional pap smears in a large, high-risk U.S. west coast minority population. Acta Cytol. 2009;53(02):153–159. Doi: 10.1159/000325117
21 Zhao C, Florea A, Onisko A, Austin RM. Histologic follow-up results in 662 patients with Pap test findings of atypical glandular cells: results from a large academic womens hospital laboratory employing sensitive screening methods. Gynecol Oncol. 2009;114(03):383–389. Doi: 10.1016/j.ygyno.2009.05.019
22 Lai CR, Hsu CY, Tsay SH, Li AF. Clinical significance of atypical glandular cells by the 2001 Bethesda System in cytohistologic correlation. Acta Cytol. 2008;52(05):563–567. Doi: 10.1159/000325598
23 Norman I, Hjerpe A, Dillner J. Risk of high-grade lesions after atypical glandular cells in cervical screening: a population-based cohort study. BMJ Open. 2017;7(12):e017070. Doi: 10.1136/bmjopen-2017-017070

Salvage Nipple-sparing Mastectomy for Patients with Breast Cancer Recurrence: A Case Series of Brazilian Patients

Mastectomia preservadora de mamilo para pacientes com recidiva de câncer de mama: Uma série de casos de pacientes brasileiras

Antônio Luiz Frasson[1] Martina Lichtenfels[2] Fernanda Barbosa[1] Alessandra Borba Anton de Souza[2] Ana Beatriz Falcone[1] Isabela Miranda[2] Betina Vollbrecht[2] Carolina Malhone[1] José Yoshikazu Tariki[1]

[1] Hospital Israelita Albert Einstein, São Paulo, SP, Brazil
[2] Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil

Address for correspondence Antônio Luiz Frasson, MD, PhD, rua Ipiranga 6.690, sala 714, Porto Alegre, RS, 90610-000, Brazil (e-mail: alfrasson.af@gmail.com).

Rev Bras Ginecol Obstet 2022;44(5):489–496.

Abstract

Objective Few studies analyzed the safety of salvage nipple-sparing mastectomy (NSM) for local relapse treatment. We evaluated the outcomes of patients with indications for mastectomy who chose to undergo NSM for ipsilateral breast tumor recurrence (IBTR).

Methods Between January 2001 and December 2018, we evaluated 24 women who underwent NSM for local relapse after conservative surgery.

Results The patients were followed up for a mean time of 132 months since the first surgery. After the NSM, 5 (20.8%) patients were diagnosed with local recurrence and only 1 (4.2%) patient died. The patients presented 4.8% (2) of partial and 2.4% (1) of total nipple necrosis.

Conclusion In this long-term follow-up since the first surgery, we observed low rates of complication and good survival, although associated with high local recurrence in patients diagnosed with IBTR undergoing NSM as salvage surgery. We demonstrated that NSM may be considered after IBTR for patients who did not want to undergo total mastectomy.

Keywords
- neoplasm recurrence
- subcutaneous mastectomy
- segmental mastectomy

Resumo

Objetivo Há poucos estudos sobre a segurança de se realizar adenomastectomia (*nipple-sparing mastectomy*, NSM, em inglês) para tratamento de recidiva local. O objetivo deste estudo foi avaliar os resultados de pacientes com indicação para mastectomia que optaram por se submeter a NSM para o tratamento de recorrência local.

Métodos Foram analisadas 24 pacientes submetidas a NSM para tratamento de recidiva local após tratamento conservador entre janeiro de 2001 e dezembro de 2018.

Palavras-chave
- neoplasias da mama
- mastectomia subcutânea
- mastectomia segmental

received
July 13, 2021
accepted
November 18, 2021
published online
February 24, 2022

DOI https://doi.org/10.1055/s-0042-1743098.
ISSN 0100-7203.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resultados As pacientes foram acompanhadas por um período médio de 132 meses a partir da primeira cirurgia. Após a NSM, 5 (20,8%) pacientes foram diagnosticadas com recorrência local, e apenas 1 paciente foi a óbito. As pacientes apresentaram 4,8% de necrose parcial e 2,4% de necrose total do mamilo.

Conclusão Em um longo período de acompanhamento desde a primeira cirurgia, foram observadas baixas taxas de complicação pós-operatória e boa sobrevida, porém, associadas com uma alta taxa de recorrência local em pacientes submetidas a NSM para tratamento de recidiva local após cirurgia conservadora. Neste estudo, demonstrou-se que a NSM pode ser considerada uma opção cirúrgica para pacientes que não querem se submeter a mastectomia total.

Introduction

Several factors are related to a higher risk of developing ipsilateral breast tumor recurrence (IBTR), such as high tumor grade, positive excision margins, and younger age.[1,2] Tumor recurrence can be associated to the aggressiveness and progression of the disease. Total mastectomy is the standard surgical treatment for IBTR after breast-conserving surgery (BCS); however, studies have demonstrated that salvage BCS presents oncological safety, and can be used as an alternative to salvage mastectomy in selected patients.[3–5]

Nipple-sparing mastectomy (NSM) is a conservative mastectomy approach for early breast cancer, with oncological safety and good aesthetic satisfaction.[6,7] The initial indications for NSM excluded patients with previous radiation, ptosis, high body mass index (BMI), and macromastia, although these contraindications have been challenged. Different authors have expanded the classic indications for NSM for patients with previous breast surgery/irradiation, neoadjuvant chemotherapy, and short tumor-nipple distance, and showed safety and low complication rates associated.[8–11] However, there are few data about the suitability of performing NSM with immediate reconstruction for the treatment of recurrent disease.[12,13] High complication rates were evidenced in patients with a history of previous BCS followed by radiation.[14–16] Therefore, the quality of the skin and previous adjuvant radiotherapy (RT) should be considered for reconstruction in this setting.

Aiming to highlight a possible conservative approach, the objective of the present retrospective study is to report our experience with NSM after local recurrence for patients currently indicated for mastectomy, with no involvement of the skin or the nipple-areolar complex (NAC) involvement, who opt to perform NSM.

Methods

The present retrospective study was performed according to the institutional ethical guidelines, and received approval from the ethics committees of Hospital São Lucas and Hospital Albert Einstein. The study was performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent was waived by the institutional review board because of the retrospective characteristic of the study.

Patients with IBTR following BCS with an indication for mastectomy with no skin or NAC involvement, and who did not accept NAC resection, were considered to undergo NSM. The risks and benefits from the surgeries were explained to the patients, and they chose to undergo NSM. All patients were operated on by the same surgeon, the data was retrospectively evaluated by the medical chart, and the patients' follow-up was updated during the appointments. Patients with complete data from at least six months follow-up after the salvage surgery were included in the study. From the 348 therapeutic NSMs performed between January 2001 and December 2018, 24 (6.8%) met the inclusion criteria. All patients underwent standard staging examinations, such as radiography or computed tomography (CT) scans of the chest, ultrasound, or CT scans of the abdomen and pelvis, and bone scintigraphy before the salvage surgery. A total of 17 patients underwent bilateral surgeries, 1 patient presented ductal carcinoma in situ (DCIS), 1 patient, invasive ductal carcinoma (IDC) in the contralateral breast, and 15 patients chose contralateral surgery for prophylaxis or symmetrization. All patients had a previous BCS and presented IBTR at the time of the salvage NSM. The data from the previous surgery and previous treatment are listed in ►**Table 1**.

The patients were followed through clinical examinations at least every six months during the first five years, and yearly thereafter. Other imaging and laboratory tests were left at the discretion of the treating oncologists. Nipple necrosis was defined as any nipple ischemia requiring surgical intervention such as debridement, repair, and skin grafting. The recurrences were diagnosed through clinical examinations and routine imaging tests, and we considered the first relapse presented by the patient as recurrence. All the breast recurrences were biopsied to confirm the tumor. Invasive or in-situ local recurrence was defined as recurrence in the same breast and/or ipsilateral axilla.

All of the procedures were performed under general anesthesia. The NSM skin incision was chosen in accordance with the method of reconstruction and the considerations of the physician. The glandular tissue was removed, leaving only fat tissue to preserve blood supply and reduce the risk of flap necrosis. It is important to highlight that flap thickness

Table 1 Previous axillary surgery and systemic treatment in patients undergoing breast-conserving surgery

	N	%
Previous breast-conserving surgery	24	100
Previous axillary surgery		
Sentinel lymph node biopsy	13	54.2
Axillary lymph node dissection	8	33.3
No axillary surgery	1	4.2
No information	2	8.3
Number of positive lymph nodes		
0	19	79.2
1	2	8.3
2	1	4.2
No information	2	8.3
Previous treatment		
Hormone therapy	12*	54.6
Chemotherapy	9*	40.9
Radiotherapy	24	100
Anti-human epidermal growth factor receptor-2 (HER2) therapy	2*	9

Note: *Missing data: hormone therapy – $n = 2$; chemotherapy – $n = 2$; and anti-HER2 therapy – $n = 2$.

varies among patients, since it is based on the amount of subcutaneous fat present in the breast. An intraoperative histopathological examination of frozen sections of the retroareolar tissue was performed to confirm the absence of malignancy in the retroareolar and superficial margins. The margins of glandular tissue dissected were also evaluated by the pathologist. If there were positive margins, a new resection was performed to achieve negative margins. No cutoff point for margin status was used.

Sentinel lymph node biopsy (SLNB) was performed when indicated. Immediate breast reconstruction was performed using silicone prosthetic implants or tissue expanders. Inframammary incision was performed in patients who did not need skin excision for ptosis correction. When the patient presented excess skin that needed to be removed, our option was to make a vertical incision between the areola and the inframammary fold. At the end of the reconstruction, we used a mastopexis technique, such as periareolar, vertical, and sometimes transversal scar at the basis of the breast if excessive skin remains. The option with less morbidity and that best replaces the resected breast volume is the use of silicone breast implants. The placement of the implant was through the retromuscular plane in all cases, without the use of matrix (►**Fig. 1**).

Descriptive statistics were used to summarize patient characteristics. The quantitative variables were expressed as means and ranges, while the categorical variables were expressed as absolute and relative frequencies. The rates of disease-free survival (DFS) were summarized using the Kaplan-Meier method and displayed graphically. For a comparison of the median time until the occurrence of the event, the log-rank test was performed. The significance level to claim statistical difference between the groups was set at 0.05. All analyses were performed using the Statistical Analysis System (SAS, SAS Institute Inc., Cary, NC, United States) software, version 9.4.

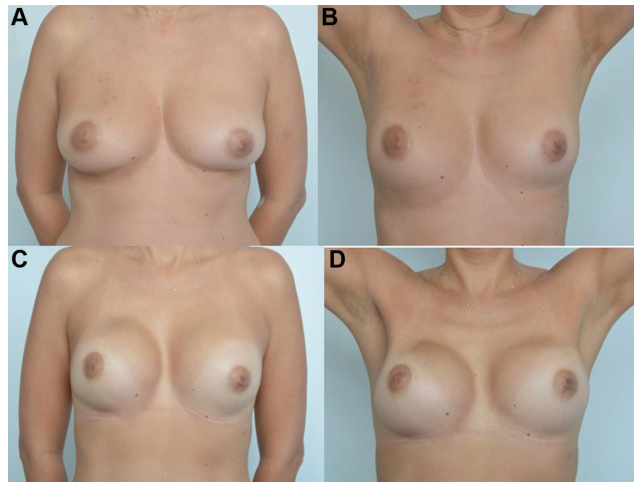


Fig. 1 Cosmetic result of the nipple-sparing mastectomy after previous breast-conserving surgery followed by radiotherapy. (**A**,**B**) Preoperative; (**C**,**D**) postoperative: immediate reconstruction with permanent implants.

Results

Between 2001 and 2018, we observed 71 patients with IBTR after previous BCS. A total of 28 (39.4%) patients underwent repeated BCS, 15 (21.2%) patients underwent total mastectomy, and another 28 (39.4%) patients with an indication for mastectomy with no skin or NAC involvement who chose to undergo NSM. Out of these 28 patients submitted to NSM, 4 were lost to follow-up (< 6 months after the NSM); therefore, we analyzed 24 patients.

The mean duration of the follow-up from the first BCS until the NSM salvage surgery was of 132 months, and the mean time until recurrence after the BCS surgery was of 111 months. In the first surgery, 13 (54.2%) patients underwent SLNB, 8 (33.3%), axillary lymph node dissection (ALND), 1 (4.2%) did not undergo axillary surgery, and data was missing from 2 (8.3%) patients. In total 19 patients presented negative sentinel lymph node (SLN), and 3, positive SLN. All patients were submitted to RT after BCS.

The mean duration of the follow-up after the salvage surgery was of 40 months. The patients' median age at the time of the salvage surgery was 49 years. Overall, 9 (37.5%) patients presented positive familial history of breast cancer, and 1 (4.2%), of ovarian cancer.

Most patients (17; 70.8%) underwent bilateral procedures: 1 (5.9%) patient due to the diagnosis of invasive cancer in both breasts, 1 (5.9%) case of DCIS in both breasts, and 15 (88.2%) patients without disease in the contralateral breast, mostly for prophylactic or esthetic reasons to avoid asymmetry and to achieve a better esthetic result. Frozen sections

of the undersurface of the areolar flap of every patient were extracted, and the samples were tumor-free upon analysis. The rates of axillary dissection were low (4.2%), 16 (66.7%) patients underwent SLNB, and the lymph nodes were not evaluated in 7 (29.2%) patients because of previous axillary dissection. All patients were clinically node negative at the time of recurrence. The mean size of the invasive tumor was 2.19 cm, and all tumors were grades 2 or 3. The reconstruction was performed using silicone prosthetic implants for 22 (91.7%) patients, and tissue expander only in 2 (8.3%) cases (►**Table 2**).

Out of the 41 NSMs performed, 4 (9.6%) complications occurred, including 1 (2.4%) infection, 2 (4.8%) cases of partial nipple necrosis, and 1 (2.4%) case of total nipple necrosis (►**Table 3**). The patient with total nipple necrosis was treated through the conservative approach, and recovered completely, maintaining the nipple.

During the mean follow-up of 40 months (range: 6 to 156 months) after the NSM, 5 (20.9%) patients were diagnosed with local recurrence, being 1 (4.1%) in the NAC. None of the patients presenting local relapse underwent reirradiation. Bone metastasis was observed in 1 (4.1%) patient, and 1 (4.1%) patient developed a new primary kidney tumor. The relapses are shown in ►**Table 3**. The characteristics of the local recurrences are shown in ►**Table 4**.

The overall survival rate was of 95.8%, and 1 patient died from progression of the breast cancer. ►**Figure 2** shows the rates of DFS, which was defined as the time from the performance of the NSM until invasive or in situ, local, regional, or distant recurrence, the development of a second primary tumor, or death from any cause. Overall survival was defined as the time from the performance of BCS to death from any cause.

Discussion

The suitability of NSM for the treatment of recurrent disease after BCS and whole-breast radiation was evidenced at a short-term follow-up with low complication rates, successful preservation of the NAC and satisfactory oncological outcomes.[13] However, the safety of performing immediate reconstruction in the salvage surgery is still under investigation, and few studies have been published. The present is the first study to show the outcomes of a case series of Brazilian patients diagnosed with IBTR after a previous conservative surgery, who underwent NSM with immediate reconstruction as a salvage surgery (►**Chart 1**).

Some tumor characteristics, such as size and molecular subtype, were lost due to the long-term follow-up since the first surgery; therefore, this data was not evaluated. After the first surgery, the mean time until recurrence was of 111 months. All patients presented IBTR and had an indication for mastectomy; however, they presented no skin or NAC involvement, and chose to undergo salvage NSM. The patients were informed about the risks and benefits of both surgeries, and they decided not to undergo mastectomy. Most patients were young, half of them were premenopausal, and presented large and high-grade invasive tumors. Their

Table 2 Nipple-sparing mastectomy and systemic treatment

Nipple-sparing mastectomy	n = 24	(%) (100)
Median age in years (range)	49 (36–78)	–
Menopausal status		
Premenopausal	12	50
Postmenopausal	12	50
Unilateral surgery	7	29.2
Bilateral surgery	17	70.8
In-situ contralateral breast cancer	1	5.9
Invasive contralateral breast cancer	1	5.9
Prophylactic contralateral nipple-sparing mastectomy	15	88.2
Axillary surgery		
Sentinel lymph node biopsy	16	66.7
Axillary lymph node dissection	1	4.2
No surgery	7	29.2
Mean lesion size (cm)	2.19	
Histology		
Invasive ductal carcinoma	14	58.4
Invasive lobular carcinoma	5	20.8
Ductal carcinoima in situ	5	20.8
Grade		
1	0	0
2	12	63.2
3	7	36.8
Molecular subtype		
ER +/PR +/HER2-	11	58
ER +/PR +/HER2+	4	21
ER-/PR-/HER2+	2	10.5
ER-/PR-/HER2-	2	10.5
Systemic treatment		
Hormone therapy		
Tamoxifen	5	20.8
Aromatase inhibitor	9	37.5
No	10	41.7
Unknown		
Chemotherapy		
Neoadjuvant	2	8.3
Adjuvant	9	37.5
No	13	54.2
Unknown		
Anti-HER2 therapy		
Trastuzumab	3	12.5
Double block	3	12.5
No	18	75
Unknown		
Radiotherapy		
Yes	6	25
No	18	75
Unknown		

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; PR, progesterone receptor. Table 3 Complication rates and recurrence after nipple-sparing mastectomy

Table 3 Complication rates and recurrence after nipple-sparing mastectomy

Complications	n = 41*	%
Infection	1	2.4
Partial nipple necrosis	2	4.8
Total nipple necrosis	1	2.4
Recurrences	**n = 24**	**%**
Local recurrence	5	20.9
Same breast/same quadrant	1	–
Same breast/other quadrant	3	–
Nipple-areolar complex	1	–
Distant metastasis	1	4.1
New primary tumor		1 4.1

Note: * The complications were calculated by the number of procedures performed ($n = 41$).

decision to undergo NSM patients might be related to the young age and the esthetic outcomes related to the surgery.[17] Galimberti et al.,[18] in their study, found that 72.1% of the patients undergoing NSM aged < 50 years, and 77.1% were premenopausal. The maintenance of the NAC confers a significant improvement in sexual, physical and psychosocial satisfaction in breast cancer patients undergoing NSM compared with skin-sparing mastectomy (SSM).[19]

Many patients underwent bilateral surgeries, and almost 90% of them did not have a diagnosis of cancer in the contralateral breast, and chose the surgery for prophylaxis or esthetic reasons, basically symmetry. Women choose to undergo the prophylactic procedure aiming to optimize the oncologic outcome, despite the fact that the literature shows no benefit in terms of survival.[20,21] Contralateral mastectomy is associated with young age, significant family history of breast or ovarian cancer, high level of schooling, and great worry about recurrence, the same characteristics we have observed in our patients who decided to undergo contralateral surgery.[22]

The number of patients with no lymph node assessment was high (29.2%) in the salvage surgery; however, all of them were submitted to a previous axillary surgery in the first surgical procedure, and the preoperative images did not evidence suspicious lymph nodes. Patients with previous breast surgery and complete axillary dissection do not need further axillary surgery.[23] The patients previously submitted to SLNB during the first surgery who presented clinically-negative axilla at the time of recurrence underwent a new SLNB (66.7%).

Our rate of complications was low (9.6%), and in line previous studies[24] that showed no increase in postoperative

Table 4 Characteristics of local recurrence after nipple-sparing mastectomy

		Second recurrence – after NSM				
Time until the first recurrence after BCS (months)	**Time until the second recurrence after NSM (months)**	**Age (years)**	**Location of the recurrence**	**New surgery**	**Pathology**	**Survival**
12	9	41	Same breast/other quadrant	Total mastectomy	IDC: bifocal; 4.5 cm and 0.9 cm; grade 3; ER-/PR-/HER2+	Alive
27	6	59	Same breast/other quadrant	Total mastectomy	DCIS: 2.8 cm; multifocal; grade 3	Alive
55	41	50	Same breast/other quadrant	Total mastectomy	IDC: 0.9 cm and 1.4 cm; bifocal; grade 3; ER +/PR +/HER2+	Alive
75	32	48	NAC	BCS	DCIS: multifocal; grade 3	Alive
117	83	50	Same breast/same quadrant	Total mastectomy	DCIS: multifocal; grade 2	Alive

Abbreviations: BCS, breast-conserving surgery; DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; PR, progesterone receptor; IDC, invasive ductal carcinoma; NAC, nipple-areolar complex; NSM, nipple-sparing mastectomy; PR, progesterone receptor.

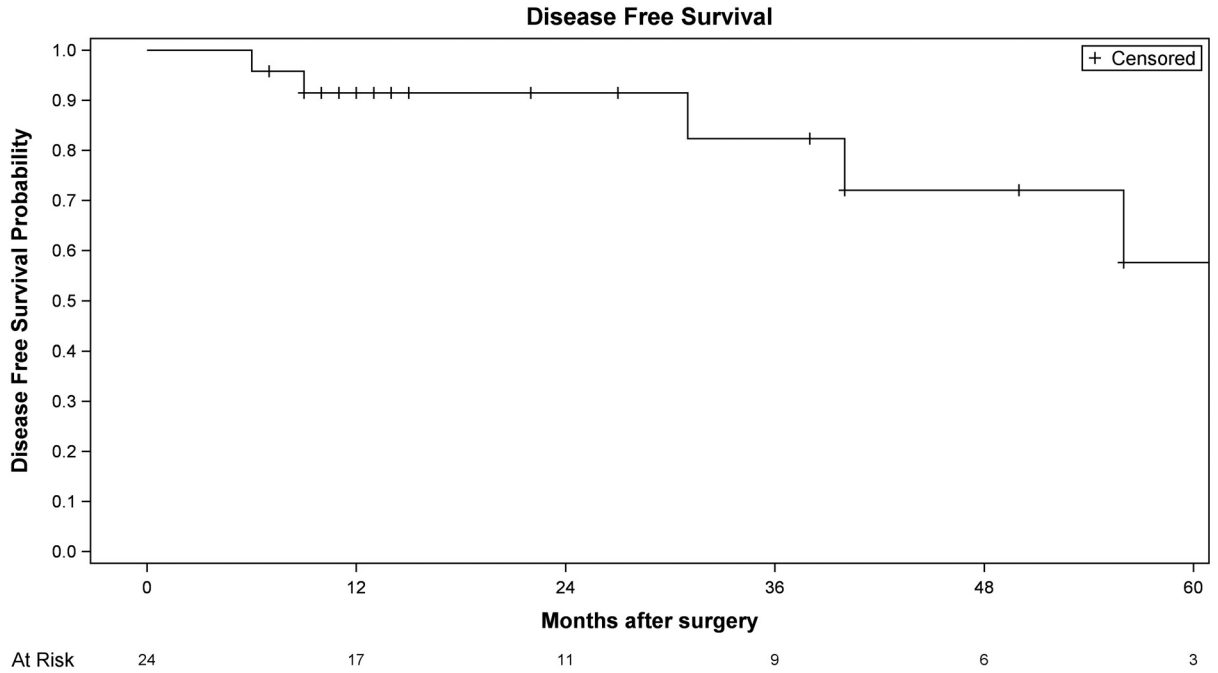


Fig. 2 Disease-free survival of breast cancer patients.

complications in patients undergoing NSM after a previous BCS. Murphy et al.[13] evaluated 19 patients who underwent NSM for the treatment of recurrent breast cancer, and observed complications requiring intervention in two patients, one with flap necrosis and one with seroma. Despite the retrospective nature of the present study, the complications and relapses from the NSM performed by our team were well documented in the medical charts.

Most of our patients were submitted to reconstruction with silicone implants (91.7%) and only 2 (9%) presented capsular contracture that caused breast asymmetry. These patients underwent a new surgery with capsular resection and a silicone prothesis exchange.

We observed 5 (20.8%) patients diagnosed with local recurrence in a mean follow-up of 40 months after the salvage surgery. Murphy et al.[13]did not observed any cases of cancer recurrence in patients undergoing NSM for the treatment of IBTR; however, their follow-up was shorter compared with the present study, with a median of 14.6 months.[13] Lee et al.[12] evaluated the oncological safety and survival of 18 patients who underwent NSM and immediate reconstruction for recurrence after BCS, and compared them with 127 patients who underwent NSM as the primary treatment for breast cancer. The patients undergoing a secondary NSM had mean age of 45 years, the majority was diagnosed with IDC (61.1%), none presented invasive lobular carcinoma (ILC), 53.8% presented stage-I tumors, 30.8% Tis, and no grade-3 tumors. Most of the patients (77.8%) in the secondary NSM group underwent preoperative radiotherapy. The authors[12] found similar rates of surgical complications and outcomes between the two groups during a mean follow-up of 45 months. The rates of local recurrence was of 5.6% in the secondary NSM group, against 3.1% in the primary NSM group. At the end of the follow-up, all patients in the secondary group and 97.6% in the primary group were alive.[12] The rate of local recurrence found in this study[12] was lower than the one observed in the present study; however, in our cohort there were more cases of ILC (21%) and high-grade tumors (graded 2 or 3), which are associated with an increased risk of relapse. Tumor grade is one of the parameters used to determine survival in all cases of breast cancer, and a high histologic grade has been associated with a high recurrence score on oncotype Dx.[25] The ILC histology is also related to higher risk of recurrence, with worse outcomes after 5 years and disease-specific survival compared with IDC.[26]

In the CALOR trial,[27] the authors evaluated the effectiveness of adding chemotherapy after surgery to treat isolated locoregional recurrence (ILRR). In the study,[27] 40% of the included patients underwent a previous mastectomy, and mosts presented ER-positive ILRR. In a 10-year follow-up, the authors observed a rate of DFS of 70% among patients who underwent chemotherapy, and of 34% among patients who did not. However, for patients with ER-positive tumors, the chemotherapy presented no benefits. The overall survival was of 73% in ER-negative ILRRs, and of 76% in ER-positive cases who underwent chemotherapy.[27] In the present study, the survival rate was high: only one patient died from disease progression in a long-term follow-up since the first surgery. Compared with the CALOR trial,[27] which included patients with previous mastectomy, our patients presented a better prognostic, since all of them underwent previous BCS followed by RT. It is expected that patients with ER-positive tumors present delayed recurrence and death after treatment. In the present study, the mean duration of the follow-up after the salvage surgery was of 40 months, and this could have influenced the high survival rates found among our population.

Chart 1 Previous studies on NSM for local recurrence after BCS

Authors (year)	Number of patients	Complication rates	Recurrence rates	Survival	Follow-up (months)
Cordeiro et al. (2012)[14]	121 patients who underwent NSM after recurrence + RT; 1.578 patients who underwent NSM for early cancer	Flap necrosis: 18% x 7.7%; infection: 8.3% x 4.8%; hematoma: 0.8% x 1.8%	NA	NA	NA
Lam et al. (2015)[15]	22	Seroma: 13.6%; bleeding: 45.%; delayed wound healing: 4.5%; infection: 4.5%	LR: 2	NA	NA
Murphy et al. (2017)[13]	21	Postoperative, requiring intervention: 2; flap necrosis: 1; seroma: 2	0%	100%	Median: 14.6
Lee et al. (2019)[12]	18 patients who underwent NSM after recurrence; 127 patients who underwent NSM for early cancer	Infecion: 5.6% x 3.9%; nipple necrosis: 11.1% x 17.3%	LR: 5.6% x 3.1% Metastasis: 0% x 5.5% Contralateral BC: 5.6% x 0.8%	100% x 97.6%	Mean: 45.5 × 45.3

Abbreviations: BCS, breast-conserving surgery; NA, not applicable; NSM, nipple-sparing mastectomy; RT, radiotherapy; BC, breast cancer; LR, local recurrence.

The present study has limitations, including the retrospective design of the analysis, the small sample size, and the process of selection of patients, which did not include thoses with incomplete data and those submitted to surgeries other than BCS as the first treatment. We did not compare the results of the NSM with those of the repeated BCS or total mastectomy, the standard treatment, because of the small sample size. Our aim was to highlight the possibility of performing NSM to treat recurrence in patients who did not want to undergo mastectomy and had no indication for BCS. Future studies comparing the outcomes of the different surgeries to treat IBTR are needed.

Conclusion

In a mean follow-up of 40 months after NSM, we observed ~ 20% local recurrence after the conservative approach in the management of local relapse in a case series of Brazilian patients. We also highlight a high survival rate in patients diagnosed with IBTR after a previous conservative surgery who underwent NSM as salvage procedure in a long-term follow-up since the first surgery. The complication rates were low. Therefore, we suggest that NSM may be performed after IBTR for patients with an indication for mastectomy with no skin or NAC involvement, who do not wish to undergo mastectomy to avoid a mutilating surgery.

Conflict of Interests

The author Antônio Luiz Frasson has received a speaker honorarium from Roche. The other authors have no conflict of interests to declare.

Acknowledgments

The present research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

References

1 Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. Int J Radiat Oncol Biol Phys. 2014;88(03):553–564. Doi: 10.1016/j.ijrobp.2013.11.012

2 Vrieling C, van Werkhoven E, Maingon P, Poortmans P, Weltens C, Fourquet A, et al; European Organisation for Research and Treatment of Cancer, Radiation Oncology and Breast Cancer Groups. Prognostic Factors for Local Control in Breast Cancer After Long-term Follow-up in the EORTC Boost vs No Boost Trial: A Randomized Clinical Trial. JAMA Oncol. 2017;3(01):42–48. Doi: 10.1001/jamaoncol.2016.3031

3 Walstra CJEF, Schipper RJ, Poodt IGM, van Riet YE, Voogd AC, van der Sangen MJC, Nieuwenhuijzen GAP. Repeat breast-conserving therapy for ipsilateral breast cancer recurrence: A systematic review. Eur J Surg Oncol. 2019;45(08):1317–1327. Doi: 10.1016/j.ejso.2019.02.008

4 Sellam Y, Shahadi ID, Gelernter I, Zippel D, Sklair-Levy M, Symon Z, et al. Local recurrence of breast cancer: Salvage lumpectomy as an option for local treatment. Breast J. 2019;25(04):619–624. Doi: 10.1111/tbj.13290

5 Smanykó V, Mészáros N, Újhelyi M, Fröhlich G, Stelczer G, Major T, et al. Second breast-conserving surgery and interstitial brachytherapy vs. salvage mastectomy for the treatment of local recurrences: 5-year results. Brachytherapy. 2019;18(03):411–419. Doi: 10.1016/j.brachy.2019.02.004

6 Howard MA, Sisco M, Yao K, Winchester DJ, Barrera E, Warner J, et al. Patient satisfaction with nipple-sparing mastectomy: A prospective study of patient reported outcomes using the BREAST-Q. J Surg Oncol. 2016;114(04):416–422. Doi: 10.1002/jso.24364

7 Bailey CR, Ogbuagu O, Baltodano PA, Simjee UF, Manahan MA, Cooney DS, et al. Quality-of-life outcomes improve with nipple-sparing mastectomy and breast reconstruction. Plast Reconstr Surg. 2017;140(02):219–226. Doi: 10.1097/PRS.0000000000003505

8 Jadeja P, Ha R, Rohde C, Ascherman J, Grant R, Chin C, et al. Expanding the criteria for nipple-sparing mastectomy in patients with poor prognostic features. Clin Breast Cancer. 2018;18(03):229–233. Doi: 10.1016/j.clbc.2017.08.010

9 Young WA, Degnim AC, Hoskin TL, Jakub JW, Nguyen MD, Tran NV, et al. Outcomes of > 1300 nipple-sparing mastectomies with immediate reconstruction: the impact of expanding indications on complications. Ann Surg Oncol. 2019;26(10):3115–3123. Doi: 10.1245/s10434-019-07560-z
10 Wengler CA, Valente SA, Al-Hilli Z, Woody NM, Muntean JH, Abraham J, et al. Determinants of short and long term outcomes in patients undergoing immediate breast reconstruction following neoadjuvant chemotherapy. J Surg Oncol. 2017;116(07): 797–802. Doi: 10.1002/jso.24741
11 Alsharif E, Ryu JM, Choi HJ, Nam SJ, Kim SW, Yu J, et al. Oncologic outcomes of nipple-sparing mastectomy with immediate breast reconstruction in patients with tumor-nipple distance less than 2.0 cm. J Breast Cancer. 2019;22(04):613–623. Doi: 10.4048/jbc.2019.22.e48
12 Lee CH, Cheng MH, Wu CW, Kuo WL, Yu CC, Huang JJ. Nipple-sparing mastectomy and immediate breast reconstruction after recurrence from previous breast conservation therapy. Ann Plast Surg. 2019;82(1S, Suppl 1):S95–S102. Doi: 10.1097/SAP.0000000000001696
13 Murphy BL, Boughey JC, Hieken TJ. Nipple-sparing mastectomy for the management of recurrent breast cancer. Clin Breast Cancer. 2017;17(04):e209–e213. Doi: 10.1016/j.clbc.2016.10.011
14 Cordeiro PG, Snell L, Heerdt A, McCarthy C. Immediate tissue expander/implast breast reconstruction after salvage mastectomy for cancer recurrence following lumpectomy/irradiation. Plast Reconstr Surg. 2012;129(02):341–350. Doi: 10.1097/PRS.0b013e318205f203
15 Lam TC, Hsieh F, Salinas J, Boyages J. Can an immediate 2-stage breast reconstruction be performed after previous conservative surgery and radiotherapy? Plast Reconstr Surg Glob Open. 2015;3 (07):e473. Doi: 10.1097/GOX.0000000000000436
16 Al-Hilli Z, Grobmyer SR. Management strategies for locally recurrent breast cancer: redo-lumpectomy, redo-sentinel node biopsy, redo-radiation. Ann Surg Oncol. 2019;26(10):3018–3024. Doi: 10.1245/s10434-019-07545-y
17 Wang M, Huang J, Chagpar AB. Can I keep my nipple? Factors influencing the surgical decision between skin-sparing and nipple-sparing mastectomy. Am Surg. 2019;85(07):768–771. Doi: 10.1177/000313481908500741
18 Galimberti V, Morigi C, Bagnardi V, Corso G, Vicini E, Fontana SK, et al. Oncological outcomes of nipple-sparing mastectomy: a single-center experience of 1989 patients. Ann Surg Oncol. 2018;25(13):3849–3857. Doi: 10.1245/s10434-018-6759-0
19 Yoon-Flannery K, DeStefano LM, De La Cruz LM, Fisher CS, Lin LY, Coffua LS, et al. Quality of life and sexual well-being after nipple sparing mastectomy: A matched comparison of patients using the breast Q. J Surg Oncol. 2018;118(01):238–242. Doi: 10.1002/jso.25107
20 Wong SM, Freedman RA, Sagara Y, Aydogan F, Barry WT, Golshan M. Growing use of contralateral prophylactic mastectomy despite no improvement in long-term survival for invasive breast cancer. Ann Surg. 2017;265(03):581–589. Doi: 10.1097/SLA.0000000000001698
21 Bouchard-Fortier A, Baxter NN, Sutradhar R, Fernandes K, Camacho X, Graham P, et al. Contralateral prophylactic mastectomy in young women with breast cancer: a population-based analysis of predictive factors and clinical impact. Curr Oncol. 2018;25(06): e562–e568. Doi: 10.3747/co.25.4169
22 Jagsi R, Hawley ST, Griffith KA, Janz NK, Kurian AW, Ward KC, et al. Contralateral prophylactic mastectomy decisions in a population-based sample of patients with early-stage breast cancer. JAMA Surg. 2017;152(03):274–282. Doi: 10.1001/jamasurg.2016.4749
23 Burger AE, Pain SJ, Peley G. Treatment of recurrent breast cancer following breast conserving surgery. Breast J. 2013;19(03): 310–318. Doi: 10.1111/tbj.12105
24 Frederick MJ, Lin AM, Neuman R, Smith BL, Austen WG Jr, Colwell AS. Nipple-sparing mastectomy in patients with previous breast surgery: comparative analysis of 775 immediate breast reconstructions. Plast Reconstr Surg. 2015;135(06):954e–962e. Doi: 10.1097/PRS.0000000000001283
25 Singh K, He X, Kalife ET, Ehdaivand S, Wang Y, Sung CJ. Relationship of histologic grade and histologic subtype with oncotype Dx recurrence score; retrospective review of 863 breast cancer oncotype Dx results. Breast Cancer Res Treat. 2018;168(01): 29–34. Doi: 10.1007/s10549-017-4619-4
26 Chen Z, Yang J, Li S, Lv M, Shen Y, Wang B, et al. Invasive lobular carcinoma of the breast: A special histological type compared with invasive ductal carcinoma. PLoS One. 2017;12(09): e0182397. Doi: 10.1371/journal.pone.0182397
27 Wapnir IL, Price KN, Anderson SJ, Robidoux A, Martín M, Nortier JW, et al; International Breast Cancer Study Group NRG Oncology, GEICAM Spanish Breast Cancer Group, BOOG Dutch Breast Cancer Trialists' Group Breast International Group. Efficacy of chemotherapy for ER-negative and ER-positive isolated locoregional recurrence of breast cancer: final analysis of the CALOR trial. J Clin Oncol. 2018;36(11):1073–1079. Doi: 10.1200/JCO.2017.76.5719

WhatsApp and Gynecologist-Patient Interaction: Development and Validation of a Questionnaire to Assess the Stress Perceived by the Doctor

WhatsApp e a relação ginecologista-paciente: Desenvolvimento e validação de questionário para avaliar o estresse percebido pelo médico

Melissa Gonzalez Veiga[1] Rogério Tadeu Felizi[1] César Eduardo Fernandes[1] Emerson Oliveira[1]

[1] Faculdade de Medicina do ABC, Santo André, SP, Brazil

Rev Bras Ginecol Obstet 2022;44(5):497–502.

Address for correspondence Melissa Gonzalez Veiga, Av. Lauro Gomes, 2000, 09060-870, Vila Sacadura Cabral, Santo André, SP, Brazil (e-mail: dramelissaveiga@gmail.com).

Abstract

Objective Construction and validation of the WhatsApp Stress Scale (WASS), a questionnaire designed for physicians that measures how the use of smartphones and related software communication applications affects the quality of life of gynecologists who use this tool to communicate with patients.

Methods The present cross-sectional observational study analyzed 60 gynecologists according to weekly WhatsApp usage time for communication with patients and compared the data with the perception of the doctor on the use of this virtual interaction as a stressor. Physicians were equally divided into three groups: < 2 hours, 2 to 5 hours, and > 5 hours. The authors created a questionnaire in Likert scale format. The study proceeded in three phases: development of the questionnaire items, pretesting, constructing, and validity and reliability testing using factor analysis, Cronbach α coefficient, and paired *t*-test.

Results A 9-item instrument using a 5-point Likert scale was created and administered to the participants in 3 different times: T0, T1 (15 minutes after the end of T0), and T2 (15 days later). All questionnaire items possessed adequate content validity indices and the internal consistency of the instrument was satisfactory (Cronbach α 0.935; 95% confidence interval [CI]: 0.744–0.989; $p = 0.0001$). No statistically significant differences were observed in the responses between the rounds of testing, indicating good test-retest reliability. A positive association between the high frequency of WhatsApp usage for communication with patients and the stress perceived by the doctor was shown.

Conclusion The WASS is a valid and reliable instrument for assessing the use of messaging applications to communicate with patients as a stressor perceived by gynecologists.

Keywords
- mobile applications
- occupational stress
- physician-patient relations
- smartphone
- questionnaire

received
April 26, 2021
accepted
January 11, 2022
published online
April 20, 2022

DOI https://doi.org/10.1055/s-0042-1744289.
ISSN 0100-7203.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resumo

Objetivo Construção e validação do WhatsApp Stress Scale (WASS, na sigla em inglês), questionário desenvolvido para médicos que avalia como o uso do smartphones e aplicativos de comunicação afetam a qualidade de vida dos ginecologistas que usam estas ferramentas para comunicação com pacientes.

Métodos O presente estudo transversal observacional analisou 60 ginecologistas de acordo com o tempo de uso semanal do WhatsApp para comunicação com pacientes e comparou os dados de percepção dos médicos do uso desta interação virtual como agente estressor. Os profissionais foram igualmente divididos em 3 grupos: < 2 horas, de 2 a 5 horas e > 5 horas. Foi criado um questionário no formato de escala tipo Likert. O estudo procedeu em três fases: desenvolvimento dos itens do questionário, pré-teste, construção, validação de constructo e teste de confiabilidade usando análise fatorial, coeficiente alfa de Cronbach e teste t pareado.

Resultados Um instrumento com 9 itens foi criado e administrado aos participantes em 3 tempos diferentes: T0, T1 (15 minutos após o término de T0) e T2 (15 dias depois). Todos os itens possuíam validade de conteúdo adequada e a consistência interna do instrumento foi satisfatória (alfa de Cronbach 0,935; intervalo de confiança [IC] 95%: 0,744–0,989; $p = 0{,}0001$). Não foi observada diferença estatisticamente significativa entre as rodadas de teste, indicando boa confiabilidade teste-reteste. Foi demonstrada uma associação positiva entre maior tempo de uso do WhatsApp para comunicação com pacientes e estresse percebido pelos médicos.

Conclusão O WASS demonstra ser um instrumento válido e confiável para avaliar o uso de aplicativos de mensagens para comunicação médico-paciente como agente estressor percebido pelo ginecologista.

Palavras-chave

- aplicativos móveis
- estresse ocupacional
- relações médico-paciente
- smartphone
- questionário

Introduction

With the advent of the Internet, the speed of information exchange and the introduction of newer communication media have dramatically improved the healthcare sector.[1] The emergence of social media has shifted information-seeking behavior in society and the health sector is not immune from this influence.[2] The digital revolution had a profound impact on how physicians interact with patients and the community and the increased use of smartphones and related software applications has created a new era in the exchange of clinical data between patients and clinicians.[3] Recently, low-cost instant messaging services (WhatsApp Messenger [WhatsApp Inc, Menlo Park, CA, US], Skype [Skype Technologies, Luxembourg City, Luxembourg] Telegram [Telegram Messenger Inc., London, UK], etc.) have practically replaced all electronic media used before thanks to the wide availability of smartphones worldwide.[4]

Among innumerable communication applications for smartphones, WhatsApp is considered to be the most widespread and has been downloaded in 40 countries in Europe, Asia, the Middle East, and the Americas.[5] A growing number of healthcare workers have adopted WhatsApp in their daily work to share information with patients.[5] The app can be downloaded freely via the Internet and is available for all commonly used mobile platforms such as Android, iPhone, and Windows mobile.[6] Other advantages of using WhatsApp in healthcare are improvement of communication, no requirement for a computer, time saving, and the possibility of an immediate response.[3,7–9] Despite the many benefits, existing risks or disadvantages have also been reported: increase in workload by staying online 24 hours a day, disparity in the sense of urgency, worsening of professional relationships and risk of unprofessional behavior, clinical information not being included in medical records, possible issues of privacy and data protection, ethical aspects of clinical evaluations at a distance, and lack of specific legislation.[9–12] Besides, some disadvantages of using WhatssApp may be the error in the interpretation by the professionals of complaints of the patients and failures in the understanding of the recommendations by the patients.[4]

It is not unusual for the demand placed on people by the changes in modern life and the consequent need to adjust to these changes to end up inducing a situation of conflict, anxiety, anguish, and emotional destabilization.[13] Stress ends up as a direct consequence of persistent efforts to adapt to the existential situation.[13] The association between smartphone use and increased stress was suggested by many studies.[10,14] Referred to as "communication overload," Thomée et al.[15] found that this pressure to be constantly available was associated with higher smartphone use – to meet the expectation – and that this pressure was associated with feelings of guilt, stress, and depression.

Psychological distress, such as depression and anxiety, has become a major workplace mental health problem and could be associated with several symptoms and possible consequences among various professions.[16] For instance, depression could result in low productivity, absenteeism, job

turnover, and economic costs, whereas anxiety, when it becomes excessive and persistent, is frequently accompanied by physiological symptoms such as headache, sweating, fatigue, or exhaustion.[16,17] Additionally, psychological distress among healthcare workers impairs not only their own health, but also imperils the health and safety of their patients.[18] However, to date, little research has examined the actual psychological experience of technostress itself. Thus, the present study aimed to present the construction and validation of the WhatsApp Stress Scale (WASS), a questionnaire designed for physicians that measures how WhatssApp use affects the wellbeing and quality of life of gynecologists who routinely use this tool as a means of communicating with patients.

Methods

We conducted a cross-sectional observational study between August 2019 and July 2020 that was previously submitted to and approved by the Research Ethics Committee of the Faculdade de Medicina do ABC (FMABC, in the Portuguese acronym) under number 3.528.229. The population sample consisted of 60 gynecologists selected by convenience; the participants were actively recruited through the research of the own database of the group and were randomly invited. The inclusion criteria were as follows: agreement to participate in the study according to the informed consent form and gynecologists working in the state of São Paulo, Brazil, who use WhatsApp as a means of communication with patients. The authors developed the questionnaire after a thorough literature review and the items were generated based on the currently available literature and their basic research issue.[3,11,12] The questionnaire included general demographics and nine questions that examined the perception of doctors on the use of this virtual interaction as a stressor, according to the weekly WhatsApp usage time for communication with patients. The items were measured by a Likert scale ranging from 1 to 5 points (1, never; 2, almost never; 3, sometimes; 4, frequently; and 5, very frequently), and 9 items with scores ranging from 9 to 45 (the higher the score, the grater the perception of the use of the virtual communication with patients as a stressor). The 9-item list of the questionnaire is shown in ►**Chart 1**.

After the participants signed the informed consent form, demographic data were collected, such as age, gender, marital status, parity, physical activity habits, and graduate year. Next, the physicians answered the WASS questionnaire in a self-administered manner. The instrument was applied at 3 different times: the first, defined as T0, overseen by researcher A; the second, called T1, occurred 15 minutes after the end of T0, and was overseen by researcher B; and the third, 15 days later, called T2, when the instrument was completed via WhatsApp after being sent by researcher A. Regarding the psychometric properties to measure the questionnaires, the variables analyzed were internal consistency, test-retest reliability, and interobserver reliability. Internal consistency evaluates the correlation between the items and is determined from the subscale scores and the total score. A higher value indicates greater correlation between various items of the scale. A retest was performed 15 days after the first application of the questionnaire. The interobserver reliability was assessed by applying the instrument 15 minutes after the first interview. Finally, the discriminant validity was evaluated by applying the questionnaire in the three groups studied. The data were tabulated in Google Drive spreadsheets (Google LLC, Mountain View, CA, US). The software Prism version 8.4.1 (GraphPad Software, San Diego, CA, US) and IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, USA) were used for analysis. The normality of the data was analyzed by the Kolmogorov-Smirnov test and, as appropriate, analysis of variance (ANOVA), the Kruskal-Wallis test, and the Dunn test were used to compare continuous variables. The chi-squared test was used to compare categorical variables. The sample size was not calculated due to the extensive variability of formulas suggested to generate the minimum number of subjects for studies involving the validation of questionnaires.[19] The internal consistency of the instrument was calculated in the form of Cronbach α coefficient by measuring the 9 questionnaires items (> 0.9: excellent; 0.7–0.9: acceptable to good; 0.6–0.7: questionable; 0.5–0.6: poor; and < 0.5: unacceptable).[20] The test-retest reliability was calculated with the intraclass correlation coefficient (ICC), which allows us to determine whether the studied tool is reliable for comparing the scores obtained at T0 and T2 (intraobserver) and at T0 and T1 (interobserver). When $ICC = 0$, the questionnaire is not reproducible; when $ICC = 1$, the questionnaire has maximum reproducibility; an $ICC < 0.4$ means that the reproducibility is poor; an $ICC \geq 0.75$, excellent reproducibility; and for $0.4 \leq ICC < 0.75$ the reproducibility is satisfactory.[21] All statistical tests were two-tailed, with a significance level of 5%.

Results

We included 60 gynecologists who were equally divided into 3 research groups according to the weekly WhatsApp usage

Chart 1 Questionnaire items

How often did you answer messages unrelated to urgent matters?
How often did you feel irritated by the messages?
How often did you feel nervous about being asked out of working hours?
How often did you feel uncomfortable with the lack of limits of the patient?
How often did you notice a decrease in patience when having to reply to messages?
How often did you feel insecure about this type of communication that does not have specific regulations or legal support?
How often were you bothered by believing that this type of communication trivializes the medical service?
How often did you feel irritated at not being paid to work through these tools?
How often did you realize that being available to work with these tools interfered with your quality of life?

Table 1 Demographic characteristics

Variable	< 2 hours ($n = 20$)	2–5 hours ($n = 20$)	> 5 hours ($n = 20$)	*p-value*
Age[a]	44.2 ± 9.5	46.7 ± 9.5	41.8 ± 6.8	0.23
Gender[b]				
Female	16 (80)	14 (70)	15 (75)	0.76
Male	4 (20)	6 (30)	5 (25)	
Marital Status[b]				
Married	12 (60)	14 (70)	12 (60)	0.75
Single	8 (40)	6 (30)	8 (40)	
Child[b]				
Yes	11 (55)	16 (80)	11 (55)	0.16
No	9 (45)	4 (20)	9 (45)	
Physical Activity[b]				
Yes	9 (45)	8 (40)	12 (60)	0.41
No	11 (55)	12 (60)	8 (40)	
Graduate Year[b]				
≤ 15 years	5 (25)	3 (15)	7 (35)	0.34
> 15 years	15 (75)	17 (85)	13 (65)	
Weekly Workload[b]				
≤ 30 hours	2 (10)	4 (20)	2 (10)	0.56
> 30 hours	18 (90)	16 (80)	18 (90)	

[a]Values presented as mean and standard deviation. Statistical test: analysis of variance (ANOVA).
[b]Values presented as numbers and percentages. Statistical test: chi-squared test.

time for communication with patients: ≤ 2 hours (GI), 2 to 5 hours (GII), and > 5 hours (GIII). Participants in GII had a higher mean age than those in GI and GIII (46.7 ± 9.5 versus 44.2 ± 9.5 and 41.8 ± 6.8 years old, respectively; $p = 0.23$). GII also had a greater proportion of individuals who were married (70%; $p = 0.75$) and had at least 1 child (80%; $p = 0.16$). More than half of the doctors self-identified as a female in all groups ($p = 0.76$). The prevalence of physical activity was higher in GIII ($p = 0.41$). Most participants in GI, GII and GIII had been working for > 15 years as a doctor (75, 85, and 65%, respectively; $p = 0.34$) and had a weekly workload of > 30 hours (90, 80, and 90%, respectively; $p = 0.56$). ►**Table 1** shows the demographic characteristics of the study population in more detail.

Doctors who reported spending more hours a week communicating with patients via WhatsApp had higher levels of stress ($p = 0.0024$). Highest stress scores did not correlate with gender, marital status, having a child or graduate year. However, there was a significant association between age and perceived stress. Younger physicians had higher stress scores. ►**Table 2** shows the analysis of the WASS scores in the three groups studied. Discriminant validity was demonstrated.

The internal consistency values of the WASS questionnaire were found for all items, and for the overall score, the Cronbach coefficient was 0.935 (95% confidence interval [CI]: 0.744–0.989; $p = 0.0001$), showing excellent internal consistency. Therefore, the reliability of the instrument was adequate. Finally, no differences were observed in the test–retest comparison of the WASS questionnaire in the intra- or interobserver evaluation. The ICC results were 0.838 and 0.847, respectively, showing excellent reproducibility (ICC > 0.75) (►**Table 3**).

Table 2 Discriminant validity of the WhatsApp Stress Scale questionnaire between groups

< 2 hours	2–5 hours	> 5 hours	*p-value*
32 (15–45)	34 (16–45)	35.5 (25–45)	0.0024

[a]Values presented as median, minimum and maximum, range. Statistical test: Kruskal-Wallis and Dunn multiple comparison test. Multiple comparisons: GIII > GII ($p = 0.0457$) and GIII > GI ($p = 0.0023$).

Table 3 Test-retest intraobserver and interobserver reliability of the WhatsApp Stress Scale

Intraobserver ICC; 95%CI; *p-value*	Interobserver ICC; 95%CI; *p-value*
0.838; 0.731–0.903; 0.0001	0.847; 0.742–0.909; 0.0001

Abbreviations: CI, confidence interval; ICC, intraclass correlation coefficient.

Discussion

The advent of telemedicine has allowed physicians to deliver medical treatment to patients from a distance. Mobile apps such as WhatsApp Messenger came as a novel concept in all fields of social life, including medicine, offering and disseminating scientific and technological information.[5,22] Because of the quick development and widespread use of mobile phones and of their vast effect on communication and interactions in work and private life, it is important to study possible negative health effects of exposure to them.[14] However, in different countries of the world, few investigations have been conducted on the attitudes and opinions of physicians about the use of social media in the healthcare field.[22] The present study aimed to develop and validate a questionnaire to assess the effects of WhatsApp use on the wellbeing and quality of life of gynecologists who routinely use this tool as a means of communicating with patients.

The widespread use of technology and the electronic environment in the healthcare system and its effect on physicians have been suggested by some prior research, but according to our knowledge, this is the first study to date to look at WhatsApp as a stressor for physicians in the context of the doctor-patient relationship.[23] The process of developing the WASS resulted in a 9-item questionnaire. The face validity was satisfactory, and a good discriminant validity was shown. The instrument also showed good internal and external reliability, demonstrating that the questionnaire is measuring the wellbeing and quality of life of

gynecologists who use WhatsApp to communicate with patients consistently and reproducibly.

We found that the highest stress scores among gynecologists were associated with more hours spent communicating with patients via WhatsApp. Similarly, studies have shown prospective associations between instant messaging and perceived stress.[24,25] Considering the variables examined, there appeared to be a significant difference of stress scores across age groups. The present study found that younger respondents demonstrated the highest levels of stress, which is in line with the findings of Ragu-Nathan et al.[26] that technostress decreased as age increased. The assessment of workload was based on self- reporting; thus, it is possible that those professionals reporting higher levels of stress perceived that they worked more hours. Therefore, the effect of age on the perceived stress warrants further investigation.

In terms of gender, male and female gynecologists did not differ significantly in their perceived stress, contrary to previous research that found clear associations for women, in whom chatting online was associated with prolonged stress and symptoms of depression.[25] Our results did not correspond with those of previously conducted studies that concluded that the prevalence of physical activity may have some impact on improving mental health and quality of life.[27] There were no significant differences in perceived stress related to marital status, having children or graduate year. Panagopoulou et al.[28] found that work hours are not a predictor of stress, which is in line with our results, which show that the raw objective data may not be the only appropriate variable to correlate with stress.

More and more studies have linked the overuse of the Internet and of smartphones to lower life satisfaction and higher stress.[29–31] Stress poses a substantial problem for the wellbeing of physicians and for the quality of healthcare and is likely to be harmful to relationships with patients. There is ample evidence that doctors who are under high levels of stress deliver poorer patient care and make potentially critical mistakes.[28,32] Identifying the risk factors of stress may prevent medical errors from occurring and increase the satisfaction with health care. Our findings serve as a reminder that this relationship between the use of smartphones to communicate with patients and stress exists, allowing gynecologists to be aware of this association in their daily lives.

There were some limitations in the development of the present questionnaire. The sample size of the study is relatively small; a larger sample could have highlighted missing aspects. Besides, the instrument was applied in specialists in the same area of expertise, which could limit the generalizability of the study. In addition, the construct validity of the instrument was not assessed, as correlations between our scale and existing, validated assessment tools of quality of life were not established.

Conclusion

The present questionnaire was found to be a valid and reliable instrument with a high internal consistency for the evaluation of WhatsApp usage in the patient-doctor interaction as a stressor for gynecologists who routinely use this tool to communicate with patients.

Contributors
Veiga M. G. contributed to the conception and design of the work, helped with interpretation of data for the work and wrote the manuscript in consultation with Felizi R. T. and Oliveira E.. Fernandes C. E. and Oliveira E. conceived the study, helped with interpretation of data for the work and performed the analytic calculations. Veiga M. G., Felizi R. T., and Oliveira E. performed the analysis of the material obtained and helped with the interpretation of data for the work. All authors provided critical revision for important intellectual content, discussed the results, and contributed to the final approval of the version to be published. All of them agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or the integrity of any part of the work are appropriately investigated and resolved.

Conflicts to Interest
None to declare.

References

1 Hazzam J, Lahrech A. Health care professionals' social media behavior and the underlying factors of social media adoption and use: quantitative study. J Med Internet Res. 2018;20(11): e12035. Doi: 10.2196/12035
2 Fox S, Duggan M. Mobile Health 2012 [Internet]. Washington (DC):Pew Research Center's Internet & American Life Project;2012 [cited 2021 Feb 12]. Available from: https://www.pewresearch.org/internet/wp-content/uploads/sites/9/media/-Files/Reports/2012/PIP_MobileHealth2012_FINAL.pdf
3 Petruzzi M, De Benedittis M. WhatsApp: a telemedicine platform for facilitating remote oral medicine consultation and improving clinical examinations. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;121(03):248–254. Doi: 10.1016/j.oooo.2015.11.005
4 Krynski L, Goldfarb G, Maglio I. Technology-mediated communication with patients: WhatsApp Messenger, e-mail, patient portals. A challenge for pediatricians in the digital era. Arch Argent Pediatr. 2018;116(04):e554–e559. Doi: 10.5546/aap.2018.eng.e554
5 Giordano V, Koch H, Godoy-Santos A, Dias Belangero W, Esteves Santos Pires R, Labronici P. WhatsApp Messenger as an adjunctive tool for telemedicine: an overview. Interact J Med Res. 2017;6 (02):e11. Doi: 10.2196/ijmr.6214
6 Graziano F, Maugeri R, Iacopino DG. Telemedicine versus WhatsApp: from tradition to evolution. Neuroreport. 2015;26(10): 602–603. Doi: 10.1097/WNR.0000000000000393
7 Kelahmetoglu O, Firinciogullari R, Yagmur C. Efficient utility of WhatsApp: from computer screen to the surgeon's hand to determine maxillofacial traumas. J Craniofac Surg. 2015;26(04): 1437. Doi: 10.1097/SCS.0000000000001627
8 Kamel Boulos MN, Giustini DM, Wheeler S. Instagram and WhatsApp in health and healthcare: an overview. Future Internet.. 2016;8(03):37. Doi: 10.3390/fi8030037
9 De Benedictis A, Lettieri E, Masella C, et al. WhatsApp in hospital? An empirical investigation of individual and organizational determinants to use. PLoS One. 2019;14(01):e0209873. Doi: 10.1371/journal.pone.0209873
10 Yun H, Kettinger WJ, Lee CC. A new open door: the smartphone's impact on work-to-life conflict, stress, and resistance. Int J

Electron Commerce. 2012;16(04):121–152. Doi: 10.2753/JEC1086-4415160405
11 Daniel F, Jabak S, Sasso R, Chamoun Y, Tamim H. Patient-physician communication in the era of mobile phones and social media apps: cross-sectional observational study on lebanese physicians' perceptions and attitudes. JMIR Med Inform. 2018;6(02):e18. Doi: 10.2196/medinform.8895
12 Leão CF, Coelho ME, Siqueira AO, Rosa BA, Neder PR. O uso do WhatsApp na relação médico-paciente. Rev Bioet. 2018;26(03):412–419. Doi: 10.1590/1983-80422018263261
13 Ballone GJ. Estresse: o que é isso? [Internet]. 2015 [cited 2021 Feb 15]. Available from: https://psiqweb.net/index.php/estresse-2/estresse/
14 Thomée S, Härenstam A, Hagberg M. Mobile phone use and stress, sleep disturbances, and symptoms of depression among young adults–a prospective cohort study. BMC Public Health. 2011;11:66. Doi: 10.1186/1471-2458-11-66
15 Thomée S, Dellve L, Härenstam A, Hagberg M. Perceived connections between information and communication technology use and mental symptoms among young adults - a qualitative study. BMC Public Health. 2010;10:66. Doi: 10.1186/1471-2458-10-66
16 Wang Y, Wang P. Perceived stress and psychological distress among chinese physicians: The mediating role of coping style. Medicine (Baltimore). 2019;98(23):e15950. Doi: 10.1097/MD.0000000000015950
17 Cocker F, Nicholson JM, Graves N, Oldenburg B, Palmer AJ, Martin A, et al. Depression in working adults: comparing the costs and health outcomes of working when ill. PLoS One. 2014;9(09):e105430. Doi: 10.1371/journal.pone.0105430
18 Hall LH, Johnson J, Watt I, Tsipa A, O'Connor DB. Healthcare staff wellbeing, burnout, and patient safety: a systematic review. PLoS One. 2016;11(07):e0159015. Doi: 10.1371/journal.pone.0159015
19 Danielsen AK, Pommergaard HC, Burcharth J, Angenete E, Rosenberg J. Translation of questionnaires measuring health related quality of life is not standardized: a literature based research study. PLoS One. 2015;10(05):e0127050. Doi: 10.1371/journal.pone.0127050
20 Cronbach LJ. Coefficient alpha and the internal structure of tests. Psychometrika. 1951;16(03):297–334. Doi: 10.1007/BF02310555
21 Cicchetti DV. Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. Psychol Assess. 1994;6(04):284–290. Doi: 10.1037/1040-3590.6.4.284
22 Alanzi T, Al-Yami S. Physicians' attitude towards the use of social media for professional purposes in Saudi Arabia. Int J Telemed Appl. 2019;2019(07):6323962. Doi: 10.1155/2019/6323962
23 Shanafelt TD, Dyrbye LN, Sinsky C, et al. Relationship between clerical burden and characteristics of the electronic environment with physician burnout and professional satisfaction. Mayo Clin Proc. 2016;91(07):836–848. Doi: 10.1016/j.mayocp.2016.05.007
24 van den Eijnden RJ, Meerkerk GJ, Vermulst AA, Spijkerman R, Engels RC. Online communication, compulsive Internet use, and psychosocial well-being among adolescents: a longitudinal study. Dev Psychol. 2008;44(03):655–665. Doi: 10.1037/0012-1649.44.3.655
25 Thomée S, Eklöf M, Gustafsson E, Nilsson R, Hagberg M. Prevalence of perceived stress, symptoms of depression and sleep disturbances in relation to information and communication technology (ICT) use among young adults - an explorative prospective study. Comput Human Behav. 2007;23(03):1300–1321. Doi: 10.1016/j.chb.2004.12.007
26 Ragu-Nathan TS, Tarafdar M, Ragu-Nathan BS, Tu Q. The consequences of technostress for end users in organizations: conceptual development and validation. Inf Syst Res. 2008;19(04):417–433. Doi: 10.1287/isre.1070.0165
27 Cherubal AG, Suhavana B, Padmavati R, Raghavan V. Physical activity and mental health in India: A narrative review. Int J Soc Psychiatry. 2019;65(7-8):656–667. Doi: 10.1177/0020764019871314
28 Panagopoulou E, Montgomery A, Benos A. Burnout in internal medicine physicians: Differences between residents and specialists. Eur J Intern Med. 2006;17(03):195–200. Doi: 10.1016/j.ejim.2005.11.013
29 Lachmann B, Sindermann C, Sariyska RY, Luo R, Melchers MC, Becker B, et al. The role of empathy and life satisfaction in internet and smartphone use disorder. Front Psychol. 2018;9:398. Doi: 10.3389/fpsyg.2018.00398
30 Lachmann B, Sariyska R, Kannen C, Stavrou M, Montag C. Commuting, life-satisfaction and internet addiction. Int J Environ Res Public Health. 2017;14(10):1176. Doi: 10.3390/ijerph14101176
31 Lachmann B, Sariyska R, Kannen C, Cooper A, Montag C. Life satisfaction and problematic Internet use: Evidence for gender specific effects. Psychiatry Res. 2016;238:363–367. Doi: 10.1016/j.psychres.2016.02.017
32 Firth-Cozens J, Greenhalgh J. Doctors' perceptions of the links between stress and lowered clinical care. Soc Sci Med. 1997;44(07):1017–1022. Doi: 10.1016/s0277-9536(96)00227-4

Effect of Surgical Treatment for Deep Infiltrating Endometriosis on Pelvic Floor Disorders: A Systematic Review with Meta-analysis

Efeito do tratamento cirúrgico para endometriose infiltrante profunda nas disfunções do assoalho pélvico: Uma revisão sistemática com metanálise

Mirian Vieira Fraga[1] Cristina Laguna Benetti-Pinto[1] Daniela Angerame Yela[1] Ticiana Alves de Mira[1] Luiz Gustavo Oliveira Brito[1]

[1] Department of Obstetrics and Gynecology, School of Medical Sciences, Universidade Estadual de Campinas, Campinas, SP, Brazil

Address for correspondence Luiz Gustavo Oliveira Brito, MD, PhD, Rua Alexander Fleming, 101, Cidade Universitária, Campinas, SP, Brazil (e-mail: lgobrito@unicamp.br).

Rev Bras Ginecol Obstet 2022;44(5):503–510.

Abstract

Objectives To evaluate the impact of surgical treatment of deep infiltrative endometriosis (DIE) on pelvic floor dysfunction (urinary incontinence [UI], pelvic organ prolapse [POP], fecal incontinence [FI)] or constipation, and sexual function [dyspareunia]).

Data Source The present systematic review was performed in the PubMed database. For the selection of studies, articles should be published by January 5, 2021, without language restriction.

Study Selection Six randomized controlled studies that evaluated surgical treatment for DIE and the comparison of different surgical techniques were included.

Data Collection The studies were selected independently by title and abstract by two authors. Disagreements were resolved by a third author. All included studies were also evaluated according to the Cochrane risk of bias tool and the quality of the evidence was analyzed using the GRADE criteria. Subgroup analysis by different treatments and follow-up periods was also performed.

Results Six studies were included in the quantitative analysis. The risk of bias between studies showed an uncertain risk of bias for most studies, with concealment of allocation being the least reported category. The quality of the evidence was considered low. High heterogeneity was found between the studies. No study has evaluated UI or POP comparatively before and after surgery.

Conclusion Dyspareunia and FI have improved after the surgical procedure, but it was not possible to demonstrate which surgical technique was related to these outcomes as there was surgical heterogeneity. This diversity was found across data, with the recommendation of future prospective studies addressing pelvic floor disorders with DIE.

Keywords

- systematic review
- endometriosis
- fecal incontinence
- urinary incontinence
- pelvic floor

received
April 2, 2021
accepted
November 3, 2021
published online
February 17, 2022

DOI https://doi.org/10.1055/s-0042-1742293.
ISSN 0100-7203.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resumo

Objetivos Avaliar o impacto do tratamento cirúrgico para endometriose infiltrante profunda (EIP) nas disfunções do assoalho pélvico (incontinência urinária [IU], prolapso de órgãos pélvicos [POP], incontinência fecal [IF] ou constipação e função sexual [dispareunia]).

Fonte de Dados A presente revisão sistemática foi realizada na base de dados PubMed. Para a seleção dos estudos, os artigos deveriam ser publicados até 5 de janeiro de 2021, sem restrição de idioma.

Seleção dos Estudos Foram incluídos seis estudos randomizados e controlados que avaliaram o tratamento cirúrgico para EIP e a comparação de diferentes técnicas cirúrgicas.

Coleta de Dados Os estudos foram selecionados de forma independente por título e resumo por dois autores. As discordâncias foram avaliadas por um terceiro autor. Todos os estudos incluídos foram avaliados de acordo com a ferramenta Cochrane de risco de viés e a qualidade de evidência foi analisada usando os critérios GRADE. A análise de subgrupo por diferentes tratamentos e períodos de acompanhamento também foi realizada.

Resultados Seis estudos foram incluídos na análise quantitativa. O risco de viés mostrou um risco incerto de viés para a maioria dos estudos, sendo a ocultação da alocação a categoria menos relatada. A qualidade de evidência foi considerada baixa. Alta heterogeneidade foi encontrada entre os estudos. Nenhum estudo avaliou a IU ou o POP comparativamente antes e após a cirurgia.

Conclusão A dispareunia e a IF melhoraram após o procedimento cirúrgico, mas não foi possível demonstrar qual técnica cirúrgica esteve relacionada a estes desfechos, pois houve heterogeneidade cirúrgica. Esta diversidade foi encontrada nos dados, com a recomendação de estudos prospectivos futuros abordando distúrbios do assoalho pélvico com EIP.

Palavras-chave

- revisão sistemática
- endometriose
- incontinência fecal
- incontinência urinária
- assoalho pélvico

Introduction

Endometriosis affects 10% of the female population. Its main symptoms are pelvic pain and infertility. For pain, women may refer dysmenorrhea, chronic pelvic pain, dyschezia, dysuria, and dyspareunia.[1] For deep infiltrative endometriosis (DIE), gastrointestinal manifestations (between 3.8 and 37%)[2] can be more intense and with major repercussions. The urinary tract can be involved (bladder endometriosis) in between 0.3 and 12% of the cases and may also compromise the quality of life of women.[3]

The literature has several systematic reviews on the impact of conservative and/or surgical treatment of DIE. However, pelvic floor dysfunctions before and after treatment of endometriosis are not so deeply explored. When surgery is performed without focusing on nerve-sparing techniques or without carefully revising the anatomy, the risk for urinary incontinence (UI), fecal incontinence (FI), and other dysfunctions are possibly increased. An observational study assessing 138 women with DIE has shown that the presence of endometriosis in the bladder was an independent predictor of low bladder compliance, whereas the presence of endometriosis in the parametrium was predictor of voiding dysfunction.[4–6] A recent systematic review has found that colorectal surgery for endometriosis has a significant impact on urinary function regardless of the technique.[6] We can even find in the literature an association between bladder endometriosis and UI.[5]

However, we do not have data pooled and analyzed into a systematic fashion, with analysis of the quality of evidence about pelvic floor dysfunctions and DIE or bladder endometriosis. Given that, we sought to systematically review the literature for studies that addressed pelvic floor dysfunctions with DIE before and/or after treatment.

Methods

Search Strategy

The present systematic review was performed according to the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines[7] (►**Fig. 1**) and was registered in the PROSPERO database (CRD42020197049).

We have included randomized controlled studies that assessed surgical treatment for DIE and have compared the utilized techniques. We have excluded all studies that did not analyze pelvic floor dysfunctions, case reports, animal and/or experimental studies. The following outcomes were included: UI or FI, defined by self-report or any measurable,

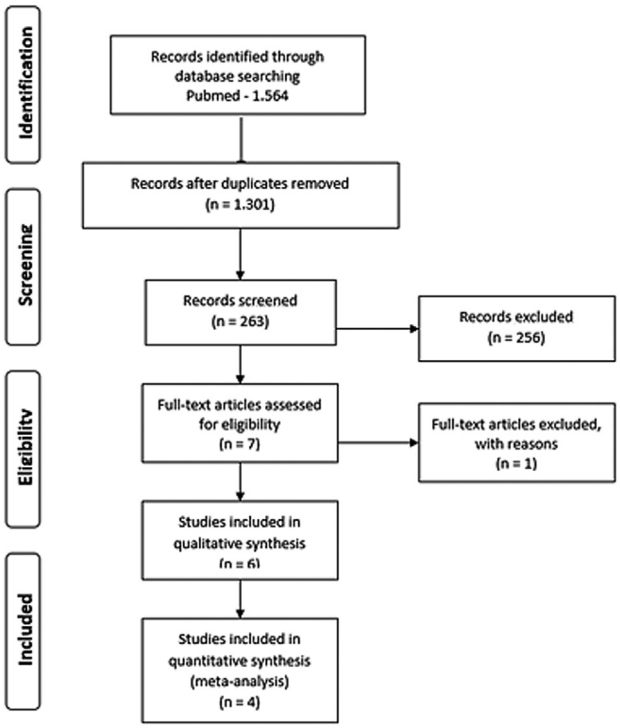


Fig. 1 Flowchart diagram of identified studies.

validated, or nonvalidated scale or questionnaire, following the IUGA/ICS recommendations for pelvic floor dysfunction terminology; pelvic organ prolapse (POP), whether symptomatic or by physical examination, constipation, and dyspareunia. Quality of life questionnaires related to pelvic floor dysfunctions were also included.

We have consulted the PubMed database on 5 January, 2021; no studies were excluded due to language restrictions. The following strategy was utilized: (((((((*urinary incontinence*) OR (*incontinence*)) OR (*fecal incontinence*)) OR (*constipation*)) OR (*pelvic organ prolapse*)) OR (*prolapse*)) OR (*urodynamics*)) OR (*pelvic floor muscle*)) OR (*dyspareunia*) AND (*endometriosis*). We intended to produce a broad search strategy because we hypothesized that we would have difficulties to retrieve data.

Study Selection, Data Extraction, and Risk of Bias

Studies were independently selected by title and abstract by two authors (Fraga M. V. and TAAM). Discordances were solved by a third author (Brito L. G. O.). Data extraction was performed in a previous spreadsheet pilot-tested and blinded for both authors. All included studies were also assessed according to the Cochrane risk of bias tool[8,9] and the quality of evidence was analyzed by the GRADE criteria.[9] Risk of bias analyzes five domains (selection, attrition, report, and other biases). The GRADE criteria consider the strength of other recommendations according to the presented variables.

Data Analysis

Meta-analysis was considered when at least two studies could be pooled. Heterogeneity was classified according to the i^2 test[10] and a random-effect model was applied to data when i^2 was $> 50\%$. Continuous variables were described as mean difference plus standard deviation (SD). Some outcomes were described as median plus interquartile ranges (IQRs) and their data were transformed into mean plus SD according to the following formula (median = mean, SD = IQR/1.35). Dichotomous variables were transformed into odds ratio (OR) plus 95% confidence intervals (CIs) with lower and upper limits. A subgroup analysis before and after treatment was performed for each treatment and pooled into forest plots. No funnel plots were built to assess publication bias as we did not have enough studies to perform this analysis. Statistical analysis was revised by Review Manager version 5.4 (The Cochrane Collaboration, Copenhagen).

Results

Study Selection and Characteristics

►**Fig. 1** depicts the process for data selection and extraction. After excluding duplicates, 1,301 studies were selected, and after another screening, 83 studies were fully read. Finally, 6 studies were selected, comprising 346 women. All manuscripts included women with DIE.[11–16]

Four studies were performed in France,[11–14] one in Poland[15] and one in Italy.[16] For assessing dyspareunia, the visual analogic scale (VAS) [11–13]; the numeric classification scale,[15] and the multidimensional punctuation system of Andersch[16] were used. For gastrointestinal symptoms, we have found the following questionnaires: Knowles – Eccersley – Scott (KESS) symptom questionnaire, gastrointestinal index of quality of life (GIQLI), and Wexner score.[12–14] For urinary symptoms, we have found the Urinary Symptom Profile (USP).[12–14] None of the studies criteria assessed UI and POP comparatively before and after surgery. Most studies analyzed dyspareunia.[11–13,15,16] Only three studies[12–14] have assessed the complaints of FI.

The surgical techniques compared were laparoscopically assisted or open colorectal resection surgery[11]; conservative surgery (shaving or disc excision) or radical rectal surgery (segmental resection)[12–14]; laparoscopy treatment using electroablation versus CO_2 laser ablation,[15] and conservative surgery alone or conservative surgery and presacral neurectomy.[16]

The primary outcomes of the studies were characterized by the relief of dyspareunia and the evaluation of gastrointestinal symptoms (constipation and fecal loss). The other outcomes proposed by the review were not analyzed as they were not found during data selection/extraction.

Risk of Bias and GRADE Evaluation

Three studies reported having performed a sample size calculation.[12,14,16] Two studies[12,13] included the intention to treat analysis. Three studies[14–16] presented uncertain risk for randomization. For allocation bias, Daraï et al.[11] had an uncertain risk and Roman et al.[12] presented a low risk, while the others had a high risk. One study[15] reported high risk of bias and two were categorized as low-risk.[11,12] Regarding the

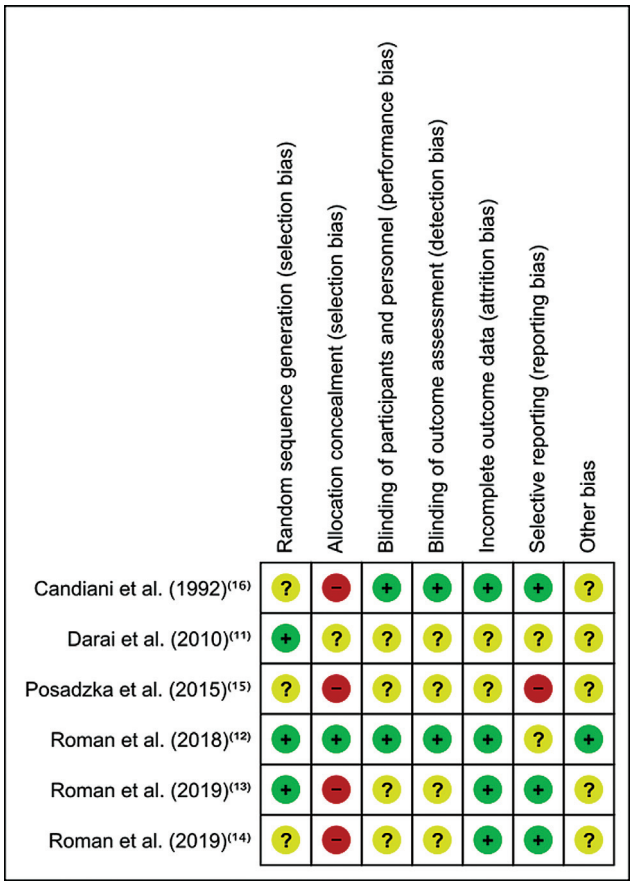


Fig. 2 Risk of bias summary.

rest of risk of bias, only Roman et al.[12] reported low risk of bias, whereas the others were labeled uncertain (►**Fig. 2**).

About the quality of evidence and the strength of recommendation according to the GRADE criteria, the studies presented a very low quality of evidence regarding reducing dyspareunia (MD: 1.18; 95%CI: 1.46–1.90; 3 studies, 167 women) and gastrointestinal complaints (KESS: MD: 1.63 for constipation; 95%CI: 1.82–1.43; 3 studies, 355 women; WEXNER: MD 0.25 for FI; 95%CI: 0.38–0.11; 3 studies, 355 women; GIQLI: MD 26.56 of gastrointestinal quality of life; 95% CI: 25.74–27.38; 3 studies, 355 women).

Results from Individual Studies

►**Chart 1** describes the general characteristics of the studies selected for the review.

Dyspareunia

Five studies[11–13,15,16] evaluated dyspareunia, with only one[16] specifying having assessed dyspareunia in depth. Daraï et al.,[11] comparing laparoscopically assisted or open colorectal resection surgery techniques, found a significant improvement in dyspareunia after surgery, with a median pain of 1 (0 to 8) ($p < 0.0001$), but with no difference between the techniques.

Roman et al.[12] evaluated the results after conservative surgery (shaving or disc excision) and radical rectal surgery (segmental resection), with no difference between groups after 24 months (median dyspareunia of 3 (2 to 3) and 4 (3 to 6), respectively; $p = 1.00$). In another study by the same group,[13] comparing shaving, disc excision or segmental resection 5 years after the surgery, they demonstrated a reduction in dyspareunia, with no statistically significant difference between the surgical techniques.

Posadzka et al.[15] compared electroablation versus laparoscopy CO2 laser ablation and found an improvement in dyspareunia at 3 months after surgery; however, at 6 months, there was an increase in the symptom score within both groups.

Candiani et al.[16] compared the surgical techniques of conservative surgery alone or conservative surgery with presacral neurectomy. The authors have found a reduction in moderate and severe dyspareunia and an increase in the number of asymptomatic women in both groups. However, they have concluded that presacral neurectomy did not add significant improvement in the performance of conservative surgery alone.

Gastrointestinal Symptoms

Only three studies[12–14] evaluated the complaint of FI, classifying it as an involuntary loss of gas or feces, and they are from the same group. Roman et al.[12] compared shaving/disc excision versus segmental resection and, after 24 months, they found an improvement in FI symptoms within both groups, but with no difference between them ($p = 0.83$). They also used assessment of gastrointestinal symptoms using the GIQLI score (low scores are related to a worse result) and, after treatment, the scores increased in both groups, but with no significant difference between them ($p = 0.64$). Wexner scores before and after treatment behaved the same way ($p = 0.42$).

The second study[13] presented a longer follow-up period (5 years) and the authors have also noticed symptom improvement, but with no difference between groups ($p = 0.42$). The presurgical evaluation using the GIQLI, KESS, and Wexner score questionnaires showed improvement in the functional results, but with no difference between the groups. A third study[14] has found the same results.

Subgroup Meta-analysis

In the subgroup meta-analysis, it can observed that there was a decrease in dyspareunia after surgical intervention (MD: -0.82 [- 1.05–- 0.59] ($p < 0.00001$) (►**Fig. 3**); however, an important heterogeneity is found as each study represents a different intervention (Chi^2: 30.31; I^2: 87%). The same can be observed for constipation (►**Fig. 4**) (assessed by the Kess questionnaire) (►**Fig. 4a**) and FI (assessed by the Wexner scale) (►**Fig. 4b**); there was an improvement for both (MD: -1.63 [- 1.82–- 1.43]; $p < 0.00001$; MD: - 0.25 [- 0.38–- 0.11]; $p = 0.006$), with high heterogeneity (I^2: 98 and 64%). We can observe the same pattern for gastrointestinal quality of life, with the improvement of the GIQLI questionnaire (MD: 26.56 [25.74–27.28]; $p = 0.0003$), with high heterogeneity (I^2: 74%) (►**Fig. 4c**).

Chart 1 General characteristics of the included studies

Author/ Year	Sample	Intervention	Follow-up	Assessment methods	Preoperative PFDs	FI	UI	Dyspareunia	POP
Daraï et al. (2010)[11]	*n* =52 Laparoscopy (*n* = 26) versus open surgery (*n* = 26)	Laparoscopy versus open surgery	1 and 6 months, then every 6 months up to 3 years	1.**Pain** VAS	There is no report in the study	There is no report in the study	There is no report in the study	When the overall result was assessed, there was a reduction in pain in both groups. However, when analyzed separately, the reduction of the complaint was not significant	There is no report in the study
Roman et al. (2018)[12]	*n*= 60 Conservative surgery (*n* = 27) versus Radical surgery (*n* = 33)	Conservative surgery versus radical rectal resection	6-month intervals for 2 years	1.**Fecal Incontinence**- GIQLI, Kess and Wexner score 2. **Urinary Incontinence** USP score 3. **Pain and quality of life** VAS and SF-36	Patients presented gastrointestinal disorders such as fecal incontinence and gas loss, in addition to dyspareunia in both groups studied	Both groups had gastrointestinal disorders after the 24-month evaluation, with no significant difference for the types of surgery	There is no report in the study	Despite the reduction in VAS in the groups studied, there was no significant difference for the types of surgery	There is no report in the study
Roman et al. (2019)[13]	*n*= 55 Excision (*n* = 27) versus Resection (*n* = 28)	Excision versus Colorectal segmental resection	5 years	1.**Fecal Incontinence** GIQLI, Kess, and Wexner score 2.**Urinary Incontinence** USP score 3. **Pain and quality of life** VAS and SF-36	Patients presented gastrointestinal disorders such as fecal incontinence and gas loss, in addition to dyspareunia in both groups studied	Both groups had gastrointestinal disorders after a 5-year assessment. Despite the improvement when compared with preoperative values, there was no significant difference between the groups	There is no report in the study	Despite the reduction in VAS in the groups, there was no significant difference for the types of surgery	There is no report in the study
Roman et al. (2019)[14]	*n* = 60 Conservative surgery (*n* = 27) versus segmental resection (*n* = 33)	Conservative surgery versus segmental resection	6,12,18 and 24 months	1.**Fecal Incontinence** GIQLI, Kess and Wexner score 2.**Urinary Incontinence** USP score	Patients had gastrointestinal disorders such as fecal incontinence and gas loss in both groups. The groups were not analyzed separately regarding the type of surgery	Both groups showed significant improvement after an evaluation when compared together. When analyzed separately, there was no significant difference between groups	There is no report in the study	There is no report in the study	There is no report in the study
Posadzka et al. (2015)[15]	*n*= 48 Electroablation (*n* = 33) versus CO2 laser ablation (*n* = 15)	Electroablation of endometriosis versus CO2 laser ablation	3 and 6 months	1. **Pain** NRS	Both groups had dyspareunia.	There is no report in the study	There is no report in the study	After an initial improvement verified in 3 months, the complaint worsened significantly in the exam of 6 months for the CO2 laser group. For the electroablation group, the complaint also increased significantly, 50% of the patients reported a level $\geq$ 10 points after 6 months	There is no report in the study
Candiani et al. (1992)[16]	*n* = 71 Conservative surgery (*n* = 36) versus Presacral neurectomy (*n* = 35)	Conservative surgery versus Presacral neurectomy	12 months	1. **Pain** Andersch and Milsom Multidimensional Scoring System	Both groups had dyspareunia (mild, moderate, and severe)	There is no report in the study	There is no report in the study	Although not significant, there was a reduction in complaints in both groups	There is no report in the study

Abbreviations: GIQLI, Gastrointestinal Quality of Life index; KESS, Knowles Eccersley Scott Symptom; NRS, Numerical Rating Scale; SF-36, Short Form Health Survey 36; USP, Urinary Symptom Profile; VAS, Visual Analogue Scale.

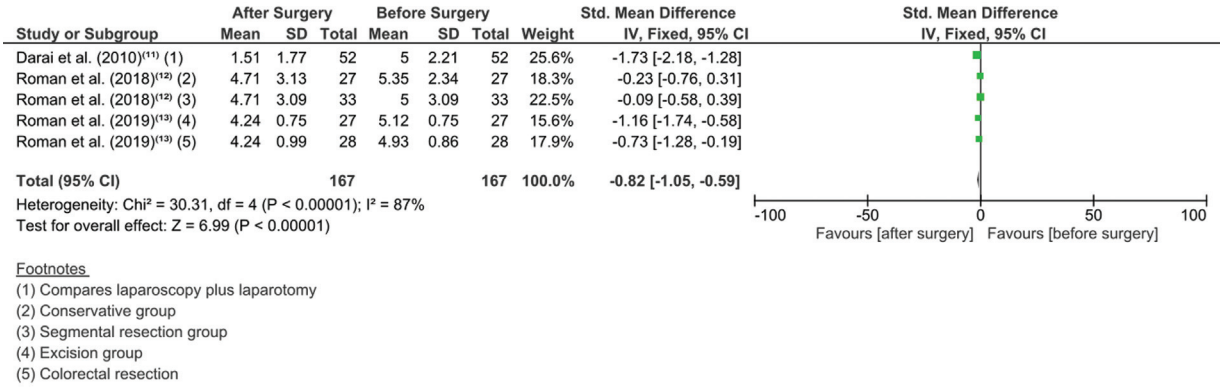


Fig. 3 Subgroup analysis for dyspareunia comprising two studies across each group before and after surgery.

Discussion

Although the present review found studies that addressed the effect of the surgical treatment of DIE on pelvic floor dysfunctions, the heterogeneity of the studies did not make it possible to gather and analyze all the data. Within the subgroup analysis, it was possible to observe the benefits of surgical treatment for some pelvic floor disorders (dyspareunia and FI), but without superiority for a technique. According to the GRADE tool, the quality of the evidence was very low for both symptoms evaluated, that is, reduction of dyspareunia and improvement of gastrointestinal symptoms. None of the selected studies evaluated the presence and/or alteration of UI and POP.

Among the studies that analyzed dyspareunia, although most of them suggested a reduction in this symptom after surgical treatment, one of them[15] revealed a resurgence of the symptom at the same level after 6 months, indicating the need for long-term evaluations. Through the meta-analysis, it was possible to confirm the results presented individually by the authors; however, the high heterogeneity among them is noteworthy. In the same direction, a recent systematic review that included only two surgical techniques (laparoscopic excision compared with laparoscopic ablation) for endometriosis and their effects on dyspareunia showed that both reduced the symptom, with no difference between the two techniques.[17]

Likewise, we can point out that studies are scarce in the analysis of the dyspareunia response; they are even more restricted to gastrointestinal symptoms, such as FI. Although we have demonstrated, through meta-analysis, the improvement of symptoms of FI, the evidence is also not robust enough to indicate the superiority of one technique over another, with important heterogeneity between studies. Considering non-comparative studies, Erdem et al.,[18] in a cohort study of 48 women with DIE, assessed long-term functional results (postoperative bowel movement and FI) after rectal resection, showing improvement in FI. A cohort study by Riiskjaer et al.[19] that evaluated 128 patients, before and after laparoscopic intestinal resection, also observed an improvement in the evacuation procedure 1 year after surgery.

Gastrointestinal symptoms usually present before surgical intervention, according to some authors, can predict postoperative results, which are worse the greater the severity of symptoms, indicating that surgical removal of the lesions may not completely reduce the symptoms.[20,21] Such data indicate that symptoms related to the pelvic floor should be evaluated before the surgical procedure. Their presence can directly interfere with functional results after surgery, requiring long-term follow-up.

We did not find data regarding dysfunctions related to UI and POP that could be included in a robust methodological analysis, although the literature draws attention to the risk of impaired urinary control when DIE is surgically treated.[22] Considering the extent of endometriotic lesions and the extent of surgical procedures performed, a potential effect on such pelvic floor dysfunctions may occur.

Considering that one of the most important indications for the surgical treatment of DIE is the control of pain symptoms, the present review has its main strength in demonstrating that surgeries, regardless of the technique used, can reduce dyspareunia and intestinal complaints, but also it has its greatest weaknesses when it demonstrates the great heterogeneity between the studies about the comparator group and the different instruments used to evaluate the results, as well as differences between the follow-up period across studies. Thus, groups of experts must meet and indicate methodologies that guide the authors when planning and executing prospective controlled studies to treat symptomatic women with DIE, evaluating the possible implications on pelvic floor dysfunctions.

Conclusion

Dyspareunia and FI improved after the surgical procedure, but it was not possible to demonstrate which surgical technique was related to these outcomes, as there was surgical heterogeneity. This diversity was found in the data, recommending future prospective studies addressing UI, POP and FI so that more robust evidence can be provided to health professionals about the association of DIE and pelvic floor disorders.

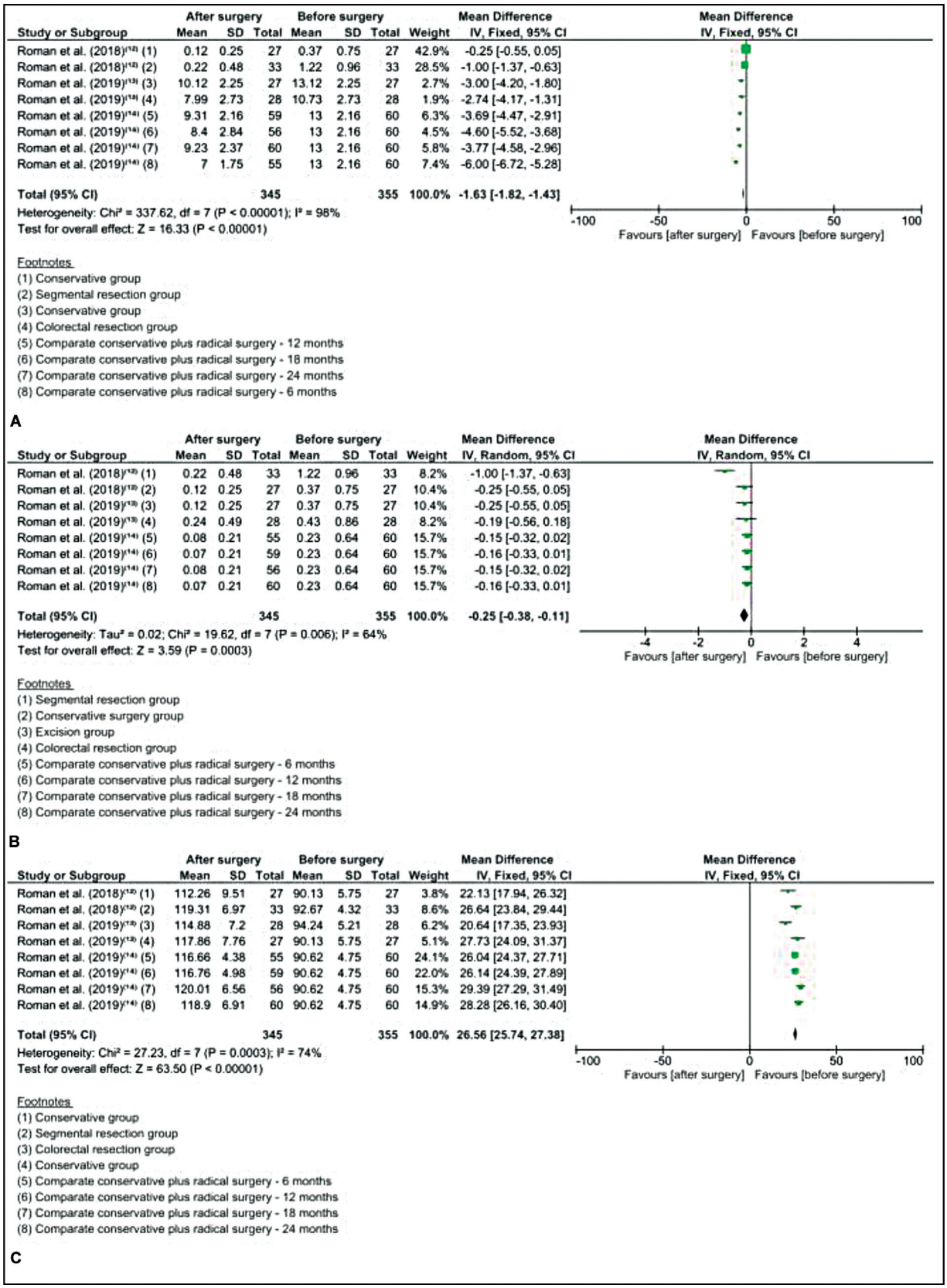


Fig. 4 Subgroup analysis for gastrointestinal symptoms. (**A**) Subgroup analysis for gastrointestinal symptoms (KESS questionnaire) comprising two studies across each group before and after surgery. (**B**) Subgroup analysis for gastrointestinal symptoms (WEXNER questionnaire) comprising two studies across each group before and after surgery. (**C**) Subgroup analysis for gastrointestinal symptoms (GIQLI questionnaire) comprising two studies across each group before and after surgery.

Conflict of Interests
The authors have no conflict of interests to declare.

References

1 Falcone T, Flyckt R. Clinical management of endometriosis. Obstet Gynecol. 2018;131(03):557–571. Doi: 10.1097/AOG.0000000000002469
2 Kiesel L, Sourouni M. Diagnosis of endometriosis in the 21st century. Climacteric. 2019;22(03):296–302. Doi: 10.1080/13697137.2019.1578743
3 Márki G, Bokor A, Rigó J, Rigó A Physical pain and emotion regulation as the main predictive factors of health-related quality of life in women living with endometriosis. Hum Reprod. 2017;32(07):1432–1438. Doi: 10.1093/humrep/dex091
4 de Resende Júnior JAD, Crispi CP, Cardeman L, Buere RT, Fonseca MF. Urodynamic observations and lower urinary tract symptoms associated with endometriosis: a prospective cross-sectional observational study assessing women with deep infiltrating disease. Int Urogynecol J Pelvic Floor Dysfunct. 2018;29(09):1349–1358. Doi: 10.1007/s00192-017-3531-0
5 Leone Roberti Maggiore U, Ferrero S, Salvatore S. Urinary incontinence and bladder endometriosis: conservative management. Int Urogynecol J Pelvic Floor Dysfunct. 2015;26(01):159–162. Doi: 10.1007/s00192-014-2487-6
6 Vesale E, Roman H, Moawad G, Benoit L, Touboul C, Darai E, et al. Voiding dysfunction after colorectal surgery for endometriosis: a systematic review and meta-analysis. J Minim Invasive Gynecol. 2020;27(07):1490–1502.e3. Doi: 10.1016/j.jmig.2020.07.019
7 Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647. Doi: 10.1136/bmj.g7647
8 Olivo SA, Macedo LG, Gadotti IC, Fuentes J, Stanton T, Magee DJ. Scales to assess the quality of randomized controlled trials: a systematic review. Phys Ther. 2008;88(02):156–175. Doi: 10.2522/ptj.20070147
9 Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al; GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490. Doi: 10.1136/bmj.328.7454.1490
10 Higgins JP, Thomas J, Chandler Jet al , Eds. Cochrane handbook for systematic reviews of interventions. 2nd ed. Chichester: John Wiley & Sons; 2019
11 Daraï E, Dubernard G, Coutant C, Frey C, Rouzier R, Ballester M. Randomized trial of laparoscopically assisted versus open colorectal resection for endometriosis: morbidity, symptoms, quality of life, and fertility. Ann Surg. 2010;251(06):1018–1023. Doi: 10.1097/SLA.0b013e3181d9691d
12 Roman H, Bubenheim M, Huet E, Bridoux V, Zacharopoulou C, Daraï E, et al. Conservative surgery versus colorectal resection in deep endometriosis infiltrating the rectum: a randomized trial. Hum Reprod. 2018;33(01):47–57. Doi: 10.1093/humrep/dex336
13 Roman H, Tuech JJ, Huet E, Bridoux V, Khalil H, Hennetier C, et al. Excision versus colorectal resection in deep endometriosis infiltrating the rectum: 5-year follow-up of patients enrolled in a randomized controlled trial. Hum Reprod. 2019;34(12):2362–2371. Doi: 10.1093/humrep/dez217
14 Roman H, Bubenheim M, Huet E, Bridoux V, Zacharapoulou C, Collinet P, et al. Baseline severe constipation negatively impacts functional outcomes of surgery for deep endometriosis infiltrating the rectum: Results of the ENDORE randomized trial. J Gynecol Obstet Hum Reprod. 2019;48(08):625–629. Doi: 10.1016/j.jogoh.2019.03.013
15 Posadzka E, Jach R, Pityński K, Jablonski MJ. Treatment efficacy for pain complaints in women with endometriosis of the lesser pelvis after laparoscopic electroablation vs. CO2 laser ablation. Lasers Med Sci. 2015;30(01):147–152. Doi: 10.1007/s10103-014-1630-4
16 Candiani GB, Fedele L, Vercellini P, Bianchi S, Di Nola G. Presacral neurectomy for the treatment of pelvic pain associated with endometriosis: a controlled study. Am J Obstet Gynecol. 1992;167(01):100–103. Doi: 10.1016/s0002-9378(11)91636-6
17 Pundir J, Omanwa K, Kovoor E, Pundir V, Lancaster G, Barton-Smith P. Laparoscopic excision versus ablation for endometriosis-associated pain: an updated systematic review and meta-analysis. J Minim Invasive Gynecol. 2017;24(05):747–756. Doi: 10.1016/j.jmig.2017.04.008
18 Erdem S, Imboden S, Papadia A, Lanz S, Mueller MD, Gloor B, et al. Functional outcomes after rectal resection for deep infiltrating pelvic endometriosis: long-term results. Dis Colon Rectum. 2018;61(06):733–742. Doi: 10.1097/DCR.0000000000001047
19 Riiskjaer M, Greisen S, Glavind-Kristensen M, Kesmodel US, Forman A, Seyer-Hansen M. Pelvic organ function before and after laparoscopic bowel resection for rectosigmoid endometriosis: a prospective, observational study. BJOG. 2016;123(08):1360–1367. Doi: 10.1111/1471-0528.13975
20 Comptour A, Chauvet P, Canis M, Grémeau A-S, Pouly J-L, Rabischong B, et al. Patient quality of life and symptoms after surgical treatment for endometriosis. J Minim Invasive Gynecol. 2019;26(04):717–726. Doi: 10.1016/j.jmig.2018.08.005
21 Fritzer N, Tammaa A, Haas D, Oppelt P, Renner S, Hornung D, et al. When sex is not on fire: a prospective multicentre study evaluating the short-term effects of radical resection of endometriosis on quality of sex life and dyspareunia. Eur J Obstet Gynecol Reprod Biol. 2016;197:36–40. Doi: 10.1016/j.ejogrb.2015.11.007
22 Turco LC, Tortorella L, Tuscano A, Palumbo MA, Fagotti A, Uccella S, et al. Surgery-related complications and long-term functional morbidity after segmental colo-rectal resection for deep infiltrating endometriosis (ENDO-RESECT morb). Arch Gynecol Obstet. 2020;302(04):983–993. Doi: 10.1007/s00404-020-05694-0

Burch Procedure: A Historical Perspective

Procedimento de Burch: Uma perspectiva histórica

Gisele Vissoci Marquini[1] Zsuzsanna Ilona Katalin de Jarmy di Bella[1] Marair Gracio Ferreira Sartori[1]

[1] Department of Gynecology, Universidade Federal de São Paulo, São Paulo, SP, Brazil.

Rev Bras Ginecol Obstet 2022;44(5):511–518.

Address for correspondence Gisele Vissoci Marquini, Gynecologist and Urogynecologist from Universidade de São Paulo, Rua Napoleão de Barros, 608, 04024-002, Vila Clementino, São Paulo, SP, Brazil (e-mail: giselemarquini@gmail.com).

Abstract

Introduction The Burch procedure (1961) was considered the gold standard treatment for stress urinary incontinence (SUI) before the midurethral slings (MUSs) were introduced, in 2001.

Objective This historical perspective of the Burch's timeline can encourage urogynecological surgeons to master the Burch technique as one of the options for surgical treatment of SUI.

Search Strategy and Selection Criteria A bibliographic search was performed in the PubMed and National Library of Medicine (NIH) databases with the terms *Burch colposuspension* AND *history* AND *stress urinary incontinence* in the last 20 years. The original article by Burch (1961) was included. The references were read by three authors. The exclusion criterion was studies in non-English languages. Biomedical Library Special Collections were included as historical relevant search.

Data Collection, Analysis and Main Results Some modifications of the technique have been made since the Burch procedure was first described. The interest in this technique has been increasing due to the negative publicity associated with vaginal synthetic mesh products. Twenty-nine relevant articles were included in the present review article, and numerous trials have compared Burch colposuspension with MUS.

Conclusion This historical perspective enables the scientific community to review a standardized technique for SUI. Burch colposuspension should be considered an appropriate surgical treatment for women with SUI, and an option in urogynecological training programs worldwide.

Keywords

- surgical therapy
- stress urinary incontinence
- surgery
- history
- burch colposuspension

Resumo

Introdução O procedimento de Burch (1961) foi considerado o tratamento padrão ouro para a incontinência urinária de esforço (IUE) antes da introdução dos slings de uretra média (SUMs), em 2001.

Objetivo Esta perspectiva histórica da linha do tempo do procedimento de Burch pode encorajar os cirurgiões uroginecológicos a dominar a técnica deste procedimento como uma das opções para o tratamento cirúrgico da IUE.

Estratégia de busca e critérios de seleção A busca bibliográfica foi realizada nas bases de dados PubMed e National Library of Medicine (NIH) com os termos *Burch colposuspension* AND *history* AND *stress urinary incontinence* nos últimos 20 anos. O

received
May 4, 2021
accepted
November 3, 2021
published online
February 18, 2022

DOI https://doi.org/10.1055/s-0042-1744312.
ISSN 0100-7203.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

artigo original de Burch (1961) foi incluído. As referências foram analisadas por três autores com exclusão de estudos em idiomas diferentes do inglês. Coleções de bibliotecas biomédicas foram incluídas por ordem de relevância histórica.

Coleta de dados, análise e principais resultados Algumas modificações de técnica foram realizadas desde que o procedimento de Burch foi inicialmente descrito. O interesse por essa técnica vem aumentando devido à publicidade negativa associada aos produtos de tela sintética vaginal. Vinte e nove artigos relevantes foram incluídos, e vários estudos compararam a colposuspensão de Burch com SUMs.

Conclusão Essa perspectiva histórica possibilita à comunidade científica revisar uma técnica padronizada para a IUE. A colposuspensão de Burch pode ser considerada um tratamento cirúrgico adequado para mulheres com IUE, e uma opção em programas de treinamento uroginecológico em todo o mundo.

Palavras-chave
- terapia cirúrgica
- incontinência urinária de esforço
- cirurgia
- história
- Burch colposuspension

Introduction

Stress urinary incontinence (SUI) is a prevalent condition that interferes with women's health-related quality of life. It is generally attributable to urethral hypermobility as a result of diminished urethral support, although there can also be a component of urethral sphincter weakness. In women with incontinence secondary to urethral hypermobility, retropubic colposuspension surgery (or urethropexy) is a traditional repair that surgically elevates and reinforces the periurethral tissue.[1]

There are several colposuspension techniques, although none is as commonly performed as the Burch procedure. The Burch procedure was first described by Dr John Chistopher Burch in 1961.[2] Burch colposuspension was considered as the gold standard retropubic colposuspension surgical treatment before Ulmsten and Petros[3] presented the tension-free vaginal tape (TVT) procedure in 1995. Consecutively, Delorme[4] practiced the transobturator tape (TOT) (outside-in) procedure in 2001, commonly known as midurethral sling (MUS). Although the colposuspension procedure was once considered the gold standard in the treatment of SUI, its number has waned since the turn of the 21st century, following the introduction of the MUS.[1]

Notwithstanding, in 2011, the Food and Drug Administration (FDA) issued a notification on the serious complications associated with transvaginal mesh for the surgical treatment for pelvic organ prolapse (POP).[5–7] Unfortunately, the negative publicity associated with vaginal synthetic mesh products has extended to MUSs for treatment of SUI. Subsequently, the interest in colposuspension procedures has been rekindled as women and practitioners alike sought alternative surgical treatment options for SUI. As a result, the Burch procedure, a satisfactory correction of almost all types of cystocele by the abdominal approach, continues to have a place in the operative armamentarium of the gynecologists and urologists.[1,2] In addition, Burch colposuspension is still a frequently performed and efective surgical procedure for SUI, especially when there is a need for concomitant pelvic surgery. With the advancements in laparoscopic techniques, laparoscopic Burch colposuspension is gaining popularity as a non-mesh alternative, minimally invasive SUI surgery, which is as effective as open surgery.[8–10]

Given this scenario, the present historical perspective aims to write a narrative review, a systematic search on the history of the Burch procedure. This review can encourage urogynecological surgeons to master the Burch technique as one of the options for the surgical treatment of SUI.

Methods

To compose the timeline of Burch's surgery, a bibliographic search was performed in the PubMed and National Library of Medicine (NLM) databases with the terms *Burch colposuspension* AND *history* AND *stress urinary incontinence* in the last 20 years (2001–2021), since the advent of mid-urethral slings. The last date of search was included due to the original Burch's article (Burch, 1961).[2] The references were read by three authors. The exclusion criterion was studies in non-English languages. Biomedical Library Special Collections[11] were included as historical relevant search. Twenty-seven recommended studies were included based on a qualitative or exploratory research strategy in areas in which there is little accumulated and systematized knowledge, with higher level of evidence. The studies included historical articles on biographies and the first publication of the cited technique. Two other studies were included before the study's inclusion date because they were relevant historical publications.[3,12]

Results and Discussion

Burch's Origins: Dr. John Christopher Burch and his Legacy

John Christopher Burch, eldest son of Dr. Lucius E. Burch and Sarah Polk (Cooper) Burch, was born on July 21, 1900, in Nashville, TN. He attended Vanderbilt University from 1917 to 1919 and then entered medical school, graduating in 1923

Fig. 1. Dr. John C. Burch (1900-1977): professor at Vanderbilt Medical School. He served as the Chair of the department of obstetrics and gynecology. **Source:** Vanderbilt University.[11]

as Founder's medalist. After completing residence programs in Boston and New York and studying in Europe, he returned to Nashville in 1926 to begin his practice at the Burch Clinic and to begin his long career of teaching at Vanderbilt Medical School.[11]

Dr. Burch is remembered for his service as Dean of the Vanderbilt Medical School from 1914 to 1925 and chairman of the department of obstetrics and gynecology until 1945. He served as professor not only in the field of urogynecology, but also obstetrics and gynecology. In 1965, as shown in ►**Figure 1**, he became emeritus.[11,13]

During his career, Dr. Burch authored more than 150 articles. His book *Hysterectomy* is considered a classic. During World War II, he served as chief of the surgical service at Brooke General Hospital in Fort Sam Houston, Texas. Over his long career at Vanderbilt, John Burch taught some 2,000 medical students and trained more than 300 interns and residents.[11] Dr. John C. Burch possessed a rare combination of medical talents. He was a beloved teacher and practitioner and a skilled surgeon and researcher. Burch's kind disposition and proximity to the students were remarkable, as demonstrated in the ►**Figure 2**, in which caricatures of

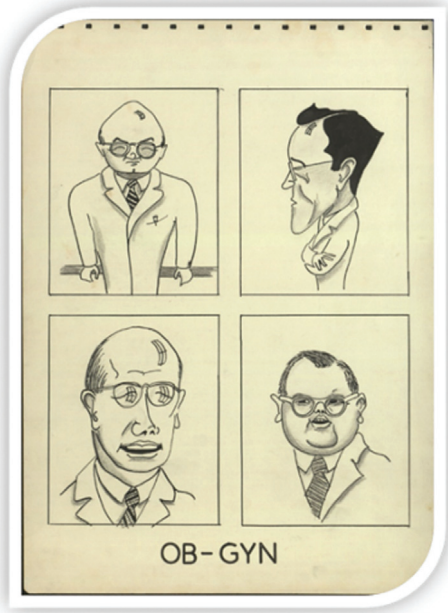


Fig. 2. Vanderbilt Medical School. Description: Caricatures of faculty members of the department of obstetrics and gynecology, by medical student Wallace Clyde (1954). Clockwise, from the top left: John Burch, Claiborne Williams, Howard Morgan, Edwin Williams. **Source:** Vanderbilt University.[11]

faculty members of the department of obstetrics and gynecology were drawn by a medical student and presented at a departament meeting.[11]

Currently, The Vanderbilt University is considered one of the top 15 universities in the United States and one of the top 50 in the world. ►**Figures 3 A** and **B** show an aerial view of the Vanderbilt Medical Center Campus in 1938 and 2019, respectively.

In 1961, John C. Burch[2] presented a modified colposuspension technique. The first retropubic suspension for the treatment of SUI, also known as Marshall-Marchetti-Krantz (MMK), was described in 1949 by Marshall et al.[14], with the peri-

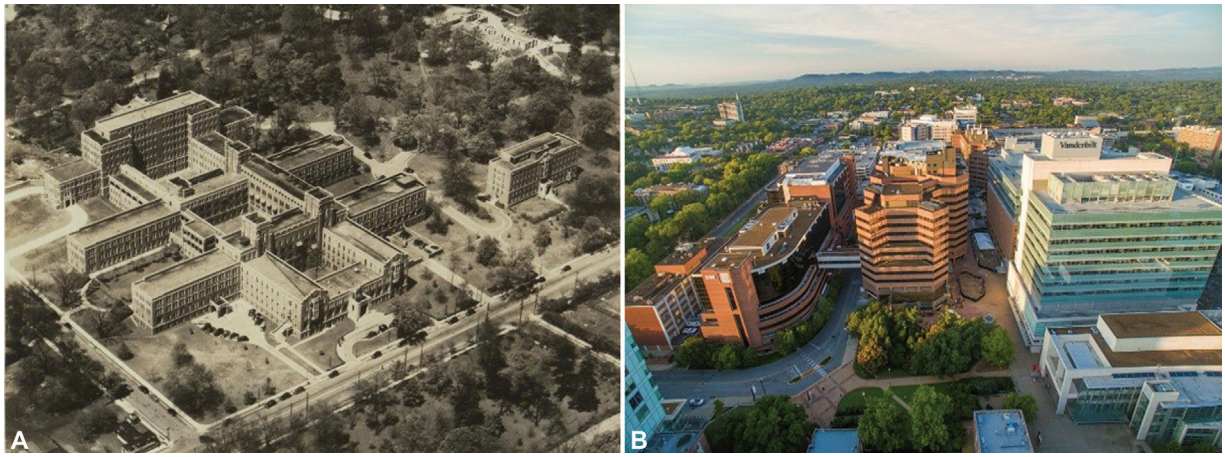
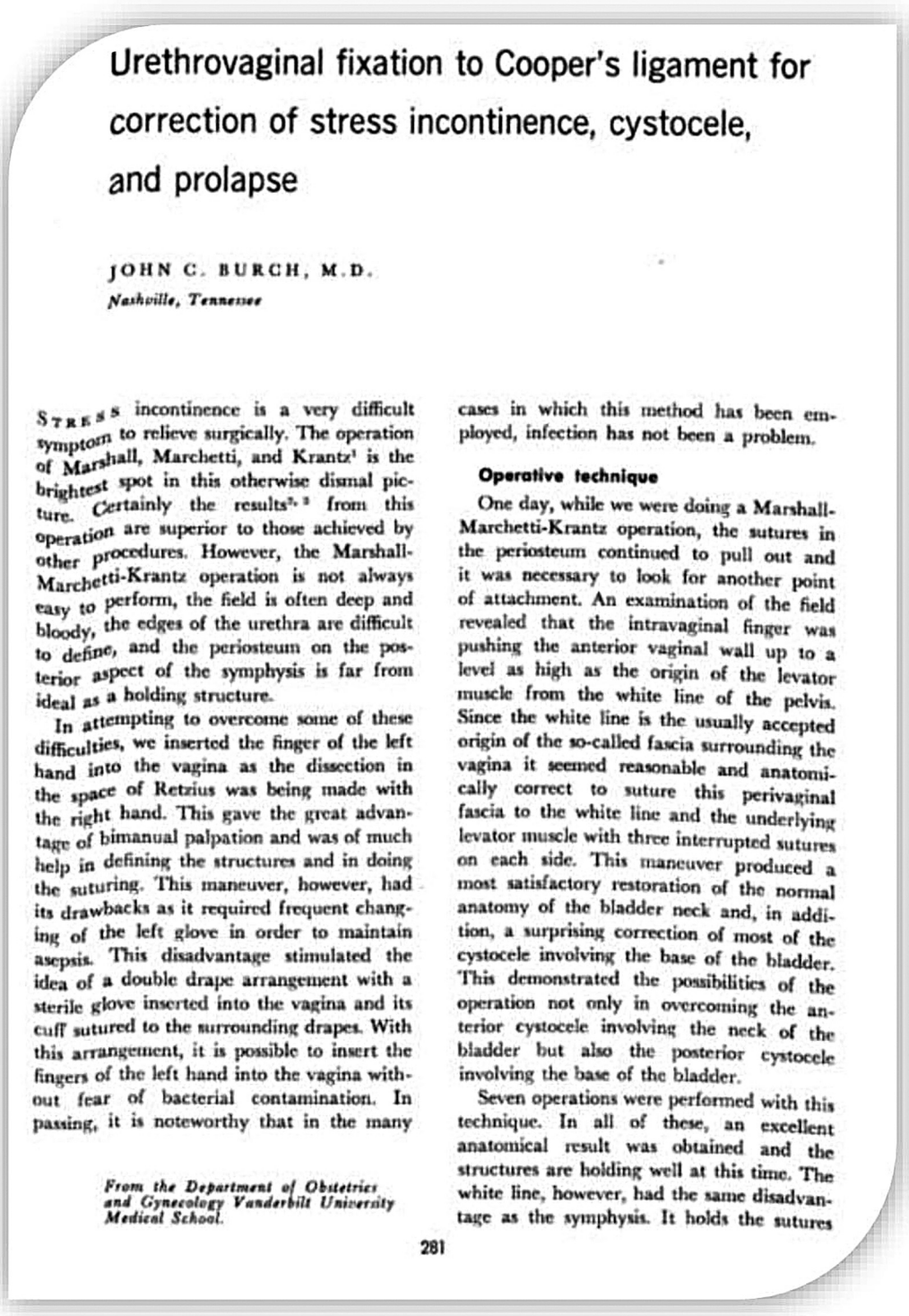


Fig. 3. A - Aerial view of Vanderbilt Medical Center Campus, Nashville, TN, 1938. This aerial view of what is now the Medical Center campus shows the Vanderbilt Hospital and Medical School as it looked after the construction of the D-wing (top left), in 1938. **B -** Aerial view of Vanderbilt Medical Center Campus, Nashville, Tennessee, 2019. **Source:** Vanderbilt University.[11]

urethral tissue being sutured to the posterior face of the pubic symphysis. Burch performed the surgical procedure fixing the periurethral/perivesical tissues to the Cooper's ligament.[13,15] In his original article, Burch initially advocated for attaching the paravaginal fascia to the tendinous arch of the fascia pelvis, as shown in ►**Figure 4**.[4] This point of attachment was later changed to the Cooper ligament in order to provide a more secure fixation. The MMK procedure fixes the bladder neck to the periosteum of the symphysis pubis. Historically, the MMK procedure has similar rates of short-term cure as those of the Burch procedure; however, it carries a risk of osteitis pubis (0.7%) that is not present with the Burch technique.[1,16]



Urethrovaginal fixation to Cooper's ligament for correction of stress incontinence, cystocele, and prolapse

JOHN C. BURCH, M.D.
Nashville, Tennessee

STRESS incontinence is a very difficult symptom to relieve surgically. The operation of Marshall, Marchetti, and Krantz[1] is the brightest spot in this otherwise dismal picture. Certainly the results[2, 3] from this operation are superior to those achieved by other procedures. However, the Marshall-Marchetti-Krantz operation is not always easy to perform, the field is often deep and bloody, the edges of the urethra are difficult to define, and the periosteum on the posterior aspect of the symphysis is far from ideal as a holding structure.

In attempting to overcome some of these difficulties, we inserted the finger of the left hand into the vagina as the dissection in the space of Retzius was being made with the right hand. This gave the great advantage of bimanual palpation and was of much help in defining the structures and in doing the suturing. This maneuver, however, had its drawbacks as it required frequent changing of the left glove in order to maintain asepsis. This disadvantage stimulated the idea of a double drape arrangement with a sterile glove inserted into the vagina and its cuff sutured to the surrounding drapes. With this arrangement, it is possible to insert the fingers of the left hand into the vagina without fear of bacterial contamination. In passing, it is noteworthy that in the many cases in which this method has been employed, infection has not been a problem.

From the Department of Obstetrics and Gynecology Vanderbilt University Medical School.

Operative technique

One day, while we were doing a Marshall-Marchetti-Krantz operation, the sutures in the periosteum continued to pull out and it was necessary to look for another point of attachment. An examination of the field revealed that the intravaginal finger was pushing the anterior vaginal wall up to a level as high as the origin of the levator muscle from the white line of the pelvis. Since the white line is the usually accepted origin of the so-called fascia surrounding the vagina it seemed reasonable and anatomically correct to suture this perivaginal fascia to the white line and the underlying levator muscle with three interrupted sutures on each side. This maneuver produced a most satisfactory restoration of the normal anatomy of the bladder neck and, in addition, a surprising correction of most of the cystocele involving the base of the bladder. This demonstrated the possibilities of the operation not only in overcoming the anterior cystocele involving the neck of the bladder but also the posterior cystocele involving the base of the bladder.

Seven operations were performed with this technique. In all of these, an excellent anatomical result was obtained and the structures are holding well at this time. The white line, however, had the same disadvantage as the symphysis. It holds the sutures

Fig. 4. First page of the original article by Burch– 1961. **Source:** Delorme (2001).[4]

Classic Description of Burch Colposuspension

The following steps describe the original Burch procedure (1961).[2]

"The dissection to expose Cooper's ligament and the fascia surrounding the vagina begins by breaking through the endoabdominal fascia, which descends from the anterior abdominal wall onto the symphysis and superior ramus of the pubic bone. The most convenient breakthrough site is at the lower angle of the abdominal wound and, when the fascia is broken through, the fingers rest on the bare bone of the symphysis. Now with the left index finger in the vagina and continuing· in this plane, the endoabdominal fascia is stripped from Cooper's ligament and the side wall of the pelvis by the right hand. This plane is relatively avascular and keeping in it avoids the rupture of many small vessels and prevents a most troublesome ooze. In working downward to the fascia surrounding the vagina, the right hand sweeps the endoabdominal fascia from the lateral structures with a lateral and superior motion. When the lateral edge of the vagina becomes apparent, further medial dissection will usually outline to some degree the edge of the bladder.[2]

The distinctness of the bladder edge is not always sharp, especially in the obese, and in passing the suture into the perivaginal fascia, one can easily penetrate the bladder.[2]

For suture material, number 2 chromic catgut has so far proved satisfactory. Perhaps stainless-steel wire or even fascia may be the eventual choice. The point on the vagina through which the needle and suture have been passed is now matched to Cooper's ligament, and the needle is passed through this ligament and tied by the assistant as the operator pushes up with the intravaginal finger. Three such sutures are passed on each side. The abdomen is closed, the legs retracted and perineorrhaphy and posterior colporrhaphy done if indicated."[2]

The relevant step in the development of the operation was the utilization of the Cooper ligament as a point of fixation. This strong thick band of fibrous tissue runs along the superior surface of the superior ramus of the pubic bone and is ideal from the standpoint of both passing and holding a suture.[2] Burch noticed that this maneuver produced a most satisfactory restoration of the normal anatomy of the bladder neck and, in addition, a surprising correction of most of the cystocele involving the base of the bladder.[2]

Burch's Variations and Outcomes

Variations of the description of the classic Burch technique can be explained in didatic steps[1,9,17]:

1. Either a Pfannenstiel or straight midline subumbilical incision is made (at least 5 cm).
2. The retropubic space is exposed, and the peritoneum is swept superiorly. The periurethral fat is removed for adequate visualization of the anterolateral vaginal wall.
3. A Foley catheter is inserted per the urethra, and the balloon is inflated. With an index finger in the vagina and gentle traction on the catheter, the bladder neck with the Foley balloon is palpable. With an assistant providing exposure by retracting the bladder medially and superiorly, the endopelvic and vaginal fascia are visible.
4. Two (or 3) absorbable stitches are then placed through the endopelvic and vaginal fascial complex, using the index finger to determine the appropriate depth (care should be taken to not violate the vaginal mucosa). The most cephalad suture is usually placed at the level of the bladder neck (2 cm lateral), and sutures are placed about 1 cm apart caudally.
5. The vaginal sutures are then placed through the Cooper ligament and tied loosely (2- to 4-cm suture bridge between the vagina and the Cooper ligament) in a tension-free manner.[1,9,17]

According to Burch,[2] his experience with the Cooper ligament urethrovaginal suspension indicates that it is a superior operation for SUI. It achieves a remarkable degree of correction of the deformity of cystocele and provides, for the first time, a satisfactory correction of almost all types of cystocele by the abdominal approach. It can be combined with abdominal hysterectomy and perineorraphy in the treatment of uterine prolapse, but, in these cases, the danger of the subsequent development of enterocele must be recognized, and appropriate precautions must be taken.[2]

The critical aspects of the Burch procedure, regardless of surgical approach, are to obtain adequate exposure and to avoid reapproximating tissue under undue tension. The surgical goal is to loosely approximate the Cooper ligament to the periurethral tissue in order to allow postoperative adhesion formation that provides broad support for the urethra and bladder neck. To date, there are no randomized trials to suggest superiority of one suture type over another; however, most surgeons use absorbable suture. In addition, reviews have shown no difference in outcomes whether placing 2, 3, or 4 sutures per side, although, as mentioned above, it has been demonstrated that one suture per side is insufficient.[1] It is also critical to understand that although the Burch colposuspension does suspend the bladder neck and may repair small cystoceles, it is insuficient for repairing significant anterior pelvic organ prolapse (POP). Hence, women with significant prolapse defects with concomitant SUI undergoing colposuspension should additionally have a dedicated cystocele repair.[1,9]

Over the years, several authors and surgeons have presented numerous modifications of the original operation described by Burch.[17] The procedure was further modified by Tanagho,[12] in 1976, to its current state, in which the paravaginal sutures are placed further laterally from the urethra, and a looser approximation of tissues is undertaken. Over time, Burch colposuspension has been adapted for laparoscopy and modifications of the original technique, such as synthetic mesh use to secure paraurethral support, have been introduced.[17]

The wealth of data from comparative and observational studies assessing the outcome of Burch colposuspension has been reported in numerous textbooks and structured

summary publications.[17,18] Since it first description in 1961, there has been a multitude of randomized controlled trials including Burch colposuspension. Fifty-five trials involving a total of 5,417 women have been included in the current Cochrane review about open retropubic colposuspension.[9]

Numerous trials have compared Burch colposuspension with MUS. Several observational and randomized studies have showed similar eficacy and lower morbidity for MUS procedures compared to Burch colposuspension.[8–10,17] Others have cited that there was no statistically significant difference in subjective cure rates, but the objective cure rates tended to be higher for MUS.[19–22] Even if the definition of objective cure varied widely between available studies, many of them still report that MUSs (retropubic slings or transobturator slings) are superior to Burch colposuspension surgery.[10,17,23,24] According to those outcomes, patients receiving midurethral tapes have significantly higher overall and objective cure rates than those receiving Burch colposuspension. In addition, in a survey among professionals, Burch colposuspension would have been chosen only by a minority of surgeons.[23–25]

In general, bladder injury, voiding dysfunction, and hematoma can be reported equally with Burch colposuspension or midurethral tapes. Midurethral slings may exhibit a much higher risk of intraoperative complications, such as bladder perforation and urinary retention, than the Burch procedure.[23,24] On the other side, the MUS placement was associated with shorter operating time, length of hospitalization, and time for resuming normal activity.[19–22] However, even if the length of hospital stay may be longer for Burch colposuspension, with this technique, there is no possibility of mesh extrusion as a complication.[23,24]

Basically, data on long-term effectiveness and adverse events are, however, limited, especially around the comparative adverse events profiles of MUS and non-MUS procedures. A better understanding of complications after surgery for SUI is imperative.[24]

Although mesh slings remain a strong option to surgical treatment for SUI, there has been renewed interest in autologous fascial slings (AFSs) for the treatment of SUI, because of the investigations of mesh safety for POP.[26,27] The fascial sling is an effective operative technique in patients who have undergone previous operations for incontinence and a second non-synthetic mesh option for SUI. A retrospective study, with a robust sample of women (463 patients), evaluated whether the conventional AFS was superior or equal to the readjustable transobturator sling in efficacy and safety in women with SUI, and it showed that both techniques had similar subjective efficacy rates. However, the transobturator sling demonstrated fewer postoperative surgical complications when compared with the AFS, such as morbidity of wound infection or hematoma.[26]

Currently, regulations surrounding the use of mesh implants for POP differ depending on the country and can influence the number of procedures of synthetic slings for SUI. Although in the United States of America (USA), the United Kingdom (UK), Canada, Australia, New Zealand, and France, transvaginal mesh implants for POP have been removed from the market, in most mainland European countries, Asia, and South America, they are still available as a surgical option for POP correction.[28]

Then, it is expected that in the USA, the UK, Australia, New Zealand, Canada, and France, with the removal or the restriction of transvaginal mesh implants as a surgical option for POP, the spectrum of urogynecological operations, including surgeries for SUI, might be greatly affected. Conventional transvaginal native tissue repair and abdominal (open, laparoscopic) surgical procedures, as well as Burch colposuspension or non-synthetic mesh procedures are expected to be increasingly performed. This requires appropriate training of younger physicians.[28]

According to this scenario, a strong point in the study is the heterogeneous source of historical research current overview of Burch's surgery. Encouraging the study of this established technique can rescue an effective surgical option for SUI in a setting of valorization of individualized conducts.

A limitation of the present study is the non-systematic methodology. The search for a historical description of Burch's surgery overlooked classic articles without a systematic review. However, these documents deserve to be part of the knowledge of the urogynecological surgeon due to the scientific contribution in the development of surgical techniques throughout the century in urogynecology.

The authors believe that the limitation of the non-systematized methodology does not detract from the study because the objective was to demonstrate, through a collection of its history, a surgical treatment option for urinary incontinence. A technique that has survived for more than 50 years, still recommended today, carries its scientific value.

The Burch colposuspension has a 50-plus year history demonstrating strong long-term outcomes with minimal complications. Iterations of the procedure, including laparoscopic, robotic, and mini-incisional approaches, appear to have equal efficacy to the open procedure. Although the current use of the Burch colposuspension has waned with the growing shift toward sling surgery, it continues to have a role in the treatment of SUI.

Specifically, given satisfactory long-term outcomes over the course of the last half-century, it seems that the Burch colposuspension should be considered an appropriate surgical treatment for any woman with SUI, especially in settings where vaginal access is limited, where intra-abdominal surgery is already planned, or if mesh is contraindicated.[1,9,17,29]

On the other side, the National Institute for Care and Health Excellence (NICE) guidelines include amongst their recommendations that laparoscopic Burch colposuspension should not be used as a routine procedure for the treatment of SUI in women. It was highlighted, that the procedure should be performed only by surgeons with appropriate training as well as expertise working in a multidisciplinary team, and women should be advised about the limited evidence.[29]

Conclusion

Finally, the Burch procedure has an ongoing role in the surgical repair of female SUI and should remain in the surgical repertoire of female pelvic medicine and reconstructive surgeons. The authors suggest new long-term follow-up studies for the association of the Burch colposuspension technique in the setting of laparoscopic, robotic, or minimally invasive urogynecological surgery. The science has no answer, so far, whether urogynecology has started a journey back to the future by revitalizing the Burch procedure. However, in light of such a development, training in both open and laparoscopic Burch colposuspension should nowadays be provided in urogynecological fellowship and training programs worldwide.

Conflict of Interests
The authors have no conflict of interests to declare.

References

1 Sohlberg EM, Elliott CS. Burch Colposuspension. Urol Clin North Am. 2019;46(01):53–59. Doi: 10.1016/j.ucl.2018.08.002
2 Burch JC. Urethrovaginal fixation to Cooper's ligament for correction of stress incontinence, cystocele, and prolapse. Am J Obstet Gynecol. 1961;81(02):281–290. Doi: 10.1016/s0002-9378(16)36367-0
3 Ulmsten U, Petros P. Intravaginal slingplasty (IVS): an ambulatory surgical procedure for treatment of female urinary incontinence. Scand J Urol Nephrol. 1995;29(01):75–82. Doi: 10.3109/00365599509180543
4 Delorme E. [Transobturator urethral suspension: mini-invasive procedure in the treatment of stress urinary incontinence in women]. Prog Urol. 2001;11(06):1306–1313French.
5 Drain A, Khan A, Ohmann EL, Brucker BM, Smilen S, Rosenblum N, et al. Use of concomitant stress incontinence surgery at time of pelvic organ prolapse surgery since release of the 2011 notification on serious complications associated with transvaginal mesh. J Urol. 2017;197(04):1092–1098. Doi: 10.1016/j.juro.2016.11.087
6 Rac G, Younger A, Clemens JQ, Kobashi K, Khan A, Nitti V, et al. Stress urinary incontinence surgery trends in academic female pelvic medicine and reconstructive surgery urology practice in the setting of the food and drug administration public health notifications. Neurourol Urodyn. 2017;36(04):1155–1160. Doi: 10.1002/nau.23080
7 Ghoniem G, Hammett J. Female pelvic medicine and reconstructive surgery practice patterns: IUGA member survey. Int Urogynecol J Pelvic Floor Dysfunct. 2015;26(10):1489–1494. Doi: 10.1007/s00192-015-2734-5
8 Asıcıoglu O, Gungorduk K, Besımoglu B, Ertas IE, Yildirim G, Celebi I, et al. A 5-year follow-up study comparing Burch colposuspension and transobturator tape for the surgical treatment of stress urinary incontinence. Int J Gynaecol Obstet. 2014;125(01):73–77. Doi: 10.1016/j.ijgo.2013.09.026
9 Lapitan MC, Cody JD. Open retropubic colposuspension for urinary incontinence in women. Cochrane Database Syst Rev. 2012;(06):CD002912. Doi: 10.1002/14651858.CD002912.pub5
10 Akdemir Y, Dincer F, Buyukuysal C, Ozmen U, Harma M, Harma MI. Comparison of outcomes of Burch colposuspension and transobturator tape and single incision needleless procedures (Dyna-Mesh®-SIS minor) for the surgical treatment of female stress urinary incontinence patients who underwent combined pelvic reconstructive surgery or hysterectomy. Int Urol Nephrol. 2020;52(09):1665–1673. Doi: 10.1007/s11255-020-02549-0
11 Vanderbilt University Jean and Alexandre Heard Library Annete & Irwin Eskind Biomedical Library Special Collections. Special Collections and University Archives. History of Medicine [Internet] 2020 [cited 2020 Oct 24]. Available from: https://www.library.vanderbilt.edu/specialcollections/history-of-medicine/
12 Tanagho EA. Colpocystourethropexy: the way we do it. J Urol. 1976;116(06):751–753. Doi: 10.1016/s0022-5347(17)58997-1
13 Powell JL. The Burch procedure. J Pelvic Surg.. 2001;7(03):130–132
14 Marshall VF, Marchetti AA, Krantz KE. The correction of stress incontinence by simple vesicourethral suspension. Surg Gynecol Obstet. 1949;88(04):509–518
15 Novara G, Artibani W, Barber MD, Chapple CR, Costantini E, Ficarra V, et al. Updated systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence. Eur Urol. 2010;58(02):218–238. Doi: 10.1016/j.eururo.2010.04.022
16 Smith AR, Dmochowski R, Hilton P, Rovner E, Nilsson CG, Reid FM, et al.Committee 14. Surgery for urinary incontinence in women. In: Abrams P, Cardozo L, Khoury S, editors. Incontinence. Plymouth: Health Publications; 2009:1191–272
17 Veit-Rubin N, Dubuisson J, Ford A, Dubuisson JB, Mourad S, Digesu A. Burch colposuspension. Neurourol Urodyn. 2019;38(02):553–562. Doi: 10.1002/nau.23905
18 Cardozo L, Staskin D. Textbook of female urology and urogynecology. 4th ed. Boca Raton: CRC Press; 2016
19 Persson J, Teleman P, Etén-Bergquist C, Wølner-Hanssen P. Cost-analyzes based on a prospective, randomized study comparing laparoscopic colposuspension with a tension-free vaginal tape procedure. Acta Obstet Gynecol Scand. 2002;81(11):1066–1073. Doi: 10.1034/j.1600-0412.2002.811112.x
20 Ustün Y, Engin-Ustün Y, Güngör M, Tezcan S. Tension-free vaginal tape compared with laparoscopic Burch urethropexy. J Am Assoc Gynecol Laparosc. 2003;10(03):386–389. Doi: 10.1016/s1074-3804(05)60268-x
21 Paraiso MF, Walters MD, Karram MM, Barber MD. Laparoscopic Burch colposuspension versus tension-free vaginal tape: a randomized trial. Obstet Gynecol. 2004;104(06):1249–1258. Doi: 10.1097/01.AOG.0000146290.10472.b3
22 Jelovsek JE, Barber MD, Karram MM, Walters MD, Paraiso MF. Randomised trial of laparoscopic Burch colposuspension versus tension-free vaginal tape: long-term follow up. BJOG. 2008;115(02):219–225, discussion 225. Doi: 10.1111/j.1471-0528.2007.01592.x
23 Lazarou G, Minis E, Grigorescu B. Outcomes of stress urinary incontinence in women undergoing TOT versus Burch colposuspension with abdominal sacrocolpopexy. Int Urogynecol J Pelvic Floor Dysfunct. 2019;30(02):245–250. Doi: 10.1007/s00192-018-3668-5
24 Imamura M, Hudson J, Wallace SA, MacLennan G, Shimonovich M, Omar MI, et al. Surgical interventions for women with stress urinary incontinence: systematic review and network meta-analysis of randomised controlled trials. BMJ. 2019;365:l1842. Doi: 10.1136/bmj.l1842
25 Giarenis I, Thiagamoorthy G, Zacchè M, Robinson D, Cardozo L. Management of recurrent stress urinary incontinence after failed midurethral sling: a survey of members of the International Urogynecological Association (IUGA). Int Urogynecol J Pelvic Floor Dysfunct. 2015;26(09):1285–1291. Doi: 10.1007/s00192-015-2696-7
26 Brito LG, Rodrigues HL, Carvalho MA, Magnani PS, Lopes AH, Sabino-de-Freitas MM. Comparison of the efficacy and safety of surgical procedures utilizing autologous fascial and transobturator slings in patients with stress urinary incontinence. J Reprod Med. 2013;58(1-2):19–24
27 Mahdy A, Ghoniem GM. Autologous rectus fascia sling for treatment of stress urinary incontinence in women: A review of the

literature. Neurourol Urodyn. 2019;38(Suppl 4):S51–S58. Doi: 10.1002/nau.23878

28 Ng-Stollmann N, Fünfgeld C, Gabriel B, Niesel A. The international discussion and the new regulations concerning transvaginal mesh implants in pelvic organ prolapse surgery. Int Urogynecol J Pelvic Floor Dysfunct. 2020;31(10):1997–2002. Doi: 10.1007/s00192-020-04407-0

29 Chapple CR, Cruz F, Deffieux X, Milani AL, Arlandis S, Artibani W, et al. Consensus statement of the European Urology Association and the European Urogynaecological Association on the use of implanted materials for treating pelvic organ prolapse and stress urinary incontinence. Eur Urol. 2017;72(03):424–431. Doi: 10.1016/j.eururo.2017.03.048

Doppler Ultrasound of the Umbilical Artery: Clinical Application

Ultrassonografia Doppler da artéria umbilical: Aplicação clínica

Ana Sá Rocha[1] Ana Rosa Araújo Andrade[2] Maria Lúcia Moleiro[2] Luís Guedes-Martins[1,2,3,4]

[1] Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal
[2] Departamento da Mulher e da Medicina Reprodutiva, Centro Materno Infantil do Norte, Centro Hospitalar Universitário do Porto EPE, Porto, Portugal
[3] Departamento da Mulher e da Medicina Reprodutiva, Centro Materno Infantil do Norte, Unidade de Investigação e Formação, Porto, Portugal
[4] Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal

Address for correspondence Ana Sá Rocha, MD, R. Jorge de Viterbo Ferreira, 228, 4050-313, Porto, Portugal (e-mail: rochasaana@gmail.com).

Rev Bras Ginecol Obstet 2022;44(5):519–531.

Abstract

Objective To provide a survey of relevant literature on umbilical artery Doppler ultrasound use in clinical practice, technical considerations and limitations, and future perspectives.

Methods Literature searches were conducted in PubMed and Medline, restricted to articles written in English. Additionally, the references of all analyzed studies were searched to obtain necessary information.

Results The use of this technique as a routine surveillance method is only recommended for high-risk pregnancies with impaired placentation. Meta-analyses of randomized trials have established that obstetric management guided by umbilical artery Doppler findings can improve perinatal mortality and morbidity. The values of the indices of Umbilical artery Doppler decrease with advancing gestational age; however, a lack of consensus on reference ranges prevails.

Conclusion Important clinical decisions are based on the information obtained with umbilical artery Doppler ultrasound. Future efforts in research are imperative to overcome the current limitations of the technique.

Keywords
- doppler
- placenta
- umbilical artery
- fetal surveillance
- placental insufficiency

Resumo

Objetivo Compilar informação relevante proveniente da literatura atual sobre a ultrassonografia Doppler das artérias umbilicais (AUs) na prática clínica, considerações e limitações técnicas e perspectivas futuras.

Métodos A pesquisa bibliográfica foi realizada nos bancos de dados PubMed e Medline e restringiu-se a artigos escritos na língua inglesa. Recorreu-se também à bibliografia dos artigos selecionados, quando necessário, para obter informação relevante.

Resultados A utilização desta técnica como método de vigilância de rotina está apenas recomendada em gravidezes de alto risco com disfunção placentar. Metanálises

Palavras-chave
- doppler
- placenta
- artéria umbilical
- vigilância fetal
- insuficiência placentária

received
July 5, 2021
accepted
November 18, 2021
published online
April 11, 2022

DOI https://doi.org/10.1055/s-0042-1743097.
ISSN 0100-7203.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

de estudos randomizados mostraram que o seguimento obstétrico baseado nos achados do Doppler da artéria umbilical pode melhorar a mortalidade e a morbilidade perinatal. É consensual que os valores dos índices Doppler da AU decrescem com o avanço da idade gestacional. No entanto, há ainda muita incerteza quanto aos valores de referência.

Conclusão As informações obtidas através da AU Doppler US são a base para muitas decisões clínicas importantes. Trabalhos de investigação nesta área são essenciais para tentar colmatar atuais limitações da técnica.

Introduction

The umbilical arteries (UAs) play a key role in the regulation of the fetoplacental circulation. In the UAs, nerve regulation is absent and its tonus depends uniquely on locally released or circulating vasoactive substances, as well as on ions, such as calcium (Ca^{2+}) and potassium (K^{+}).[1–7] They lead the deoxygenated blood from the fetus to the placenta during systole and diastole, and together with the umbilical vein, which conducts the blood on the opposite direction, the exchange of nutrients, respiratory gases, and metabolites between the mother and the fetus, is guaranteed.[8]

To ensure normal intrauterine growth, there are some conditions that must be met: normal umbilical cord architecture and function; adequate placental perfusion; a healthy fetus and a favorable maternal condition; availability of nutrients and absence of pregnancy-related or non-related diseases.[1,8,9] Any abnormality in any of these prerequisites can potentially lead to intrauterine growth restriction (IUGR), with its inherent increased risk of perinatal mortality and morbidity in the short and long term.[1,9–14]

The main cause of IUGR is placental insufficiency,[9] which is associated with an increased resistance to blood flow in the placental vasculature, restricting the blood supply to the fetus and inducing compensatory responses with hemodynamic changes.[9,15,16] The onset of IUGR can occur anytime during pregnancy, and strict fetal surveillance is required after the diagnosis to determine when staying in the womb represents a greater risk of adverse perinatal outcomes than being born.[10,17–20]

Doppler ultrasound (US) of the UA provides useful information regarding the blood flow features within the arteries and is a well-established surveillance method in high-risk pregnancies due to impaired placentation.[11,20–22] In high-risk pregnancies, it is estimated that the use of Doppler US has allowed a decrease in the risk of perinatal death by $\sim$ 29%.[20]

The physical principle behind the Doppler US technology is named after The Doppler Effect, which is defined as the variation in the frequencies transmitted to and received from US waves between two objects when at least one is moving.[23,24] In obstetrics, the constant object is the transducer, and the red blood cells of the uterofetoplacental circulation are the shifting reflectors that produce the returning signal echoes.[23]

Spectral Doppler US is a speed-time spectral recording, presenting as flow velocity waveforms (FVWs).[25] It enables the quantification of the peak systolic velocity (PSV) and of the end-diastolic velocity (EDV) of blood flow within the UA, with which three indices can be obtained: the pulsatility index (PI), the resistance index (RI), and the systolic/diastolic ratio (S/D).[26,27] These indices are considered to be indirect measures of the resistance to blood flow of the placental vasculature.[1,11,28–30] Therefore, values not expected for the gestational age indicate placental dysfunction and fetal distress.[15,26,28,31]

The UA Doppler US is widely used in fetal surveillance because it is a noninvasive, economical, simple, and reproducible method.[8,12,13,15] However useful, this technic has some limitations, including the potential to cause considerable anxiety in families and clinicians, further diagnostic testing, and early (possibly very preterm) birth.[11] Moreover, it has been found that many studies reporting reference ranges for UA Doppler are based in methodologies with much heterogeneity.[20,31]

The aim of the present review is to provide a survey of the relevant literature on UA Doppler US in the clinical practice, its technical considerations and limitations, and to explore future perspectives.

Methods

The present research aimed to include studies that focused on the applicability of UA Doppler US in pregnancy management. To compose the present review, thorough literature searches were conducted in the PubMed and Medline databases, restricted to articles written in the English language. The screening of articles was performed using the following terms from the Medical Subject Heading of the Index Medicus as keywords: *Doppler ultrasound* AND/OR *umbilical artery*. The list of obtained articles was revised and the ones dealing with placental evaluation, placental insufficiency, fetal/pregnancy surveillance, and IUGR were chosen for further revision. Articles found by cross-referencing that met the inclusion criteria were also included.

All identified studies were screened for these inclusion criteria: (1) published in English (2) with full-text available, (3) UA Doppler US application in pregnancy.

A selection of the articles was performed. First, articles were filtered by reviewing titles and abstracts using the same

inclusion criteria. Second, the remaining articles were accessed based on the full text. Studies that did not meet all the inclusion criteria were excluded.

Results

Umbilical Artery Waveform Analysis

Concerning the UA, the standard Spectral Doppler US FVW pattern presents as a "sawtooth" pattern, revealing a unidirectional, continuous, and pulsatile flow toward the placenta (►**Fig. 1**). Its pattern can be distinguished from that of the umbilical vein since the UV FVW are continuous and non-pulsatile throughout the cardiac cycle.[32,33] In the "sawtooth" pattern of the UA, the highest point corresponds to the PSV, the lowest point corresponds to the EDV, and TAV stands for time-averaged velocity. These parameters enable the calculation of three indices: S/D Ratio: PSV/EDV; PI: (PSV - EDV)/TAV; RI: (PSV - EDV) / PSV.[23] In the clinical practice, the PI is the most commonly used.[34]

In low-risk pregnancies, the fetoplacental circulation presents itself with a placental high resistance to flow until the 20th week; thereafter, it gradually decreases and becomes a low-resistance system.[8] This phenomenon occurs from the end of the 2nd trimester due to the progressive placental villi maturation, greater width and wall compliance of the umbilical vessels along with greater fetal cardiac output and blood pressure.[35,36] Consequently, an acceleration in the EDV occurs and a proportional decrease in the three indices mentioned above is expected.[37] A deviation from the expected indices may signal an underlying placental dysfunction, and it indicates an increased risk of fetal demise,[31,38–40] regardless of the Doppler technique used.[35,41]

Pathological UA FVW has a progressive pattern of alterations, depending on the severity of the disorder: the EDV of the waveform becomes reduced (positive end-diastolic velocities [PEDV]), might disappear (absent end-diastolic velocities [AEDV]) (►**Fig. 2**), and can even reverse (reversed end-diastolic velocities [REDV]) (►**Fig. 3**), while PSV is not affected.[37,40,42] In these cases, the PI is more indicated for the interpretation of FVW findings[35] and it starts to increase only when 40% of the placental vascular tree remains functioning.[43]

While an AEDV flow before the 15th week is a normal physiological finding,[44] a REDV flow during the 1st trimester is associated with chromosomal abnormalities, fetal cardiovascular defects, and significant mortality.[45–49] However, as stated by Bellver et al.,[50] the latter "is not always an ominous sign."

Once present, the AEDV can stabilize or gradually evolve to REDV.[51] In a small number of cases, an AEDV can ameliorate and normalize spontaneously around the 27th week of gestation, although it is still unknown how to predict in which fetuses it will happen.[51] Antenatal administration of betamethasone to IUGR fetuses with absent or reversed end-diastolic velocity (AREDV) has also been correlated with the returning of the EDV and the stabilization of the resistance in the ductus venosus. By converting the AREDV to a normal flow, the outcome greatly improves, reverting the constant hypoxemia and acidosis to a better oxygenative status.[52] However, this positive effect of betamethasone is not seen in all cases, and the favorable response of the responding fetuses has not yet been understood.[52]

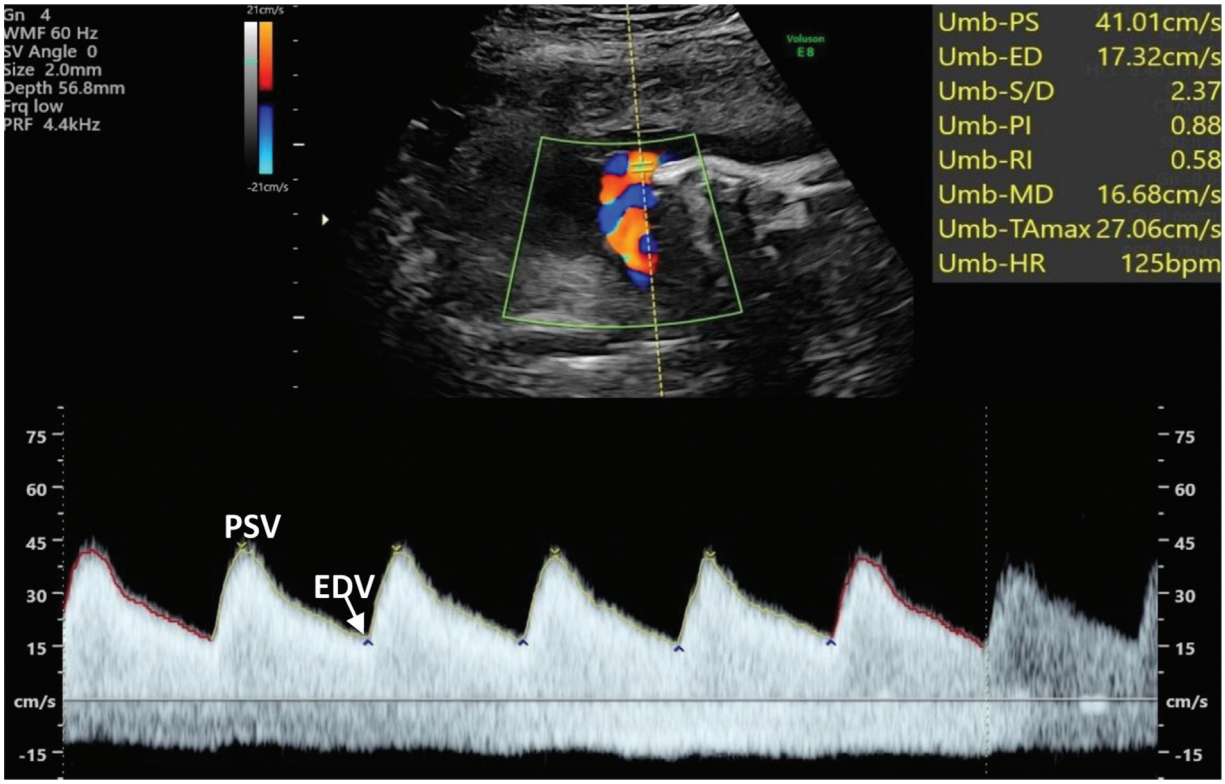


Fig. 1 Normal umbilical artery flow velocity waveform tracings obtained during the 3rd trimester. End diastolic velocities are present and are high; PSV - peak systolic velocity; EDV - end-diastolic velocity.

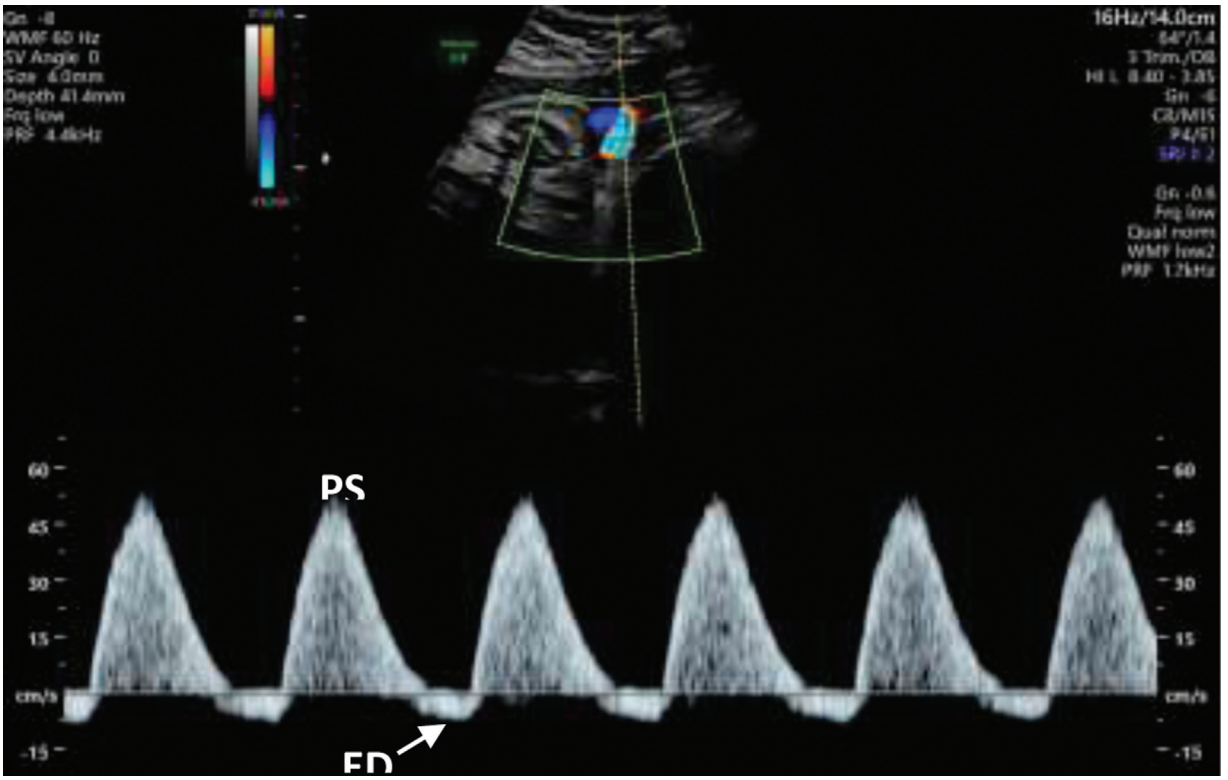


Fig. 2 Abnormal umbilical artery flow velocity waveform tracings obtained during the 2nd trimester. End diastolic velocities are absent, defining this pattern as AEDV. PSV - peak systolic velocity; EDV - end-diastolic velocity; AEDV - Absent end-diastolic velocity

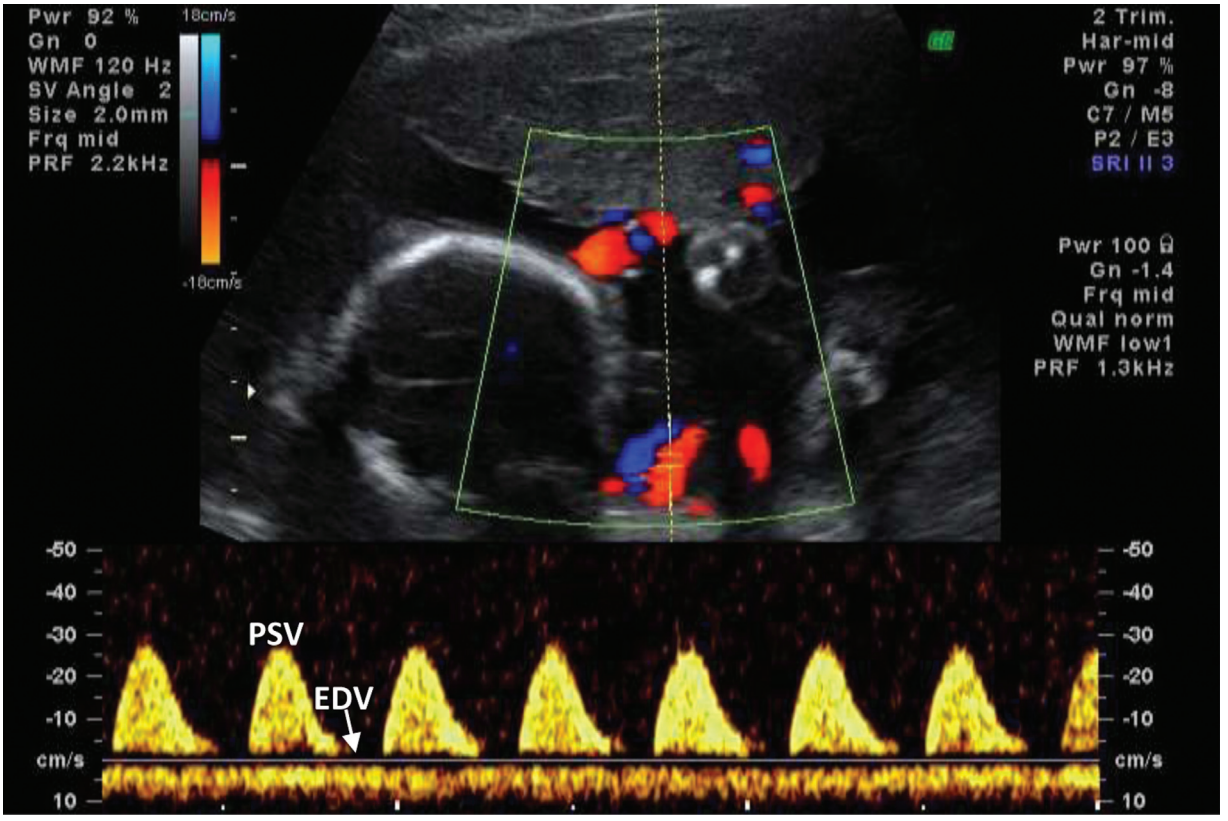


Fig. 3 Abnormal umbilical artery flow velocity waveform tracings obtained in a 3rd trimester pregnancy. End diastolic velocities are below the baseline, defining this pattern as REDV. PSV: peak systolic velocity; EDV: end-diastolic velocity; REDV: Reversed end-diastolic velocity

Absent or reversed end-diastolic velocity is frequently associated with marginal placental-end cord insertion,[1,53] which can be accurately diagnosed by Color Doppler US during the 2nd trimester.[12] Furthermore, in IUGR fetuses with AREDV, there is an increased expression of estrogen receptor-β within the fetoplacental endothelium, misbalancing the vascular tonus mediators and favoring vasoconstriction.[1,54,55] Being a vasodilator and smooth muscle relaxant,[56] the administration of intravenous or transdermal nitroglycerine causes a decrease in placental resistance to flow. This results in decreased PI, RI and S/D ratio in UA and Uterine artery (UtA) Doppler US, thus improving the outcomes.[56,57]

When compared with PEDV, AREDV fetuses have a higher incidence of low birthweight, worse Apgar scores, and oligohydramnios; greater number of labor inductions and caesarean sections due to fetal distress; admissions to neonatal intensive care unit; fetal demise; perinatal mortality and morbidity,[58–62] as well as long-term neurological impairment.[14,63–65] The lower the gestational age and fetal weight at birth, the more severe are the neonatal complications.[58] Specifically, fetuses with trisomy 21 have higher prevalence of AREDV, along with the presence of maternal malperfusion, delayed villous maturation and fetal vascular malperfusion, shortened umbilical cord, congenital cardiac anomalies, which frequently result in growth restriction, and death *in utero*.[66]

In IUGR fetuses, when in the presence of PEDV, an expectant attitude and close monitoring with weekly UA assessment is suggested, while in the presence of AREDV, after an acceptable gestational age is achieved, pregnancy termination seems to be the safest option to attain a better perinatal outcome.[37,58] Based on a recent meta-analysis, the 2021 International Federation of Gynecology and Obstetrics (FIGO) initiative on fetal growth suggested the application of UA Doppler findings as relative delivery criteria from 30 weeks onward for REDV and from 32 weeks onward for AEDV.[39,67]

The analysis of FVW can alert obstetricians to other pathological entities in addition to placental disorders. A period of deceleration during a larger period of acceleration, or the opposite, is called *notching*.[68] A systolic notch in the UA FVW suggests the presence of an umbilical cord abnormality, such as an UA narrowing, an abnormal cord insertion, cord entanglement (in twin pregnancies) or a true knot. True knots, which are the major cause of notching, can impair the flow supply to the fetus and lead to adverse outcomes. The notching magnitude strongly correlates to how tight the knot is and it depends on the type of FVW being measured (envelope versus centerline), as well as on the location downstream of the constriction where the FVW is being measured.[68]

Also worth of consideration are the results of a study conducted in 2006 by Struijk et al.,[69] in which the magnitude-squared coherence function between the UtA and UA FVW was found to improve the early identification of preeclampsia during the mid-trimester. However, it has no applicability in the prediction of IUGR or of pregnancy-induced hypertension.[69]

Umbilical Artery Doppler Reference Ranges

There is a consensus that UA PI decreases linearly with advancing gestational age in uncomplicated singleton pregnancies.[15,31,35,70–75] (►**Table 1**) (►**Fig. 4**).

However, the same percentile values were not obtained for each corresponding gestational age.[15,31,35,70–75] The same could be inferred about UA RI (►**Table 2**) (►**Fig. 5**).[72–75]

Gathering values obtained in three different geographical areas, Drukker et al.[72] proposed universal charts for UA PI. They considered that uncomplicated pregnancies in excellent health, nutritional, and environmental conditions for fetal growth have similar fetoplacental function and, consequently, similar Doppler indices regardless of the country of origin and of the inherent characteristics of its population.[72] On the other hand, Ciobanu et al.[71] suggested that the *a priori* risk related to maternal characteristics and medical history should be taken into account as maternal age, body mass index, smoking, parity, and racial origin have significant impact on UA PI. Moreover, Widnes et al.[26] considered the influence of fetal gender and proposed gestational age-dependent gender reference ranges, as they found that female fetuses have a more pulsatile UA from the 20th week to the 37th week, and higher heart rates from the 26th week.

In the case of fetuses with a single umbilical artery, Contro et al.[77] found the UA PI to be 20% lower than in those with a normal 3-vessel umbilical cord. This disparity remained constant between the 23rd and 40th gestational weeks. Thus, lower reference values in such cases may allow a more accurate interpretation of Doppler measurements.[77]

Concerning twin pregnancies, Mulcahy et al.[78] described the UA PI and RI to be consistently higher, from early pregnancy, in both monochorionic (MC) and dichorionic (DC) twins in comparison with singletons. Also among twin pregnancies, MC twins tend to demonstrate slightly higher values of UA PI and RI compared with DC twins.[78] These findings are supported by Casati et al.,[79] who proposed uncomplicated MC-specific Doppler charts, which include UA PI values. Since singleton Doppler reference ranges are not suitable for interpreting findings in twin pregnancies, further studies on both complicated and uncomplicated twin gestations and their perinatal and long-term outcomes are needed.[78,79]

Maternal glucose loading[80] and fetal behavior state were found not to influence UA PI value measurements if adjusted to the fetal heart rate.[80,81] Although smoking during pregnancy is associated with an increased risk of adverse outcomes,[82–84] smoking habits seem not to influence fetal Doppler parameters.[85] A curious finding is that the left UA appears to have higher impedance to flow and as few as 2% of the pregnancies have both arteries with similar Doppler indices.[86]

There is currently a wide variety of reference charts on UA Doppler indices, which could be explained, at least in part, by the heterogeneity in the methodological quality of the reports. Major methodological and statistical bias, found in some reports aiming to establish UA Doppler reference values, must be considered when examining this subject.[31] Even the studies with the highest methodological quality have significant discrepancy in cutoff values, which may signify important differences in clinical practice when using

Table 1 Values of the 95th centile for umbilical artery pulsatility index in studies reporting reference ranges

Gestational age (weeks)	Drukker et al.[72]	Acharya et al.[73]	Ciobanu et al.[71]	Srikumar et al.[75]	Ayoola et al.[74]	Baschat et al.[76]
18				1.62	1.402	
19		1.66		1.66	1.395	
20		1.62	1.553	1.55	1.388	1.31
21		1.58	1.526	1.53	1.381	1.27
22		1.54	1.499	1.54	1.375	1.28
23		1.5	1.472	1.41	1.368	1.12
24	1.38	1.47	1.446	1.42	1.361	1.21
25	1.37	1.44	1.42	1.31	1.354	1.13
26	1.35	1.41	1.395	1.24	1.348	1.11
27	1.34	1.38	1.371	1.32	1.341	1.07
28	1.32	1.35	1.346	1.33	1.334	1.05
29	1.3	1.32	1.322	1.25	1.327	1.11
30	1.28	1.29	1.299	1.08	1.321	1.04
31	1.26	1.27	1.275	1.12	1.314	0.99
32	1.24	1.25	1.252	1.1	1.307	0.93
33	1.21	1.22	1.229	1.15	1.3	0.92
34	1.19	1.2	1.207	1.2	1.294	0.89
35	1.16	1.18	1.184	1.05	1.287	0.91
36	1.14	1.16	1.162	1.05	1.28	0.93
37	1.11	1.14	1.14	1	1.273	0.95
38	1.08	1.12	1.118	1.08	1.267	0.89
39	1.06	1.1	1.097	0.95	1.26	1.01
40	1.03	1.09	1.075	0.82		0.75
41		1.07	1.053			

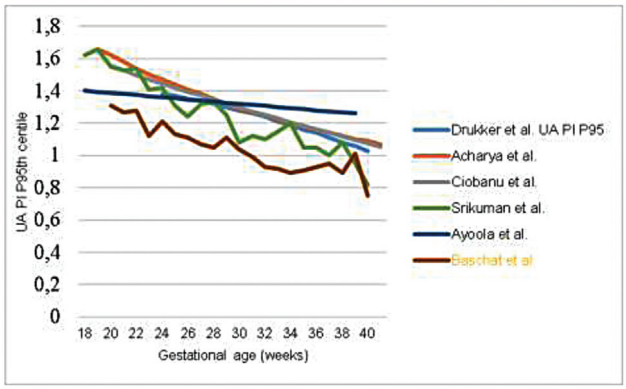


Fig. 4 Comparison of the 95th percentile of the umbilical artery pulsatility index in studies reporting reference ranges. UA: Umbilical artery; PI: Pulsatility index

one cutoff value in preference to another.[31] When evaluating the potential impact of such variability on the clinical management of small for gestational age (SGA) fetuses, Ruiz-Martinez et al.[87] found the rate of labor inductions to vary from 2.1 to 33.7%, depending on which reference chart of the UA PI was used and considering the PI cutoff > 95th percentile, as recommended in current clinical guidelines.[88] This example illustrates the magnitude of the impact that heterogeneous cutoff values have on decision-making in important clinical issues.[87] Another example is presented by Drukker et al.,[72] who found the 95th percentile values of UA PI to range between 1.28 and 1.48 at 32 weeks and between 1.03 and 1.40 at 39 weeks of pregnancy in different studies, illustrating a considerable uncertainty about what is a normal and expected cutoff value.[72]

Umbilical Artery Doppler as a Screening Test in Low-Risk Pregnancies

According to Alfirevic et al.,[11] the methods traditionally used in low-risk pregnancies to assess fetal well-being (symphysis-fundal height measurement, fetal movements charts, and cardiotocography) have no proven ability to positively impact the low incidence and preventable adverse perinatal outcomes. Therefore, UA Doppler US was tested as a routine screening tool in low-risk pregnancies. In such pregnancies, UA Doppler US demonstrated low prognostic value concerning the risk of fetal demise, neonatal acidosis or decreased Apgar score.[89] Also, at term, an abnormal UA Doppler result in these cases can only have one consequence to improve the health of the newborn: intensified monitoring

Table 2 Values of the 95th percentile for umbilical artery resistance index in studies reporting reference ranges

Gestational age (weeks)	Drukker et al.[72]	Acharya et al.[73]	Srikumar et al.[75]	Ayoola et al.[74]
18			0.9	0.781
19		0.88	0.86	0.778
20		0.87	0.82	0.775
21		0.85	0.84	0.772
22		0.84	0.83	0.769
23		0.83	0.81	0.766
24	0.78	0.82	0.79	0.763
25	0.77	0.81	0.77	0.76
26	0.77	0.8	0.75	0.758
27	0.76	0.79	0.78	0.755
28	0.76	0.78	0.76	0.752
29	0.75	0.77	0.76	0.749
30	0.75	0.76	0.7	0.746
31	0.74	0.76	0.71	0.743
32	0.73	0.75	0.73	0.74
33	0.72	0.74	0.73	0.737
34	0.71	0.73	0.74	0.734
35	0.7	0.72	0.66	0.732
36	0.69	0.71	0.66	0.729
37	0.68	0.7	0.65	0.726
38	0.67	0.7	0.68	0.723
39	0.66	0.69	0.62	0.72
40	0.65	0.68	0.58	
41		0.67		

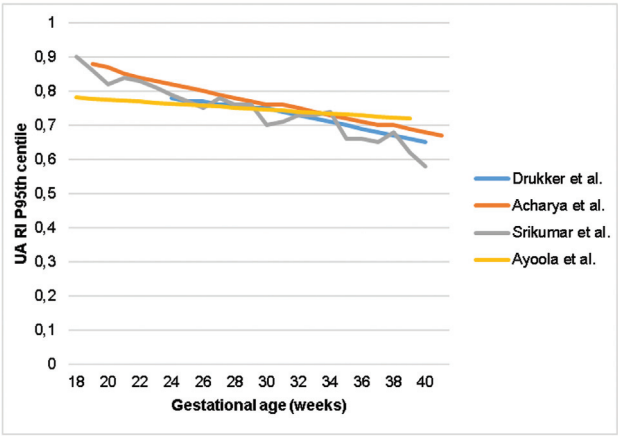


Fig. 5 Comparison of the 95th percentile of the umbilical artery resistance index in studies reporting reference ranges; UA: Umbilical artery; RI: Resistance index

with possible elective delivery in the event of deteriorating fetal distress.[90] Considering its low predictable value and its cost of time, money and considerable anxiety of the parents, nowadays the routine screening of low-risk pregnancies with UA Doppler US is not recommended.[11,15,90,91]

In contrast, according to Nkosi et al.,[92] in developing countries and small centers with less financial resources, the routine use of Umbiflow (a continuous-wave Doppler machine) to screen low-risk pregnancies from the 28th to the 32nd week is beneficial. It allowed greater recognition of increased UA RI and AREDV patterns up to 5 to 10 times more than expected.[92] The identification of these fetuses at risk, among the until then considered low-risk pregnancies, led to an adequate and active management of those pregnancies and to an improvement in perinatal outcomes, avoiding several unexplained stillbirths.[92,93]

Aiming to predict the perinatal outcome of low-risk pregnancies whose fetuses are suspected of IUGR, Gudmundsson et al.[94] proposed a new Doppler index: the placental pulsatility index. It combines the PI value of UA and UtA to evaluate the complete placental vascular impedance, and the authors suggest it has greater efficiency to predict adverse perinatal outcomes than UA and UtA alone.[94]

Umbilical Artery Doppler as a Screening Test in High-Risk Pregnancies

In contrast to low-risk pregnancies, the UA Doppler US is recommended as a routine surveillance method to assess

fetal well-being in high-risk pregnancies. Especially in pregnancies complicated by placental dysfunction, as in IUGR or pre-eclampsia, UA Doppler US works as a predictive test for fetal compromise.[20,22,95,96] Its applicability in other high-risk groups such as diabetes mellitus, post-term, and uncomplicated dichorionic twin pregnancy is still uncertain.[20,97–99]

The UA Doppler parameters are used to monitor fetal status and response to stress in pre-eclampsia and other hypertensive disorders related to pregnancy. However, it is the UtA PI that better predicts its future development[100,101] and anticipates adverse outcomes related to the condition.[102]

Fetuses with estimated fetal weight (EFW) $< 10^{th}$ centile are considered to be small for gestational age (SGA) and are at increased risk of fetal demise and poor perinatal outcomes when compared with non-SGA fetuses.[20,103,104] Some of these are constitutionally small healthy fetuses, whereas others are failing to reach their potential weight due to an underlying condition – IUGR fetuses.[11,20,105] Still, fetuses failing to reach their growth potential may or may not be SGA.[20,106]

The criteria for diagnosing IUGR due to placental insufficiency include UA Doppler measurements.[107] There are 2 subtypes of IUGR, depending on whether the onset is before or after the 32^{nd} week,[107] both of which have distinguishable Doppler patterns and postnatal outcomes.[10,108] The early-onset IUGR (E-IUGR) is more frequently associated with early-onset pre-eclampsia[109,110] and a classical sequence of deterioration of Doppler indices is present.[111–114] First, the UA PI increases to abnormally high values and then the middle cerebral artery PI starts decreasing as the cardiovascular redistribution occurs. As the downstream impedance to flow keeps increasing, the EDV within the UA decreases and AREDV pattern settles down. These are followed by an abnormal ductus venosus FVW and fetal heart insufficiency.[111–114] The presence of an AREDV pattern or an EFW $< 3^{rd}$ centile, before the 32^{nd} week, establishes the diagnosis of E-IUGR by itself.[107] In E-IUGR fetuses, the decision of labor induction based on fetal monitoring with non-stress test and ductus venosus Doppler seems to be associated with better results at 2 years of age.[17,38]

The late-onset IUGR (L-IUGR) is more prevalent and has a lower mortality rate than E-IUGR[108]; however, the undetected cases constitute the major cause of unexplained stillbirth.[11,103,115] In this subtype of IUGR, the UA Doppler indices remain unchanged or minimally elevated, not being reliable for diagnosis.[108] After the 32^{nd} week, the combination of biometrical parameters with Doppler measurements is more reliable than either one alone when differentiating the SGA at low-risk from those at high-risk for adverse outcomes.[108] These Doppler measurements must include the UA, the middle cerebral artery and the UtA as a multivessel screening in all pregnancies at high risk for placental dysfunction in the 3^{rd} trimester.[108,116] Finding both normal cerebroplacental ratio (CPR) and UtA Doppler indices, in fetuses presenting with an EFW $> 3^{rd}$ centile, confirms the low-risk status and the managing protocol of constitutionally small fetuses is appropriate.[108] When Doppler indices suggest placental insufficiency (UA PI $> 95^{th}$ centile or CPR $< 5^{th}$ centile), an EFW $< 10^{th}$ centile, or crossing > 2 quartiles on growth charts, has to be present to establish a high-risk status for late-SGA. However, an EFW $< 3^{rd}$ centile alone, after the 32^{nd} week, establishes the diagnosis by itself.[107]

Selective IUGR in DC twin pregnancies can also be monitored using UA Doppler US as it presents a flow progression pattern similar to that of IUGR in singleton pregnancies. In contrast, and due to the interdependent circulation, selective IUGR in MC twin pregnancies does not exhibit such pattern and the UA Doppler US is not a reliable tool to predict a possible deterioration of fetal status.[117] However, in MC pregnancies, a classification system based on the presence or absence of EDV in the UA in the affected twin guides its subsequent management.[117,118] Thus, twin pregnancies benefit from fetal well-being assessment with the UA Doppler US when there is a growth discordance, twin-to-twin transfusion syndrome, or IUGR.[119,120]

In pregnancies complicated by gestational diabetes,[121] or with pre-existing diabetes mellitus without vascular disease, the non-stress test was found to be better than the UA Doppler US at predicting adverse perinatal outcomes.[98,121] Only those complicated with vasculopathy due to diabetes could benefit from periodic UA Doppler US monitoring.[98]

Discussion

The UA Doppler US has acquired an unquestionable importance as a fetal well-being surveillance method over the years and it is widely used in the clinical practice today.

In low-risk pregnancies, the placental impedance to flow is low and enables a continuous blood flow within the UA.[8,37] Placental insufficiency compromises this low-resistance system at the expense of the EDV. The higher the placental resistance, the lower the UA EDV, and the normal FVW "sawtooth" pattern progressively deteriorates into PEDV, AEDV, and ultimately into REDV patterns. These abnormal patterns are recognized as ominous and anticipatory signs of poor obstetric outcomes.[37,39,40,42,58,122] Likewise, the UA Doppler indices depend on EDV, and the PI, RI, and S/D ratio values are considered indirect measures of placental vasculature resistance to blood flow.[1,11,28–30]

Concerning low-risk pregnancies, the routine use of UA Doppler US for fetal surveillance is not recommended.[11,90,91] Nonetheless, this assumption is based on studies conducted approximately 30 years ago. Therefore, it would be paramount to replicate these investigations with more accurate methodologies to determine whether there would be changes to the current knowledge or a corroboration of past conclusions.

In high-risk pregnancies, the UA Doppler US allows an accurate risk assessment for adverse outcomes and helps in the decision-making toward minimization of perinatal mortality and morbidity.[8,11,15] Current guidelines strongly recommend the routine use of this tool in high-risk pregnancies affected by placental insufficiency, such as those with IUGR and pregnancy-related hypertensive disorders.[20,22,95,96] However, during the 3^{rd} trimester, placental insufficiency develops under normal UA Doppler indices;[108] therefore, when suspected, other methods must be used to assess fetal well-being.[10,108,116] Regarding this issue, the TRUFFLE group is currently conducting

a study (the TRUFFLE 2 study) aiming to address which monitoring methods and thresholds are ideal for determining the delivery of L-IUGR fetuses.[123] The role of UA Doppler US for fetal surveillance in high-risk pregnancies due to other precipitating factors requires further investigation.[20,31,97–99,124]

Health improvements are not due to the application of the UA Doppler US itself but, rather, the result from the decision-making based on the information provided by this technology. Also, the success of Doppler measurements depends on the efficiency to spot abnormal and suspicious findings. Reference ranges are essential to establish which values of UA Doppler parameters must be considered normal and abnormal. Surprisingly, this is the point where less consensus exists. Although all studies agree that the values decrease with advancing gestational age, their proposed cutoff values differ significantly.[15,31,35,70–75] Studies on the methodological quality of reports proposing reference ranges have shown major methodological and statistical biases.[31,87] This may explain why so many different reference ranges have already been proposed. Another factor that may contribute to this variability is the wide range of variables that may influence UA Doppler indices. These can be fetal, maternal, or pregnancy-related variables, whose impact may be different when studied individually or in interaction. Given this and considering the potential impact of such variability on clinical decisions, the lack of consensus on reference ranges should incite scientific discussion. A universal chart was recently proposed aiming to standardize UA Doppler indices globally.[72] Although it sounds promising, future studies reporting its efficacy in different populations around the globe are paramount to state a conclusion.

Conclusion

The UA Doppler US is an invaluable screening tool for high-risk pregnancies and on which important clinical decisions depend. Future investments in research are imperative to attempt to overcome the current limitations of the technique.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Su EJ. Role of the fetoplacental endothelium in fetal growth restriction with abnormal umbilical artery Doppler velocimetry. Am J Obstet Gynecol. 2015;213(4, Suppl)S123–S130. Doi: 10.1016/j.ajog.2015.06.038

2 Lorigo M, Mariana M, Feiteiro J, Cairrao E. How is the human umbilical artery regulated? J Obstet Gynaecol Res. 2018;44(07): 1193–1201. Doi: 10.1111/jog.13667

3 Salemme S, Rebolledo A, Speroni F, Petruccelli S, Milesi V. L, P-/Q- and T-type Ca2+ channels in smooth muscle cells from human umbilical artery. Cell Physiol Biochem. 2007;20(1-4):55–64. Doi: 10.1159/000104153

4 Milesi V, Raingo J, Rebolledo A, Grassi de Gende AO. Potassium channels in human umbilical artery cells. J Soc Gynecol Investig. 2003;10(06):339–346. Doi: 10.1016/s1071-5576(03)00117-5

5 Reilly FD, Russell PT. Neurohistochemical evidence supporting an absence of adrenergic and cholinergic innervation in the human placenta and umbilical cord. Anat Rec. 1977;188(03): 277–286. Doi: 10.1002/ar.1091880302

6 Fox SB, Khong TY. Lack of innervation of human umbilical cord. An immunohistological and histochemical study. Placenta. 1990; 11(01):59–62. Doi: 10.1016/s0143-4004(05)80443-6

7 Poston L, McCarthy AL, Ritter JM. Control of vascular resistance in the maternal and feto-placental arterial beds. Pharmacol Ther. 1995;65(02):215–239. Doi: 10.1016/0163-7258(94)00064-a

8 Krzyżanowski A, Kwiatek M, Gęca T, Stupak A, Kwaśniewska A. Modern ultrasonography of the umbilical cord: prenatal diagnosis of umbilical cord abnormalities and assessement of fetal wellbeing. Med Sci Monit. 2019;25:3170–3180. Doi: 10.12659/MSM.913762

9 Sankaran S, Kyle PM. Aetiology and pathogenesis of IUGR. Best Pract Res Clin Obstet Gynaecol. 2009;23(06):765–777. Doi: 10.1016/j.bpobgyn.2009.05.003

10 Mureşan D, Rotar IC, Stamatian F. The usefulness of fetal Doppler evaluation in early versus late onset intrauterine growth restriction. Review of the literature. Med Ultrason. 2016;18(01): 103–109. Doi: 10.11152/mu.2013.2066.181.dop

11 Alfirevic Z, Stampalija T, Medley N. Fetal and umbilical Doppler ultrasound in normal pregnancy. Cochrane Database Syst Rev. 2015;(04):CD001450. Doi: 10.1002/14651858.CD001450.pub4

12 Sun J, Wang L, Li Y. Clinical value of color doppler ultrasound in prenatal diagnosis of umbilical cord entry abnormity. Pak J Med Sci. 2016;32(06):1414–1418. Doi: 10.12669/pjms.325.10518

13 Tanis JC, Boelen MR, Schmitz DM, Casarella L, van der Laan ME, Bos AF, et al. Correlation between Doppler flow patterns in growth-restricted fetuses and neonatal circulation. Ultrasound Obstet Gynecol. 2016;48(02):210–216. Doi: 10.1002/uog.15744

14 Baschat AA. Neurodevelopment after fetal growth restriction. Fetal Diagn Ther. 2014;36(02):136–142. Doi: 10.1159/000353631

15 Figueira CO, Surita FG, Dertkigil MS, Pereira SL, Bennini JR Jr., Morais SS, et al. Fetal Hemodynamic parameters in low risk pregnancies: Doppler velocimetry of uterine, umbilical, and middle cerebral artery. ScientificWorldJournal. 2016;2016:1693704. Doi: 10.1155/2016/1693704

16 Richardson BS, Bocking AD. Metabolic and circulatory adaptations to chronic hypoxia in the fetus. Comp Biochem Physiol A Mol Integr Physiol. 1998;119(03):717–723. Doi: 10.1016/s1095-6433(98)01010-1

17 Frusca T, Todros T, Lees C, Bilardo CMTRUFFLE Investigators. Outcome in early-onset fetal growth restriction is best combining computerized fetal heart rate analysis with ductus venosus Doppler: insights from the Trial of Umbilical and Fetal Flow in Europe. Am J Obstet Gynecol. 2018;218(2S, 2s):S783–S789. Doi: 10.1016/j.ajog.2017.12.226

18 Vollgraff Heidweiller-Schreurs CA, De Boer MA, Heymans MW, Schoondmade LJ, Bossuyt PMM, Mol BWJ, et al. Prognostic accuracy of cerebroplacental ratio and middle cerebral artery Doppler for adverse perinatal outcome: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018;51(03):313–322. Doi: 10.1002/uog.18809

19 Bakalis S, Akolekar R, Gallo DM, Poon LC, Nicolaides KH. Umbilical and fetal middle cerebral artery Doppler at 30-34 weeks' gestation in the prediction of adverse perinatal outcome. Ultrasound Obstet Gynecol. 2015;45(04):409–420. Doi: 10.1002/uog.14822

20 Alfirevic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database Syst Rev. 2017;6(06):CD007529. Doi: 10.1002/14651858.CD007529.pub4

21 American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics and the Society forMaternal-FetalMedicin. ACOG Practice Bulletin No. 204: fetal growth restriction. Obstet Gynecol. 2019;133(02):e97–e109. Doi: 10.1097/AOG.0000000000003070

22 Berkley E, Chauhan SP, Abuhamad ASociety for Maternal-Fetal Medicine Publications Committee. Doppler assessment of the

fetus with intrauterine growth restriction. Am J Obstet Gynecol. 2012;206(04):300–308. Doi: 10.1016/j.ajog.2012.01.022
23 Oglat AA, Matjafri MZ, Suardi N, Oqlat MA, Abdelrahman MA, Oqlat AA. A review of medical Doppler ultrasonography of blood flow in general and especially in common carotid artery. J Med Ultrasound. 2018;26(01):3–13. Doi: 10.4103/JMU.JMU_11_17
24 Moorthy RS. Doppler ultrasound. Med J Armed Forces India. 2002;58(01):1–2. Doi: 10.1016/S0377-1237(02)80001-6
25 Wood MM, Romine LE, Lee YK, Richman KM, O'Boyle M, Paz DA, et al. Spectral Doppler signature waveforms in ultrasonography: a review of normal and abnormal waveforms. Ultrasound Q. 2010;26(02):83–99. Doi: 10.1097/RUQ.0b013e3181dcbf67
26 Widnes C, Flo K, Wilsgaard T, Kiserud T, Acharya G. Sex differences in umbilical artery Doppler indices: a longitudinal study. Biol Sex Differ. 2018;9(01):16. Doi: 10.1186/s13293-018-0174-x
27 Nelson TR, Pretorius DH. The Doppler signal: where does it come from and what does it mean? AJR Am J Roentgenol. 1988;151 (03):439–447. Doi: 10.2214/ajr.151.3.439
28 Mone F, McConnell B, Thompson A, Segurado R, Hepper P, Stewart MC, et al. Fetal umbilical artery Doppler pulsatility index and childhood neurocognitive outcome at 12 years. BMJ Open. 2016;6 (06):e008916. Doi: 10.1136/bmjopen-2015-008916
29 Trudinger BJ, Stevens D, Connelly A, Hales JR, Alexander G, Bradley L, et al. Umbilical artery flow velocity waveforms and placental resistance: the effects of embolization of the umbilical circulation. Am J Obstet Gynecol. 1987;157(06):1443–1448. Doi: 10.1016/s0002-9378(87)80241-7
30 Giles WB, Trudinger BJ, Baird PJ. Fetal umbilical artery flow velocity waveforms and placental resistance: pathological correlation. Br J Obstet Gynaecol. 1985;92(01):31–38. Doi: 10.1111/j.1471-0528.1985.tb01045.x
31 Oros D, Ruiz-Martinez S, Staines-Urias E, Conde-Aguiedo A, Villar J, Fabre E, et al. Reference ranges for Doppler indices of umbilical and fetal middle cerebral arteries and cerebroplacental ratio: systematic review. Ultrasound Obstet Gynecol. 2019;53(04): 454–464. Doi: 10.1002/uog.20102
32 Hecher K, Campbell S. Characteristics of fetal venous blood flow under normal circumstances and during fetal disease. Ultrasound Obstet Gynecol. 1996;7(01):68–83. Doi: 10.1046/j.1469-0705.1996.07010068.x
33 Najafzadeh A, Dickinson JE. Umbilical venous blood flow and its measurement in the human fetus. J Clin Ultrasound. 2012;40 (08):502–511. Doi: 10.1002/jcu.21970
34 Bhide A, Acharya G, Bilardo CM, Brezinka C, Cafici D, Hernandez-Andrade E, et al. ISUOG practice guidelines: use of Doppler ultrasonography in obstetrics. Ultrasound Obstet Gynecol. 2013;41(02):233–239. Doi: 10.1002/uog.12371
35 Bahlmann F, Fittschen M, Reinhard I, Wellek S, Puhl A. Blood flow velocity waveforms of the umbilical artery in a normal population: reference values from 18 weeks to 42 weeks of gestation. Ultraschall Med. 2012;33(07):E80–E87. Doi: 10.1055/s-0031-1299294
36 Trudinger BJ, Giles WB, Cook CM, Bombardieri J, Collins L. Fetal umbilical artery flow velocity waveforms and placental resistance: clinical significance. Br J Obstet Gynaecol. 1985;92(01): 23–30. Doi: 10.1111/j.1471-0528.1985.tb01044.x
37 Todros T, Piccoli E, Rolfo A, Cardaropoli S, Guiot C, Gaglioti P, et al. Review: Feto-placental vascularization: a multifaceted approach. Placenta. 2011;32(Suppl 2):S165–S169. Doi: 10.1016/j.placenta.2010.12.020
38 Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, Derks JB, et al; TRUFFLE Group. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). Ultrasound Obstet Gynecol. 2013;42(04):400–408. Doi: 10.1002/uog.13190
39 Caradeux J, Martinez-Portilla RJ, Basuki TR, Kiserud T, Figueras F. Risk of fetal death in growth-restricted fetuses with umbilical and/or ductus venosus absent or reversed end-diastolic velocities before 34 weeks of gestation: a systematic review and meta-analysis. Am J Obstet Gynecol. 2018;218(2S):S774–82.e21, 782.e21. Doi: 10.1016/j.ajog.2017.11.566
40 Kalache KD, Dückelmann AM. Doppler in obstetrics: beyond the umbilical artery. Clin Obstet Gynecol. 2012;55(01):288–295. Doi: 10.1097/GRF.0b013e3182488156
41 Giles WB, Lingman G, Marsál K, Trudinger BJ. Fetal volume blood flow and umbilical artery flow velocity waveform analysis: a comparison. Br J Obstet Gynaecol. 1986;93(05):461–465
42 Marsál K. Rational use of Doppler ultrasound in perinatal medicine. J Perinat Med. 1994;22(06):463–474
43 Thompson RS, Trudinger BJ. Doppler waveform pulsatility index and resistance, pressure and flow in the umbilical placental circulation: an investigation using a mathematical model. Ultrasound Med Biol. 1990;16(05):449–458. Doi: 10.1016/0301-5629(90)90167-b
44 Fisk NM, MacLachlan N, Ellis C, Tannirandorn Y, Tonge HM, Rodeck CH. Absent end-diastolic flow in first trimester umbilical artery. Lancet. 1988;2(8622):1256–1257. Doi: 10.1016/s0140-6736(88)90854-9
45 Borrell A, Martinez JM, Farre MT, Azulay M, Cararach V, Fortuny A. Reversed end-diastolic flow in first-trimester umbilical artery: an ominous new sign for fetal outcome. Am J Obstet Gynecol. 2001; 185(01):204–207. Doi: 10.1067/mob.2001.114872
46 Borrell A, Costa D, Martinez JM, Farré MT, Palacio M, Mortera C, Fortuny A, et al. Reversed end-diastolic umbilical flow in a first-trimester fetus with congenital heart disease. Prenat Diagn. 1998; 18(10):1001–1005. Doi: 10.1002/(sici)1097-0223(1998100)18:10<1001:aid-pd395>3.0.co;2-v
47 Martinez Crespo JM, Comas C, Borrell A, Puerto B, Antolin E, Ojuel J, et al. Reversed end-diastolic umbilical artery velocity in two cases of trisomy 18 at 10 weeks' gestation. Ultrasound Obstet Gynecol. 1996;7(06):447–449. Doi: 10.1046/j.1469-0705.1996.07060447.x
48 Murta CG, Moron AF, Avila MA. Reversed diastolic umbilical artery flow in the first trimester associated with chromosomal fetal abnormalities or cardiac defects. Obstet Gynecol. 2000;95(6 Pt 2):1011–1013. Doi: 10.1016/s0029-7844(99)00603-1
49 Comas C, Carrera M, Devesa R, Muñoz A, Torrents M, Ribas I, et al. Early detection of reversed diastolic umbilical flow: should we offer karyotyping? Ultrasound Obstet Gynecol. 1997;10(06): 400–402. Doi: 10.1046/j.1469-0705.1997.10060400.x
50 Bellver J, Lara C, Rossal LP, Remohí J, Pellicer A, Serra V. First-trimester reversed end-diastolic flow in the umbilical artery is not always an ominous sign. Ultrasound Obstet Gynecol. 2003;22 (06):652–655. Doi: 10.1002/uog.922
51 Simonazzi G, Curti A, Cattani L, Rizzo N, Pilu G. Outcome of severe placental insufficiency with abnormal umbilical artery Doppler prior to fetal viability. BJOG. 2013;120(06):754–757. Doi: 10.1111/1471-0528.12133
52 Piazze J, Dillon KC, Cerekja A. Betamethasone effects on umbilical arteries and ductus venosus Doppler velocity waveforms in growth-restricted fetuses. J Matern Fetal Neonatal Med. 2012; 25(07):1179–1182. Doi: 10.3109/14767058.2011.624216
53 Nordenvall M, Ullberg U, Laurin J, Lingman G, Sandstedt B, Ulmsten U. Placental morphology in relation to umbilical artery blood velocity waveforms. Eur J Obstet Gynecol Reprod Biol. 1991;40(03):179–190. Doi: 10.1016/0028-2243(91)90115-2
54 Su EJ, Ernst L, Abdallah N, Chatterton R, Xin H, Monsivais D, et al. Estrogen receptor-β and fetoplacental endothelial prostanoid biosynthesis: a link to clinically demonstrated fetal growth restriction. J Clin Endocrinol Metab. 2011;96(10):E1558–E1567. Doi: 10.1210/jc.2011-1084
55 Su EJ, Lin ZH, Zeine R, Yin PReierstad Innes JE, et al. Estrogen receptor-beta mediates cyclooxygenase-2 expression and vascular prostanoid levels in human placental villous endothelial cells. Am J Obstet Gynecol. 2009;200(04):427.e1–427.e8. Doi: 10.1016/j.ajog.2009.01.025

56 Gupta S, Chauhan M, Sen J, Nanda S. Effect of transdermal nitroglycerine on Doppler velocity waveforms of the uterine, umbilical and fetal middle cerebral arteries in patients with chronic placental insufficiency: a prospective RCT. J Clin Diagn Res. 2017;11(07): QC13–QC17. Doi: 10.7860/JCDR/2017/21438.10282

57 Mishra M, Sawhney R, Kumar A, Bapna KR, Kohli V, Wasir H, et al. Cardiac surgery during pregnancy: continuous fetal monitoring using umbilical artery Doppler flow velocity indices. Ann Card Anaesth. 2014;17(01):46–51. Doi: 10.4103/0971-9784.124141

58 Yildirim G, Turhan E, Aslan H, Gungorduk K, Guven H, Idem O, et al. Perinatal and neonatal outcomes of growth restricted fetuses with positive end diastolic and absent or reversed umbilical artery doppler waveforms. Saudi Med J. 2008;29 (03):403–408

59 Karsdorp VH, van Vugt JM, van Geijn HP, Kostene PJ, Arduini D, Montenegro N, et al. Clinical significance of absent or reversed end diastolic velocity waveforms in umbilical artery. Lancet. 1994;344 (8938):1664–1668. Doi: 10.1016/s0140-6736(94)90457-x

60 Al Hamayel NA, Baghlaf H, Blakemore K, Crino JP, Burd I. Significance of abnormal umbilical artery Doppler studies in normally grown fetuses. Matern Health Neonatol Perinatol. 2020;6:1. Doi: 10.1186/s40748-020-0115-7

61 Tolu LB, Ararso R, Abdulkadir A, Feyissa GT, Worku Y. Perinatal outcome of growth restricted fetuses with abnormal umbilical artery Doppler waveforms compared to growth restricted fetuses with normal umbilical artery Doppler waveforms at a tertiary referral hospital in urban Ethiopia. PLoS One. 2020;15 (06):e0234810. Doi: 10.1371/journal.pone.0234810

62 Byun YJ, Kim HS, Yang JI, Kim JH, Kim HY, Chang SJ. Umbilical artery Doppler study as a predictive marker of perinatal outcome in preterm small for gestational age infants. Yonsei Med J. 2009; 50(01):39–44. Doi: 10.3349/ymj.2009.50.1.39

63 Valcamonico A, Danti L, Frusca T, Soregaroli M, Zucca S, Abrami F, et al. Absent end-diastolic velocity in umbilical artery: risk of neonatal morbidity and brain damage. Am J Obstet Gynecol. 1994;170(03):796–801. Doi: 10.1016/s0002-9378(94)70285-3

64 Valcamonico A, Accorsi P, Battaglia S, Soregaroli M, Beretta D, Frusca T. Absent or reverse end-diastolic flow in the umbilical artery: intellectual development at school age. Eur J Obstet Gynecol Reprod Biol. 2004;114(01):23–28. Doi: 10.1016/j.ejogrb.2003.09.033

65 Brütsch S, Burkhardt T, Kurmanavicius J, Bassler D, Zimmermann R, Natalucci G, et al. Neurodevelopmental outcome in very low birthweight infants with pathological umbilical artery flow. Arch Dis Child Fetal Neonatal Ed. 2016;101(03):F212–F216. Doi: 10.1136/archdischild-2014-307820

66 Corry E, Mone F, Segurado R, Downey P, McParland P, McAuliffe FM, et al. Placental disease and abnormal umbilical artery Doppler waveforms in trisomy 21 pregnancy: A case-control study. Placenta. 2016;47:24–28. Doi: 10.1016/j.placenta.2016.09.001

67 Melamed N, Baschat A, Yinon Y, Athanasiadis A, Mecacci F, Figueras F, et al. FIGO (international Federation of Gynecology and obstetrics) initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction. Int J Gynaecol Obstet. 2021;152(Suppl 1):3–57. Doi: 10.1002/ijgo.13522

68 Tejada-Martínez AE, Borberg CJ, Venugopal R, Carballo C, Moreno WA, Quintero RA. Computational fluid dynamic analysis of flow velocity waveform notching in umbilical arteries. Am J Physiol Regul Integr Comp Physiol. 2011;300(01):R76–R84. Doi: 10.1152/ajpregu.00864.2009

69 Struijk PC, Fernando KL, Mathews VJ, Steegers EAP, Wladimiroff JW, Clark EB, et al. Application of the magnitude-squared coherence function between uterine and umbilical flow velocity waveforms for predicting placental dysfunction: a preliminary study. Ultrasound Med Biol. 2007;33(07):1057–1063. Doi: 10.1016/j.ultrasmedbio.2007.01.012

70 Dias T, Abeykoon S, Mendis P, Gunawardena C, Pragasan G, Padeniya T, et al. Fetal Doppler reference values in women with a normal body mass index. Ceylon Med J. 2019;64(02): 59–65. Doi: 10.4038/cmj.v64i2.8888

71 Ciobanu A, Wright A, Syngelaki A, Wright D, Akolekar R, Nicolaides KH. Fetal Medicine Foundation reference ranges for umbilical artery and middle cerebral artery pulsatility index and cerebroplacental ratio. Ultrasound Obstet Gynecol. 2019;53(04): 465–472. Doi: 10.1002/uog.20157

72 Drukker L, Staines-Urias E, Villar J, Barros FC, Carvalho M, Munim S, et al. International gestational age-specific centiles for umbilical artery Doppler indices: a longitudinal prospective cohort study of the INTERGROWTH-21st Project. Am J Obstet Gynecol. 2020;222(06):602.e1–602.e15. Doi: 10.1016/j.ajog.2020.01.012

73 Acharya G, Wilsgaard T, Berntsen GK, Maltau JM, Kiserud T. Reference ranges for serial measurements of umbilical artery Doppler indices in the second half of pregnancy. Am J Obstet Gynecol. 2005;192(03):937–944. Doi: 10.1016/j.ajog.2004.09.019

74 Ayoola OO, Bulus P, Loto OM, Idowu BM. Normogram of umbilical artery Doppler indices in singleton pregnancies in south-western Nigerian women. J Obstet Gynaecol Res. 2016;42(12): 1694–1698. Doi: 10.1111/jog.13114

75 Srikumar S, Debnath J, Ravikumar R, Bandhu HC, Maurya VK. Doppler indices of the umbilical and fetal middle cerebral artery at 18-40 weeks of normal gestation: A pilot study. Med J Armed Forces India. 2017;73(03):232–241. Doi: 10.1016/j.mjafi.2016.12.008

76 Baschat AA, Gembruch U. The cerebroplacental Doppler ratio revisited. Ultrasound Obstet Gynecol. 2003;21(02):124–127. Doi: 10.1002/uog.20

77 Contro E, Cataneo I, Morano D, Farina A. Reference charts for umbilical Doppler pulsatility index in fetuses with isolated two-vessel cord. Arch Gynecol Obstet. 2019;299(04):947–951. Doi: 10.1007/s00404-019-05086-z

78 Mulcahy C, McAuliffe FM, Breathnach F, Geary M, Daly S, Higgins J, et al. Umbilical and fetal middle cerebral artery Doppler reference ranges in a twin population followed longitudinally from 24 to 38 weeks' gestation. Ultrasound Obstet Gynecol. 2014;44(04):461–467. Doi: 10.1002/uog.13302

79 Casati D, Pellegrino M, Cortinovis I, Spada E, Lanna M, Faiola S, et al. Longitudinal Doppler references for monochorionic twins and comparison with singletons. PLoS One. 2019;14(12): e0226090. Doi: 10.1371/journal.pone.0226090

80 Haugen G, Bollerslev J, Henriksen T. Human umbilical and fetal cerebral blood flow velocity waveforms following maternal glucose loading: a cross-sectional observational study. Acta Obstet Gynecol Scand. 2016;95(06):683–689. Doi: 10.1111/aogs.12913

81 Mulders LG, Muijsers GJ, Jongsma HW, Nijhuis JG, Hein PR. The umbilical artery blood flow velocity waveform in relation to fetal breathing movements, fetal heart rate and fetal behavioural states in normal pregnancy at 37 to 39 weeks. Early Hum Dev. 1986;14(3-4):283–293. Doi: 10.1016/0378-3782(86)90191-x

82 Soneji S, Beltrán-Sánchez H. Association of maternal cigarette smoking and smoking cessation with preterm birth. JAMA Netw Open. 2019;2(04):e192514. Doi: 10.1001/jamanetworkopen.2019.2514

83 Tikkanen M, Nuutila M, Hiilesmaa V, Paavonen J, Ylikorkala O. Prepregnancy risk factors for placental abruption. Acta Obstet Gynecol Scand. 2006;85(01):40–44. Doi: 10.1080/00016340500324241

84 Reeves S, Bernstein I. Effects of maternal tobacco-smoke exposure on fetal growth and neonatal size. Expert Rev Obstet Gynecol. 2008;3(06):719–730. Doi: 10.1586/17474108.3.6.719

85 Stalzer A, Seybold D, Hossino D, Broce M, Calhoun B. Doppler screening and predictors of adverse outcomes in high risk pregnancies affected by tobacco. Reprod Toxicol. 2017; 67:10–14. Doi: 10.1016/j.reprotox.2016.11.006

86 Janeczek S, Karlman R, MacMillan W. Left versus right intra-abdominal umbilical arteries: comparison of their Doppler waveforms. J Ultrasound Med. 2012;31(05):679–683. Doi: 10.7863/jum.2012.31.5.67

87 Ruiz-Martinez S, Papageorghiou AT, Staines-Urias E, Villar J, Gonzalez de Agüero R, Oros D. Clinical impact of Doppler reference charts to manage fetal growth restriction: need for standardization. Ultrasound Obstet Gynecol. 2020;56(02): 166–172. Doi: 10.1002/uog.20380

88 ACOG Practice bulletin no. 134: fetal growth restriction. Obstet Gynecol. 2013;121(05):1122–1133. Doi: 10.1097/01.AOG.0000429658.85846.f9

89 Bolz N, Kalache KD, Proquitte H, Slowinski T, Hartung JP, Henrich W, et al. Value of Doppler sonography near term: can umbilical and uterine artery indices in low-risk pregnancies predict perinatal outcome? J Perinat Med. 2013;41(02):165–170. Doi: 10.1515/jpm-2012-0042

90 Doppler French Study Group. A randomised controlled trial of Doppler ultrasound velocimetry of the umbilical artery in low risk pregnancies. Br J Obstet Gynaecol. 1997;104(04):419–424. Doi: 10.1111/j.1471-0528.1997.tb11492.x

91 Goffinet F, Paris-Llado J, Nisand I, Bréart G. Umbilical artery Doppler velocimetry in unselected and low risk pregnancies: a review of randomised controlled trials. Br J Obstet Gynaecol. 1997; 104(04):425–430. Doi: 10.1111/j.1471-0528.1997.tb11493.x

92 Nkosi S, Makin J, Hlongwane T, Pattinson RC. Screening and managing a low-risk pregnant population using continuous-wave Doppler ultrasound in a low-income population: A cohort analytical study. S Afr Med J. 2019;109(05):347–352. Doi: 10.7196/SAMJ.2019.v109i5.13611

93 Hugo EJ, Odendaal HJ, Grove D. Evaluation of the use of umbilical artery Doppler flow studies and outcome of pregnancies at a secondary hospital. J Matern Fetal Neonatal Med. 2007;20 (03):233–239. Doi: 10.1080/14767050601134926

94 Gudmundsson S, Flo K, Ghosh G, Wilsgaard T, Acharya G. Placental pulsatility index: a new, more sensitive parameter for predicting adverse outcome in pregnancies suspected of fetal growth restriction. Acta Obstet Gynecol Scand. 2017;96(02): 216–222. Doi: 10.1111/aogs.13060

95 FitzGerald DE, Drumm JE. Non-invasive measurement of human fetal circulation using ultrasound: a new method. BMJ. 1977;2 (6100):1450–1451. Doi: 10.1136/bmj.2.6100.1450

96 Morris RK, Malin G, Robson SC, Kleijnen J, Zamora J, Khan KS. Fetal umbilical artery Doppler to predict compromise of fetal/neonatal wellbeing in a high-risk population: systematic review and bivariate meta-analysis. Ultrasound Obstet Gynecol. 2011;37(02):135–142. Doi: 10.1002/uog.7767

97 Vayssière C, Benoist G, Blondel B, Deruelle P, Favre R, Gallot D, et al; French College of Gynaecologists and Obstetricians. Twin pregnancies: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF). Eur J Obstet Gynecol Reprod Biol. 2011;156(01):12–17. Doi: 10.1016/j.ejogrb.2010.12.045

98 Graves CR. Antepartum fetal surveillance and timing of delivery in the pregnancy complicated by diabetes mellitus. Clin Obstet Gynecol. 2007;50(04):1007–1013. Doi: 10.1097/GRF.0b013e31815a63cc

99 de Rochambeau B, Jabbour N, Mellier G. [Umbilical Doppler velocimetry in prolonged pregnancies]. Rev Fr Gynécol Obstet. 1992;87(05):289–294French.

100 Adekanmi AJ, Roberts A, Akinmoladun JA, Adeyinka AO. Uterine and umbilical artery doppler in women with pre-eclampsia and their pregnancy outcomes. Niger Postgrad Med J. 2019;26(02): 106–112. Doi: 10.4103/npmj.npmj_161_18

101 Velauthar L, Plana MN, Kalidindi M, Zammora J, Thilaganathan B, Illanes SE, et al. First-trimester uterine artery Doppler and adverse pregnancy outcome: a meta-analysis involving 55,974 women. Ultrasound Obstet Gynecol. 2014;43(05):500–507. Doi: 10.1002/uog.13275

102 Shen G, Huang Y, Jiang L, Gu J, Wang Y, Hu B. Ultrasound prediction of abnormal infant development in hypertensive pregnant women in the second and third trimester. Sci Rep. 2017;7:40429. Doi: 10.1038/srep40429

103 Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: population based study. BMJ. 2013;346:f108. Doi: 10.1136/bmj.f108

104 Pilliod RA, Cheng YW, Snowden JM, Doss AE, Caughey AB. The risk of intrauterine fetal death in the small-for-gestational-age fetus. Am J Obstet Gynecol. 2012;207(04):318.e1–318.e6. Doi: 10.1016/j.ajog.2012.06.039

105 Figueras F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis, and management. Am J Obstet Gynecol. 2011;204(04):288–300. Doi: 10.1016/j.ajog.2010.08.055

106 Bardien N, Whitehead CL, Tong S, Ugoni A, McDonald S, Walker SP. Placental insufficiency in fetuses that slow in growth but are born appropriate for gestational age: a prospective longitudinal study. PLoS One. 2016;11(01):e0142788. Doi: 10.1371/journal.pone.0142788

107 Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker N, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol. 2016;48 (03):333–339. Doi: 10.1002/uog.15884

108 Figueras F, Caradeux J, Crispi F, Eixarch E, Peguero A, Gratacos E. Diagnosis and surveillance of late-onset fetal growth restriction. Am J Obstet Gynecol. 2018;218(2S, 2s):S790–, 802.e1. Doi: 10.1016/j.ajog.2017.12.003

109 Mifsud W, Sebire NJ. Placental pathology in early-onset and late-onset fetal growth restriction. Fetal Diagn Ther. 2014;36(02): 117–128. Doi: 10.1159/000359969

110 Yinon Y, Kingdom JC, Odutayo A, Moineddin R, Drewlo S, Lai V, et al. Vascular dysfunction in women with a history of pre-eclampsia and intrauterine growth restriction: insights into future vascular risk. Circulation. 2010;122(18):1846–1853. Doi: 10.1161/CIRCULATIONAHA.110.948455

111 Turan OM, Turan S, Gungor S, Berg C, Moyano D, Gembruch U, et al. Progression of Doppler abnormalities in intrauterine growth restriction. Ultrasound Obstet Gynecol. 2008;32(02): 160–167. Doi: 10.1002/uog.5386

112 Baschat AA, Gembruch U, Harman CR. The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsens. Ultrasound Obstet Gynecol. 2001;18(06): 571–577. Doi: 10.1046/j.0960-7692.2001.00591.x

113 Hecher K, Bilardo CM, Stigter RH, Ville Y, Hackelöer BJ, Kok HJ, et al. Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. Ultrasound Obstet Gynecol. 2001;18(06): 564–570. Doi: 10.1046/j.0960-7692.2001.00590.x

114 Ferrazzi E, Bozzo M, Rigano S, Bellotti M, Morabito A, Pardi G, et al. Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely growth-restricted fetus. Ultrasound Obstet Gynecol. 2002;19 (02):140–146. Doi: 10.1046/j.0960-7692.2002.00627.x

115 Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. BMJ. 2005;331(7525):1113–1117. Doi: 10.1136/bmj.38629.587639.7C

116 Geerts L, Van der Merwe E, Theron A, Rademan K. Placental insufficiency among high-risk pregnancies with a normal umbilical artery resistance index after 32weeks. Int J Gynaecol Obstet. 2016;135(01):38–42. Doi: 10.1016/j.ijgo.2016.03.038

117 Townsend R, Khalil A. Twin pregnancy complicated by selective growth restriction. Curr Opin Obstet Gynecol. 2016;28(06): 485–491. Doi: 10.1097/GCO.0000000000000326

118 Gratacós E, Lewi L, Muñoz B, Acosta-Rojas R, Hernandez-Andrade E, Martinez JM, et al. A classification system for selective intrauterine growth restriction in monochorionic pregnancies according to umbilical artery Doppler flow in the smaller twin.

Ultrasound Obstet Gynecol. 2007;30(01):28–34. Doi: 10.1002/uog.4046

119 Maulik D, Mundy D, Heitmann E, Maulik D. Evidence-based approach to umbilical artery Doppler fetal surveillance in high-risk pregnancies: an update. Clin Obstet Gynecol. 2010; 53(04):869–878. Doi: 10.1097/GRF.0b013e3181fbb5f5

120 Morin L, Lim KDIAGNOSTIC IMAGING COMMITTEE SPECIAL CONTRIBUTOR GENETICS COMMITTEE MATERNAL FETAL MEDICINE COMMITTEE. Ultrasound in twin pregnancies. J Obstet Gynaecol Can. 2011;33(06):643–656. Doi: 10.1016/S1701-2163(16)34916-7

121 Niromanesh S, Shirazi M, Eftekhariyazdi M, Mortazavi F. Comparison of umbilical artery Doppler and non-stress test in assessment of fetal well-being in gestational diabetes mellitus: A prospective cohort study. Electron Physician. 2017;9(12): 6087–6093. Doi: 10.19082/6087

122 Malhotra N, Chanana C, Kumar S, Roy K, Sharma JB. Comparison of perinatal outcome of growth-restricted fetuses with normal and abnormal umbilical artery Doppler waveforms. Indian J Med Sci. 2006;60(08):311–317. Doi: 10.4103/0019-5359.26607

123 Lees C. Perinatal and 2 year neurodevelopmental outcome in late preterm fetal compromise: the TRUFFLE 2 Randomised Trial [Study protocol] [Internet]. 2020 [cited 2021 Jan 12]. Available from: https://www.fundingawards.nihr.ac.uk/award/NIHR127976

124 D'Antonio F, Patel D, Chandrasekharan N, Thilaganathan B, Bhide A. Role of cerebroplacental ratio for fetal assessment in prolonged pregnancy. Ultrasound Obstet Gynecol. 2013;42(02): 196–200. Doi: 10.1002/uog.12357

Risks and Benefits of Breastfeeding in COVID-19: Integrative Literature Review

Riscos e benefícios da amamentação na COVID-19: Revisão integrativa da literatura

Ana Clara Alves de Carvalho[1] Gabriel Campos Carvalhaes Reis[1]
João Guilherme de Moura Oliveira[1] Raquel Ferreira Borges[1]

[1] Departamento de Medicina, Pontifícia Universidade Católica de Minas Gerais, Contagem, MG, Brazil

Rev Bras Ginecol Obstet 2022;44(5):532–539.

Address for correspondence João Guilherme de Moura Oliveira, Aluno de Graduação em Medicina, Rua Rio Comprido, Bairro Cinco, 32010-025, Contagem, MG, Brazil (e-mail: jgmoura.oliveira@gmail.com).

Abstract

Objective The present article seeks to consolidate existing knowledge on breastfeeding during the SARS-CoV-2 pandemic.

Data source Articles from 2020 and 2021 collected from the PubMed, CAPES, Virtual Health Library, Google Scholar, SciELO, and UpToDate databases were analyzed. Books and government documents published in the last decade (2010–2020) were also consulted.

Study Selection Sixteen works were used in the present study. The date of publication and discussion of SARS-CoV-2 transmission through breast milk were the inclusion criteria. Thus, articles containing repeated information or with no relevance to add to the production were excluded. Data collection comprised critical reading and synthesis of the main information obtained on the subject, which were performed for the preparation of the present study. The research took place in the period from March 27 to April 2, 2021.

Synthesis of the data Breast milk has diverse benefits for both the nursing mother and the infant. The presence of viral RNA by real-time polymerase chain reaction (RT-PCR) in milk from disease-positive mothers has been detected in a few cases, and infant infections in these conditions suggest oral transmission of maternal or third-party origin. The virulence of the novel coronavirus in human milk is not confirmed, while significant amounts of exclusive antibodies are.

Conclusion Lactation in the context of COVID-19 has shown greater benefits than risks of vertical transmission. Therefore, it should be encouraged when possible.

Keywords
- COVID-19
- SARS-CoV-2 infection
- breastfeeding
- vertical infectious disease transmission
- immunology

received
June 30, 2021
accepted
September 20, 2021
published online
February 9, 2022

DOI https://doi.org/10.1055/s-0041-1741031.
ISSN 0100-7203.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resumo

Objetivo O presente artigo procura consolidar os conhecimentos existentes sobre o aleitamento materno durante a pandemia do SARS-CoV-2.

Fonte de dados Foram analisados os artigos de 2020 e 2021 recolhidos dos bancos de dados PubMed, CAPES, Biblioteca Virtual de Saúde, Google Scholar, SciELO e bases de dados UpToDate. Livros e documentos governamentais publicados na última década (2010–2020) também foram consultados.

Seleção de estudos Dezesseis obras foram utilizadas no presente estudo. A data de publicação e discussão sobre a transmissão do SARS-CoV-2 através do leite materno foram os critérios de inclusão. Assim, foram excluídos os artigos que continham informações repetidas ou sem relevância para a produção.

Coleta de dados Para a preparação do presente estudo, foram realizadas leituras críticas e síntese das principais informações obtidas sobre o tema. A pesquisa ocorreu no período de 27 de março a 2 de abril de 2021.

Síntese dos dados O leite materno tem diversos benefícios tanto para a mãe quanto para o lactente. A presença de RNA viral por reação em cadeia de polimerase em tempo real (RT-PCR, na sigla em inglês) no leite de mães positivas foi detectada em alguns casos, e as infecções infantis nestas condições sugerem transmissão oral de origem materna ou de terceiros. A virulência do novo coronavírus no leite humano não está confirmada, enquanto quantidades significativas de anticorpos exclusivos sim.

Conclusão A lactação no contexto da COVID-19 mostrou maiores benefícios do que os riscos de transmissão vertical. Por conseguinte, deve ser encorajada sempre que possível.

Palavras-chave

- COVID-19
- infecção por SARS-CoV-2
- aleitamento materno
- transmissão vertical de doenças infecciosas
- imunologia

Introduction

In the epilogue of December 2019 and in the advent of the year 2020, the world witnessed the rise of severe acute respiratory syndrome (SARS) caused by a new variant of coronavirus – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – which was declared in January 2020 by the World Health Organization (WHO) as an epidemiological pandemic situation. This etiologic agent was responsible for naming a new disease classification known as Coronavirus disease 2019 (COVID-19), which is considered a public health emergency of international concern (EPII). Moreover, this health condition has become one of the main causes of increased mortality rates, as well as of increased efforts by the most diverse centers of medical practice and research in attempts to understand the disease and its therapeutic approach.[1]

In general terms, the clinical manifestations of COVID-19 are variable, a reality that demands great attention from healthcare teams. The most common symptoms of the disease are typical of a flu-like syndrome, and involve cough, fever, dyspnea, myalgia, and, in some cases, abdominal pain and diarrhea. So far, it has been observed that the disease most frequently affects adults and the elderly, although it is already known that pregnant women, mothers, newborns, and children can also develop it in its aggravating form. However, it is known that the expressivity of these same aspects can be mild and even asymptomatic, although many cases can evolve to severe acute respiratory syndrome, septic shock, and multiple organ failure.[1,2] In this perspective, the clinical evolution of the disease can be associated to the degree of inflammatory response in the organism of the infected individual, since the higher the degree, the greater the tissue damage and, consequently, the functional compromise of the affected regions.[3]

Regarding the transmissibility of the virus, it is known that it enters the body mainly through inhalation of infected air. Moreover, it can enter the body due to contact of the individual with contaminated surfaces (food packaging and other solid objects).[4] In the midst of a scenario of an international health crisis, the debate involving breastfeeding during the pandemic period has arisen in the scientific community. Several publications have already been published in scientific platforms, whose contents investigate not only the possibilities of vertical transmission of the virus through the placenta and breast milk, but also antibody production and its transmission through breastfeeding. Under this bias, the attention in relation to pregnant and postpartum women has increased, since they can also develop COVID-19, especially women in the last trimester of pregnancy.[5]

Breastfeeding is described in the literature as a practice that brings benefits to both mother and child. Being exclusive until the first 6 months of life, breastfeeding is able to fully nourish the newborn, promote hydration, transmit antibodies, and develop bonds of affection between the infant and the mother.[6] However, for the purposes of this action to actually be achieved, direct contact between mother and child is essential. In this sense, this reality has brought doubts to the scientific community regarding the transmission of SARS-CoV-2 from

the nursing mother to the child, since there is not only a transfer of fluids (breast milk), but also an exchange of aerosols and droplets through the air. Therefore, in a scenario where the etiologic agent of COVID-19 is transmitted mainly by this route, the indication or not of breastfeeding is conflicting.[7]

In view of the above, the present work aims to perform a literature review regarding the practice of breastfeeding in the period of the COVID-19 pandemic. This is justified by the possibility of updating and consolidating the knowledge in question.

Methods

This is an integrative literature review on the relationship between maternal breastfeeding and the transmission of the new coronavirus through this practice. The present study was conducted in Belo Horizonte, state of Minas Gerais, Brazil, in April and March 2021. The guiding question was: "how can SARS-CoV-2 infection affect the practice of breastfeeding, considering its risks and benefits?" Thus, the research was outlined in four stages. In the first, a bibliographic search was conducted in the main databases and through the reading of books, protocols, and guides as complementary material that contemplated the theme for the construction of the study. In the second stage, the articles were selected, which guided the third phase, which was consolidated by the elaboration of a critical review of each material, followed by the writing of the present paper – the fourth stage.

First, the search for articles and scientific research was conducted in the following databases: PubMed, CAPES, Virtual Health Library (VHL), Google Scholar, SciELO, and UpToDate. The keywords *breastmilk*, *breastfeeding*, and COVID-*19* were used in conjunction with the Health Sciences Descriptor (DeCS) *breastfeeding*. Along with these searches, a search was performed in the SciELO database with the keywords COVID-*19* AND *breastfeeding*. In addition, books and other documents from the Ministry of Health were read, all from the last decade (2010–2020).

The selection of studies, in turn, was guided by articles that addressed the evidence on the transmission of SARS-CoV-2 through breast milk and the transmissibility of the virus in question, in addition to prioritizing articles published between the second half of 2020 and the beginning of 2021. In the background, articles were selected from reading their titles and abstracts. Finally, it is worth mentioning that articles containing repeated information or without relevance to add to the production were excluded. A total of 16 works were used.

Therefore, from the selected scientific articles and the complementary material, the third and fourth steps were performed: a critical reading and the synthesis of the main information obtained about the theme for the preparation of the present study. The research took place between March 27 and April 2, 2021, while the discussion of the theme and the preparation of the article took place between April and May, 2021.

Results

A total of 31 studies were selected from the reading of titles and abstracts. Then, a second choice was performed from the complete reading of the articles, with 12 studies being selected for the production of the work in question. From the total of selected articles, there are 8 review articles; 1 standard operating procedure; 1 comment; 1 prospective study; 1 protocol; 1 epidemiological surveillance guide; 1 food guide, and 1 letter . Besides these, one book on epidemiological approach and materials from the Ministry of Health published in the last decade were complementary to the preparation of the present work. A total of 16 books were used in the preparation of the research and are shown in ►**Table 1**.

Discussion

The Benefits of Breastfeeding

There is a consensus in the literature that breastfeeding designates benefits for both the nursing mother and the infant. These advantages can be attested to by increased quality of life and reduced maternal and infant morbidity and mortality.

In this context, there is evidence that reinforces the significant decrease in the incidence of diseases, linked, above all, to poor prognoses in the neonatal, postnatal, and childhood phases. In line with this fact, it is observed that lactation is responsible for increasing the intellectual coefficient and preventing dental bone disorders, allergies, and chronic conditions in adolescence and adulthood.[8,9]

Another point widely discussed in all the studies analyzed is the immunological, anti-inflammatory, and anti-infective properties of natural food from the mother. Thus,

breastfeeding in the context of COVID-19 is an important resource to control the increase in virulence,[9] which is the ability of the etiologic agent to cause infection.[10] Regarding immunological benefits, breast milk has antimicrobial properties. Moreover, it is primarily responsible for the 48% decrease in necrotizing enterocolitis in infants, highlighted in a cohort study.[9]

The antimicrobial, anti-inflammatory, and immune system modulating actions can be conferred by mucin, lactalbumin, lactadherin, lactoferrin, amino acids, casein, and tryptophan, present in breast milk. These substances promote activation and proliferation of phagocytic cells, such as macrophages, dendritic cells, and apoptotic cells. In addition, they mediate the development of cells that secrete cytokines and regulatory proteins of the cell cycle and cell division that are important in the response of the inflammatory process.[9]

The proliferation and activation of B and T lymphocytes are also ensured by breast milk through the release of immunomodulatory peptides. Casein, lactalbumin, and tryptophan are notable nutrients in this role. The latter is also related to the prevention of chronic conditions involving the gastrointestinal tract. Furthermore, these components act on the child's development by modulating the secretion of metabolic precursors.[9]

The protection of the intestinal mucosa by barrier formation, the proliferation and maturation of tissue cells, and the homeostasis of the microbiota are modulated by the components of breast milk. In this sense, mucin, casein,

Table 1 Studies used in the construction of the present article

Title	Authors	Date of publication	Study	Brief description
The Effect of Coronavirus Disease 2019 on Cardiovascular Disease	Askin et al.[1]	2020	Review article	The article addresses the pathophysiology of the disease and delves into the risk of its evolution within vascular comorbidities. Finally, it was used for the introduction of the theme and epidemiological contextualization.
Protocolo de Manejo Clínico do Coronavírus (COVID-19) na Atenção Primária à Saúde	Ministério da Saúde[2]	2020	Protocol	The protocol addresses the acute condition of COVID-19 within the full clinical spectrum, and provides guidance for therapy.
Severe COVID-19: understanding the role of immunity, endothelium, and coagulation in clinical practice	Brandão et al.[3]	2020	Review article	The article presents an association between COVID-19 and the endothelial involvement that this health condition causes in this tissue. In addition, it illustrates the immunophysiology of the disease.
Alimentos, Sars CoV-2 e Covid-19: contato possível, transmissão improvável	Franco et al.[4]	2020	Review article	The article discusses the possibility of SARS-CoV-2 transmission through food, and was used to contextualize this aspect.
Guia de Vigilância Epidemiológica: Emergência de saúde pública de importância nacional pela doença pelo coronavírus 2019	Ministério da Saúde[5]	2021	Epidemiological surveillance guide	The document addresses the epidemiology of COVID-19 by specific age groups, and was used to contextualize the risk scenario for pregnant women from a prevalence and death perspective.
Guia Alimentar para crianças brasileiras menores de 2 anos	Ministério da Saúde[6]	2019	Food guide	The document presents a dietary guideline for Brazilian children <2 years old and objectively addresses breastfeeding, as well as its benefits and an explanation of how to proceed.
[BREASTFEEDING x COVID-19: Elaboration of a SOP for the stages of extraction and storage of breast Milk]	Fernandes et al.[7]	2020	Standard operating procedure	The standard operating procedure guides how breastfeeding should be performed in times of COVID-19. Care at the time of breast milk extraction is the main issue addressed.
Guidance on breastfeeding during the Covid-19 pandemic	Calil et al.[8]	2020	Review article	The article addresses the importance of breastfeeding, the existing data regarding transmission, the guidelines of the public health agencies, and possible scenarios in the health condition of mother and child to guide the practice under discussion.
Breastfeeding importance and its therapeutic potential against SARS-CoV-2	Vasques et al.[9]	2021	Review article	The article presents scientific data regarding the benefits of breastfeeding, especially considering the immunological resources in the context of COVID 19.
Epidemiologia	Gordis L[10]	2017	Book	The book was used to support epidemiological concepts in the context of disease transmission. Chapter 2 was used.
Transmission of SARS-CoV-2 through breast milk and breastfeeding: a living systematic review	Centeno-Tablante et al.[11]	2021	Review article	The paper is a literature review of evidence of SARS-CoV-2 in breast milk. The authors address several studies that present statistical data and health

(*Continued*)

Table 1 (*Continued*)

Title	Authors	Date of publication	Study	Brief description
				conditions of mothers and children on COVID-19 and breastfeeding.
Susceptibility to COVID-19 in pregnancy, labor, and postpartum period: immune system, vertical transmission, and breastfeeding	Vale et al.[12]	2021	Review article	The article addresses questions about the pathophysiology of COVID-19, especially in pregnant and postpartum women. They discuss a little about vertical transmission, and put the focus of research on the guidelines for mothers and children in the postpartum period.
Covid-19 and breastfeeding: what's the risk?	Hand et al.[13]	2020	Comment	The paper affirms the numerous benefits that breastfeeding promotes in the health of mother and child. In addition, statistical data on the presence and transmission of SARS-CoV-2 in breast milk is also emphasized.
Breastfeeding during the COVID 19 pandemic – a literature review for clinical practice	Lubbe et al.[14]	2020	Review article	The study, with a clinical practice oriented approach, addresses the possible scenarios regarding mother and child conditions in the context of COVID-19. It also highlights data on the transmission of SARS-CoV-2 through breast milk.
Characterization of SARS-CoV-2 RNA, antibodies, and neutralizing capacity in milk produced by women with COVID-19	Pace et al.[15]	2021	Prospective study	The article presents a study conducted in mothers who were infected with SARS-CoV-2, discussing the presence of virus RNA, specific antibodies, and neutralizing ability against the novel coronavirus in the breast milk samples tested.
Antibodies in the breast milk of a maternal woman with COVID-19	Dong et al.[16]	2020	Letter	The paper presents a case report that takes into consideration the clinical findings in puerperae and neonates who tested positive for COVID-19. The focus of the discussion was on breastfeeding.

lactoferrin, amino acids, and tryptophan are mainly responsible for this effector mechanism. Therefore, it is observed that these nutrients create a favorable environment for the growth and development of the beneficial intestinal microbiota, which prevents infections and inflammation by reducing inflammatory cytokines. In addition, they regulate the motility of the gastrointestinal tract.[9]

Lactadherin and lactoferrin also play an important role in antiparasitic actions and in the neutralization of antigens, preventing their colonization. These substances promote the secretion of interleukin-10 and transforming growth factor beta (TGF-β) by regulatory T lymphocytes, which are cell adhesion molecules that inhibit binding to pathogens. The latter, in particular, has shown promising results regarding the neutralization of cell receptors, which may confer prevention of COVID-19.[9,10]

The presence and transfer of specific antibodies, including those compatible with SARS-CoV-2, are also important points to note in favoring immune competence. Immunoglobulins A (IgA) have been identified in the breast milk of infected mothers, which can be transferred to their children and remain reactive for a period of ~7 months. These are important antibodies for preventing severe cases of the disease, as well as respiratory and gastrointestinal disorders. Thus, the immunological benefits outweigh the risks of breastfeeding due to the presence of these peptides, considering also a possible pre-exposure to the virus by mother-child contact.[8,9,11,12]

Added to this, the increased expression of type I interferon in infants is related to the practice of breastfeeding. This importance is consolidated in the benefits for fighting COVID-19, analyzed in two studies in which poor prognosis of this new disease in patients in whom the deficiency of this protein is conditional.[13]

Notwithstanding the benefits to the infant, breastfeeding contributes to the health of the mother. According to some studies,[8] it is possible to observe that such an act causes a decrease in postpartum bleeding, aids in weight loss, and is a natural contraceptive method. Moreover, they highlight its preventive potential against breast and ovarian cancers, type II diabetes mellitus, and postpartum depression.

It is also important to highlight that maternal breastfeeding is related to the bond between mother and child. This condition causes an increase in the quality of life by

promoting the mental health of the puerperal woman, especially in the period of social

distance which is conferred.[9] Therefore, the separation of the two parties can be associated to adverse effects on mental health.[14]

The risks associated with early weaning, which is characterized by the interruption of lactation before the first 6 months of life, are discussed. Thus, lower incidence of infections are observed; hospitalization rates decreased by 5% per month of breastfeeding; and increased proliferation and differentiation rates of cells and biomolecules responsible for antigenic protection barriers were observed. Furthermore, it was shown that breastfeeding time is indirectly related to the proportion of morbidity and mortality and serious conditions. Thus, it is concluded that the absence of exclusive breastfeeding can serve as a "gateway" to infections, especially those caused by SARS-CoV-2, in addition to causing intestinal inflammation.[9]

To reaffirm the benefits, the analyzed studies assess that the use of formula as a substitute should be avoided. In this context, it is important to point out that errors associated with the handling of formulae cause absence in the necessary nutritional coverage. The presence of coagulant proteins that hinder digestion and cause a decrease in immunological power when compared to natural food should also be highlighted. From this perspective, the use of formula is also associated with the development of milk protein allergies.[8,13]

Finally, issues related to economics and availability should be considered in the discussion. Regarding breast milk, it is a clean, safe, complete, ready, and easily accessible food. Moreover, the high cost involved in the purchase of formula, as well as the possibility of its shortage in the current context, is not a reason for concern on the part of nursing mothers and their families. In this context, an analysis of the absence or interruption of breastfeeding designated the loss of 341.3 billion USD annually, when considering the maternal and infant morbidity and mortality that could be avoided, the cost of purchasing the substitute for human milk, and cognitive loss.[8–13]

In view of the above, it is concluded that breastfeeding brings significant benefits to the mother and the child. Thus, on May 27, 2020, the World Health Organization (WHO) updated the Interim Guidance on Clinical Management of COVID-19. In this decision, the institution reaffirmed that the benefits of this exclusive practice up to the first 6 months and complementary up to 2 years old outweigh the risks of maternal-to-child transmission of SARS-CoV-2 through human milk and poor outcomes of COVID-19 in infants and newborns.[11]

Evidence for Sars-Cov-2 in Milk, Vertical Transmission, Antibodies, and Viral Neutralization

In 37 studies, 19 out of 77 evaluated children were diagnosed with COVID-19 by viral RNA and antibody detection.[11] Of these, 10 were certainly fed with breast milk. In another study with 79 samples, several infants tested positive for RT-PCR SARS-CoV-2 were exclusively fed milk that was negative for the same test.[11] All had contact with COVID-19-positive third parties. Furthermore, out of the 77 mothers analyzed, 59 of them tested negative for RT-PCR. Another relevant point is that three positive milk samples were collected during the symptomatic phase of the mother. Another 43 negatives were collected during the symptomatic or convalescent phase. This indicates the possibility that SARS-CoV-2 is not transmitted through breast milk during the acute phase, when maternal viremia is expected to be higher, or during the convalescent phase. After 4 to 5 weeks of infection, no milk samples positive for SARS-CoV-2 were identified, indicating that the alveoli do not denote a viral reservoir.[11]

Importantly, the aforementioned research has limitations, since the milk extraction and analysis process were not detailed, which may suggest exogenous contamination. In addition, it is not possible to estimate the virulence of breast milk, since the viral culture technique was not tested; similarly, it is worth pointing out another study that showed the impossibility of culture from detected SARS-CoV-2. It is also important to investigate the possibility of this condition changing during lactation, since breast milk changes at different stages.[11]

From maternal collections, the main hypothesis of infection and transmission between mother and child is orally or through infected instruments, suggesting that lactation is safe when it comes to virulence. The mother should be aware of the existing data regarding vertical and breastfeeding transmissions, besides the fact that there are newborns who become infected, probably by the oral route, but have a good prognosis. Thus, personal protective measures and breast hygiene should be strictly followed. Moreover, the researchers do not state that there is a possibility of vertical transmission, but they also do not rule out this possibility.[12]

Influenza was used to exemplify how breastfeeding can contribute to protect the child if the mother is infected. In this context, the passage of IgA is possible through breastfeeding and can remain in the organism of the infant for up to 6 months. Another important point to be discussed is that breastfeeding provides increased type I interferon in infected individuals, which classifies such a response as innate antiviral to influenza, and not to respiratory syncytial virus or to human metapneumovirus.[13]

A study of 6 women after their first lactation, for example, revealed 100% negative results for detection of SARS-CoV-2 viral RNA by RT-PCR. In addition, another survey of 19 women also failed to demonstrate the presence of the virus in maternal samples. In contrast, SARS-CoV-2 secretory immunoglobulin A (SIgA) was found to be present in the milk of 80% of mothers previously infected with the SARS-CoV-2. These analyses have also shown that, despite obtaining negative results in PCR test (polymerase chain reaction) specific for SARS-CoV-2, there is presence of these immunoglobulins in breast milk.[13]

It was also possible to identify SARS PCR-positive maternal samples from three different women. However, the results obtained were negative on days 3, 14 and 14, respectively. Like the mothers, the children in the study tested positive for the viral gene, despite their good clinical condition. Furthermore, it cannot be said that the infection was

caused by the virus present in the milk. The authors of this study state that it is still difficult to confirm the possibility of mother-to-child perinatal transmission through breastfeeding, and that it may occur rarely.[13]

Not far from this scenario, it is necessary to point out that, in Italy, two newborns had positive pharyngeal swab results for SARS-CoV-2 days after birth, but one of them was asymptomatic and the other had mild symptoms. From the analysis of the breast milk with negative result for SARS-CoV-2, the hypothesis was that a third person infected the mother and the newborn at the same time after birth. Another episode is that of a 13-week-old Chinese newborn who – after presenting with weak signs of COVID-19–tested positive for the presence of viral RNA, as did his mother. Breast milk samples did not detect the presence of the virus, but rather of antibodies against COVID-19. It is noteworthy that both the mother and the newborn were exposed to a third person, who also tested positive for the disease, suggesting that the infection occurred through the oral route.[13]

Following up on the discussion about immunoglobulins, a prospective study – with a repeated measures longitudinal design – analyzed 18 women who had COVID-19 confirmed by laboratory diagnoses. With this, 37 human milk samples were collected and analyzed, and none of them had detectable SARS-CoV-2 RNA. In addition, 76% of the breast milk samples had IgA for SARS-CoV-2, and 80% of these samples contained class G immunoglobulins (IgG) for the same virus, with concentrations of the former being higher compared with the latter. Another important point is that 62% of the samples were able to neutralize the virulence of the etiologic agent in vitro, in contrast with samples collected prior to the pandemic, none of which showed such potential. Finally, 70 breast swabs were tested and only 8 showed evidence of SARS-CoV-2 RNA.[15]

The results of the analyzed studies suggest that breastfeeding does not transmit SARS-CoV-2 from the mother with mild to moderate COVID-19 symptoms to her child. However, transmission through the skin of the breast is possible. It is noteworthy that no SARS-CoV-2 RNA was found in the breast after washing, evidencing that individual protection measures during breastfeeding and milk extraction reduce the rate of contamination to the infant. Furthermore, the literature shows that the concentrations of immunoglobulins specific for SARS-CoV-2 are directly linked to the viral neutralization potential. Therefore, these results may serve as a rationale encouraging the continuation or initiation of breastfeeding in women with nonsevere COVID-19.[15]

To exemplify the data in question, it is suggested to approach a study built from the follow-up of a mother who tested positive for COVID-19 and her son, who has high rates of anti-SARS-CoV-2 class M immunoglobulin (IgM), which highlights the possibility of antibody transfer through breastfeeding. It was pointed out that the mother, still pregnant when she was admitted to the hospital, was symptomatic for COVID-19 and, therefore, underwent imaging and molecular testing in an attempt to make a diagnosis. X-rays were taken, which revealed irregular ground-glass opacities in the left lung, consistent with clinical management protocols for this acute condition. The positive smear for RT-PCR was obtained from the upper airway.[16]

The delivery of the approached pregnant woman occurred under normal conditions, with all properly paramented. The newborn presented with excellent birth conditions, and soon after delivery, a pharyngeal sample was collected for molecular testing, which tested negative. High levels of IgA anti-SARS-CoV-2 were found in the maternal milk, which denotes the protective nature of the milk. Immunoglobulin G was also detected in the newborn, but with a decline after one and a half months.[16]

In a similar vein, another study establishes the modulation of the imune in COVID-19. In this study, 100% of mothers who had recovered from COVID-19 had developed SIgA specific for SARS-CoV-2, and 99% of these proteins were reactive for the peak protein of the virus in another smaller assay. These immunoglobulins can remain in breast milk 7 months after birth and confer prevention of COVID as well as decreased symptoms in the 1st year of life if the infant becomes infected. In addition, they are optimal for recovering severe cases of the disease, are resistant to proteolysis, and may confer protection from respiratory and intestinal diseases. Thus, breastfeeding may protect against SARS-CoV-2 infection at a level that lessens the impact on the intestinal mucosa and its severity. Accordingly, research has shown that cessation of this exclusive practice can serve as a "gateway" to infections, particularly those caused by SARS-CoV-2, in addition to causing intestinal inflammation.[9]

Therefore, we conclude that there is no relevant evidence of the presence of SARS-CoV-2 in breast milk by means of the RT-PCR laboratory test and that, in the positive samples, it was not possible to perform viral culture to evaluate the infectious capacity, so that virulence is not observed. This fact suggests that the main means of transmission of SARS-CoV-2 from mother to infant is still oral, and that human milk is a means of passive immunization, since it presents antibodies against the pathogen. Therefore, it is evident that the benefits of breastfeeding outweigh the possible risks of contamination by SARS-CoV-2 and that this practice should be encouraged, but with a shared decision between mother, family members, and health professionals.

Conclusion

In the present study, the relationship between breastfeeding and the potential for transmission of SARS-CoV-2 during the current pandemic scenario was evaluated. Thus, it was observed that the benefits provided by lactation, both for the mother and the infant, outweigh the risks associated with this practice in COVID-19-positive women. In this context, little evidence of SARS-CoV-2 in human milk from COVID-19- positive mothers has been observed. Furthermore, infection in children and in neonates suggests oral transmission, since the virulence of natural food has not been confirmed. It is important to note that antibodies unique to SARS-CoV-2 were detected in the analyzed samples. Finally, it can be concluded that, based on evidence suggesting the impossibility of transmission of SARS-CoV-2 through breast

milk, breastfeeding should be encouraged. In this process, however, the autonomy, the desire, and the well-being of the mother and of the child must be assured during the decision-making process, which must be indispensably shared.

Conflict of Interests
The authors have no conflict of interests to declare.

Acknowledgments
The authors are grateful to Eduardo Ribeiro Hemeto and Wilma Dantas Pereira for their relevance in recognizing the research as an integrative literature review.

References

1 Askin L, Tanrıverdi O, Askin HS. The effect of Coronavirus Disease 2019 on cardiovascular disease. Arq Bras Cardiol. 2020;114(05): 817–822. Doi: 10.36660/abc.20200273
2 Ministério da Saúde. Secretaria de Atenção Primária à Saúde. Protocolo de manejo clínico do Coronavírus (COVID-19) na atenção primária à saúde: Versão 7 [Internet]. 2020 [cited 2021 Mar 28]. Available from: https://saude.rs.gov.br/upload/arquivos/202004/14140606-4-ms-protocolomanejo-aps-ver07abril.pdf
3 Brandão SCS, Godoi ETAM, Ramos JOX, de Melo LMMP, Sarinho ESC. Severe COVID-19: understanding the role of immunity, endothelium, and coagulation in clinical practice. J Vasc Bras. 2020;19:e20200131. Doi: 10.1590/1677-5449.200131
4 Franco BD, Landgraf M, Pinto UM. Alimentos, Sars-CoV-2 e Covid-19: contato possível, transmissão improvável. Estud Av. 2020;34 (100):189–202. Doi: 10.1590/s0103- 4014.2020.34100.012
5 Ministério da Saúde. Secretaria de Vigilância em Saúde. Guia de vigilância epidemiológica: emergência de saúde pública de importância nacional pela doença pelo coronavírus 2019: COVID-19 [Internet]. Brasília (DF): Ministério da Saúde; 2021 [cited 2021 Mar 29]. Available from: https://www.gov.br/saude/pt-br/coronavirus/publicacoes-tecnicas/guias-e-planos/guia-de-vigilancia-epidemiologica-covid-19
6 Ministério da Saúde. Secretaria de Atenção Primaria à Saúde. Departamento de Promoção da Saúde. Guia alimentar para crianças brasileiras menores de 2 anos [Internet]. Brasília (DF): Ministério da Saúde; 2019 [cited 2021 Apr 1]. Available from: http://189.28.128.100/dab/docs/portaldab/publicacoes/guia_da_crianca_2019.pdf
7 Fernandes E, Sousa J, Silva R, Serquiz A. [BREASTFEEDING x COVID-19: elaboration of a SOP for the stages of extraction and storage of breast milk]. Rev Extensão Soc.. 2020;12(01):30–45. Doi: 10.21680/2178-6054.2020v12n1ID20791
8 Calil VMLT, Krebs VLJ, Carvalho WB. Guidance on breastfeeding during the Covid-19 pandemic. Rev Assoc Med Bras (1992). 2020; 66(04):541–546. Doi: 10.1590/1806-9282.66.4.541
9 Vasques da Costa A, Purcell Goes C, Gama P. Breastfeeding importance and its therapeutic potential against SARS-CoV-2. Physiol Rep. 2021;9(03):e14744. Doi: 10.14814/phy2.14744
10 Gordis L. Epidemiologia. 5a ed. Rio de Janeiro: Thieme Revinter; 2017
11 Centeno-Tablante E, Medina-Rivera M, Finkelstein JL, Rayco-Solo P, Garcia-Casal MN, Rogers L, et al. Transmission of SARS-CoV-2 through breast milk and breastfeeding: a living systematic review. Ann N Y Acad Sci. 2021;1484(01):32–54. Doi: 10.1111/nyas.14477
12 Vale AJ, Fernandes AC, Guzen FP, Pinheiro FI, de Azevedo EP, Cobucci RN. Susceptibility to COVID-19 in pregnancy, labor, and postpartum period: immune system, vertical transmission, and breastfeeding. Front Glob Womens Health.. 2021;2:602572. Doi: 10.3389/fgwh.2021.602572
13 Hand IL, Noble L. Covid-19 and breastfeeding: what's the risk? J Perinatol. 2020;40(10):1459–1461. Doi: 10.1038/s41372-020-0738-6
14 Lubbe W, Botha E, Niela-Vilen H, Reimers P. Breastfeeding during the COVID-19 pandemic - a literature review for clinical practice. Int Breastfeed J. 2020;15(01):82. Doi: 10.1186/s13006- 020–00319–3
15 Pace RM, Williams JE, Järvinen KM, Belfort MB, Pace CDW, Lackey KA, et al. Characterization of SARS-CoV-2 RNA, antibodies, and neutralizing capacity in milk produced by women with COVID-19. mBio. 2021;12(01):e03192–e20. Doi: 10.1128/mBio
16 Dong Y, Chi X, Hai H, Sun L, et al. Antibodies in the breast milk of a maternal woman with COVID-19. Emerg Microbes Infect. 2020;9 (01):1467–1469. Doi: 10.1080/22221751.2020.1780952

Dietary Patterns during Pregnancy and Gestational Weight Gain: A Systematic Review

Padrões alimentares durante a gravidez e ganho de peso gestacional: Uma revisão sistemática

Larissa Bueno Ferreira[1] Cecília Viana Lobo[2] Aline Elizabeth da Silva Miranda[2]
Brenda da Cunha Carvalho[2] Luana Caroline dos Santos[2]

[1] Child and Adolescent Health, Federal University of Minas Gerais, Faculdade de Medicina/UFMG, Belo Horizonte, MG, Brazil
[2] Nutrition Departament, Federal University of Minas Gerais, Escola de Enfermagem/UFMG, Belo Horizonte, MG, Brazil

Address for correspondence Larissa Bueno Ferreira, PhD in Health Science, Av. Alfredo Balena, 190, 30130-100, Belo Horizonte, MG, Brazil (e-mail: labuenoferreira@gmail.com).

Rev Bras Ginecol Obstet 2022;44(5):540–547.

Abstract

The present systematic review (PROSPERO: CRD42020148630) hypothesizes the association of excessive weight gain during pregnancy with dietary patterns composed of ultraprocessed foods. Thus, the objective was to investigate the association between dietary patterns after analysis and weight gain during pregnancy. The search for articles was performed in nine databases. Two reviewers selected the articles in the databases and extracted from them the data used in the review. Two scales were used to evaluate the quality of the selected studies: New Castle-Ottawa Quality Assessment for cohort-based studies and Appraisal tool for Cross-Sectional Studies (AXIS) for cross-sectional-based studies. In total, 11 studies were identified with sample size variation ($n = 173–5,733$). Women presenting more adherence to healthy and traditional patterns (fruits, vegetables, salads, nuts, and dairy) recorded less excessive gestational weight gain (GWG). Higher intake of mixed patterns and western patterns rich in ultraprocessed foods were associated with a higher prevalence of excessive GWG (24.48–55.20%). Gestational dietary patterns a posteriori-derived that have presented ultraprocessed components rich in fat and sugars presented association with high GWG; healthy and traditional dietary patterns were related to better mother-child health conditions, such as adequate GWG.

Keywords
- gestational dietary patterns
- weight gain
- pregnancy
- pregnant women
- diets

Resumo

A presente revisão sistemática (PROSPERO: CRD42020148630) tem como hipótese que o ganho de peso excessivo durante a gravidez está associado aos padrões alimentares compostos por alimentos ultraprocessados. Desta forma, objetivou-se investigar a associação entre o padrão alimentar a posteriori e o ganho de peso durante a gestação. A busca de artigos foi realizada em nove bases de dados. Dois revisores selecionaram os artigos nestas bases e extraíram as informações utilizadas na revisão. Duas escalas foram utilizadas para avaliar a qualidade dos estudos selecionados: Escala de Avaliação da Qualidade de New Castle-Ottawa para estudos baseados em coortes e a

Palavras-chave
- padrões alimentares gestacionais
- ganho de peso
- gravidez
- gestantes
- dietas

received
April 5, 2021
accepted
January 11, 2022
published online
April 28, 2022

DOI https://doi.org/10.1055/s-0042-1744290.
ISSN 0100-7203.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Ferramenta de Avaliação de Estudos Transversais (escala AXIS) para estudos transversais. No total, foram identificados 11 trabalhos com variação do tamanho amostral ($n = 173–5.733$). As mulheres que apresentaram maior adesão aos padrões alimentares saudáveis e tradicionais (frutas, hortaliças e vegetais, nozes e laticínios) apresentaram menor ganho de peso gestacional (GPG). A maior ingestão de padrões alimentares mistos e ocidentais ricos em alimentos ultraprocessados foi associada a uma maior prevalência de GPG excessivo (24,48–55,20%). Os padrões alimentares gestacionais derivados a posteriori que apresentaram componentes ultraprocessados ricos em gordura e açúcares apresentaram associação com o maior GPG; os padrões alimentares saudáveis e tradicionais foram relacionados a melhores condições de saúde materno-infantil, como GPG adequado.

Introduction

Dietary patterns capture the interaction and cumulative effect of various foods and nutrients and can be easily interpreted by the population and, therefore, are particularly important in public health. It is important to note that people do not eat isolated nutrients. Instead, they eat meals that consist of a variety of foods with complex combinations of nutrients that are likely to be interactive or synergistic.[1]

Dietary patterns can be based on indices, assessed a priori using dietary indices to measure adherence to a predefined dietary pattern, or data-driven—assessed a posteriori, in which dietary patterns are statistically derived based on food intake reported by a population.[2]

The *a posteriori* method is considered more robust, making it possible to find the real dietary patterns of the study population, without making any assumption of protection or harmful effects on health.[3]

Maternal nutrition during pregnancy is an important determinant for both maternal and infant outcomes. The examination of dietary patterns emerged as a more holistic approach to capture the complex interactions between nutrients and food, congruent with the dietary guidelines adopted by health agencies and international references.[4]

Among the outcomes of the pregnancy period, gestational weight gain (GWG) is an important predictor of adverse maternal and child health outcomes. Inadequate or excessive weight gain can lead to undesirable health conditions for the mother or children,[5] with different prevalences of inadequate weight gain among populations. In the United States, only 32% of women who give birth to babies at term meet GWG recommendations of the Institute of Medicine (IOM).[6]

Inadequate GWG is related to preterm birth, low weight at birth, and difficulty to start breastfeeding.[4,5,7] Moreover, excessive weight gain is associated with unfavorable outcomes such as gestational diabetes, gestational high blood pressure, cesarean section surgery, and child obesity.[7–9] In addition, a systematic review and meta-analysis[10] found that excessive GWG was also associated with both cesarean surgery and fetal macrosomia. Besides, excessive GWG helps worsening the global obesity outbreak, a fact that can lead to a great economic burden in both developed and developing countries.[5]

Different factors can influence weight gain, with an emphasis on the eating patterns of the mother throughout pregnancy. Studies show an association between dietary patterns and GWG in western populations.[11,12]

Therefore, the most likely hypothesis is that excessive weight gain during pregnancy is associated with dietary patterns composed of ultraprocessed foods.

Thus, the aim of the present study is to investigate the association between a posteriori dietary patterns and analysis of weight gain during pregnancy. In addition, the present study aims to update the practices of health professionals to improve care during pregnancy. This makes room for a better understanding of the association between dietary patterns and better health outcomes.

Methods

A preliminary search was performed in the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE) through PubMed, PROSPERO, and Cochrane Library to assure article authenticity, and no reviews about the topic were found. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA) were adopted.[13]

Nine databases were searched, including the MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, Web of Science, Virtual Health Library (BVS, in the Portuguese acronym), Latin American and Caribbean Health Sciences Literature (LILACS), Spanish Bibliographic Index of Health Sciences (IBECS), Scientific Eletronic Library Online (SciELO), and SciFinder databases.

The following terms, words, and combinations of words were searched: (*dietary patterns* OR *dietary intake patterns* OR *patterns of food consumption* OR *food profile* AND *pregnancy* OR *pregnant women* OR *gravid* OR *gestation* AND *gestational weight gain* OR *weight gain* OR *postpartum period*), as well as its translations into Spanish and Portuguese. The PROSPERO registration was performed under number CRD42020148630.

The studies were screened by title and then by abstract by two reviewers. The full texts of all selected studies were critically reviewed based on the inclusion and exclusion criteria. The inclusion criteria considered for the present review study were: (a) original articles; (b) studies using a posteriori dietary patterns derived as exposure variable and GWG as outcome variable; and (c) published between 2009 and January 2021. The exclusion criteria were: (a) articles that examined only individual nutrients or foods; (b) articles that used a priori dietary pattern analysis; (c) articles that featured dietary patterns concerning periods other than pregnancy; (d) duplicate articles in the databases; (e) experimental and animal studies.

The quality of the selected full-text articles was rated by two reviewers independently using the New Castle-Ottawa Quality Assessment for cohort-based studies and the Appraisal tool for Cross-Sectional Studies (AXIS) for cross-sectional-related studies.

The New Castle-Ottawa Quality Assessment scale assesses eight study items divided into three domains: selection, comparability, and outcome. The scoring system ranges from 0 to n stars – $\geq$ 6 stars are considered good scores. The AXIS scale takes into account 20 items, which are divided into 5 domains: introduction, methods, results, discussion, and others. Scores in the AXIS scale range from 0 to 20 points, and scores – $\geq$ 15 points are considered good. Other authors adopted similar cutoff points.[14–16]

All articles used in the present review recorded good scores (►**Chart 1**); therefore, they were considered of good quality.

The data were entered into a Microsoft Excel, version 16 (Microsoft Corporation, Redmond, WA, USA) spreadsheet and exported to the IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA). Article inclusion and data extraction were made in an independent way; result comparisons were performed through the Kappa test. Disagreements were solved by consensus between reviewers—a third reviewer should be requested in case of disagreement between peers.

The following information were extracted: authors, publication year, city and country, study design, sample size, method to identify dietary patterns, dietary patterns identified, main results, and inadequate and/or excessive GWG prevalence.

Results

We identified 984 articles, 973 (98.88%) of which were considered unsuitable for the preparation of the present material. For the present review, 11 articles addressing dietary patterns and GWG were considered eligible (►**Fig. 1**). The Kappa test result (0.887) pointed toward excellent agreement between reviewers.

Five studies were performed in Europe,[6,17–21] one in North America,[19] one in South America,[11] one in South Africa,[22] and three in Asia.[5,23,24] Nine (81.82%) of the 11 assessed studies followed a cohort-based design to find the assessed data, whereas 2 of them (18.18%) were cross-sectional-based studies. The samples in these studies ranged from 173 to 5,733 participants (►**Chart 1**).

All studies selected to compose the present review have used a food frequency questionnaire (FFQ) to assess the food intake of women. A posteriori dietary patterns were derived out through principal components analysis (PCA) on the majority ($n = 9$). One study used Clusters analysis to determinate the patterns, and another study used reduced rank regression (RRR) (►**Chart 2**).

Association between Food Patterns and Gestational Weight Gain

Seven studies showed positive associations between dietary patterns and GWG. A study performed by Uusitalo et al.[17] showed that two out of seven dietary patterns (fast-food and traditional breads) had positive association with the GWG rate. Only the fast-food pattern, rich in ultraprocessed foods like sweets, soft drinks, hamburgers, pizza, and other fast-foods, remained GWG-significant after the models were adjusted to all confounding factors, including maternal age

Chart 1 Features of articles included in the systematic review

Authors, year	City/Country	Design	Sample (n)	Instruments used for quality evaluation	Score*
Wei et al. (2019)[5]	China	Cohort	5733	New Castle-Ottawa Quality Assessment Scale	*********
Suliga et al. (2018)[6]	Poland	Cross-sectional	458	Appraisal tool for Cross-Sectional Studies (AXIS)	16
Alves-Santos et al. (2018)[11]	Rio de Janeiro, Brazil	Cohort	173	New Castle-Ottawa Quality Assessment Scale	********
Shin et al. (2016)[12]	United States	Cross-sectional	391	Appraisal tool for Cross-Sectional Studies (AXIS)	19
Uusitalo et al. (2009)[17]	Finland	Cohort	3360	New Castle-Ottawa Quality Assessment Scale	*********
Tielemans et al. (2015)[18]	Netherlands	Cohort	3374	New Castle-Ottawa Quality Assessment Scale	*********
Maugeri et al. (2019)[20]	Catania, Italy	Cohort	232	New Castle-Ottawa Quality Assessment Scale	******
Cano-Ibáñez et al. (2020)[21]	Spain	Cohort	533	New Castle-Ottawa Quality Assessment Scale	*********
Wrottesley et al. (2017)[22]	South Africa	Cohort	538	New Castle-Ottawa Quality Assessment Scale	*******
Angali et al. (2020)[23]	Iran	Cohort	488	New Castle-Ottawa Quality Assessment Scale	********
Itani et al. (2020)[24]	United Arab Emirates	Cohort	242	New Castle-Ottawa Quality Assessment Scale	********

Note: *New Castle-Ottawa Quality Assessment Scale: score, 0 to 9 stars – 6 stars, or more, were considered good scores; Appraisal tool for Cross-Sectional Studies (AXIS): score, 0 to 20–15 points, or more, were considered good scores

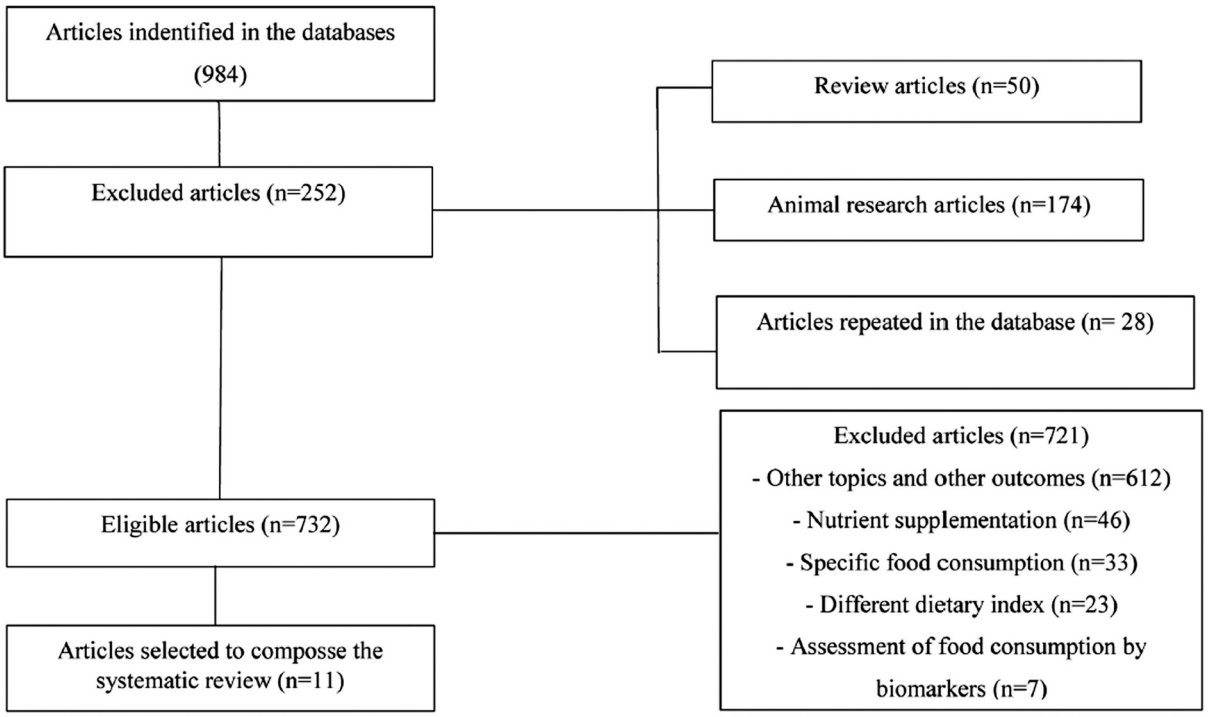


Fig. 1 Flowchart describing the article-selection process for the systematic review.

at delivery, pregestational body mass index (BMI), parity, residence location, vocational education, smoking, and birthweight ($\beta = 0.010$; $p = 0.004$).[17]

Tielemans et al.[18] presented a prevalence of 43% of women with excessive GWG. They did not find associations between higher adherence to the dietary patterns and GWG prevalence; however, women recording higher scores for the "margarine, sugar, and snacks" pattern had a higher prevalence of excessive GWG than the ones in the lowest quartile (odds ratio [OR] Q4: 1.45; 95% confidence interval [CI]: 1.06–1.99). This pattern was also significantly associated with higher weight in normal weight women (mean 0.30; 95% CI: 0.07–0.52; $p < 0.05$) throughout pregnancy.

Although Maugeri et al.[20] did not find associations between dietary patterns and GWG in the univariate analyses, they performed a linear regression model adjusted to age, weight at delivery, gestational duration, educational level, working status, smoking, parity, newborn gender, and total energy intake. This model showed a positive trend of GWG across tertiles of the western dietary pattern—high consumption of red meat, fries, dipping sauces, salty snacks, and alcoholic drinks ($\beta = 1.217$; se = 0.487; $p = 0.013$). They found no associations between excessive GWG and adherence to the prudent dietary pattern in the assessed population.

Wei et al.[5] found a prevalence of 31.3% of women with excessive GWG. The "richer in fish, beans, nuts, and yogurt" pattern was the one that registered the greater proportion of participants (23.2%), while the richer in fruits pattern registered the lowest proportion (11.2%). The "richer in fruits" pattern was positively correlated to GWG in both the total GWG and GWG rates. The other patterns did not present significant correlation with GWG. The "richer in fruits" pattern was associated with excessive GWG after adjustments to confounders such as maternal age, educational level, prepregnancy BMI, and parity.

Wrottesley et al.[22] found a prevalence of 55% of women presenting excessive GWG. In the total sample of pregnant women, only the "mixed" pattern (characterized by high consumption of grains, nuts, and dairy as well as added sugar and sweet spreads) showed significant and positive association with the GWG rate in both crude and adjusted models (adjusted to other patterns, parity, marital status, and total energy intake). This positive association was maintained in obese women for all models (Model 1: 25–11.4 g/week; $p = 0.029$; Model 2: 23–11.4 g/week; $p = 0.042$; Model 3: 24–11.6 g/week; $p = 0.041$) but was not observed in normal weight or overweight women.

The western pattern was significantly associated with a higher weight gain rate in normal weight women in all models. To the GWG category analysis, in crude logistic regression, a higher western diet pattern score was associated with increased odds of excessive weight gain in normal weight women.

In a study conducted with Emirati and Arab women, Angali et al.[23] identified two dietary patterns: "fast food with high fat" pattern, which included pasta, vermicelli, broken wheat, high-fat organ meats, high-fat dairy, sugary cool drinks, and ultraprocessed meats (salami and sausage), and the "vegetable, fruit, and protein" pattern. The higher the adherence to the "fast food with high fat" pattern, the covariance adjusted analysis and unadjusted multiple regression analysis indicated that the this pattern was a significant positive predictor of increase in GWG in the 1st

Chart 2 Identified dietary patterns, main results, and inadequate and/or excessive gestational weight gain prevalence

Authors, years	Dietary patterns method	Identified dietary patterns	Main results	Excessive GWG	Inadequate GWG
Suliga et al. (2018)[6]	PCA	"Prudent" "Varied" "Unhealthy"	Prudent Women with excessive GWG presented less adherence to this pattern (OR 0.47; $p = 0.033$)	32.97%	21.83%
Alves-Santos et al. (2018)[11]	RRR	"Common- Brazilian" "Western"	There was no association between the identified dietary patterns and GWG	34.68%	*
Shin et al. (2016)[12]	PCA	"Healthy" "Mixed" "Western"	Mixed Higher adherence to this pattern was associated with greater odds of inadequate GWG when compared with lower adherence (AOR 4.72 95%CI 1.07–20.94)	51.15%	28.39%
Uusitalo et al. (2009)[17]	PCA	"Healthy" "Fast Food" "Traditional bread" "Traditional meat" "Low-fat" "Coffee" "Alcohol and Butter"	Fast food pattern Positively associated with GWG rate ($\beta = 0.010$, $p = 0.004$) Alcohol and butter pattern Inversely associated with GWG rate ($\beta = -0.010$, $p < 0.0001$)	*	*
Tielemans et al. (2015)[18]	PCA	"Vegetable, oil and fish" "Nuts, high-fiber cereals and soy" "Margarine, sugar and snacks"	Margarine, sugar and snacks Higher scores on this pattern resulted in a higher prevalence of excessive GWG (OR 1.45 95%CI 1.06–1.99)	24.48%	13.60%
Maugeri et al. (2019)[20]	PCA	"Western" "Prudent"	Western The adherence to this pattern was associated with greater GWG ($\beta = 1.217$, $p = 0.013$)	27.59%	31.46%
Wrottesley et al. (2017)[22]	PCA	"Traditional" "Mixed" "Western"	Mixed Significant and positive association with GWG rate ($\beta = 22$ $p = 0.004$)	55.20%	23.79%

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; GWG, gestational weight gain; OR, odds ratio; p: significance level; PCA, principal component analysis; RRR: reduced rank regression.
*Not informed by the study.

(adjusted b = 0.009; 95%CI: 0.001–0.017) and 3rd trimester of pregnancy (adjusted b = 0.029; 95%CI: 0.012–0.049). On the other hand, in the fully adjusted quartile regression model, women in the highest quartile (Q99) of the "vegetable, fruit, and protein" pattern showed a negative and significant association (adjusted β = - 1; 95%CI: - 1.97–- 0.03).

Likewise, Itani et al.[24] found two dietary patterns, the *diverse* pattern, characterized by high inputs of fruits, vegetables, mixed dishes, meats, dairy products, grains, vegetables, and nuts, and the *western* pattern, rich in ultraprocessed foods (sweets, sugar-sweetened drinks, fast-food, and added sugars). The western pattern was associated with excessive GWG (OR: 4.04; 95%CI: 1.07–15.24) and GWG rate (OR: 4.38; 95%CI: 1.28–15.03), while the diverse pattern decreased the risk of inadequate GWG (OR: 0.24; 95%CI: 0.06–0.97) and GWG rate (OR: 0.28; 95%CI: 0.09–0.90).

Three studies found dietary patterns with protective effect in terms of GWG. Wrottesley et al.[22] showed that the *traditional* pattern (high in whole grains, legumes, vegetables, and traditional meat) had significant, inverse associations with the GWG rate in the crude model, and to parity and marital status adjusted (model 1: - 2 7; 11.1 g/week; $p = 0.015$; model 2: - 27; 11.5 g/week; $p = 0.02$); however, this association was no longer significant after adjustment for total energy intake. In line with these findings, the study conducted by Suliga et al.[6] showed that in women with excessive GWG, a lower adherence to the *prudent* pattern was noted in comparison with other participants in the study. The *prudent* pattern found in this study (high intake of whole grains, vegetables, legumes, sea fish, milk, and dairy products, and avoiding snacking between meals) is similar in terms of composition to the *traditional* pattern described by Wrottesley et al.[22]

In addition, Cano-Ibáñez et al.[21] found moderate evidence for an association between the Mediterranean eating pattern, considered a healthy eating pattern (vegetables, olive oil, whole grains, and nuts) and lower GWG trajectories (0.06; 95%CI: - 0.11–- 0.04) and better nutrient adequacy.

One study found that the *mixed* pattern also showed significant associations with inadequate GWG.[12] In the physical activity level-adjusted model, women in the highest tertile of the *mixed* pattern (high intake of meat, dairy products, fruits, vegetables, potatoes, nuts and seeds, and sweets) had significantly greater odds of inadequate GWG

when compared with those in the lowest tertile (AOR: 4.72; 95%CI:1.07–20.94). Women in the midtertile of the *mixed* pattern presented a lower OR of excessive GWG compared with those in the lowest tertiles (OR: 0.39; 95%CI: 0.15–0.99). The other patterns did not show significant GWG associations.

Dietary Pattern Association and other Outcomes

The assessed studies also associated GWG and dietary patterns with other maternal and child health outcomes.

Suliga et al.[6] found in the crude model a positive association between an increased risk of excessive GWG and prepregnancy BMI $\geq$ 25 kg/m2 (OR = 6.44; $p < 0.001$) and with giving up smoking (OR = 9.07; $p = 0.004$). A lower risk of excessive GWG was associated with being underweight prepregnancy compared with having a normal BMI (OR = 0.17; $p = 0.020$). In the adjusted model, the factor increasing the risk of inadequate GWG was being underweight prepregnancy (OR= 2.61; $p = 0.018$), but this risk was significantly lower in the third, or subsequent, pregnancy compared with the first one (OR = 0.39; $p = 0.042$).

Maugeri et al.[20] showed that prepregnancy weight and BMI decreased across tertiles of the *prudent* dietary pattern ($p = 0.043$ and $p = 0.019$, respectively). In fact, women presenting higher adherence to this pattern were less likely to be overweight or obese ($p = 0.007$). Linear regression results confirmed the negative association between prepregnancy BMI and adherence to the *prudent* dietary pattern after adjustments regarding age, educational level, employment status, smoking, total energy intake, and gestational age at recruiting ($\beta = -0.631$; se = 0.318; $p = 0.038$). Women in the 3rd tertile of the *prudent* dietary pattern showed lower prepregnancy BMI than the ones in the 1st tertile ($\beta = -1.347$; se = 0.598; $p = 0.024$).

Angali et al.[23] identified that women with pregestational BMI > 25 kg/m^2 had more adherence to the "vegetable, fruit, and protein" pattern than those with low adherence (3rd tercil versus 1st tercil). On the other hand, women with normal weight and underweight showed a greater tendency to the *fast food with high fat* pattern (3rd tercil versus 1st tercil).

Wrottesley et al.[22] did not find any association between BMI in the 1st gestational semester and the dietary patterns identified in their research.

The multiple adjusted longitudinal analyses conducted by Alves-Santos et al.[11] showed that higher adherence to the common-Brazilian dietary pattern was directly associated with adiponectin concentrations ($\beta = 1.07$; 95%CI: 0.17–1.98). On the other hand, highest adherence to the western dietary pattern was negatively associated with adiponectin throughout pregnancy (high versus low tertile of adherence $\beta = -1.11$; 95%CI - 2.00–- 0.22) and directly associated with leptin concentrations ($\beta = 64.9$; 95%CI: 22.8–107.0).

Finally, Cano-Ibáñez et al.[21] identified that, regardless of the GWG, the Mediterranean dietary pattern showed moderate evidence of a greater likelihood of achieving an adequate dietary fiber intake, vitamins B9, D and E, and iodine ($p < 0.05$).

Discussion

To the best of our knowledge, this is the first review addressing dietary patterns a posteriori-derived and their association with GWG. The studies were performed especially in European and Asian countries, and the most used method was the principal components analysis. The high prevalence of inadequacy and/or excess of GWG (35.10 to 55.20%) is the last one confirming the hypothesis about the dietary pattern composed of ultraprocessed foods and its outcomes in the weight gain of pregnant woman, proves the importance of better understand the process, both in the health of women and children.

Dietary patterns are not exactly the same in studies; however, it is clear from published studies that certain dietary patterns like *western*/*unhealthy*, *healthy*/*prudent*/*Mediterranean,* and *traditional* are often found.[24] The assessed studies were similar in the association of dietary patterns that shows higher caloric density[12,18,19,22,24] with greater chances of excessive GWG outcomes, as well as patterns presenting healthier and more traditional components[6,21,22] being associated with lower GWG.

The *healthy*/*prudent*/*Mediterranean* dietary patterns were characterized by high consumption of whole grains, vegetables, legumes, sea fish, olive oil, and nuts.[6,21] Accordingly, the Dietary Guidelines for the Brazilian Population has, as one of its recommendations, that the base of a healthy diet should be in natura or minimally processed food, mostly from vegetal origin.[25,26] The recommendation also mentions the need of reducing the intake of ultraprocessed food, which is often found in the western and unhealthy patterns.

A diet rich in vitamins, minerals, fibers and antioxidants can stimulate the immune system and detoxification of enzymes, improve cholesterol synthesis, modulate hormone metabolism, and stimulate antioxidant defenses.[17] Besides, some studies link the intake of healthy food with healthier life habits, such as regular exercise, which can result in weight adequacy. Thus, promoting a healthy lifestyle during prenatal consultations is an excellent strategy for adequate weight gain during pregnancy.[21]

The study conducted by Wei et al.,[5] found out that the richer in fruits pattern was positively correlated to GWG. However, observing other components of this pattern, it was also possible to find a high presence of Cantonese dessert (sugar, rice flour, honey, whole milk). The presence of this type of high caloric intake in the pattern could explain the positive correlation to GWG, in compliance with the other presented results.

Unhealthy dietary patterns consist mainly of sweets, refined cereal, fast foods, salty snacks, red meat, fries, sugar-sweetened beverages, and alcoholic drinks.[20,23,24] The intake of unhealthy dietary patterns throughout pregnancy might be associated with excessive GWG due to its unbalanced offer of energy, and macro and micronutrients, thus contributing to undesired outcomes such as inadequate fetal growth, excessive fat accumulation, and metabolic complications.[17]

Although some studies have shown a relationship between dietary patterns and GWG, and food consumption is

one of the main factors causing inadequate or excessive GWG, other aspects of it must be taken into consideration. Pregestational BMI, and genetic and environmental factors (involving for instance the offer of, access to, and availability of food, and the context capable of promoting and impairing physical activities), as well as regular exercise by women, can also influence the herein addressed process. Thus, a dietary pattern alone may not be able to make a pregnant women develop inadequate or excessive GWG, a fact that could explain studies that did not find associations or that had their associations weakened by the adjusted models.

In addition to the data found in relation to GWG, dietary patterns during pregnancy also seem to influence weight gain in the years following the baby delivery. A cohort study performed in Norway found out that the adherence to the New Nordic Diet resulted in lower postgestational BMI and lower weight gain in the following 8 years after child delivery when compared with women who had low adherence to this diet.[27] The New Nordic Diet consists in a dietary pattern similar to that of traditional, healthy, and *prudent* patterns (fruits, roots, cabbage, potatoes, oat porridge, whole grains, wild fish, game meat, berries, milk and water).[28] The study concluded that adherence to the Norwegian eating guidelines, or adherence to Nordic diet guidelines recommended to pregnant women, are associated with lower postpartum weight retention.

It is known that dietary patterns can change based on the country or on the assessed population; however, other studies have also associated unhealthy, *western*, and sugar/fat-rich patterns with negative outcomes throughout pregnancy, whereas healthy or *traditional* patterns presented the best health outcomes. Kibret et al.[9] performed a review and meta-analysis and found that dietary patterns based on high fruit intake are associated with reduced chances to reach adverse results throughout pregnancy.

Other studies highlighted the relationship between gestational dietary patterns and pregnancy outcomes besides GWG, such as fertility, gestational diabetes mellitus, fetal growth, depression symptoms and preterm birth.[25,29,30] Such findings point out the magnitude of unhealthy dietary pattern influence on mother/child health outcomes. Shin et al.[19] assessed data from the National Research in Health and Nutrition and found a connection between high intake of refined grains, fat, addition sugar, and low intake of fruits and vegetables during pregnancy and greater chances to develop gestational diabetes mellitus.

The limitations of this systemic review must be recognized. The number of studies selected for this review was not large (only eleven studies fell within its scope) and the design of primary studies. In addition, the selected articles did not contain the necessary subsidies for the preparation of a meta-analysis. The time frame used for the study can also be considered a limitation, not using the Embase database, since more studies could be performed before that and on other platforms. However, this study also has several strengths. It is recognized that observational studies can be greatly influenced by confounding factors, such as lifestyle and sociodemographic variables, which can vary among different cultures and countries. This information was taken into account to minimize the confusion bias.

Conclusion

Gestational dietary patterns a posteriori-derived that present ultraprocessed components rich in fat and sugars seem to be associated with excessive GWG, while healthy and traditional dietary patterns have been associated with better maternal and child health conditions, such as adequate GWG, term birth, and babies with adequate birth weight. However, the scarcity of studies on this topic points out the need for further investigation about the subject. Findings in the present review reinforce the importance of providing nutritional assistance to pregnant women during gestation and highlight the role played by public health policies focused on food and nutrition to encourage adhesion to healthier dietary patterns, which contributes to better maternal and newborn health outcomes.

Conflict of Interests
The authors have no conflict of interests to declare.

Acknowledgments
The financial support provided by the Coordination for the Improvement of Higher Education Personnel (CAPES - Financial code 001), Foundation for Research Support of the State of Minas Gerais (FAPEMIG) and National Council for Scientific and Technological Development (CNPq - Research Productivity fellow (301555/2019–2) and Universal Notice 2016 (406644/2016–0).

References

1 Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol. 2002;13(01):3–9. Doi: 10.1097/00041433-200202000-00002
2 Chia AR, Chen LW, Lai JS, Wong CH, Neelakantan N, van Dam RM, Chong MFF. Maternal dietary patterns and birth outcomes: a systematic review and meta-analysis. Adv Nutr. 2019;10(04): 685–695 Doi: 10.1093/advances/nmy123
3 Carvalho CA, Fonsêca PC, Nobre LN, Priore SE, Franceschini SD. Metodologias de identificação de padrões alimentares a posteriori em crianças brasileiras: revisão sistemática. Ciênc Saúde Coletiva. 2016;21(01):143–154. Doi: 10.1590/1413-81232015211.18962014
4 Arora P, Tamber Aeri B. Gestational weight gain among healthy pregnant women from Asia in comparison with Institute of Medicine (IOM) guidelines-2009: a systematic review. J Pregnancy. 2019;2019:3849596. Doi: 10.1155/2019/3849596
5 Wei X, He JR, Lin Y, Lu M, Zhou Q, Li S, et al. The influence of maternal dietary patterns on gestational weight gain: A large prospective cohort study in China. Nutrition. 2019;59:90–95 Doi: 10.1016/j.nut.2018.07.113
6 Suliga E, Rokita W, Adamczyk-Gruszka O, Pazera G, Cieśla E, Głuszek S. Factors associated with gestational weight gain: a cross-sectional survey. BMC Pregnancy Childbirth. 2018;18(01): 465. Doi: 10.1186/s12884-018-2112-7
7 Santos S, Voerman E, Amiano P, Barros H, Beilin LJ, Bergström A, et al. Impact of maternal body mass index and gestational weight gain on pregnancy complications: an individual participant data meta-analysis of European, North American and Australian

cohorts. BJOG. 2019;126(08):984–995 Doi: 10.1111/1471-0528.15661
8 Gaillard R, Durmuş B, Hofman A, Mackenbach JP, Steegers EA, Jaddoe VW. Risk factors and outcomes of maternal obesity and excessive weight gain during pregnancy. Obesity (Silver Spring). 2013;21(05):1046–1055. Doi: 10.1002/oby.20088
9 Kibret KT, Chojenta C, Gresham E, Tegegne TK, Loxton D. Maternal dietary patterns and risk of adverse pregnancy (hypertensive disorders of pregnancy and gestational diabetes mellitus) and birth (preterm birth and low birth weight) outcomes: a systematic review and meta-analysis. Public Health Nutr. 2018;1–15. Doi: 10.1017/s1368980018002616
10 Godoy AC, Nascimento SL, Surita FG. A systematic review and meta-analysis of gestational weight gain recommendations and related outcomes in Brazil. Clinics (São Paulo). 2015;70(11): 758–764. Doi: 10.6061/clinics/2015(11)08
11 Alves-Santos NH, Cocate PG, Eshriqui I, Benaim C, Barros EG, Emmett PM, Kac G. Dietary patterns and their association with adiponectin and leptin concentrations throughout pregnancy: a prospective cohort. Br J Nutr. 2018;119(03):320–329 Doi: 10.1017/S0007114517003580
12 Shin D, Lee KW, Song WO. Dietary patterns during pregnancy are associated with gestational weight gain. Matern Child Health J. 2016;20(12):2527–2538. Doi: 10.1007/s10995-016-2078-x
13 Moher D, Liberati A, Tetzlaff J, Altman DGPRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006–1012. Doi: 10.1016/j.jclinepi.2009.06.005
14 Schoth DE, Blankenburg M, Wager J, Broadbent P, Zhang J, Zernikow B, and Liossi C. Association between quantitative sensory testing and pain or disability in paediatric chronic pain: protocol for a systematic review and meta-analysis. BMJ Open. 2019;9(10):e031861 Doi: 10.1136/bmjopen-2019-031861
15 Giannopoulou EZ, Doundoulakis I, Antza C, Christoforidis A, Haidich AB, Kotsis V, Stabouli S. Subclinical arterial damage in children and adolescents with type 1 diabetes: A systematic review and meta-analysis. Pediatr Diabetes. 2019;20(06): 668–677 Doi: 10.1111/pedi.12874
16 Islam MA, Khandker SS, Alam F, Kamal MA, Gan SH. Genetic risk factors in thrombotic primary antiphospholipid syndrome: A systematic review with bioinformatic analyses. Autoimmun Rev. 2018;17(03):226–243. Doi: 10.1016/j.autrev.2017.10.014
17 Uusitalo U, Arkkola T, Ovaskainen ML, Kronberg-Kippilä C, Kenward MG, Veijola R, et al. Unhealthy dietary patterns are associated with weight gain during pregnancy among Finnish women. Public Health Nutr. 2009;12(12):2392–2399 Doi: 10.1017/S136898000900528X
18 Tielemans MJ, Erler NS, Leermakers ET, van den Broek M, Jaddoe VWV, Steegers EAP, et al. A priori and a posteriori dietary patterns during pregnancy and gestational weight gain: the Generation R Study. Nutrients. 2015;7(11):9383–9399 Doi: 10.3390/nu7115476
19 Shin D, Lee KW, Song WO. Dietary patterns during pregnancy are associated with risk of gestational diabetes mellitus. Nutrients. 2015;7(11):9369–9382. Doi: 10.3390/nu7115472
20 Maugeri A, Barchitta M, Favara G, La Rosa MC, La Mastra C, San Lio RM, and Agodi A. Maternal dietary patterns are associated with pre-pregnancy body mass index and gestational weight gain: results from the "Mamma & Bambino" cohort. Nutrients. 2019;11 (06):1308–1320 Doi: 10.3390/nu11061308
21 Cano-Ibáñez N, Martínez-Galiano JM, Luque-Fernández MA, Martín-Peláez S, Bueno-Cavanillas A, Delgado-Rodríguez M. Maternal dietary patterns during pregnancy and their association with gestational weight gain and nutrient adequacy. Int J Environ Res Public Health. 2020;17(21):7908. Doi: 10.3390/ijerph17217908
22 Wrottesley SV, Pisa PT, Norris SA. The influence of maternal dietary patterns on body mass index and gestational weight gain in urban Black South African women. Nutrients. 2017;9 (07):732. Doi: 10.33390/nu9070732
23 Angali KA, Shahri P, Borazjani F. Maternal dietary pattern in early pregnancy is associated with gestational weight gain and hyperglycemia: A cohort study in South West of Iran. Diabetes Metab Syndr. 2020;14(06):1711–1717. Doi: 10.1016/j.dsx.2020.08.008
24 Itani L, Radwan H, Hashim M, Hasan H, Obaid RS, Ghazal HA, et al. Dietary patterns and their associations with gestational weight gain in the United Arab Emirates: results from the MISC cohort. Nutr J. 2020;19(01):36 Doi: 10.1186/s12937-020-00553-9
25 Ocké MC. Evaluation of methodologies for assessing the overall diet: dietary quality scores and dietary pattern analysis. Proc Nutr Soc. 2013;72(02):191–199. Doi: 10.1017/S0029665113000013
26 Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Atenção Básica. Guia alimentar para a população brasileira [Internet]. 2a ed. Brasília (DF): Ministério da Saúde; 2014 [cited 2021 Feb 12]. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/guia_alimentar_populacao_brasileira_2ed.pdf
27 Skreden M, Hillesund ER, Wills AK, Brantsæter AL, Bere E, Øverby NC. Adherence to the New Nordic Diet during pregnancy and subsequent maternal weight development: a study conducted in the Norwegian Mother and Child Cohort Study (MoBa). Br J Nutr. 2018;119(11):1286–1294. Doi: 10.1017/s0007114518000776
28 von Ruesten A, Brantsæter AL, Haugen M, Meltzer HM, Mehlig K, Winkvist A, Lissner L. Adherence of pregnant women to Nordic dietary guidelines in relation to postpartum weight retention: results from the Norwegian Mother and Child Cohort Study. BMC Public Health. 2014;14:75 Doi: 10.1186/1471-2458-14-75
29 Chen X, Zhao D, Mao X, Xia Y, Baker PN, Zhang H. Maternal dietary patterns and pregnancy outcome. Nutrients. 2016;8(06):351. Doi: 10.3390/nu8060351
30 Zareei S, Homayounfar R, Naghizadeh MM, Ehrampoush E, Rahimi M. Dietary pattern in pregnancy and risk of gestational diabetes mellitus (GDM). Diabetes Metab Syndr. 2018;12(03):399–404. Doi: 10.1016/j.dsx.2018.03.004

febrasgo
Federação Brasileira das Associações de Ginecologia e Obstetrícia

FEBRASGO POSITION STATEMENT

Initial evaluation in the climacteric

Number 5 - May 2022
DOI: https://doi.org/10.1055/s-0042-1750282

The National Specialty Commission on Climateric of the Brazilian Federation of Gynecology and Obstetrics Associations (FEBRASGO) endorses to this document. The content production is based on scientific studies on a thematic proposal and the findings presented contribute to clinical practice.

Key points

- Climacteric syndrome is a set of signs and symptoms resulting from the interaction between sociocultural, psychological and endocrine factors occurring in aging women. Its diagnosis is clinical in women with the expected age group for ovarian hypofunction. The term "menopause" refers to the date of the woman's last menstrual bleeding episode and is defined retrospectively.
- Women in menopausal transition have disease prevention and health promotion needs. Hypoestrogenism associated with aging and metabolic syndrome can lead to lower quality of life and increased occurrence of cardiovascular disease.
- The medical consultation of climacteric women is an excellent opportunity of screening for chronic diseases and neoplasms.
- Complementary evaluation for climacteric women must be carried out judiciously. The benefit and risk of each test must be considered. Complementary tests without a specific definition of a diagnostic and therapeutic plan should be avoided.
- Menopausal hormone therapy (HT) may be indicated to treat climacteric symptoms. Detailed clinical history and rational complementary exams are essential to define the therapeutic plan and follow-up of women undergoing HT.

Recommendations

- For women over 45 years of age with symptoms suggestive of hypoestrogenism such as typical hot flashes, the diagnosis of climacteric syndrome is clinical. The date of menopause is defined retrospectively, after 12 months of amenorrhea in a woman over 45 years of age. When in doubt, two doses of follicle-stimulating hormone (FSH) 4-6 weeks apart are recommended. Values above 25 mIU/mL indicate the beginning of menopausal transition. For women under 45 years of age who complain of irregular uterine bleeding pattern and infrequent menstrual cycles, the performance of complementary tests for investigation is recommended.
- The diagnosis of genitourinary syndrome of menopause should be made proactively, with questioning directed to urogenital symptoms associated with a thorough gynecological examination.
- In women at usual risk, breast cancer screening should begin at age 40. Mammography is the recommended exam yearly (if normal). In women with dense breasts, ultrasound should be considered as a supplement to mammography. Breast cancer screening can be interrupted when life expectancy is less than seven years or if there are no clinical conditions for diagnosis or treatment.
- Cervical cancer screening is performed using periodic oncotic cytology. After performing two consecutive negative cytology tests at annual intervals, it is recommended to do the exam every three years. Screening can be stopped after age 64 if the patient has two consecutive negative tests in the previous five years. The gynecological physical examination should be part of the periodic gynecological evaluation regardless of the woman no longer having an indication for cervical cancer screening.
- Requesting pelvic and transvaginal ultrasound for women (at usual risk) without signs or symptoms suggestive of disease is not cost-effective. For symptomatic women, such as those with abnormal uterine bleeding, postmenopausal vaginal bleeding, or abdominal discomfort, transvaginal pelvic ultrasound is cost-effective and is the initial complementary test of choice to evaluate uterine and ovarian diseases.
- For women at normal risk and over 50 years of age, colorectal cancer screening is recommended.

- Screening for risk factors for cardiovascular disease, including hypertension, diabetes mellitus, obesity, smoking and dyslipidemia, should always be considered in the consultation of climacteric women. Researching all criteria for the definition of metabolic syndrome is essential. Menopausal transition is a window of vulnerability for the development of mood swings, such as depressive disorder. Identifying women with depressive symptoms is important to institute the appropriate therapy.
- Bone densitometry is recommended for screening for osteoporosis in all women aged 65 years and older. Densitometry is also indicated for climacteric women under 65 years of age who have at least one risk factor for osteoporosis. The FRAX-Brasil, analyzed according to the recommendation of the National Osteoporosis Guideline Group (NOGG), can also be used to assess the need for densitometry.
- Sexually transmitted infections (STIs) during menopause and postmenopause cannot be underestimated. Behavioral counseling and treatment of genitourinary syndrome of menopause are important tools to decrease the risk of STIs. Screening for STIs should be performed based on each patient's clinical history data.
- Thyroid diseases are prevalent in aging women and can increase morbidity and mortality. Clinical evaluation of the thyroid should be performed routinely during physical examination of climacteric women. Women over 60 years of age or with symptoms of thyroid dysfunction should be evaluated initially with a thyroid-stimulating hormone (TSH) measurement.

Background

The transition between reproductive and non-reproductive stages in a woman's life is called climacteric.[1] At this stage, women have numerous needs for disease prevention and health promotion, and physicians must be aware of a series of conducts aimed at optimizing the quality of life.[2] The gynecological consultation is an excellent opportunity to meet these needs. A review of the pertinent literature on the subject was performed in order to systematize the initial workup during the gynecological consultation of climacteric women. The most relevant results are shown below, divided into: diagnosis of menopause and climacteric syndrome; opportunistic screening of chronic diseases and neoplasms; specific tests aimed at women undergoing menopausal HT.

How are menopause and climacteric syndrome diagnosed?

Aging leads to progressive ovarian failure, determining the interruption of ovulatory cycles and cessation of menstrual bleeding. With the objective of standardizing the definition of the different stages of reproductive aging, the STRAW system, Stages of Reproductive Aging Workshop, was developed.[3] The characterization of the reproductive period, menopausal transition and postmenopausal period is performed based on patterns of symptoms and laboratory findings.

The date of the woman's last menstrual bleeding episode is defined as menopause.[1] It occurs at 51 years of age, on average, and 90% of women experience menopause between 45 and 55 years of age.[4] Its definition is performed retrospectively after 12 months of amenorrhea in women in the expected age group for the menopausal transition.[4] Premature ovarian failure is a syndrome resulting from the loss of ovarian activity before 40 years of age.[5] This condition affects approximately 1% of women.[6] Menopause between 40 and 45 years of age affects approximately 5% of women and has been called early menopause.[6]

The term "climacteric syndrome" refers to the set of symptoms and signs resulting from the interaction between sociocultural, psychological and endocrine factors that occur in aging women.[1] Its diagnosis is based on a detailed anamnesis complemented by a thorough physical examination.[2]

Vasomotor symptoms, also known as hot flashes, are the most frequently associated with menopausal transition. They consist of sudden sensations of heat in the central region of the body, most notably in the region of the face, chest and neck, and last an average of three to four minutes.[7] There is often an increase in heart rate, peripheral vasodilation, elevation of skin temperature and sweating. They can be associated with insomnia when occurring at night.[8]

Women often seek care due to changes in the menstrual cycle in the menopausal transition. As a consequence of decreased ovarian production of inhibin B at the end of the fourth decade of life, an increase in serum concentrations of FSH and estradiol may occur at the beginning of the cycle, causing a shortening of the follicular phase. Progesterone level in the luteal phase also decreases given the deterioration of the quality of the corpus luteum. One of the first signs of reduced ovarian reserve is the shortening of the interval between menstruations.[9]

Over the years, the process of follicular depletion continues and anovulation becomes more and more frequent. Due to the lack of progestational opposition, the interval between menstrual cycles is longer, passing to 40 to 50 days. The increase in the interval between menstrual cycles occurs at 47 years of age, on average.[9] Longer episodes of amenorrhea begin to

occur, interrupted by episodes of menstrual bleeding of variable volume. This menstrual bleeding pattern can last from one to three years before menopause.[9]

For women over 45 years of age with complaints suggestive of hypoestrogenism, such as vasomotor symptoms and typical changes in menstrual pattern (infrequent uterine bleeding), the diagnosis of climacteric syndrome is clinical and does not require confirmation by other complementary tests.[2] In case of doubts if symptoms are resulting from a drop in ovarian estradiol production, FSH measurement in the early follicular phase can confirm the diagnosis. Values above 25 mIU/mL may indicate the beginning of menopausal transition, although concentrations may have great daily variability during this phase.[9] When necessary, two dosages at four to six weeks interval should be performed.[2] For women under 45 years of age who complain of abnormal uterine bleeding with an irregular pattern and infrequent menstrual cycles, even if the clinical picture is compatible with hypoestrogenism, a complementary evaluation is recommended for investigation of symptoms and exclusion of other causes of menstrual irregularity.[9]

How screening for chronic diseases and neoplasms in the climacteric should be?

During the climacteric, an individual evaluation of each woman is essential to meet her needs for disease prevention and health promotion.[2] Next, details on screening for gynecological malignancies, colorectal cancer, risk factors for cardiovascular disease, osteoporosis, depression and sexually transmitted infections (STIs) are presented.

How to screen for breast cancer?

Breast cancer is the second most frequent neoplasm among Brazilian women, with an estimated incidence of 66,280 new cases for each year of the 2020-2022 triennium, corresponding to an estimated risk of 61.61 new cases per 100,000 women.[10] The objective of screening is to reduce the need for mutilating procedures and increase survival.[11] Mammographic screening can reduce breast cancer mortality by approximately 20% and reduce the risk of advanced-stage breast tumors in women over 50 years of age.[12] Breast ultrasound should not be used as the only screening method due to the lack of studies in women at normal risk, but it should be used as a complementary method to mammography in women with dense breasts. The use of magnetic resonance imaging is not recommended as a screening method in women at normal risk.[13]

Breast cancer screening can present risks such as overdiagnosis, overtreatment, and false-positive results.[14] The shared decision between physician and patient should be considered to define the age of onset, periodicity, and when to stop screening. Febrasgo suggests that breast cancer screening starts at age 40 for women at normal risk. Mammography is the recommended exam yearly (if normal). Breast cancer screening can be interrupted when life expectancy is less than seven years or when there are no clinical conditions for the diagnosis or treatment of a woman with an abnormal test result (Chart 1).[13] The screening in patients at high-risk for breast cancer is outside the scope of this publication.

Chart 1. Recommendations for breast cancer screening in women at usual risk

Febrasgo/SBM/CBR	
Clinical examination by a health professional	Recommended
Self-exam	Recommended
Recommended age to start mammography	40 years
Frequency of mammography	Yearly
Recommended age to end mammography screening	Discontinue when life expectancy < 7 years or there are no clinical conditions for diagnosis/treatment of altered exam

How to screen for cervical cancer?

Cervical cancer is the fourth most frequent neoplasm among Brazilian women, with an estimated 16,590 new cases for each year of the 2020-2022 triennium and an estimated risk of 15.43 cases per 100,000 women.[10] The Brazilian Ministry of Health recommends the Pap smear test as the method of choice for screening for precursor lesions.[15] It is recommended to start collection at 25 years of age for women who have already started sexual activity with an year interval between the first two exams. If the first two results are normal, collection is performed at a three-year interval. If the patient has two consecutive negative tests in the last five years, cytological screening can be interrupted after the age of 64 if the woman has never had a history of pre-invasive precursor lesion, including if there is a change of sexual partner.[15] For women in this age group who have never been screened, two Pap smears at one to three year-intervals are recommended before stopping the screening.[15] Menopause genitourinary syndrome, previously known as urogenital atrophy,[11] can lead to the occurrence of results such as “atypical squamous cells of undetermined significance” (ASC-US) in cytopathological examinations of the cervix. The use of topical estrogen for at least 21 days before the next collection can be useful in these cases.[16] The use of human papillomavirus (HPV) detection tests associated with cytology is recommended by some national and international soci-

eties for women from the age of 30 years. As it is more sensitive and has a high negative predictive value, the screening strategy including the HPV test allows increasing the interval between collections from three to five years when both results are negative.[16] Women without a history of precursor cancer lesions of the cervix can stop screening after performing a total hysterectomy for benign disease.[15] It is extremely important to maintain the periodical gynecological clinical evaluation by means of gynecological examination regardless of cytopathological examination.

Should gynecological pelvic ultrasound be routinely requested as a screening test?

To date, there is no scientific evidence to justify screening for ovarian cancer and endometrial cancer in women at normal risk for these neoplasms.[17-19] Therefore, the request for pelvic ultrasound for women with this risk profile who do not present signs and symptoms suggestive of ovarian or uterine diseases does not demonstrate a good cost-benefit relationship.[17-19] Among the adverse events of screening in women at normal risk, is the high number of false positives, that is, surgeries and possible associated complications in women who do not have cancer.[20] Note that in symptomatic women, such as those with abnormal perimenopausal uterine bleeding, postmenopausal vaginal bleeding or abdominal discomfort, transvaginal pelvic ultrasound examination is the initial complementary test of choice to assess uterine and ovarian diseases.[11]

How to screen for colorectal cancer?

Colorectal cancer is the third most frequent neoplasm among Brazilian women, with an estimated 20,470 new cases in the 2020-2022 period and an estimated risk of 19.03 cases per 100,000 women.[10] Reducing mortality due to the disease is possible by identifying asymptomatic neoplasms at an early stage through screening. Complementary tests are classified as structural, for example, colonoscopy, and non-structural, for example, fecal occult blood. In cases of positive results in a non-structural test, diagnostic confirmation by colonoscopy is necessary.[21] Screening schemes must be adapted to the resources available in each region. According to the World Health Organization, screening for fecal occult blood from the age of 50 should be performed in countries that can guarantee diagnostic confirmation and treatment.[22] In Brazil, the Ministry of Health considers that people at normal risk for colorectal cancer should be screened from the age of 50 using an yearly fecal occult blood test or colonoscopy with no established frequency.[23] This screening scheme may differ depending on the regional context. The American Cancer Society recommends that screening in patients at normal risk begins at 45 years of age, performed with structural or non-structural tests (Chart 2).[21] The North American Menopause Society (NAMS) considers that from the age of 50, colonoscopy every ten years (if the test result is considered normal) is an appropriate screening regimen for patients at normal risk for colon cancer.[6] Note that suspected cases of colorectal disease should be referred for evaluation by the specialist physician. Screening for patients at high risk for colorectal cancer is outside the scope of this publication.

Chart 2. Colorectal cancer screening

Organization	Population screened	Screening options
Ministry of Health[23]	Women at normal risk aged between 50 and 75 years	Non-structural tests: - Annual or biennial fecal occult blood Structural tests: - Colonoscopy if positive fecal occult blood
American Cancer Society[21]	Women aged 45 to 75 years if life expectancy is greater than 10 years. For women aged 76 to 85, individualization based on patient preferences, life expectancy, and previous screening history	Structural tests: - Colonoscopy every 10 years - Flexible sigmoidoscopy every 5 years - CT virtual colonoscopy every 5 years Non-structural tests: - Annual fecal occult blood - Annual immunochemical fecal test - Fecal DNA every 3 years

Source: Wolf et al.[21] and Ministry of Health.[23]

How to screen for risk factors for cardiovascular disease?

After menopause, the beneficial effect of endogenous estrogen on the cardiovascular system is mitigated, and the number of cardiovascular events increases.[24] Screening of risk factors such as diabetes mellitus, arterial hypertension, dyslipidemia, smoking, and obesity is essential for risk stratification and development of treatment plans (Chart 3).

The joint consideration of the therapeutic history and the different individual risk factors is useful for a better determination of the cardiovascular prognosis. Risk calculation tools for the occurrence of events such as myocardial infarction and stroke are available for use. The Brazilian Guideline for Cardiovascular Prevention of the Brazilian Society of Cardiology recommends using the Framingham Global Risk Score as an assessment tool.[25]

Chart 3. Screening of risk factors for cardiovascular disease according to the Ministry of Health

Risk factor	Recommendation	Comments
Dyslipidemia	Screening from 45 years of age in women at high risk for CVD	Screening intervals of every 4-6 years. Age to stop screening not well defined
Obesity	BMI calculation during visits to health services	If BMI changed, plan individual or group behavioral intervention with advice on diet and exercise Waist circumference ≥ 89 cm is considered high and indicative of higher cardiovascular risk
Diabetes mellitus	If there are no risk factors, screen from age 45 with no defined periodicity (possibly every 3-5 years).	Glycosylated hemoglobin (%) Normal: <5.7 Glucose intolerance: 5.7 to 6.4 Diabetes: ≥ 6.5 Fasting blood glucose (mg/dL) Normal: <100 Glucose intolerance: 100 to 125 Diabetes ≥ 126
Arterial hypertension	Screening in adults (>18 years). Frequency not established	Obtain measurements outside the hospital or clinical setting to confirm the diagnosis. > two measurements on two or more visits over a period of one or more weeks
Smoking	Questioning about tobacco use for all adults.	Brief five-step approach (the five A's): 1. Address the use of tobacco; 2. Advise quitting through a clear and personalized message; 3. Assess willingness to quit smoking; 4. Offer assistance to quit; 5. Arrange conditions for patient follow-up and support.

CVD: cardiovascular disease; BMI: body mass index.
Source: Ministry of Health.[23]

How to screen for osteoporosis?

Osteoporosis is often asymptomatic. Its diagnosis through bone densitometry or the documentation of an asymptomatic bone fragility fracture is essential to adopt the appropriate treatment. [26] Bone densitometry should be performed for all women over 65 years of age. Climacteric women under 65 years of age who have some risk factor for low bone mass (Chart 4) should also undergo the examination.[26]

Chart 4. Risk factors that indicate the need for bone densitometry in climacteric women under 65 years of age

Use of corticosteroids at a dose greater than 5 mg of prednisone/day (or equivalent) for 3 months or more
Low weight
Current smoking
Rheumatoid arthritis
Menopause before age 45
History of bone fragility fracture
Parents with a history of hip fracture
Alcoholism (≥ 3 alcohol units/day)

Source: Rosen and Drezner.[26]

In cases of doubt regarding the indication of bone densitometry, we recommend the analysis of the FRAX-Brasil using recommendations of the National Osteoporosis Guideline Group (NOGG).[27] The FRAX-Brasil is a computerized algorithm that calculates the probability of occurrence of major osteoporotic fracture and femoral neck fracture in ten years. FRAX and NOGG used together make it possible to select patients who would benefit from performing bone densitometry. Two intervention thresholds are considered based on age-specific fracture probability equivalent to women with a previous fragility fracture. Women classified below the lower limit do not need to undergo bone densitometry, while those above the upper limit are candidates for pharmacological treatment for osteoporosis, regardless of the results of the densitometry test. Those between the lower and upper limits must undergo bone densitometry and subsequently be reclassified according to the FRAX/NOGG.[27] FRAX-Brasil/NOGG is available for use at the following electronic address: https://abrasso.org.br/calculadora/calculadora/.

Bone fragility fractures occur in the absence of trauma or in the presence of "minor" trauma, often in the thoracolumbar spine, wrist, and hip.[26] They are the most common manifestation of osteoporosis, and may be asymptomatic in up to 70% of cases. As its diagnosis is essential to choose the appropriate therapy and reduce the risk of new fractures, thoracolumbar radiography is recommended for women with the characteristics described in Chart 5.[28]

How to screen for depression?

The menopausal transition is a window of vulnerability for the development of mood changes and depressive disorders. The risk of presenting symptoms is high during perimenopause, even in women without a

Chart 5. Indication of thoracolumbar radiography for the diagnosis of vertebral fractures in asymptomatic women

Low impact trauma fracture after 50 years
Prolonged treatment with corticosteroids
Loss of historical height[a] ≥ 4 cm or prospective height[b] ≥ 2 cm
Age greater than 70 years if spine, femoral neck or total femur BMD T-score ≤ -1.0[c]
Age between 65 and 69 years old if the spine, femoral neck or total femur BMD T-score ≤ -1.5[c]

BMD: bone densitometry
[a] Current height compared to the greatest height during adulthood. [b] Cumulative height loss measured between medical consultation intervals. [c] If bone densitometry is unavailable, radiography may be considered based on age alone.
Source: Cosman et al.[28]

personal history of depressive disorder.[29] Identifying women with depressive symptoms is important to adopt the appropriate therapy. Although there are no specific questionnaires for screening for mood disorders in menopausal women, some general screening tools such as the PHQ-9 can be used. This questionnaire is validated for Brazilian Portuguese and a score ≥ 9 identifies individuals at greater risk of having a major depressive episode.[30] Other questionnaires on climacteric symptoms, such as the Menopause Rating Scale, also incorporate questions related to mood and can be used to identify women at risk.[31] It is recommended to make the definitive diagnosis in consultation with a mental health professional.

How to screen for sexually transmitted infections?

In recent years, there has been an increase in the occurrence of STIs in climacteric and postmenopausal women. The high prevalence of menopausal genitourinary syndrome, which predisposes to bleeding during sexual intercourse, associated with greater accessibility to treatment for male erectile dysfunction, contributes to a greater chance of infection.[32] Behavioral counseling regarding condom use and treatment of the genitourinary syndrome of menopause are important tools to reduce this risk. Screening for STIs should be performed based on data from the clinical history of each patient.[6]

How to screen for thyroid disease?

Thyroid diseases are prevalent in aging women and can increase morbidity and mortality. The Latin American Thyroid Society (LATS) recommends the initial screening of women over 60 years of age for thyroid disease with a thyroid-stimulating hormone (TSH) measurement.[33] The symptoms of thyroid dysfunction are similar to those of hypoestrogenism, therefore, perimenopausal women who experience symptoms such as hot flashes, menstrual irregularity, weight gain, or depression should also have their thyroid function evaluated.[6,33] Screening for thyroid cancer in women at normal risk does not appear to be cost-effective, but clinical evaluation of the thyroid should be performed routinely during physical examination of climacteric women. When there is any change, such as a suspected goiter or nodule, thyroid ultrasound is indicated.[6,33]

What additional tests are necessary before prescribing hormone therapy and during its use?

Menopausal hormone therapy may be indicated to treat vasomotor symptoms associated with hypoestrogenism and the genitourinary syndrome of menopause, in addition to preventing bone loss and reducing the risk of bone fragility fractures.[11] The clinical history and a complete physical examination can rule out the vast majority of contraindications to the use of HT. Suspicious data in the anamnesis should be investigated with complementary exams. Note that the presence of a precursor lesion of breast cancer is a contraindication to the use of HT. Clinical breast examination in asymptomatic women has low sensitivity in the diagnosis of small lesions, which can lead to false negatives. Thus, women who will start HT should have performed a screening mammogram at the maximum of one year earlier.[11]

Some complementary exams help in choosing the best route of hormonal administration. Observational studies have shown that transdermal estrogen offers a lower risk of thromboembolic events.[34] The identification of women at greater risk of presenting already formed atheromatous plaques is important to define the best regimen for HT administration. Some international societies recommend the use of cardiovascular risk calculation instruments as an auxiliary tool in the decision on the administration of HT. The North American Menopause Society (NAMS) recommends using the tool developed by the American College of Cardiology available on the internet for use on computers or mobile devices.[35] According to NAMS, women with a risk of less than 10% in 10 years can receive HT, but those with cardiovascular risk between 5% and 10% would benefit more from the transdermal route.[8] The use of estrogen in women with high cardiovascular risk (>10% in 10 years) could destabilize atheromatous plaques and lead to thromboembolic events such as stroke and myocardial infarction.[8] Risk calculation tools use data from anamnesis, physical examination and some laboratory tests, such as total and HDL cholesterol. Therefore, measuring fasting glucose and lipid profile before starting HT is recommended. Even in women at low cardiovascular risk, the transdermal route is more appropriate when triglyceride values are above 400 mg/dL.[8]

Ensuring patient safety during medication use is critical, therefore, routine clinical evaluation should

be maintained. Cardiovascular risk factors should be reassessed periodically. Chart 3 details the screening schemes proposed by the Brazilian Ministry of Health. Orally administered estrogen can increase serum triglyceride and HDL levels, and decrease LDL levels. The effect is less evident with transdermal administration. An annual assessment of the lipid profile of women using oral HT is recommended.[11] There is no evidence that reducing the breast cancer screening interval to a period of less than one year is beneficial. It is recommended to perform mammographic screening annually. There is no evidence that the discontinuation of hormonal medication for one or two months before the mammogram improves the interpretation of the exam due to a supposed decrease in breast density.[11]

Women using systemic continuous combined HT with estrogen and progestagen are expected to have amenorrhea, even though irregular bleeding episodes may occur in the first few months of use.[36] Endometrial evaluation with transvaginal ultrasound and biopsy should be performed if there is persistent bleeding. Women using systemic continuous combined HT with amenorrhea who have a new bleeding episode and those using cyclic HT who have irregular bleeding also need endometrial evaluation.[11] Vaginal low-dose estrogen alone can be used to treat genitourinary menopausal syndrome. In these cases, the use of progestogen is not necessary, but the occurrence of abnormal uterine bleeding requires a prompt complementary endometrial investigation.[37]

Final considerations

Population aging is an established phenomenon in several countries. Aspects related to senility should be a constant reason for consultation with health professionals. The climacteric deserves to be highlighted, as it is accompanied by a series of physiological changes that imply disease prevention and health promotion needs. The medical consultation of climacteric women is an opportunity to screen for chronic diseases and neoplasms. The appropriate workup at this stage of life is one of the initial steps for physicians contributing to the quality of life of their patients.

References

1. Utian WH. Ovarian function, therapy-oriented definition of menopause and climacteric. Exp Gerontol. 1994;29(3-4):245-51. doi: 10.1016/0531-5565(94)90003-5
2. Ministério da Saúde. Instituto Sírio-Libanês de Ensino e Pesquisa. Protocolos da atenção básica: saúde das mulheres. Brasília (DF): Ministério da Saúde; 2016.
3. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab. 2012;97(4):1159-68. doi: 10.1210/jc.2011-3362
4. Welt CK. Ovarian development and failure (menopause) in normal women [Internet]. 2020 [cited 2020 Jun 21]. Available from: https://www.uptodate.com/contents/ovarian-development-and-failure-menopause-in-normal-women
5. Federação Brasileira das Associações de Ginecologia e Obstetrícia. Insuficiência ovariana prematura. São Paulo: Febrasgo; 2021. (Protocolo Febrasgo-Ginecologia, no. 26/ Comissão Nacional Especializada em Ginecologia Endócrina).
6. Shifren JL, Gass ML; NAMS Recommendations for Clinical Care of Midlife Women Working Group. The North American Menopause Society recommendations for clinical care of midlife women. Menopause. 2014;21(10):1038-62. doi: 10.1097/GME.0000000000000319
7. Voda AM. Climacteric hot flash. Maturitas. 1981;3(1):73-90. doi:10.1016/0378-5122(81)90022-0
8. Kaunitz AM, Manson JE. Management of menopausal symptoms. Obstet Gynecol. 2015;126(4):859-76. doi: 10.1097/AOG.0000000000001058
9. Casper RF. Clinical manifestations and diagnosis of menopause [Internet]. 2020 [cited 2020 Jun 21]. Available from: https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-menopause
10. Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2020: incidência de câncer no Brasil [Internet]. Rio de Janeiro: INCA; 2019 [cited 2020 Jun 1]. Available from: https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//estimativa-2020-incidencia-de-cancer-no-brasil.pdf
11. Pompei LM, Machado RB, Wender MC, Fernandes CE. Consenso Brasileiro de Terapêutica Hormonal da Menopausa – Associação Brasileira de Climatério (Sobrac). São Paulo: Leitura Médica; 2018.
12. Siu AL; U.S. Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2016;164(4):279-96. doi: 10.7326/M15-2886
13. Urban LA, Chala LF, Bauab SP, Schaefer MB, Santos RP, Maranhão NM, et al. Breast cancer screening: updated recommendations of the Brazilian College of Radiology and Diagnostic Imaging, Brazilian Breast Disease Society, and Brazilian Federation of Gynecological and Obstetrical Associations. Radiol Bras. 2017;50(4):244-9. doi: 10.1590/0100-3984.2017-0069
14. Committee on Practice Bulletins - Gynecology. Practice Bulletin Number 179: breast cancer risk assessment and screening in average-risk women. Obstet Gynecol. 2017;130(1):e1-e16. doi: 10.1097/AOG.0000000000002158
15. Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. Diretrizes brasileiras para o rastreamento do câncer do colo do útero [Internet]. 2a ed. Rio de Janeiro: INCA; 2016 [cited 2020 Jun 21]. Available from: https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//diretrizesparaorastreamentodocancerdocolodoutero_2016_corrigido.pdf
16. Federação Brasileira das Associações de Ginecologia e Obstetrícia. Rastreio, diagnóstico e tratamento do câncer de colo de útero. São Paulo: Febrasgo; 2017.
17. Menon U, Gentry-Maharaj A, Burnell M, Singh N, Ryan A, Karpinskyj C, et al. Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet. 2021;397(10290):2182-93. doi: 10.1016/S0140-6736(21)00731-5

18. Pinsky PF, Yu K, Kramer BS, Black A, Buys SS, Partridge E, et al. Extended mortality results for ovarian cancer screening in the PLCO trial with median 15years follow-up. Gynecol Oncol. 2016;143(2):270-5. doi: 10.1016/j.ygyno.2016.08.334

19. Chen L, Berek JS. Endometrial carcinoma: clinical features, diagnosis, prognosis, and screening [Internet]. 2021 [cited 2021 Jul 12]. Available from: https://www.uptodate.com/contents/endometrial-carcinoma-clinical-features-diagnosis-prognosis-and-screening

20. Committee Opinion No. 716: the role of the obstetrician-gynecologist in the early detection of epithelial ovarian cancer in women at average risk. Obstet Gynecol. 2017;130(3):e146-9. doi: 10.1097/AOG.0000000000002299

21. Wolf AM, Fontham ET, Church TR, Flowers CR, Guerra CE, LaMonte SJ, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018;68(4):250-81. doi: 10.3322/caac.21457

22. World Health Organization. Global action plan for the prevention and control of noncommunicable diseases 2013-2020. Geneva: WHO; 2013.

23. Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Atenção Básica. Rastreamento [Internet]. Brasília (DF): Ministério da Saúde; 2010 [cited 2020 Jun 23]. (Caderno de Atenção Básica; no. 29). Available from: http://189.28.128.100/dab/docs/publicacoes/cadernos_ab/abcad29.pdf

24. Lobo RA. Hormone-replacement therapy: current thinking. Nat Rev Endocrinol. 2017;13(4):220-31. doi: 10.1038/nrendo.2016.164

25. Précoma DB, Oliveira GM, Simão AF, Dutra OP, Coelho OR, Izar MC, et al. Updated Cardiovascular Prevention Guideline of the Brazilian Society of Cardiology – 2019. Arq Bras Cardiol. 2019;113(4):787-891. doi: 10.5935/abc.20190204

26. Rosen HN, Drezner MK. Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women [Internet]. 2020 [cited 2020 Jun 21]. Available from: https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-evaluation-of-osteoporosis-in-postmenopausal-women

27. Albergaria BH, Paula FJ. The Algorhytm: FRAX Brazil. Rev Bras Ginecol Obstet. 2019;41(8):467-8. doi: 10.1055/s-0039-1695027

28. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014;25(10):2359-81. doi: 10.1007/s00198-014-2794-2

29. Maki PM, Kornstein SG, Joffe H, Bromberger JT, Freeman EW, Athappilly G, et al. Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. Menopause. 2018;25(10):1069-85. doi: 10.1097/GME.0000000000001174

30. Santos IS, Tavares BF, Munhoz TN, Almeida LS, Silva NT, Tams BD, et al. Sensibilidade e especificidade do Patient Health Questionnaire-9 (PHQ-9) entre adultos da população geral. Cad Saúde Pública. 2013;29(8):1533-43. doi: 10.1590/0102-311X0014461

31. Heinemann LA, Potthoff P, Schneider HP. International versions of the Menopause Rating Scale (MRS). Health Qual Life Outcomes. 2003;1:28. doi: 10.1186/1477-7525-1-28

32. Baill IC, Castiglioni A. Health maintenance in postmenopausal women. Am Fam Physician. 2017;95(9):561-70.

33. Brenta G, Vaisman M, Sgarbi JA, Bergoglio LM, Andrada NC, Bravo PP, et al. Clinical practice guidelines for the management of hypothyroidism. Arq Bras Endocrinol Metabol. 2013;57(4):265-91. doi: 10.1590/s0004-27302013000400003

34. Mohammed K, Abu Dabrh AM, Benkhadra K, Al Nofal A, Carranza Leon BG, Prokop LJ, et al. Oral vs transdermal estrogen therapy and vascular events: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2015;100(11):4012-20. doi: 10.1210/jc.2015-2237

35. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S49-73. doi: 10.1161/01.cir.0000437741.48606.98

36. Archer DF, Pickar JH, Bottiglioni F. Bleeding patterns in postmenopausal women taking continuous combined or sequential regimens of conjugated estrogens with medroxyprogesterone acetate. Menopause Study Group. Obstet Gynecol. 1994;83(5 Pt 1):686-92.

37. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. Menopause. 2013;20(9):888-902. doi: 10.1097/GME.0b013e3182a122c2

Luiz Francisco Cintra Baccaro
Universidade Estadual de Campinas, Campinas, SP, Brazil.

Lúcia Helena Simões da Costa Paiva
Universidade Estadual de Campinas, Campinas, SP, Brazil.

Elizabeth Jeha Nasser
Departamento de Ginecologia e Obstetrícia, Faculdade de Medicina do ABC, Santo André, SP, Brazil.

Ana Lúcia Ribeiro Valadares
Universidade Estadual de Campinas, Campinas, SP, Brazil.

Célia Regina da Silva
Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil.

Eliana Aguiar Petri Nahas
Universidade Estadual Paulista "Júlio de Mesquita Filho", Botucatu, SP, Brazil.

Jaime Kulak Junior
Universidade Federal do Paraná, Curitiba, PR, Brazil.

Márcio Alexandre Hipólito Rodrigues
Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil.

Marco Aurélio Albernaz
Universidade Federal de Goiás, Goiânia, GO, Brazil.

Maria Celeste Osório Wender
Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil.

Maria Célia Mendes
Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, São Paulo, Brazil.

Rita de Cassia de Maio Dardes
Departamento de Ginecologia, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil.

Rodolfo Strufaldi
Departamento de Ginecologia e Obstetrícia, Faculdade de Medicina do ABC, Santo André, SP, Brazil.

Rogerio Cesar Bocardo
Faculdade de Medicina de Jundiaí, Jundiaí, SP, Brazil

Luciano de Melo Pompei
Departamento de Ginecologia e Obstetrícia, Faculdade de Medicina do ABC, Santo André, SP, Brazil.

Conflicts of interest: none to declare.

Instructions to Authors

Scope and policy

The material submitted for analysis cannot be simultaneously submitted for publication in other journals or previously published. In the selection of manuscripts for publication, are evaluated the originality, relevance of the theme, quality of the methodology used, and adequacy to the editorial standards adopted by the journal. The published material becomes intellectual property of the Brazilian Journal of Gynecology and Obstetrics and Febrasgo.

Manuscripts evaluation

The manuscripts submitted to the journal are received by the Editorial Office that checks the mandatory documentation and examines if the editorial norms contained in the Instructions to Authors have been fulfilled. If the process is in compliance, the manuscript is sent to the Editor-in-Chief, who will make a merit evaluation of the material. If the Editor-in-Chief concludes the work is in favorable scientific and technical conditions, the manuscript is forwarded to the Associate Editors, who will designate reviewers (double mind process) to evaluate it. Then, the reviewers' opinions and editor's instructions are sent to authors to inform them about changes to be made. Then, the authors resubmit the text with the suggested changes within the requested deadline. When resubmitting the manuscript, the requested corrections should be highlighted in yellow. In cases of disagreement with the suggestions, observations should be included in the comments balloons. Be assertive and punctual with the inquiry, and support the hypothesis with references.

IMPORTANT! Authors must comply with the deadlines, since non-attendance will result in delay of manuscript publication or even archiving of the process. At any point in the process of analysis and editing of the text, the authors may request the process suspension and withdrawal of the manuscript, except when it is accepted for publication. The concepts and statements contained in the articles are of the authors' responsibility.

Preparing a manuscript for submission

Mandatory submission documents

When submitting a manuscript to RBGO, attach the documents listed below on the ScholarOne submission platform. Note that not attaching the documents will result in cancellation of the submitted process. Mandatory documentation for online submission:

- Authorization of copyright transfer signed by all authors (scanned and attached as supplementary document) **Model;**
- In accordance with chapter XII.2 of Res. CNS 466/2012, in Brazil, research involving human subjects needs to inform the registration number referring to the Certificate of Ethical Assessment (CAAE) or the approval number of the research (CEP/CONEP) in the Ethics Committee. International manuscripts must present local ethical documentation to proceed with the submission process;
- Cover Letter: written to justify the publication. The authors should be identified, together with the title of the team that intends to publish, origin institution of the authors and intention of publication;
- Title page;
- Manuscript.

Title Page

- Title of the manuscript in English with a maximum of 18 words;
- Authors' full name without abbreviations and Orcid ID;
- Corresponding author (full name, professional mailing address and contact email);
- Institutional affiliation of each author. Example: Faculty of Medicine, University of São Paulo, Ribeirão Preto, SP, Brazil;
- **Conflicts of interest:** authors should report any potential conflicts of interest whether political, economic, of resources for research execution or intellectual property;
- **Acknowledgements:** restricted to people and institutions that contributed to research development in a relevant way. Any financial support provided by development agencies or private companies should be mentioned in the section Acknowledgments. For Brazilian authors, RBGO requests the citation of CNPq, Capes, FAPESP and other financing agencies, together with the number of research process or granted scholarships.
- **Contributions:** according to the criteria for scientific authorship of the International Committee of Medical Journal Editors (ICMJE), authorship credit must be based on three conditions met in full: 1. Substantial contributions to conception and design, data collection or analysis, and interpretation of data; 2. Writing of the article or critical review of the intellectual content; and 3. Final approval of the version to be published.

Manuscript

Instructions to Authors

The Brazilian Journal of Gynecology and Obstetrics publishes the following categories of manuscripts:

Original Articles, complete prospective, experimental or retrospective studies. Manuscripts containing original clinical or experimental research results have priority for publication.

Case Reports, of great interest and well documented from the clinical and laboratorial point of view. In the letter of referral, authors should indicate new or unexpected aspects in relation to already published cases. The text of Introduction and Discussion sections should be based on an updated bibliographic review.

Review Articles, including comprehensive reviews, meta-analysis or systematic reviews. Spontaneous contributions are accepted. The methods and procedures adopted for obtaining the text should be described, and based on recent references, including the current year. As this subject is still subject to controversy, the review should discuss the trends and lines of research under way. In addition to the text of the review, there should be an abstract and conclusions. See the 'Instructions to Authors' section for information on the text body and title page;

Letters to the Editor, dealing with editorial matters or not, but presenting relevant information to readers. Letters can be summarized by the editor, but maintaining the main points. In case of criticism to published works, the letter is sent to the authors so their reply can be published simultaneously;

Editorial, only at the publisher's invitation.

Title

When writing a scientific article, the researcher should focus on the manuscript title, which is the business card of any publication. It should be elaborated very carefully, and preferably written only after the article finalization. A good title adequately describes the manuscript content. Generally it is not a phrase, because it does not contain the subject, only verbs and arranged objects. Titles rarely contain abbreviations, chemical formulas, adjectives, names of cities, among others. The title of manuscripts submitted to RBGO must contain a maximum of 18 words.

Abstract

The abstract should provide the context or basis for the study, establish the objectives, basic procedures, main outcomes and key findings. It should emphasize new and important aspects of the study or observations. Since the abstract is the only substantive part of the article indexed in many electronic databases, authors should ensure it reflects the article content in an accurate and highlighted manner. Do not use abbreviations, symbols and references in the abstract. In case of original articles from clinical trials, authors must inform the registration number at the end of the text.

Informational abstract of structured type of original articles

Abstracts of original articles submitted to RBGO must be structured in four sections and contain a maximum of 250 words:

Objective: What was done; the question posed by the investigator.

Methods: How it was done; the method, including the material used to achieve the objective.

Results: What was found, the main findings and, if necessary, the secondary findings.

Conclusion: The conclusions; the answer to the question asked.

Informational abstract of structured type of systematic review articles

Among the included items are the review objective to the question asked, data source, procedures for selecting the studies and data collection, the results and conclusions. The abstracts of systematic review articles submitted to RBGO must be structured in six sections and contain a maximum of 250 words:

Objective: Declare the main purpose of the article.

Data sources: Describe the data sources examined, including the date, indexing terms, and limitations.

Selection of studies: Specify the number of studies reviewed and the criteria used in their selection.

Data collection: Summarize the conduct used for data extraction and how it was used.

Data synthesis: State the main results of the review and the methods used to obtain them.

Conclusions: Indicate the main conclusions and their clinical usefulness.

Informational abstract of unstructured type of review articles, except systematic reviews and case studies

It shall contain the substance of the article, covering the purpose, method, results and conclusions or recommendations. It exposes enough details so readers can decide on the convenience of reading the full text (Limit of words: 150).

Keywords

The keywords of a scientific paper indicate the thematic content of the text they represent. The main objectives of the aforementioned terms are the thematic content identification, indexing of the work in databases, and rapid location and retrieval of contents. The keyword systems used by RBGO are DeCS (Health Sciences Descriptors - Lilacs Indexer) and MeSH (Medical Subject Headings - MEDLINE-PubMed Indexer). Please choose five descriptors that represent your work on these platforms.

Manuscript body (Manuscripts submitted to RBGO must have a maximum of 4000 words. Note that tables, charts and figures in the Results section and References are not counted).

Introduction

The **Introduction** section of a scientific article has the purpose of informing what was researched and the reason for the investigation. This part of the article prepares the reader to understand the investigation and justification of its realization. The content informed in this section should provide context or basis for the study (i.e. the nature of the problem and its importance); state the specific purpose, research objective, or hypothesis tested in the study or observation. The study objective usually has a more precise focus when formulated as a question. Both the primary and secondary objectives should be clear, and any analyzes in a pre-specified subgroup should be described; provide strictly relevant references only and do not include data or conclusions of the work being reported.

Methods

According to the Houaiss dictionary, **Methods** "is an organized, logical and systematic process of research". The method comprises the material and procedures adopted in the research in order to respond to the central research question. Structure the Methods section of RBGO starting with the study design; research scenario (place and period in which it was performed); sample of participants; data collection; intervention to be evaluated (if any) and the alternative intervention; statistical methods used and the ethical aspects of the study. When thinking about the writing of the study design, reflect if it is appropriate to achieve the research objective, if the data analysis reflects the design, and if what was expected with use of the design was achieved to research the theme. Following, the guidelines used in clinical or epidemiological research that should be included in the section Methods of manuscripts sent to RBGO:

Types of study (adapted from Pereira, 2014*):

Case Report (Case study): In-depth investigation of a situation in which one or a few people are included (usually up to ten);

Case series: A set of patients (for example, more than ten people) with the same diagnosis or undergoing the same intervention. In general, these are consecutive series of patients seen in a hospital or other health institution for a certain period. There is no internal control group formed simultaneously. The comparison is made with external controls. The name of external or historical control is given to the group used to compare the results, but that was not constituted at the same time within the study: for example, the case series is compared with patients from previous years.

Transversal (or Cross-sectional) study: Investigation to determine prevalence; examine the relationship between events (exposure, disease, and other variables of interest) at any given time. Cause and effect data are collected simultaneously: for example, the case series is compared with patients from previous years.

Case-control study: Particular form of etiological investigation of retrospective approach in which the search of causes starts from the effects. Groups of individuals, respectively with and without a particular health problem are compared in relation to past exposures in order to test the hypothesis that exposure to certain risk factors is the contributing cause of the disease. For example, individuals afflicted with low back pain are compared with an equal number of individuals (control group) of the same sex and age, but without low back pain.

Cohort study: Particular form of investigation of etiological factors in which the search of effects starts from the cause; therefore, the opposite of case-control studies. A group of people is identified, and pertinent information on the exposure of interest is collected, so the group can be monitored over time, checking those who do not develop the disease in focus, and if the prior exposure is related to occurrence of disease. For example, smokers are compared to nonsmoker controls; the incidence of bladder cancer is determined for each group.

Randomized study: This has the connotation of an experimental study to evaluate an intervention hence the synonym of *intervention study*. Can be performed in a clinical setting; sometimes referred to simply as clinical trial or clinical study. It is also conducted at the community level. In clinical trials, participants are randomly assigned to form groups called study (experimental) and control (or testimony), whether submitted or not to an intervention (for example, a drug or vaccine). Participants are monitored to verify the occurrence of outcome of interest. This way, the relationship between intervention and effect is examined under controlled observation conditions, usually with double-blind evaluation. In the case of a **randomized study**, inform the number of the Brazilian Registry of Clinical Trials (REBEC) and/or the number of the International Clinical Trials Registration Platform (ICTRP/OMS) on the title page.

Ecological study: Research performed with statistics: the unit of observation and analysis is not constituted of individuals, but of groups of individuals hence the synonyms: study of groups, aggregates, clusters, statistics or community. For example, research on the variation of mortality coefficients for diseases of the vascular system and per capita consumption of wine among European countries.

Systematic Review and Meta-analysis: Type of review in which there is a clearly formulated question, explicit methods are used to critically identify, select and evaluate relevant research, and also to collect and analyze data from the studies included in the review. There is use of strategies to

limit bias in the localization, selection, critical evaluation and synthesis of relevant studies on a given topic. Meta-analysis may or may not be part of the systematic review. Meta-analysis is the review of two or more studies to obtain a global, quantitative estimate of the question or hypothesis investigated; and employs statistical methods to combine the results of the studies used in the review.

Source: *Pereira MG. Artigos Científicos – Como redigir, publicar e avaliar. Rio de Janeiro: Guanabara-Koogan; 2014.

Script for statistical review of original scientific papers

Study objective: Is the study objective sufficiently described, including pre-established hypotheses?

Design: Is the design appropriate to achieve the proposed objective?

Characteristics of the sample: Is there a satisfactory report on the selection of people for inclusion in the study? Has a satisfactory rate of responses (valid cases) been achieved? If participants were followed up, was it long and complete enough? If there was a pairing (eg. of cases and controls), is it appropriate? How did you deal with missing data?

Data Collection (measurement of results): Were the measurement methods detailed for each variable of interest? Is there a description of comparability of the measurement methods used in the groups? Was there consideration of the validity and reproducibility of the methods used?

Sample size: Has adequate information on sample size calculation been provided? Is the logic used to determine the study size described, including practical and statistical considerations?

Statistical Methods: Was the statistical test used for each comparison informed? Indicate if the assumptions for use of the test were followed. Was there information about the methods used for any other analysis? For example, subgroup analysis and sensitivity analysis. Are the main results accompanied by accuracy of the estimate? Inform the p value and confidence interval. Was the alpha level informed? Indicate the alpha level below which the results are statistically significant. Was the beta error informed? Or indicate the statistical power of the sample. Has the adjustment been made to the main confounding factors? Were the reasons that explained the inclusion of some and the exclusion of others described? Is the difference found statistically significant? Make sure there are sufficient analyzes to show the statistically significant difference is not due to any bias (eg. lack of comparability between groups or distortion in data collection). If the difference found is significant, is it also relevant? Specify the clinically important minimal difference. Make clear the distinction between statistically relevant difference and relevant clinical difference. Is it a one- or two-tailed test? Provide this information if appropriate. What statistical program is used? Inform the reference where to find it, and the version used.

Abstract: Does the abstract contain the proper article synthesis?

Recommendation on the article: Is the article in acceptable statistical standard for publication? If not, can the article be accepted after proper review?

Source: *Pereira MG. Artigos Científicos – Como redigir, publicar e avaliar. Rio de Janeiro: Guanabara-Koogan; 2014.

IMPORTANT!

RBGO joined the initiative of the International Committee of Medical Journal Editors (ICMJE) and the EQUATOR Network, which are aimed to improve the presentation of research results. Check the following international guides:

Randomized clinical trial:
http://www.consort-statement.org/downloads/consort-statement

Systematic reviews and meta-analysis: http://www.scielo.br/pdf/ress/v24n2/2237-9622-ress-24-02-00335.pdf

Observational studies in epidemiology: strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_combined.pdf

Qualitative studies: http://intqhc.oxfordjournals.org/content/19/6/349.long

Results

The purpose of the Results section is to show the study findings. It is the original data obtained and synthesized by the author with the aim to answer the question that motivated the investigation. For the writing of the section, present the results in logical sequence in the text, tables and illustrations, first mentioning the most important findings. Do not repeat all information of the tables or illustrations in the text. Emphasize or summarize only important observations. Additional or supplementary materials and technical details may be placed in an appendix where they will be accessible without interrupting the flow of the text. Alternatively, this information may be published only in the electronic version of the Journal. When data are summarized in the results section, provide numerical results not only in derived values (eg. percentages), but also in absolute values from which the derivatives were calculated, and specify the statistical methods used for their analysis. Use only the tables and figures necessary to explain the argument of the work and evaluate its foundation. When scientifically appropriate, include data analysis with variables such as age and sex. Do not exceed the maximum limit of five tables, five charts or five figures. Tables, charts and/or figures should be included in the body of the manuscript and do not count the requested limit of 4000 words.

ATTENTION!

In Case Studies, the Methods and Results sections should be replaced by the term Case Description.

Discussion

In the **Discussion** section, emphasize the new and important aspects of the study and the conclusions derived therefrom. Do not repeat details of data or other information presented in the introduction or results sections. For experimental studies, it is useful to begin the discussion by briefly summarizing the main findings, comparing and contrasting the results with other relevant studies, stating the limitations of the study, and exploring the implications of the findings for future research and clinical practice. Avoid claiming precedence and referring to incomplete studies. Do not discuss data not directly related to the results of the presented study. Propose new hypotheses when justifiable, but qualify them clearly as such. In the last paragraph of the Discussion section, cite which information of your work contributes relatively to advancement of knowledge.

Conclusion

The **Conclusion** section has the function of relating the conclusions to the objectives of the study, but authors should avoid unfounded statements and conclusions not adequately supported by data. In particular, authors should avoid making statements about economic benefits and costs unless their original includes economic analysis and appropriate data.

References

A study is based on the results of other research that preceded it. Once published, it becomes support for future work on the subject. In the report of their research, authors state the references of prior works consulted that they deem pertinent to inform readers, hence the importance of choosing good References. Properly chosen references lend credibility to the report. They are a source for convincing readers of the validity of facts and arguments presented.

Attention! For manuscripts submitted to RBGO, authors should number the references in order of entry into the manuscript and use those numbers for text citations. Avoid excessive references by selecting the most relevant for each statement and giving preference to the most recent work. Do not use hard-to-reach quotations, such as abstracts of papers presented at congresses, theses or restricted publications (non-indexed). Seek to cite the primary and conventional references (articles in scientific journals and textbooks). Do not use references such as 'unpublished observations' and 'personal communication'. Authors' publications (self-citation) should be used only if there is a clear need and relationship with the topic. In this case, include in bibliographical references only original works published in regular journals (do not cite chapters or revisions). The number of references should be 35, in exception review articles. Authors are responsible for the accuracy of data contained in the references.

Please check the Vancouver Citation Style to format your references.

*The Instructions to Authors of this journal were elaborated based in the literary work ***Artigos Científicos: Como redigir, publicar e avaliar de Maurício Gomes Pereira, Editora Guanabara Koogan, 2014.***

Submission of papers

The articles must, necessarily, be submitted electronically, according to the instructions posted on the site: http://mc04.manuscriptcentral.com/rbgo-scielo

There is no fee for submission and review articles.

Revista Brasileira de Ginecologia e Obstetrícia
Address: Brigadeiro Luiz Antonio Avenue, 3421, 01401-001, 903 room, Jardim Paulista, São Paulo, SP, Brazil.
Phone: + 55 11 5573.4919
E-mail: editorial.office@febrasgo.org.br
Home Page: https://www.thieme.com/rbgo