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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
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Editorial

Contraception for Women with Polycystic Ovary Syndrome: Dealing with a Complex Condition

Poli Mara Spritzer[1,2]

[1] Gynecological Endocrinology Unit, Division of Endocrinology, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil
[2] Department of Physiology, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

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Polycystic ovary syndrome (PCOS) is a complex condition, affecting around 9 to 13% of women at reproductive age and characterized by menstrual irregularity, ovulatory dysfunction, hyperandrogenism and polycystic ovarian morphology. Women with PCOS also present higher prevalence of obesity, cardiometabolic disturbances, such as dyslipidemia and hypertension and greater risk of impaired glucose tolerance and diabetes. Current evidence suggests that complex interactions between genetic, epigenetic, environmental, and behavioral factors contribute to the onset and to the heterogeneous clinical presentation of PCOS. In this context, and in the absence of pregnancy plans, it is essential to determine the ideal contraceptive method to offer according to the clinical, hormonal and metabolic profile of each woman.[1]

Menstrual disturbances are a very common clinical feature in women with PCOS. Effective treatment will protect the endometrium from estrogen stimulation and will significantly reduce the risk of endometrial hyperplasia and cancer. Also common are signs of clinical hyperandrogenism, namely hirsutism, acne, and hair loss, which should be considered when choosing a contraceptive method. This choice may, therefore, have advantages that are not related to contraception. As part of a holistic approach to women with PCOS, even if lifestyle changes (and weight loss for overweight and obese patients) can improve or prevent metabolic disorders, their cardiometabolic profile should also be taken into account when choosing a contraceptive method.

Combined oral contraceptive (COC) is the first-line pharmacological treatment for the management of menstrual irregularities in PCOS, offering, in addition to contraception, protection of the endometrium. In addition, COC is also recommended for treating clinical hyperandrogenism, combined or not with cosmetic treatments and/or antiandrogen drugs. COC acts by suppressing LH secretion, which induces a reduction in the ovarian production of androgens. These contraceptives also increase hepatic secretion of SHBG, thereby reducing circulating free testosterone levels.[2]

Current data do not support recommending specific estrogen-progestin combinations or types and doses of progestins that may be more effective than others in PCOS.[3,4] The effectiveness of COC depends, among other factors, on the duration of use, the severity of the clinical presentation, the adherence of patients to treatment. In this sense, COC containing a progestin with low affinity for the androgen receptor, such as those of the third generation (gestodene, desogestrel, norgestimate), and or a progestin with anti-androgen action (cyproterone acetate and drospirenone), could be preferred in the presence of signs of hyperandrogenism. However, the differences in efficacy between these molecules have not been clearly established.[3] In contrast, the lowest effective estrogen doses, such as 20–30 micrograms of ethinyl estradiol (EE) (or estradiol equivalent), should be considered, balancing efficacy and metabolic risk profile.[3] While the efficacy of different COC may be comparable, the risk of venous thromboembolic events should be considered before their prescription. Current data indicate that COC containing a second-generation progestin (levonorgestrel) or norgestimate have the lowest relative risk compared with other progestins.[5,6]

Among women with PCOS, using COC seems to have no deleterious effect on carbohydrate metabolism,[7] but long-term, good-quality longitudinal studies are needed to confirm these data. For some overweight women with PCOS and at-risk metabolic profile or risk factors for diabetes, the combination of the COC with metformin may be considered. Lifestyle changes, including a healthy diet and regular physical activity, are then essential.[3,8,9]

Although the benefits of COC in the long-term treatment of PCOS overall outweigh the risks of their use, the World Health Organization (WHO)[10] eligibility criteria for prescribing PCOS should be met. Screening for contraindications to COC is

Address for correspondence Poli Mara Spritzer, MD, PhD, Gynecological Endocrinology Unit, Division of Endocrinology, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil (e-mail: spritzer@ufrgs.br).

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therefore imperative before any prescription in women with PCOS.[10] Indeed, in case of contraindication or refusal of COC, oral progestin-only contraceptives and long-acting, non-oral contraceptives (LARC) are good alternatives for providing endometrial protection and guarantee contraception to women with PCOS. Progestin-containing LARC includes the intrauterine device locally delivering low doses of levonorgestrel, and the subcutaneous implant, which delivers etonogestrel. Injectable medroxyprogesterone acetate is also available, but the risks outweigh the benefits of this molecule in women with PCOS who have multiple cardiovascular risk factors, such as but not limited to, high blood pressure, diabetes with chronic complications.[10] After an initial period of use, progestin-only contraceptives can cause varying degrees of endometrial atrophy and amenorrhea. But, they can also be responsible for spotting or breakthrough bleeding.[11] The choice between progestin-only contraceptives or LARC needs to be individualized, as is the case for women without PCOS, respecting the patient's preference.

Although endometrial protection is assured with oral progestin-only contraceptives and LARC, this type of contraception has no effect on hyperandrogenism in women with PCOS, with the possible exception of a recently released oral drospirenone-only oral contraceptive.[12] If the choice is for using a LARC, and in the presence of hirsutism, it is possible to consider associating an anti-androgen with the contraceptive treatment. In women with PCOS who are overweight and have cardiometabolic risk factors, including insulin resistance or dysglicemia, metformin may be also added to the contraceptive.[3,8]

Regarding the copper intrauterine device, it is an effective contraceptive option and suitable for women who cannot or do not want hormonal contraception. In turn, this contraception has no effect on hyperandrogenism. Individualization of treatment is therefore recommended, combining, if necessary, an anti-androgen and/or metformin.[3]

Therefore, considering the multifaceted pattern of this clinical condition, the choice of contraception in women with PCOS should be tailored to the individual needs of each patient, which may additionally include lifestyle changes and specific treatment of comorbidities such as anti-obesity, anti-hypertensive, anti-diabetic or anti-lipid drugs, when applicable.

Conflict of Interest
None declared.

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Analysis of Variables that Influence the Success Rates of Induction of Labor with Misoprostol: A Retrospective Observational Study

Análise de variáveis que influenciam na taxa de sucesso da indução do parto com misoprostol: Um estudo observacional retrospectivo

Thayane Delazari Corrêa[1] Adriano Nascimento Barreto Junior[1] Maria Clara Mendes Batista[1] Mário Dias Corrêa Júnior[1] Henrique Vitor Leite[1]

[1] Department of Gynecology and Obstetrics, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil

Address for correspondence Thayane Delazari Corrêa, Master's degree, Av. Pres. Antônio Carlos, 6627, 31270-900, Pampulha, Belo Horizonte, MG, Brazil (e-mail: thayanedelazari@gmail.com).

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Abstract

Objective Determine the predictive criteria for success in inducing labor for live fetuses using misoprostol in pregnant women. Secondarily, the objective is to determine the rates of vaginal or cesarean delivery, duration of induction, interval of administration of misoprostol, the main causes of induction of labor and indication for operative delivery.

Methods Medical records of 873 pregnant women admitted for cervical maturation from January 2017 to December 2018 were reviewed in a descriptive observational study of retrospective analysis, considering the following response variables: age, parity, Bishop Index, doses of misoprostol, labor induction time. Logistic regression models were used to predict success with misoprostol in non-operative deliveries.

Results Of the 873 patients evaluated, 72% evolved with vaginal delivery, 23% of the cases were cesarean, 5% forceps or vacuum-extractor. For non-operative delivery the predictive variables at admission were age, parity, gestational age and dilation. During hospitalization, fewer vaginal touches, amniotomy or amniorrhexis with clear fluid lead to a shorter induction time and a greater chance of non-operative delivery. False positives and false negatives of the model were always below 50% and correct answers above 65%.

Conclusion At admission, age less than 24 years, previous normal births, lower the gestational age and greater the dilation, were predictive of greater probability of non-operative delivery. During hospitalization, the less vaginal touches and occurrence of amniotomy/amniorrhexis with clear liquid indicate shorter induction time. Future studies with a prospective design and analysis of other factors are necessary to assess the replicability, generalization of these findings.

Keywords
- obstetrics
- misoprostol
- complications of labor and delivery
- induced labor

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Resumo

Objetivo Determinar os critérios preditivos para o sucesso na indução do trabalho de parto para fetos vivos utilizando misoprostol em gestantes. Em segundo lugar, o objetivo é determinar as taxas de parto vaginal ou cesáreo, duração da indução, intervalo de administração de misoprostol, as principais causas de indução do trabalho de parto e indicação para parto operatório.

Métodos Foram revisados os prontuários de 873 gestantes internadas para amadurecimento cervical entre janeiro de 2017 e dezembro de 2018 em um estudo descritivo observacional de análise retrospectiva, considerando as variáveis-resposta: idade, paridade, Índice de Bishop, doses de misoprostol, tempo de indução do trabalho de parto. Modelos de regressão logística foram utilizados para prever o sucesso com misoprostol em partos não operatórios.

Resultados Dos 873 pacientes avaliados, 72% evoluíram com parto vaginal, 23% dos casos foram cesáreos, 5% fórceps ou vácuo-extrator. Para o parto não operatório as variáveis preditivas na internação foram idade, paridade, idade gestacional e dilatação. Durante a internação, um menor número de toques vaginais, amniotomia ou amniorrexe com líquido claro, levam a menor tempo de indução e maior chance de parto não operatório. Falsos positivos e falsos negativos do modelo sempre foram inferiores a 50% e respostas corretas acima de 65%.

Conclusão Na internação, idade menor que 24 anos, ocorrência de partos normais anteriores, menor idade gestacional e maior dilatação, foram preditivos de maior probabilidade de parto não-operatório. Durante a internação, o menor número de toques vaginais, amniotomia/amniorrexe com líquido claro indicam menor tempo de indução. Estudos futuros com design prospectivo e análise de outros fatores são necessários para avaliar a replicabilidade, generalização desses achados.

Palavras-chave

- obstetrícia
- misoprostol
- complicações do trabalho de parto
- trabalho de parto induzido

Introduction

Labor induction is one of the most performed obstetric interventions and refers to techniques of stimulation of the uterine contractions that will lead to labor.[1] According to the World Health Organization (WHO), in an assessment of maternal perinatal health, 9.6% of births worldwide need to be induced.[2]

The decision to induce labor is made when the continuity of pregnancy is associated with increased maternal or fetal risk, and there is no contraindication to vaginal delivery.[1] Successful induction of labor depends on the maturity of the cervix, which is generally assessed using the Bishop index, the best predictor of success for vaginal birth nowadays.[3] Several techniques for cervical ripening and labor induction are evaluated with the aim of reducing the cesarean section rates, with the available mechanical and pharmacological options.[4]

The main mechanical methods are: artificial rupture of membranes (amniotomy), membrane sweeping, and cervical dilators (laminaria and Krause method).[5] Pharmacological methods include prostaglandins (PGE2: dinoprostone or PGE1: misoprostol), selective modulators of progesterone receptors, oxytocin, and nitric oxide (NO) donating compounds.[6,7]

Misoprostol, a synthetic analogue of prostaglandin E1, has been used for labor induction since the 1990s and has a plasma half-life of less than one hour when administered vaginally.[8,9] It has been shown to be an effective stimulator of the myometrium of the gravid uterus by several studies. The use of misoprostol for induction of labor is still *off label*. This drug was initially approved by the FDA in an oral form (Cytotecs, Pfizer) to reduce the risk of ulcers induced by non-steroidal anti-inflammatory drugs (NSAIDs). However, this medication has been used for the past 30 years in the third trimester of pregnancy for cervical ripening and labor induction, being orally, vaginally, rectally, and sublingually applied, in high or low dose regimens, although the ideal route of use is still unknown. The doses initially used for induction of labor were empirical and ranged from 25 µg every 3 to 6 hours, to 200 µg in a single dose intravaginally or orally.[10]

Thus, as labor induction rates increase, it is of clinical importance to clearly determine the different variables that influence the safety and effectiveness of methods for inducing labor in pregnant women. As the appropriate doses of misoprostol for preparation and induction of labor in pregnant women with live fetuses are not well established, in the proposed study, the primary objective was to determine the predictive criteria for the success of labor induction with the use of misoprostol in pregnant women at the Otto Cirne Maternity Hospital of the Hospital das Clínicas of UFMG. Our secondary objective was to determine the rates of

vaginal or cesarean delivery, mean duration of induction, interval of misoprostol administration, the main causes of induction of labor, and indications for operative delivery.

Methods

A descriptive observational study of retrospective analysis was performed, with a review of the clinical records of pregnant women admitted for labor induction at the Otto Cirne Maternity of the Hospital das Clínicas of UFMG from January 2017 to December 2018.

Data were collected through the analysis of electronic and physical records of patients admitted for delivery. Pregnant women candidates for cervical ripening underwent maternal and fetal evaluation, confirming the absence of contraindications to induction of labor and vaginal delivery. The gestational age of all patients was determined by date of last menstruation or earlier ultrasound, anamnesis, and clinical examination.

The inclusion criteria in this study were patients followed-up at our service, with medical and obstetric indications for the labor induction with misoprostol in live fetuses. Exclusion criteria were based on our primary design, which was to study misoprostol labor induction in women with live fetuses. Therefore, in addition to the exclusion of women hospitalized for induction with a dead fetus on admission, induction with oxytocin without the use of misoprostol and women who had the induction initiated by legal interruption were also excluded, since fetal vitality and the newborn's outcome were not important and limiting factors of conduct for the obstetrician in these situations. Furthermore, women with contraindications to induction of labor or vaginal delivery were also excluded, as established in the HC-UFMG Obstetrics Protocol: history of previous uterine rupture, history of gynecological surgery on the uterine body (such as intramural myomectomy), active genital herpes, total placenta previa or vasa previa, cord prolapse, anomalous fetal presentations (except in fetal descent), macrosomia with estimated fetal weight greater than 4 kg, invasive cervical cancer, patient's refusal, non-reassuring fetal pattern, anomalous pelvis, some fetal congenital anomalies such as neural tube and/or abdominal wall closure defects with good neonatal prognosis, and fetal tumors that determine fetal-pelvic disproportion. Women who had used oxytocin after misoprostol and whose fetuses died during hospitalization were not excluded from this study.

Data collected from medical records were: age, parity, gestational age at admission and at delivery, days of hospitalization, maternal morbidity, induction indication, uterine height on admission, Bishop index on admission, total number of misoprostol tablets used, total number of doses of misoprostol used, analgesia, obesity according to the body-mass index (BMI), use of oxytocin during induction, maximum dose of oxytocin, type of delivery, time of delivery after beginning of induction, indication of operative delivery, Apgar index at birth (first minute) and Apgar after 5 minutes, fetal condition at birth (alive or dead), newborn weight, amniorrhexis, and clear fluid appearance, considered in admission and during labor. Maternal morbidity and indication for induction were described according to the medical records but for analysis purposes, groups were defined as described below.

Regarding maternal morbidity, as pregnant women admitted to the Hospital das Clínicas are primarily considered "High Risk" (~60%), around 85 different comorbidities were identified and divided into 8 groups: no comorbidities, hypertensive disorders, diabetes, mental disorders, heart disease, kidney disorders, infectious diseases, and "other": cholestasis, asthma, obesity, myasthenia gravis, thrombophilia, hypothyroidism, hearing loss, anemia, rheumatic fever, factor XI deficiency, congenital deafness, dermatopolymyositis, autoimmune thrombocytopenia, coagulopathy, Crohn disease, rheumatoid arthritis, adrenal adenoma, Cushing syndrome, isoimmunization, neoplasm, previous history of thrombosis, drug use, liver transplantation, systemic lupus erythematosus (SLE), epilepsy, myomatosis, pheochromocytoma, cholelithiasis, need for cerclage in pregnancy, alcoholism, Graves ophthalmopathy, hyperthyroidism, idiopathic thrombocytopenic purpura (ITP), antiphospholipid antibody syndrome (APLS), pituitary adenoma, sickle cell trait, smoking during pregnancy, maternal hydrocephalus, Hodgkin lymphoma, Von Willerbrand disease, ascites, vitiligo, pulmonary hypertension, isthmus-cervical incompetence, Turner syndrome, and history of bariatric surgery.

One point to be raised would be the lack of consensus on the concept of successful induction of labor. For example, for successful induction, the National Institute for Health and Clinical Excellence (NICE) considers achieving a vaginal delivery within 24 hours.[11] However, the WHO considers the rate of cesarean sections as an indicator of success.[2] And the Society of Obstetricians and Gynecologists of Canada (SOGC) considers vaginal delivery between 24 and 48 hours of induction as a success.[9] Other authors add "uncomplicated vaginal delivery," or "reaching the active phase of labor."[3] In our study, labor induction was considered successful when non-operative vaginal delivery occurred, without the use of forceps or vacuum extractor. Procedures with absence of uterine contractions, changes in the cervix, or complications during labor culminating in a cesarean section were considered as unsuccessful labor inductions.

The hospital chosen for the research was the Otto Cirne Maternity of UFMG's Hospital das Clínicas (UFMG-HC). This is a general, public, university hospital, which is a reference center in highly complex care for the Unified Health System of Minas Gerais (UHS/MG), with a monthly average of 190 births at the time of this study. The UFMG-HC protocol for misoprostol use determines a maximum dose of 275 mcg divided into 8 doses, as follows: 1 tablet of 25 mcg via the vaginal route every 4 hours in the first 5 doses, and 2 tablets of 25 mcg via vaginal (50 mcg) every 6 hours on the sixth, seventh, and eighth doses. Therefore, data was collected considering the number of doses, ranging from 1 to 8 doses; but the total number of pills inserted can range from 1 to 11 pills. In our study, the dose of misoprostol used was in accordance with the American College of Obstetricians and Gynecologists (ACOG) guidelines, which recommends a misoprostol dosage of 25 mcg every 3 to 6 hours (50 mcg every 6 hours may be appropriate in some situations).[5]

This research project was approved by the UFMG Research Ethics Committee (CAAE 06358919.7.0000.5149–Number 3.278.259, April 23rd, 2019) and does not present any conflict of interests.

As for the descriptive analysis, data from all patients were initially collected and recorded in Excel (Microsoft CO. Redmond, WA, USA). The statistical software R (R Foundation for Statistical Computing, Vienna, Austria) was used to set up a database and perform the statistical analyses. Data related to categorical variables were analyzed in frequency tables, which have both absolute and relative frequency. For the numerical variables, the measures of central tendency used were the mean and median; as measures of variation, we used the standard deviation (SD), the minimum value, the maximum value, and in some cases the limits of the 95% confidence intervals (95% CI) of the average.

The analyzes of the quantitative variables with the response variable (non-operative delivery) were performed using box plots[12] and the non-parametric statistical Mann-Whitney test,[13] also known as the unpaired Wilcoxon test, using the wilcox.test function in R. As for the qualitative variables, the analyzes were performed using bar graphs and the Yates chi-square test, with the chisq.test function in R.[14]

In a second step, multivariate logistic regression analysis was performed, aiming to create a predictive statistical model. Multivariate (or multiple) analyzes were performed using logistic regression techniques, with the glm function in R, which generates a final equation that can be used for future predictions, in addition to saying how much each variable influences (increases or decreases) the probability of occurrence of the event of the response variable.[14] We used the backward variable selection method, also known as variable elimination.[13] The final significance level chosen was 0.01 and not 0.05, due to how this selection method causes a possible underestimation bias of *p*-values. It is noteworthy that regardless of the result of the bivariate analyses, all variables entered the first model. Finally, the quality of the predictions of the models was evaluated through sensitivity, specificity, percentage of correct answers, and false positives and negatives.

Results

We selected 1065 patients hospitalized for labor induction at the Hospital das Clínicas of UFMG from January 2017 to December 2018. Among those, 84 pregnant women hospitalized with fetal failure and 104 pregnant women whose induction was not performed with the aid of misoprostol were excluded. The final analyzed sample contains 873 patients. No patient refused to undergo the induction process after medical advice and clarification of doubts (►**Fig. 1**).

►**Table 1** shows the mean age of patients, Bishop score on admission, number of misoprostol doses used in total, time of delivery after induction onset, Apgar score at birth and gestacional age at delivery.

The body mass index (BMI) of the participants was also evaluated; however, for only 139 of the participants was this information present in the medical record. Thus, we obtained a sample mean equal to 31.8, sample standard deviation equal to 6.69 and median equal to 31. Regarding the number of previous vaginal deliveries, 53.15% of the pregnant women had no previous vaginal delivery, approximately 25% of the

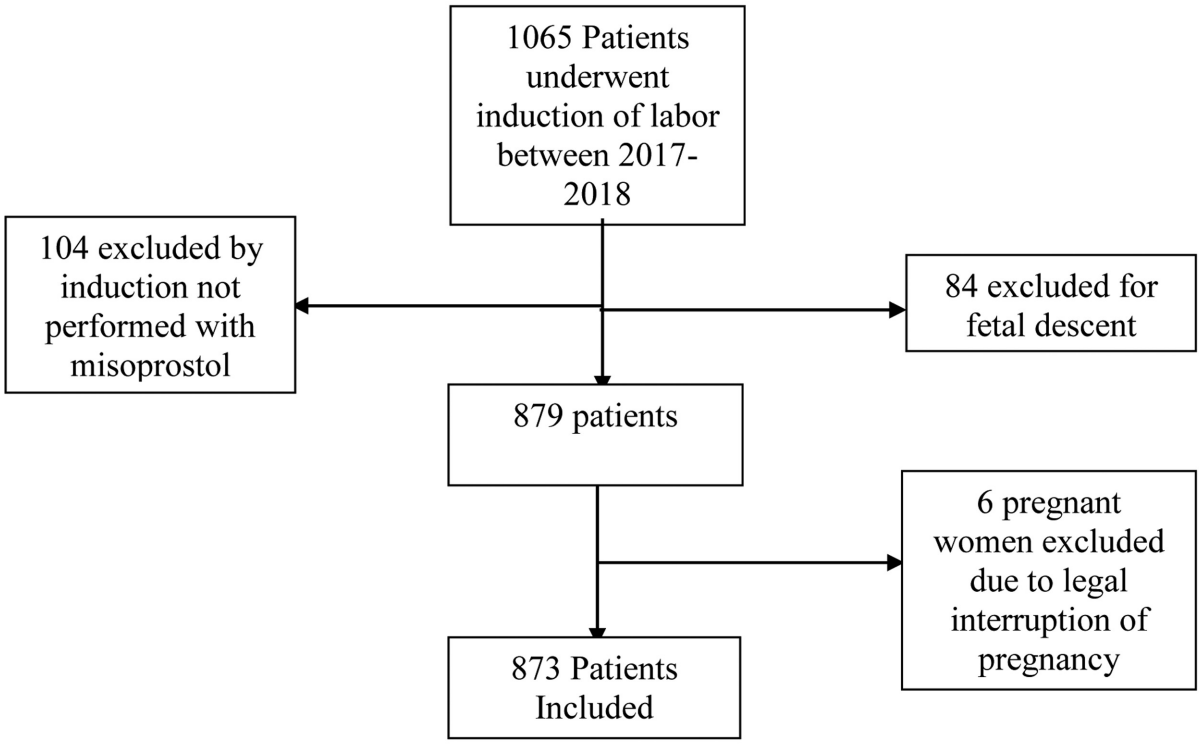

Fig. 1 Flowchart of patients selected for the study.

Table 1 Characterization of patients regarding mean age, Bishop score on admission, total number of misoprostol doses, time of delivery after induction onset, Apgar score at birth, and gestational age at delivery

	Mean	95% CI of the mean	Minimum – maximum
Age (years)	27.66 ± 6.83 (27)	(27.21; 28.12)	13–48
Bishop index at admission	1.59 ± 1.32 (1)	(1.50; 1.68)	1–6
Total number of misoprostol doses	3.59 ± 2.26 (3)	(3.44; 3.74)	1–10
Delivery time after beginning of induction (hours)	21.22 ± 13.30 (18.25)	(20.33; 22.10)	1–109
Apgar index at birth	7.85 ± 1.88 (8)	(7.72; 7.97)	0–10
Gestational age at delivery		**N (%)**	
Birth < 37 weeks		99 (11.4)	
Birth 37–41 weeks and 6 days		773 (88.5)	
Birth ≥ 42 weeks)		1 (0.1)	
Total		873 (100)	

Abbreviations: 95% CI, 95% confidence interval.

Table 2 Maternal morbidity

		Frequency
Groups	**n**	**%**
No comorbidities	356	40.8%
Hypertensive disorders	317	36.3%
Others	205	23.5%
Diabetes	127	14.6%
Infectious diseases	59	6.8%
Mental disorders	21	2.4%
Kidney disorders	21	2.4%
Heart diseases	20	2.3%
Total participants	873*	–

Note: *Patients could have more than one comorbidity, so the sum of the number of pregnant women in each group is greater than 873, which is the total number of participants.

Table 3 Childbirth outcome

Frequency		
Type of delivery	**n**	**%**
Cesarean delivery	199	22.8%
Vaginal delivery	632	72.4%
Vaginal delivery by forceps	34	3.9%
Vaginal delivery by vacuum extractor	8	0.9%
Total	873	100%

patients had one previous vaginal birth, 12.03% had two previous vaginal deliveries, and almost 5% had 3 or more previous deliveries. ►**Table 2** characterizes the patients regarding maternal morbidity, with 59.22% of the pregnant women having some comorbidity.

►**Table 3** shows the delivery outcome. It is clear that most patients who participated in the survey had non-operative vaginal delivery, which corresponds to just over 72%. The second most common type of delivery was the cesarean operation with almost 23% of the cases, followed by the forceps vaginal delivery, with approximately 4% of the deliveries, and finally the extraction vacuum vaginal delivery, which had just under 1% of the cases.

The time of delivery after the beginning of induction was also evaluated, which was timed from the insertion of the first misoprostol tablet until the birth of the newborn. We observed that 67.81% of the patients delivered within 24 hours and 26.92% delivered within 12 hours of the beginning of induction as an outcome. A considerable amount also presented delivery from 24 to 36 hours after the beginning of induction, approximately 18%. Only 4% gave birth 48 hour after the start of induction. The total average time of delivery after beginning of induction was 21.22 hours, with a sample deviation equal to 13.3. The smallest value identified was equal to 1 and the largest value equal to 109 hours. With the 95% confidence interval of the mean, we found a lower limit of 20.33 and an upper limit of 22.10. With the analysis of ►**Table 4**, we can see the main indications for labor induction, the main reason being hypertensive disorders, which affected approximately 37.46% of the patients. Antepartum amniorrhexis was the second most recurrent reason, found in 23.02% of the participants. Gestational age (18.33%) was the third most recurrent reason for labor induction, and comorbidities related to diabetes also had a significant frequency, in approximately 12.6% of the patients. The other indications occurred in a maximum of 10% of the patients. As each patient could have more than one reason for induction, the sum of frequencies in ►**Table 5** is not equal to the total number of participants.

►**Table 5** refers to the indication for operative delivery (cesarean section or instrumentalized vaginal delivery, with the use of forceps or vacuum extractor). The most recurrent indications are related to the group of acute fetal distress (34.85%), already presented, as well as induction failure (19.09%), cephalopelvic disproportion (CPD, 9.96%), and maternal exhaustion (9.96%).

Table 4 Indication of labor induction

	Frequency	
Indication	**n**	**%**
Hypertensive disorders	327	37.5%
Gestational age $\geq$ 41 weeks	160	18.3%
Antepartum amniorrhexis	201	23%
Diabetes	110	12.6%
Fetal indication	87	10%
Fetal malformations	57	6.5%
Others	55	6.3%
Severe maternal comorbidity	32	3.7%
Infectious diseases	29	3.3%
Total of participants	873	–

Notes: Fetal malformations: fetal heart disease, trisomy 13, trisomy 18, cystic adenomatoid malformation of the lung (MAC) type II, Dandy-Walker syndrome. Fetal indication: fetal macrosomia, intrauterine growth restriction (IUGR), fetal flow centralization, fetus large for gestational age (LGA), oligohydramnios, pelvic presentation, polyhydramnios.

The logistic regression analysis considering the outcome "nonoperative delivery" was performed. To adjust the final model, the database was first divided into a training base and a test base, the first having 70% of all observations (611) and the second 30% (262). Then, the selection of variables was made using the training base and following the backward method, in which the variables are extracted one by one. The equation for the probability of non-operative delivery is presented as ►**supplementary material**. The percentage of success of the predictive model in both the test base and the training base was 79.1%. This gave us confidence that there was no overfitting of the data, and the final result considered the entire database. However, although the original database contains 873 patients, as the records of some patients had missing values for some variables, 856 patients remained for evaluation of the model's prediction, as shown in ►**Table 6**.

In another template for nonoperative delivery, we chose to consider only the variables available at the time of patient's admission. The equation for the probability of non-operative delivery is presented as ►**supplementary material**. It is important to note that the three variables in common in the two results above (age, previous normal births, and gestational age at admission) have almost identical coefficients in the two models, indicating the robustness of the results. The percentage of accuracy of the predictive model was 73% in the test base and 76% in the training base, also not indicating a very big difference that could indicate an overfitting of the model to the data. Thus, the final results considered the entire database. Taking into consideration that the records of some patients had missing values for some variables, 871 patients remained for evaluation of the template's prediction, as shown in ►**Table 7**.

Table 5 Indication of surgical delivery

	Frequency		
Indication	**n**	**%**	**Total %**
Acute fetal distress	84	34.9%	9,6%
Induction failure	46	19.1%	5.3%
Maternal exhaustion	24	10%	2.8%
Cephalo-pelvic disproportion	24	10%	2.8%
Secondary arrest of dilation	21	8.7%	2.4%
Cesarean on request	8	3.3%	0.9%
Placental abruption	8	3.3%	0.9%
Macrosomy	5	2.1%	0.6%
Not informed	4	1.7%	0.5%
Acute fetal distress and maternal exhaustion	3	1.2%	0.3%
Pelvic presentation	2	0.8%	0.2%
Maternal heart disease	2	0.8%	0.2%
Twin pregnancy	2	0.8%	0.2%
IUGR with altered doppler	1	0.4%	0.1%
Induction failure and fetal macrosomia	1	0.4%	0.1%
HELLP syndrome	1	0.4%	0.1%
Provenance of hands	1	0.4%	0.1%
Fetal risk of intrapartum vaginal death	1	0.4%	0.1%
Acute fetal distress and breech presentation	1	0.4%	0.1%
Acute fetal distress and induction failure	1	0.4%	0.1%
Acute fetal distress and secondary arrest of dilation	1	0.4%	0.1%
Total	241	100%	27.6%

Abbreviations: IUGR, intrauterine growth restriction; HELLP, hemolysis, elevated liver enzymes, and low platelets. **Notes:** Induction failure: absence of labor after insertion of 8 doses of misoprostol or 11 tablets. Acute fetal distress: described in medical record as "persistent fetal bradycardia," "non reassuring fetal state ", "late deceleration in CTG" and "prolonged deceleration in CTG." The number of operative vaginal deliveries is 42 (4,8%); antepartum c-sections, 50 (5,7%); intrapartum c-sections, 149 (17%).

Table 6 Logistic regression forecast results for non-operative childbirth: final template for admission and hospitalization variables

Type of delivery	**Template (Expected Response)**		
(Response observed)	**Operative delivery**	**Non-operative delivery**	**Total**
Operative delivery	84	149	233
Non-operative delivery	30	593	623
Total	114	742	856

Notes: sensitivity = 95.2%; specificity = 36.1%; hit percentage = 79.1%; false positives = 20.1%; false negatives = 26.3%.

Table 7 Logistic regression prediction results for non-operative childbirth: final template for admission variables only

Type of delivery	Template (expected response)		
(Response observed)	Operative delivery	Non-operative delivery	Total
Operative delivery	56	185	241
Non-operative delivery	33	597	630
Total	89	782	871

Notes: sensitivity = 94.8%; specificity = 23.2%; hit percentage = 75.7%; false positives = 23.7%; false negatives = 37.1%.

Discussion

The aim of this study was to determine the predictive criteria for success in labor induction with the use of misoprostol, in addition to determining the rates of vaginal birth or cesarean operation, mean duration of induction, interval of misoprostol administration, the main causes of labor induction, and indication of operative delivery.

The association between cesarean operation and induction is reinforced by daily obstetric practice, and it is a common belief that induction of labor increases the risk of cesarean operation. However, using the appropriate comparison group, studies show that induction of labor is actually associated with a small decrease in this risk.[15] The labor induction rate between the years 2017 and 2018 at Hospital das Clínicas of UFMG was 27.8%, and the cesarean rate was 37.87% in the total number of deliveries performed.[16] Of the induced deliveries, we had a rate of caesarean section of 22.79% found in the study, which is significantly lower than the total group of patients monitored in our hospital.

This finding is in line with what is registered in the literature, and in a meta-analysis the cesarean rate was quite variable between the compared trials, with an overall trend of reduction with vaginal misoprostol (34 trials, RR (Relative Risk) 0.95, 95% CI (Confidence Interval) 0, 87 to 1.03).[17]

Regarding the time of delivery after the start of induction, we observed that almost 70% of the patients delivered within 24 hours, and approximately 27% delivered within 12 hours of the start of induction.

A randomized clinical trial demonstrated a higher proportion of women who delivered within 12 hours and within 24 hours using misoprostol combined with mechanical dilation using a Foley tube.[18]

The American College of Obstetricians and Gynecologists (ACOG) suggests that the appropriate dosage of misoprostol is 25 mcg every 3 to 6 hours (or 50 mcg every 6 hours, in some situations), the SOGC recommends 50 mcg orally with a glass of water or 25 mcg vaginally every 4 hours, while WHO recommends 25 mcg of oral misoprostol every 2 hours or 25 mcg of misoprostol vaginally every 6 hours for labor induction.[9] In our study, the dose of misoprostol used is in accordance with the ACOG, and proved to be adequate with satisfactory results.

A review on labor induction showed that the success of induction with vaginal birth increases with gestational age.[3] In our study, the most frequent types of pregnancies in the sample are those considered early term and full term, with 37.57% and 33.33% of the situations respectively, which may have influenced the best outcome.

In a prospective observational study, the main cause of induction was pregnancy $\geq$ 41 weeks, 29.8%, 17.9% with antepartum amniorrhexis, elective induction in 9.5% of the cases, followed by preeclampsia in 8.5% of cases, 8.1% with oligohydramnios, severe maternal morbidity in 7.7%, diabetes in 3.8%, severe fetal morbidity in 3.3%, and other causes $<$ 2%.[19] In our study, however, the main reason for induction were the hypertensive disorders, which affected approximately 37.46% of the patients. Followed by antepartum amniorrhexis in 23.02% of the participants. Gestational age was the third most recurrent reason for labor induction, in 18.33% of the patients, and comorbidities related to diabetes also had a significant frequency, in approximately 12.6% of the patients. The other indications occurred in 10% of the patients at most. This difference in relation to the literature may have occurred because the Hospital das Clínicas of UFMG is a high-risk referral unit.

As for the indication of cesarean, in a study of labor induction with oxytocin, misoprostol, or both, it was found that acute fetal distress played an important role in the indication of cesarean, with 35.1% correlation rates, followed by CPD with 23.4%, and 16% of induction failure.[20] In the present study, we found very similar results, with the most recurrent indications related to the group of acute fetal distress (34.85%), with induction failure in second place (19.09%), followed by CPD (9.96%), and maternal exhaustion (9.96%).

It should be noted that, in our study, these indications are not only for cesarean section, but also instrumentalized vaginal delivery, in which case the main cause was maternal exhaustion.

For induction to be successful, we generally take into account the maturity of the cervix, which is assessed using the Bishop index, the best predictor of success for vaginal birth nowadays.[3] A review that considered more than 40 articles correlated the Bishop index at the beginning of induction with its outcome, concluding that it would be a poor predictor and should not be used to decide whether or not to induce labor.[21] At the moment, however, this index remains the main tool for evaluating the uterine cervix at the beginning of induction. Our model proposes to complement this index, as it includes other variables that were not considered as predictors until now.

Regarding the logistic regression models found, for non-operative delivery, the model showed that at the time of admission, the younger maternal age, more previous normal deliveries, lower gestational age, and greater dilatation, all contribute for a higher probability of this patient undergoing non-operative delivery, which confirms the results in the literature. During hospitalization, the lower number of vaginal touches, in addition to the occurrence of amniotomy, amniorrhexis (on admission or hospitalization), and

appearance of clear fluid, were related to a higher occurrence of non-operative delivery.

For the models where the answer is non-operative delivery, the percentage of correct answers was 79% (admission and hospitalization variables) and 76% (only admission variables), which are considered high values. The percentages of false positives (35% and 42%) and false negatives (21% and 21%) were less than 50% in both models. Sensitivity was excellent in both models (95%), but specificity was low in both with 36% considering all variables (admission and hospitalization) and 23% using only admission variables. One of the reasons for this difference between sensitivity and specificity is the fact that the models predicted more non-operative deliveries than the actual total. Thus, it can be said that there was a "difficulty" of the models in identifying and predicting operative deliveries.

Overall, both logistic regression models designed here had difficulty predicting the least frequent outcome, which was operative deliveries (241 deliveries out of 873). On the other hand, false positives and false negatives were always less than 50%, and the percentage of correct answers was greater than 65%, indicating that the predictions made by such models are always more likely to be right than wrong.

A strength of this study would be that the overall clinical volume of the studied hospital and cesarean rates did not change significantly over the years spanning the study period, making the confounding factor related to temporal trends less likely. Another relevant point of this study was that we arrived at final models for predicting childbirth, with both admission and hospitalization variables.

As this is a retrospective study with review of medical records, some of the necessary patient data were not present in the medical records. Another important limitation of this study is that, although we had statistical power to detect differences in time from induction to delivery, for most outcomes—including cesarean operation, and adverse maternal and neonatal outcomes—we did not have the statistical power to discern potentially important differences between groups.

Conclusion

At admission, factors such as younger maternal age (age < 24 years), more previous normal births, lower gestational age, and greater dilatation, were all associated with a higher probability of undergoing non-operative delivery. During hospitalization, fewer vaginal touches, amniotomy and amniorrhexis with clear fluid, and shorter labor induction time were associated with a greater chance of non-operative delivery. However, despite the percentage of false positives and false negatives being always below 50% and that of correct answers being above 65%, the final models had difficulty predicting the outcome "operative delivery" because it was less frequent.

Furthermore, in our study, labor induction with misoprostol had a 15% lower cesarean incidence compared with the overall cesarean rate of our hospital in the study's period, with most patients (almost 70%) giving birth in up to 24 hours after initiation of induction, using up to 4 doses of the tablet.

The most recurrent indications for operative delivery and the main causes of labor induction in this study were similar to those found in the literature, the second differing only in the frequency and order of the results found, a fact that may have occurred because the Hospital das Clínicas of UFMG is a high-risk reference unit. Future studies in different environments, with a prospective design and analysis of other factors are needed to assess replicability, generalization of these findings, and improved prediction rates.

Contributions

All authors participated in the concept and design of the present study; in the analysis and interpretation of data; in the draft or revision of the manuscript; and all 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.

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Perioperative Outcomes in Pregnant Women Who Underwent Surgery for Adnexal Torsion

Resultados perioperatórios em mulheres grávidas submetidas a cirurgia para torção anexial

Huseyin Ekici[1] Fırat Okmen[1] Metehan Imamoglu[1,2] Ismet Hortu[1,3,4] Ali Akdemir[1,3]

[1] Department of Obstetrics and Gynecology, School of Medicine, Ege University, Izmir, Turkey
[2] Department of Obstetrics and Gynecology, School of Medicine, Yale University, New Haven, Connecticut, United States
[3] Department of Stem Cell, Institute of Health Sciences, Ege University, Izmir, Turkey
[4] Department of Molecular Pharmacology and Physiology, Morsani College of Medicine, University of South Florida, Tampa, FL, United States

Address for correspondence Ismet Hortu, Department of Obstetrics and Gynecology, School of Medicine, Ege University, 35100, Bornova, Izmir, Turkey (e-mail: ismethortu@yahoo.com).

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Abstract

Objective To evaluate clinical characteristics, maternal and fetal outcomes in pregnant women who underwent surgery for adnexal torsion (AT).

Methods All patients, who underwent surgical operation due to AT during pregnancy at the Department of Obstetrics and Gynecology, School of Medicine, Ege University between 2005 and 2020 were retrospectively investigated. Main clinical and perioperative outcomes were evaluated.

Results A total of 21 patients who underwent surgery due to AT during pregnancy were included. Of all patients, 61.9% underwent laparoscopy and the remaining 38.1% underwent laparotomy. The most common surgical procedure was adnexal detorsion in both groups (48%). Mean gestational age at the time of diagnosis, duration of surgery and hospitalization were significantly lower in the laparoscopy group, when compared with the laparotomy group ($p = 0.006$, $p = 0.001$, and $p = 0.001$, respectively.) One of the patients had an infection during the postoperative period. Spontaneous abortion was only observed in one case.

Conclusion It can be concluded that the surgical intervention implemented for the exact diagnosis and treatment of AT (laparotomy or laparoscopy) did not have an unfavorable effect on pregnancy outcomes such as abortion, preterm delivery, and fetal anomaly. However, laparoscopy may be superior to laparotomy in terms of advantages.

Keywords
- adnexal torsion
- pregnancy
- emergent surgery
- perinatal outcomes

Resumo

Objetivo Avaliar as características clínicas, e os desfechos maternos e fetais em gestantes submetidas à cirurgia de torção anexial.

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Métodos Todas as pacientes operadas por torção anexial durante a gravidez no Departamento de Obstetrícia e Ginecologia da Faculdade de Medicina da Universidade de Ege entre 2005 e 2020 foram investigadas retrospectivamente. Os principais resultados clínicos e perioperatórios foram avaliados.

Resultados Foram inclusas 21 pacientes operadas por torção anexial durante a gravidez. De todos as pacientes, 61,9% foram submetidas à laparoscopia e as 38,1% restantes foram submetidas à laparotomia. O procedimento cirúrgico mais comum foi apenas a destorção anexial em ambos os grupos (48%). A idade gestacional média no momento do diagnóstico, a duração da operação e da hospitalização foram significativamente menores no grupo de laparoscopia em comparação com o grupo de laparotomia ($p = 0,006$, $p = 0,001$ e $p = 0,001$, respectivamente.) Uma das pacientes teve uma infecção no pós-operatório. Apenas em um caso observamos aborto espontâneo.

Conclusão Pode-se concluir que a intervenção cirúrgica implementada para o diagnóstico exato e tratamento da torção anexial (laparotomia ou laparoscopia) não teve efeito desfavorável nos desfechos da gravidez, como aborto, parto prematuro e anomalia fetal. No entanto, a laparoscopia pode ser superior à laparotomia em termos de vantagens.

Palavras-chave
- torção anexial
- gravidez
- cirurgia emergente
- resultados perinatais

Introduction

Ovarian torsion is the complete or partial twisting of the pedicle on its vascular axis, which includes the ovarian arterial and venous vessels, interrupting the blood supply. If the ovarian torsion is accompanied by fallopian torsion, it is called adnexal torsion (AT). The adnexal detorsion (AD) surgery constitutes 2.7% of all gynecological emergent surgeries during pregnancy and may affect women of all ages, particularly during the reproductive period.[1–3]

The AT is rather rare during pregnancy and its incidence is between 1 and 5 in every 10,000 patients, among cases with spontaneous pregnancy.[4,5] Following the implementation of the assisted reproductive techniques (ART), the number and size of the follicular cysts increase along with the dramatic increase in the risk of torsion. The incidence of torsion may increase in up to 8%, particularly among women with ovarian hyperstimulation syndrome.[6] Although AT is usually encountered in the first trimester, it may also emerge in the second and third trimesters.[7]

Early diagnosis is crucial for the preservation of the ovarian and tubal functions and decrease of the related risks of other morbidities. Since there are no exact diagnostic and imaging criteria for the confirmation of the preoperative diagnosis of AT, immediate surgical intervention is also important to preserve ovarian tissue and fertility, and preventing the adverse pregnancy outcomes. Laparoscopy is an effective and safe surgical method mostly preferred for AT treatment in pregnant and non-pregnant women in experienced centers.[8] There are only a limited number of studies focused on the course of the AT and its effects on pregnancy outcomes.

Methods

All patients, who had undergone surgery due to AT during pregnancy at the Department of Obstetrics and Gynecology, School of Medicine, Ege University (Izmir, Turkey) between 2005 and 2020, were retrospectively investigated. The data related to the demographic characteristics, medical, surgical and obstetric history, findings of the preoperative laboratory and ultrasound examinations, surgery reports, anesthesia, and hospitalization were accessed from the patients' antenatal follow-up files. Pregnancy outcomes such as abortion, gestational age at birth, birth weight, and congenital anomalies were investigated in detail. This study was approved by the Local Ethics Committee of the School of Medicine at Ege University (Approval ID: 20–6.1T/54). Patients whose medical records related to pregnancy monitoring and delivery were not available were excluded from the study.

Regarding imaging methods, we used 2-D ultrasonography, with the Voluson-E8 (General Electric Healthcare, Wauwatosa, WI, USA), 3–9 MHz Transducer scanner and, less frequently, the magnetic resonance imaging (MRI) Magnetom Symphony (Siemens. Erlangen, Germany) 1.5-Tesla scanner. The ultrasound reports were retrospectively scanned, and the findings were divided into three groups: normal ovaries without the presence of cysts or mass, cystic ovaries, and hyperstimulated ovaries. The evaluation of the ultrasound reports showed that the short and long axis of the ovaries were measured in all patients. Furthermore, the mean ovarian diameter was measured, as the calculation of the ovarian volume was not possible. The preoperative white blood counts (WBC) and C-reactive protein (CRP) values were available for all patients. The participating patients were divided into groups according to the preferred surgical intervention (laparoscopy and laparotomy) and the trimester during which AT emerged (first trimester: 5^{th}–14^{th} gestational weeks; second trimester: 14^{th}–28^{th} gestational weeks; third trimester: 28^{th} gestational week–term). We evaluated the differences for the surgical characteristics, ultrasound findings, and pregnancy outcomes between the two groups.

In patients who went through laparoscopy, the Veress needle was inserted into the umbilicus to create pneumoperitoneum with carbon dioxide gas. In the cases of patients who had previous surgery in the medical history, had suspected periumbilical adhesions, and were in advanced gestational weeks ($\geq$ 15 weeks), the Veress needle was inserted at the Palmer point to create pneumoperitoneum. After the intraabdominal pressure reached 10 to 12 mm Hg, and the 10 to 12 mm primary trocar was placed, the surgeon decided for the placements of the assistant trocars, taking the gestational week and the size of the adnexal mass into consideration. The supine position was selected for first-trimester patients, and left lateral position for the second-trimester patients to avoid aortocaval compression syndrome. In the laparotomy group, the decision of the abdominal incision was made according to the size of the uterus, and size and location of the adnexal mass. In the cases of patients who had undergone cystectomy and salpingo-oophorectomy, all resected materials were referred to the pathological examination. The fetal heartbeat was checked with an ultrasound before and after the intervention. All operations were performed by experienced, high-volume surgeons.

The Statistical Package for the Social Sciences (SPSS, IBM Corp. Armonk, NY, USA) software, version 25.0, was used for the statistical analysis. The normal distribution of the numerical variables was analyzed with the Shapiro-Wilk test ($n < 50$). The numerical variables were given in mean $\pm$ standard deviation (SD), or median (min–max). The categorical variables were given in numbers and percentages. The independent binary sample *t*-test was used in normal distribution, and the Mann-Whitney U test was used in non-normal distribution. The Pearson Chi-square test and the Fisher exact test were used for the categorical variables.

Results

A total of 21 patients who had undergone surgery due to the AT during pregnancy were retrospectively investigated throughout the study period. The demographic and obstetric characteristics, as well as laboratory findings, were listed in ►**Table 1**. The mean gestational week at the time of diagnosis was found to be 11.9 ± 4.6 (range 6–22). In 14 patients (66.6%) the AT developed in the first trimester, and in 7 patients (33.3%) in the second trimester. Six patients (28.6%) became pregnant after ART implementations (in vitro fertilization: 3 cases; ovulation induction: 3 cases), and the remaining patients became pregnant through spontaneous conception.

The preoperative imaging examination was mainly performed with ultrasonography and, less frequently, with MRI. We observed cystic lesions in the adnexa (single, multiple or cystic teratoma) in 47.6% of the cases, ovarian enlargement without mass or cyst in 38.1% of the patients, and hyperstimulated ovaries in 14.3% of the patients. The mean ovarian diameter was 77 ± 19 mm (range 52–130). Thirteen patients had their blood flow assessed by Doppler ultrasonography and normal blood flow was observed in 6 patients, who were surgically diagnosed with AT (false-negative rate: 46%). The laboratory analysis showed that both preoperative WBC (12.368 ± 4.864 cells/μL) and CRP (1.2 ± 0.8 mg/dL) were slightly elevated.

Table 1 Demographic and clinical characteristics of the patients

Parameter	Results
Maternal age (years)	30 ± 3.9
Parity, n (%)	
Nulliparous	9 (42.8%)
Parous	12 (57.2%)
Surgical history, n (%)	
Laparoscopy	3 (14.3%)
Laparotomy	6 (28.6%)
GA at the time of torsion (weeks)	11.9 ± 4.6
GT at the time of torsion*	
First trimester	14 (66.6%)
Second trimester	7 (33.3%)
Mode of conception, n (%)	
Spontaneous conception	15 (71.4%)
Assisted reproductive technology	6 (28.6%)
Twin pregnancy	1 (4.7%)
Torsion side	
Right	13 (61.9%)
Left	8 (38.1%)
Preoperative WBC (cells/ μL)	$12{,}368 \pm 4{,}864$
Preoperative CRP (mg/dL)	1.2 ± 0.8

Abbreviations: CRP, C-reactive protein; GA, gestational age; GT, gestational trimester; WBC, white blood cell. Notes: Data are given as mean $\pm$ SD and/or percentage. * No cases were seen in third trimester.

Regardless of the gestational week, laparoscopy and laparotomy were performed in 61.9% ($n = 13/21$) and 38.1% ($n = 8/21$) of the patients, respectively. The most common surgical procedures were only adnexal detorsion (48%) (►**Fig. 1**). In one patient, who had AT in her medical history before pregnancy, adnexal fixation was performed to prevent recurrence. Histopathological examination was performed in patients who underwent cystectomy and salpingo-oophorectomy: 2 cases had dermoid cysts; 2 cases serous cysts, one case a paratubal cyst, and 1 case an inflammatory cyst. We encountered no intraoperative complications in any patients and only one second-trimester patient, who underwent laparotomy and salpingo-oophorectomy, developed an infection in the postoperative period. The comparison of the patients according to the implemented surgical method (laparoscopy or laparotomy) showed that there was a statistically significant difference between the groups for the gestational week at the time of diagnosis ($p = 0.006$), duration of surgery ($p = 0.001$), and hospitalization ($p = 0.001$). There was no statistically significant difference between the

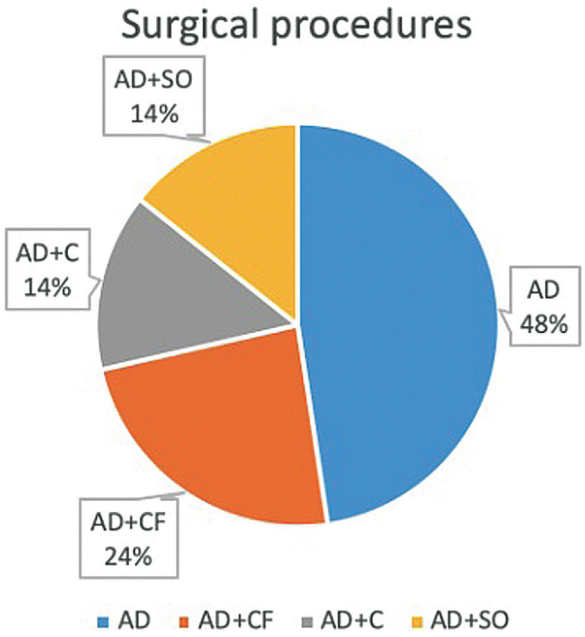

Fig. 1 Type of the surgical procedures in adnexal torsion during pregnancy. AD: Adnexal de-torsion only, CF: cyst fenestration, C: cystectomy, SO: salpingo-oophorectomy.

groups for the gestational week at delivery, birth weight, preterm birth, cesarean section, ultrasound findings, and complications (►**Table 2**).

The average gestational age at delivery was 38.1 ± 1.7 weeks (range 34–41 weeks) among women with live birth; three of the cases (14.3%) had delivered before the 37th gestational week, and the remaining 18 cases (85.7%) in the 37th gestational week or later. The rate of cesarean section was 52.4% (n = 11/21) and all indications depended on the routine fetal, obstetric, or maternal factors. The majority of the patients (95.2%) gave live birth (n = 20/21) and only in one first-trimester patient, who had undergone laparoscopy and AD, spontaneous abortion happened two weeks after surgery. We observed no fetal anomaly in women who had given live birth. The comparison of patients according to the trimester, during which surgery was performed (first trimester and second trimester), showed that there was a statistically significant difference between the groups for the duration of surgery ($p = 0.020$) and hospitalization ($p = 0.009$). There was no statistically significant difference between these groups for the abortion rates, gestational age at delivery, birth weight, preterm birth, and cesarean section (►**Table 3**).

Discussion

The AT is one of the most common emergent conditions in obstetrics and gynecology, and it challenges the clinicians because of the maternal and fetal risks.[2] Primarily, AT is suspected because of the nonspecific symptoms such as nausea and vomiting, examination findings (low-grade fever, lateralized lower abdominal pain), and imaging method findings. The definitive diagnosis is done during the surgery. Although it can occur in any trimester, it is more common in the first trimester.[7] In our study, two-third of the cases were in the first trimester. The AT is more common in the first trimester, as the functional ovarian cysts and hyperstimulated ovaries are more common in this trimester. It is relatively rare in the second and third trimesters because these cysts spontaneously regress in these trimesters. Women who underwent ovulation induction and in vitro

Table 2 Clinical and operative characteristics of the patients

Variable	Laparoscopy group	Laparotomy group	*p*-value
GA at the time of diagnosis (weeks)	9.8 ± 3.4	15.25 ± 4.6	0.006
Operation time (min)	61.6 ± 8.3(45–70)	84 ± 13.4(70–100)	0.001
Duration of hospitalization (days)	3.5 ± 1(2–5)	5.7 ± 1(4–7)	0.001
GA at birth (weeks)	38.1 ± 1.7(34–41)	37.7 ± 2(35–40)	0.549
Birthweight (g)	3,043 ± 338 (2,400–3650)	3,010 ± 292 (2,600–3530)	0.821
Preterm delivery n/N (%)	1/13 (7.7%)	2/8 (25%)	0.271
Cesarean section, n/N (%)	7/13 (53.8%)	4/8 (50%)	0.676
Ultrasonographic findings n/N			
Normal-appearing ovary without cysts	6/13 (46.2%)	2/8 (25%)	0.4
Cystic ovary	5/13 (38.4%)	5/8 (62.5%)	0.387
Hyperstimulated ovary	2/13 (15.4%)	1/8 (12.5%)	0.54
Complications			
Intraoperative n/N (%)	0/13	0/8	NA
Postoperative n/N (%)	0/13	1/8 (12.5%)	0.381

Abbreviation: GA, gestational age; NA, Not applicable. Notes: Data are given as mean ± SD and percentage. Range is given inside the parentheses.

Table 3 Comparison of surgical and obstetric characteristics at first trimester and second trimester

Variable	First trimester	Second trimester	*p*-value
Operation time (min)	63.4 ± 9.8 (45–80)	84.2 ± 15.1 (70–100)	**0.020**
Hospitalization (days)	3.7 ± 1.3(2–7)	5.5 ± 0.9 (4–7)	**0.009**
GA at delivery (weeks)	38.1 ± 1.8(34–41)	37.7 ± 1.7 (35–40)	0.601
Birthweight (g)	3,018 ± 348 (2,400–3,650)	3,052 ± 259 (2,600–3,420)	0.820
Preterm delivery, n/N (%)	1/14 (7.1%)	2/7 (28.6%)	0.186
Cesarean section, n/N (%)	7/14 (50%)	4/7 (57.1%)	0.761

Abbreviation: GA, gestational age. Notes: Data are given as mean ± SD and percentage. Range is given inside the parentheses.

fertilization are under higher risk of AT. Regarding the studies focused on the effects of AT on pregnancy, 73.2%,[4] 48.5%,[9] and 47.9%[10] of the study samples consisted of pregnancies after ART. In our study, this rate was 28.6% and this relatively low rate can be explained by the following factors: implementation of the frozen thaw cycle after the cancellation of the embryo transfer in the same cycle in patients with the hyperstimulated ovary; preference of gonadotropin-releasing hormone antagonists (GnRH antagonists) instead of gonadotropin-releasing hormone analogues (GnRH), which overstimulates the adnexa; early detection of predisposition to ovarian hyperstimulation, and implementation of the appropriate interventions.[11]

Transabdominal ultrasonography is frequently the preferred imaging method for AT. Enlarged ovary, solid/cystic/complex ovarian mass, pelvic fluid, and edematous ovarian stroma with peripherally located small follicles are the most common findings in ultrasonographic examinations.[12] The Doppler ultrasound modalities have limited use in AT due to the low sensitivity and operator-dependent usage.[13] If the findings of the ultrasonographic examination are indefinite, MRI may be useful (typically best seen on T2-weighted images).[14] In general, an ovarian diameter equal to or greater than 5 cm is strongly related with AT.[15,16] Hasson et al.[4] reported a mean ovarian diameter of 70 ± 23 mm and a false negativity rate of 61% after the ultrasonographic examination. In our study, the mean ovarian diameter was 77 ± 19 mm and the false negativity rate was 46% in the Doppler ultrasonographic evaluation. Several biochemical parameters such as leukocytosis, CRP, and erythrocyte sedimentation rate were measured in AT cases, and it was found that they were not relevant to diagnosis.[17,18] In our study, we also measured the WBC and CRP parameters and observed slightly elevated levels.

The decision for surgery during pregnancy, particularly in emergencies, is not always easy depending both on the circumstances related to surgery and possible effects of surgery on pregnancy outcomes. In the current literature, it was reported that laparoscopy did not increase the rate of the maternal and fetal complications, and it can be safely and effectively used in the diagnosis and treatment of AT.[19] For this procedure, the optimal gestational week is the second trimester, and several cases who were treated successfully with laparoscopy up to the 34th gestational week were reported.[20] In our study, regardless of gestational age, the majority of the cases (61.9%) was treated with the laparoscopic approach. Laparotomy was implemented predominantly between 2005 and 2010 and laparoscopy became more popular with the increase of medical experience with endoscopic surgery. Like in previous studies, the duration of surgery and hospitalization were shorter in cases that underwent laparoscopy.[21,22] Regarding the pregnancy outcomes, no significant difference was observed between laparoscopy and laparotomy. There was no need to convert from laparoscopy to laparotomy in any patient.

Some precautions should be taken to decrease complications during pregnancy related to these procedures, as noted in the literature. These include left lateral recumbent positioning, to minimize compression of vena cava inferior and aorta; initial port placement; and the Veress needle insertion sites should be adjusted according to the gravid's uterine size. Safer alternative sites, such as the Palmer point open technique, can be implemented to prevent devastating complications. Intra-abdominal pressure should not exceed 15 mm Hg during surgery, to minimize pressure-related complications. Moreover, the patient's carbon dioxide levels should be monitored with capnography during surgery.[23] Considering the implemented surgical procedures, AD only was usually sufficient (48%). In cases of patients with cysts, cyst fenestration or cystectomy were preferred. Histopathological examination was performed in 28.6% of the patients, and the dermoid cyst and serous cyst were the most common findings. In their study, Seo et al.[24] performed the pathological examination in 81.8% of the cases, and the most common finding was corpus luteum cyst (42.4%). In principle, only AD or fenestration were performed, particularly in first-trimester patients, to preserve the ovarian reserve, and cystectomy and salpingo-oophorectomy were avoided. In our study, we did not encounter complications in the intraoperative period and only one patient, who underwent laparotomy, developed an infection with no negative effects on the pregnancy outcome.

There are some differences between pregnant women and non-pregnant women in the management of the AT. The choice of anesthesia is generally guided by maternal indications, as well as the site and nature of the planned surgical procedure. However, most abdominal surgical

procedures, including laparoscopy, require general anesthesia and muscle relaxation. Preservation of maternal hemodynamic stability, uteroplacental blood flow, and avoidance of maternal and fetal hypoxia throughout surgery, as well as avoidance of preterm delivery, are mandatory.[25,26] General anesthesia is used for the vast majority of laparoscopic, non-obstetric surgeries in pregnancy. Endotracheal intubation with positive pressure ventilation is favored for several reasons: 1. the risk of regurgitation from increased intra-abdominal pressure; 2. the need for controlled ventilation to prevent hypercapnia; 3. the need for relatively high- and peak airway pressures; 4. the need for muscle relaxation (paralysis); and 5. the need for the placement of a nasogastric tube. In addition, when selecting anesthetic drugs, the primary goals are to preserve maternal blood pressure as well as uterine blood flow, and to minimize fetal depression.[27]

There are different studies focused on the obstetric alterations in laparoscopy and laparotomy surgeries implemented due to AT in pregnant women.[4,10,28] Oelsner et al.[21] investigated the effects of laparoscopy and laparotomy performed during pregnancy on the obstetric performance and fetal outcomes, and found that the rates of fetal anomalies, abortion, and preterm births were comparable in both groups. Dvash et al.[10] investigated the AT cases managed with laparoscopy during pregnancy and found a high rate of preterm birth. However, they associated this high rate not with laparoscopy but with multiple pregnancies. In our study, the rates of preterm birth and spontaneous abortion were 14.3% and 4.8% respectively, and we observed that the trimester during which surgery was performed in did not change the pregnancy outcomes. Additionally, the type of surgery did not affect pregnancy results either. In women who underwent surgery due to the AT during pregnancy, the timing, mode, and management of delivery were comparable to women with normal pregnancies. The decision for the cesarean section is made on fetal, maternal, and obstetric indications. In our study, the rate of cesarean section was relatively high (52.4%), and we believe this high rate was related to the increasing number of cesarean sections in our country. On the other hand, after the detorsion surgery, postoperative care and instructions following detorsion should include observation for signs of peritonitis or sepsis (fever, worsening abdominal pain, peritoneal irritation signs, hemodynamic instability, etc.), as AT is commonly seen in the first trimester of the pregnancy, and enlarged gravid uterus hinders re-torsion of the ovary during pregnancy in the late weeks.[29]

The small sample size and the retrospective nature were the main limitations of the present study. However, as AT during pregnancy is a rare disorder, to conduct a prospective study would be rather difficult. The absence of postnatal data is another limitation of our study.

Conclusion

If AT is suspected during pregnancy, regardless of the trimester, surgery should not be delayed, to preserve the ovarian and tubal functions and prevent the torsion-related complications. The surgical method (laparotomy or laparoscopy) chosen for the diagnosis and treatment does not have any negative effect on pregnancy outcomes like abortion, preterm birth, and fetal anomaly. In cases with small, simple, non-malignant cystic lesions, adnexal detorsion and cyst fenestration seem a suitable treatment to preserve the ovarian reserve. Furthermore, according to the results of the present study, obstetric outcomes of pregnant women who underwent surgery for AT are generally favorable. If the surgery can be done via laparoscopy in pregnant cases within early gestations, postoperative recovery will be better than open surgery.

Contributions
Concept: HE, IH. Design: HE, FO, MI., Data collection: HE, IH, FO. Analysis or Interpretation: AA, HE, FO., Literature search: HE, IH., Writing: HE, IH, FO.

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

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Emotional and Clinical Aspects Observed in Women with Gestational Trophoblastic Disease: A Multidisciplinary Action

Aspectos emocionais e clínicos observados em mulheres com doença trofoblástica gestacional: Uma ação multidisciplinar

Ana Carolina Gomes França[1] Elza Maria Hartmann Uberti[2] Karine Paiva Muller[2] Rodrigo Bernardes Cardoso[1] Fabiana Giguer[2] Patricia El Beitune[1] Antonio Braga[3,4]

[1] Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, RS, Brazil
[2] Irmandade da Santa Casa da Misericórdia de Porto Alegre, Porto Alegre, RS, Brazil
[3] Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil
[4] Universidade Federal Fluminense, Niterói, RJ, Brazil

Address for correspondence Ana Carolina Gomes França, Rua Sarmento Leite, 245, 90050-170, setor PPG Patologia, Porto Alegre, RS, Brazil (e-mail: acarolinagfranca@gmail.com).

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Abstract

Objective To evaluate the emotional and clinical aspects observed in women with gestational trophoblastic disease (GTD) followed-up in a reference center (RC) by a multidisciplinary team.

Methods Retrospective cohort study of the clinical records of 186 women with GTD and of the emotional aspects (EA) observed in these women by a team of psychologists and reported by the 389 support groups conducted from 2014 to 2018.

Results The women were young (mean age: 31.2 years), 47% had no living child, 60% had planned the pregnancy, and 50% participated in two or more SG. Most women (n = 137; 73.6%) reached spontaneous remission of molar gestation in a median time of 10 weeks and had a total follow-up time of seven months. In the group of 49 women (26.3%) who progressed to gestational trophoblastic neoplasia (GTN), time to remission after chemotherapy was 18 weeks, and total follow-up time was 36 months. EA included different levels of anxiety and depression, more evident in 9.1% of the women; these symptoms tended to occur more frequently in women older than 40 years ($p = 0.067$), less educated ($p = 0.054$), and whose disease progressed to GTN ($p = 0.018$), as well as in those who had to undergo multi-agent chemotherapy ($p = 0.028$) or hysterectomy ($p = 0.001$) adjuvant to clinical treatment.

Conclusion This study found several EA in association with all types of GTD. It also highlights the importance of specialized care only found in a RC, essential to support the recovery of the mental health of these women.

Keywords
- gestational trophoblastic disease
- psychological aspects
- support group
- mental health

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Resumo

Objetivo Avaliar aspectos emocionais e clínicos observados em mulheres com doença trofoblástica gestacional (DTG) acompanhadas em um centro de referência (CR), por equipe multiprofissional.

Método Estudo de coorte retrospectivo nos prontuários clínicos de 186 mulheres com DTG, e dos aspectos emocionais (AE) observados nessas mulheres pela equipe de psicólogas e registrados nos 389 grupos de apoio (GAs), ocorridos de 2014 a 2018.

Resultados As pacientes eram jovens (idade média 31,2 anos), 47% sem filhos vivos, 60% tinham desejado ou planejado esta gravidez e 50% delas participaram de dois ou mais GAs. A maioria (n = 137–73,6%) apresentou remissão espontânea da gestação molar com mediana de 10 semanas e um tempo total de seguimento de 7 meses. Quarenta e nove mulheres (26,3%) evoluíram para neoplasia trofoblástica gestacional (NTG); a mediana para atingir a remissão após tratamento com quimioterapia foi de 19 semanas e o tempo total de seguimento foi de 36 meses. Os AE incluíram variados graus de ansiedade e depressão, mais evidentes em 9,1% das nossas pacientes; tais AE tenderam a ocorrer mais em mulheres com idade acima de 40 anos ($p = 0,067$), com menor escolaridade ($p = 0,054$), com evolução para NTG ($p = 0,018$), e nas que necessitaram de tratamento quimioterápico com regime de múltiplos agentes ($p = 0,028$), ou de histerectomia complementar ao tratamento clínico ($p = 0,001$).

Conclusão Este estudo mostrou presença de vários AE associados em todos os tipos de DTG. Destaca também a importância de um atendimento psicológico especializado, somente encontrado nos CR, que é essencial para ajudar na recuperação da saúde mental dessas mulheres.

Palavras-chave

- doença trofoblástica gestacional
- aspectos psicológicos
- grupos de apoio
- saúde mental

Introduction

The emotional aspects associated with normal pregnancies have been widely studied and described, particularly when associated with high-risk gestations that may pose special risks to maternal and fetal health.[1,2] Of all pregnancy complications in Brazil, about 1:200-400 are cases of gestational trophoblastic disease (GTD). GTD is a fertilization error of cytogenetic origin that potentially leads to an obstetric near miss and may progress to gestational trophoblastic neoplasia, which may be a cause of maternal death if not treated adequately.[3–5]

These women face a great emotional impact when diagnosed with GTD. They experience the grief of a gestational loss, as well as the fear of being seriously ill and of losing their own life.[6–8] The difficulties that many women have in understanding a diagnosis of a molar gestation and its uncertain prognosis have social and psychological impacts that go beyond the diagnosis and treatment of GTD.[9] The emotional repercussions of this disease have been studied because of its particular circumstances and characteristics of GTD.[6,7] Their psychosocial impact should be understood to define directions for the improvement of the approaches adopted by multidisciplinary teams.[5,9]

According to its natural history, GTD progresses to a cure most cases. However, its psychological stressors are real for both women and their partners. Both face unexpected changes of plans: the hopes and joys of pregnancy give way to the immediate need of adaptation to deal with a potentially serious disease.[10–12] Therefore, beyond medical care, GTD reference centers (GTD-RC), where women with GTD are followed up, organize support groups (SG) to provide psychosocial support to these women.[5] The objective of a SG is to contribute to health education and promote actions to improve women's mental health during the clinical follow-up of their disease. Some studies have demonstrated the efficacy of health education also in the case of GTD, as it clarifies questions and provides support to face the disease and its impacts. It also promotes adherence to treatments and anxiety control and provides support for their reproductive future.[5,9,13–17]

Despite the importance of emotional aspects (EA) in its diagnosis, few studies have investigated the impacts of GTD, particularly the feelings associated with a pregnancy loss and a possible disease progression. Moreover, there are few studies about the potential benefits of psychotherapeutic interventions for these women.[3–8]

This study evaluated EA associated with the diagnosis and follow-up of women with GTD, as well as with different clinical outcomes and treatment modalities. In some cases, the need of complementary individual psychological support and the use of psychoactive medication were required to restore the mental health of women with GTD.

Methods

This is a retrospective cohort study to analyze data about EA collected from the records of 389 SG. Participants were 186

women with all types of GTD evaluated from 2014 to 2018 in the GTD-RC of the "Mario Totta" Maternity Ward of Irmandade Santa Casa de Misericórdia Hospital (ISCMPA), Porto Alegre, Brazil. Clinical and epidemiological data were reviewed in the medical records of the women seen in the GTD-RC, and qualitative data about EA were retrieved from the SG reports.

This study was approved by the ethics in research committee of the institution where it was conducted (CAAE 07388818.0.0000.5335 and CEP 3.209.698).

The SGs of the GTD-RC in the "Mário Totta" Maternity (MTM) of ISCMPA were first established in 1994 to provide psychosocial support in addition to medical care.[5] The SGs meet every seven to 14 days and are coordinated by the psychologist in the GTD-RC team. They also have the participation of a psychologist and a resident of the Gynecology and Obstetrics Department of ISCMPA or of the GTD-RC team. In the beginning of follow-up in the GTD-RC, all women and their families receive an explanation about the natural history of GTD and are invited and encouraged to participate in a SG. In the group, they have the opportunity to meet other women at different stages of GTD follow-up and have the chance to ask their questions and express their feelings and expectations about the disease and the future of their health.

At the time they are discharged from treatment in the GTD-RC, they are again invited to participate in a SG. At this moment, the idea is to have them share their experiences and life events and offer support and motivation to adhere to follow-up for women in the initial stages of post-molar follow-up.

When they return to the GTD-RC after a successful pregnancy, they are encouraged to participate in a SG once more, this time as representatives of a moment of hope of having a healthy pregnancy after the disease.

As the work in a SG is concluded, the psychologist in the group synthesizes the issues approached and reports on the EAs identified, which are later analyzed by the whole medical team responsible for the GTD-RC. For women that have more intense and frequent depressive symptoms or signs of anxiety, individual psychological care is offered, as well as a referral to a psychiatrist, whenever necessary. In the study period, the two psychologists who participated in this study estimated the frequency of each EA in women with spontaneous remission of GTD and in those whose disease progressed to GTN.

The data reviewed and collected from the medical records of the GTD-RC were age, age group, number of previous pregnancies, parity, number of living children, education, whether current pregnancy was planned, gestational age at diagnosis (weeks), GTD diagnostic method (imaging, clinical, histological), type of GTD (complete or partial hydatidiform mole, other GTDs), associated medical complications (such as anemia, blood transfusion, repeated curettage, laboratorial hyperthyroidism, pelvic infection and theca-lutein cysts), GTD progression (remission or GTN), time to remission (weeks), need of individual psychological care, depression or anxiety symptoms before GTN and during post-molar follow-up, total follow-up time (months) and discharge status.

GTD was diagnosed using the 2002 International Federation of Gynecology and Obstetrics (FIGO) criteria: hCG concentrations plateaued at values greater than or equal to 10%, hCG rise of more than 10% for three consecutive weeks, or histological diagnosis of choriocarcinoma.[18,19]

Clinical staging of women that progressed to GTN used the 2002 FIGO-World Health Organization (WHO) criteria. Their risk score at the time of GTN diagnosis and beginning of the treatment indicated the most adequate type of management considering the risk of developing resistance to chemotherapy: single-agent chemotherapy when the risk score was lower than or equal to 6, and multi-agent chemotherapy if the score was greater than 7.

Quantitative variables were described as means and standard deviations or medians and interquartile ranges. Categorical variables were described as absolute and relative frequencies.

The Student t-test was used to compare means. The Mann-Whitney test was used for asymmetrical variables. Proportions were compared using the Pearson chi-squared or the Fisher exact test.

A multivariate Poisson regression model was performed to control for confounding factors. This model is appropriate to estimate prevalence ratios in studies when the outcome is dichotomous. Variables significant at $p < 0.20$ in bivariate analysis were included in the multivariate analysis, but only those significant at $p < 0.10$ were kept in the final model.

The level of significance was set at 5%, and the IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY USA) was used for all statistical analyses.

Results

Sociodemographic and clinical characteristics of the 186 women followed-up in the GTD-RC of the MTM/ISCMPA are shown in ►**Table 1**. Mean age was 31.2 ± 9 years; about one third had only an elementary school education; almost half the women were nulliparous or had no living child; and pregnancy had been desired and planned in more than 60% of the cases. A possible molar pregnancy was investigated using ultrasound in 75% of the cases, and the definitive diagnosis was confirmed in 91.4% of these women. Except for transvaginal bleeding in 60% of the women, no other associated medical complications (such as anemia, blood transfusion, repeated curettage, laboratorial hyperthyroidism, pelvic infection, and theca-lutein cysts) were found in 75% of the women.

GTD evolution is described in ►**Table 2**, which shows that 50% of the women participated in two or more SGs. The disease progressed to GTN in 49 women (26.3%); almost 90% had GTN with a low risk of resistance to chemotherapy according to the 2002 FIGO/WHO criteria, and 83.6% of these cases were treated with only single-agent chemotherapy. As expected, both time to disease remission and time of follow-up were statistically greater in women with disease that progressed to GTN ($p < 0.001$). Patient recovery was

Table 1 Sociodemographic and clinical characteristics of the 186 women with GTD included in the study

Characteristics	n = 186	%
Age (in years) (mean ± SD, minimum - maximum)	31.2 ± 9	16–69
Education (N - %)		
Elementary (9 years)	52	28.0
Intermediate (12 years)	72	38.7
Higher (≥ 16 years)	62	33.3
Previous pregnancies (N - %)		
Zero	71	38.2
One	63	33.9
Two	52	28.0
Previous births (N - %)		
Zero	88	47.3
One	64	34.4
≥ Two	34	18.3
Living children (N - %)		
Zero	92	49.5
One	65	34.9
≥ Two	29	15.6
Planned or desired pregnancy (N - %)		
Yes	120	64.5
No	66	35.5
Gestational age (in weeks); mean ± SD, minimum - maximum	10.1 ± 3.8	4 - 29
Vaginal bleeding before diagnosis (N - %)		
Yes	111	59.7
No	75	40.3
GTD diagnostic method (N - %)		
Ultrasound	136	73.1
Histology only	50	26.8
Type of molar pregnancy (N - %)		
Complete hydatidiform mole	94	50.5
Partial hydatidiform mole	76	40.9
Other diagnoses	16	8.6
Associated clinical complications* (N - %)		
No	142	76.3
Yes	44	23.6

Abbreviation: GTD, gestational trophoblastic disease.
*associated clinical complications: anemia, blood transfusion, repeated curettage, laboratorial hyperthyroidism, pelvic infection and theca-lutein cysts.

confirmed in 96.2% of the cases, and 79% were discharged after all post-molar follow-up was completed.

►**Tables 3** and **4** show the association of EA related to depressive symptoms with women's clinical characteristics

Table 2 Clinical evolution of the 186 women with GTD followed up in the study

Factors evaluated	N = 186 (%)	*p*-value
Participation in SG		< 0.001
One	94 (50.5)	
≥ Two	92 (49.4)	
Evolution		
Spontaneous remission	137 (73.6)	
GTN	49 (26.3)	
Time to remission (weeks) - median [P25–P75]***		
Spontaneous remission	10 (8-12)	
GTN	19 (16-26)	
FIGO/WHO risk score (n = 49)		
Low-risk	44 (89.8)	
High-risk	5 (10.2)	
Treatment (n = 49)		
Only chemotherapy	42 (85.7)	
Chemotherapy + surgery	7(14.2)	
Chemotherapy (n = 49)		
Single-agent	41 (83.6)	
Multi-agent	8 (16.3)	
Hysterectomy and indication (n = 49)		
No	42 (85.7)	
Yes	7 (14.2)	
Age, or childbearing completed	2 (28.5)	
Associated gynecological complications	4 (57.1)	
Recurrence	1 (14.2)	
Follow-up (months) - median (P25–P75)***		
Spontaneous remission	7 (6–9)	
GTN	36 (18–60)	
Discharge status		
Medical discharge after complete follow-up	147 (79.0)	
Loss to follow-up after remission (with normal hCG concentration)	32 (17.2)	
Loss to follow-up before remission (with elevated hCG concentration)	5 (2.7)	
Transferred	1 (0.5)	
Death	1 (0.5)	

Abbreviations: FIGO, The International Federation of Gynecology and Obstetrics; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; SG, support group; WHO, World Health Organization.
***Mann-Whitney test ($p < 0.001$).

Table 3 Association between women's clinical characteristics and depressive symptoms

Variables	With depressive symptoms (n = 17)	Without depressive symptoms (n = 169)	*p*-value
Age (years)–mean ± SD	36.5 ± 10.9	30.6 ± 8.6	0.009*
Age range–n (%)			0.067**
≤ 19 years	0 (0.0)	11 (6.5)	
20–39 years	11 (64.7)	133 (78.7)	
≥ 40 years	6 (35.3)♪	25 (14.8)	
Education–n (%)			0.054**
Elementary (9 years)	9 (52.9)♪,	43 (25.4)	
Intermediate (12 years)	4 (23.5)	68 (40.2)	
College or higher (≥ 16 years)	4 (23.5)	58 (34.3)	
Planned pregnancy–n (%)	9 (52.9)	111 (65.7)	0.435**
Previous pregnancies–median (P25–P75)	1 (1–2.5)	1 (0–2)	0.012***
Number of births–median (P25–P75)	1 (0.5–2)	1 (0–1)	0.011***
Number of living children–median (P25–P75)	1 (0–2)	0 (0–1)	0.029***
Gestational age (weeks)–mean ± SD	9.9 ± 3.2	10.1 ± 3.9	0.827*
Type of molar pregnancy–n (%)			0.082**
Complete hydatidiform mole	11 (64.7)	83 (49.1)	
Partial hydatidiform mole	3 (17.6)	73 (43.2)	
Another diagnosis	3 (17.6)	13 (7.7)	
With associated medical complications–n (%)	4 (23,5)	40 (23.7)	1.000 ±

Abbreviations: GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; SD, standard deviation.
* Student *t* test; ** Chi-squared test; ***Mann-Whitney test; ↑ Fisher exact test; #statistically significant adjusted residuals ($p < 0.05$); ♪ results approaching significance.

Table 4 Association of GTD evolution with depressive symptoms

Variables	With depressive symptoms (n = 17)	Without depressive symptoms (n = 169)	*p*-value
GTD evolution–n (%)			0.018**
Spontaneous remission	8 (47.1)	128 (76.2)*	
GTN evolution	9 (52.9)*	40 (23.8)	
Time to remission (weeks)–median (P25–P75)	17 (12–27)	10.5 (8–15)	< 0.001***
GTN risk score - median (P25–P75)	6 (2–8.5)	2 (1–3)	0.008***
GTN Treatment - n (%) [N = 49]			0.224↑
Only chemotherapy	7 (77.8)	37 (92.5)	
Chemotherapy and surgery	2 (22.2)	3 (7.5)	
Type of Chemotherapy–n (%) [N = 49]			0.028↑
Single agent	5 (55.6)	36 (90.0)#	
Multi-agent	4 (44.4)#	4 (10.0)	
With adjuvant hysterectomy - n (%)	4 (23.5)	3 (1.8)	0.001↑
Discharge conditions - n (%)			0.874**
Medical discharge after complete follow-up	15 (88.2)	132 (78.1)	
Loss to follow-up after remission, with normal hCG concentration	2 (11.8)	30 (17.8)	
Loss to follow-up before remission, with elevated hCG concentration	0 (0.0)	5 (3.0)	
Death/Transferred	0 (0.0)	2 (1.2)	
Follow-up (months)–median (P25–P75)	36 (9.5–66)	8 (6–12)	< 0.001***

Abbreviations: GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; SD, standard deviation.
* Student *t* test; **Chi-squared test; ***Mann-Whitney test; ↑ Fisher exact test; #statistically significant adjusted residuals ($p < 0.05$); ♪results approaching significance.

Table 5 Multivariate Poisson regression to assess variables independently associated with depressive symptoms

Variables	Prevalence ratio (95%CI)	*p*
GTD evolution		
Spontaneous remission	1	
GTN	2.64 (0.94–7.44)	0.067
Hysterectomy	3.26 (1.11–9.58)	0.032
Number of living children	1.59 (1.09–2.33)	0.016

Abbreviation: GTN, gestational trophoblastic neoplasia.

and GTD evolution variables. Grouped data revealed that 17 women (9.1%) had one or more depressive symptoms: six (3.2%) of them received individual psychological care; five (2.7%) had a history of depression; 16 (8.6%) had symptoms during follow-up; and 14 (7.5%) needed treatment with antidepressant medication. Data were grouped to obtain a larger sample size for the analysis of associations.

The multivariate analysis revealed that the tendency to depressive symptoms was about 2.5 times greater in women whose disease progressed to GTN ($p = 0.067$) (►**Table 5**). Women that underwent hysterectomy had a three times greater probability of having depressive symptoms. For each child a woman had, this probability increased 59% (RR = 1.59).

Moreover, mean age of women whose disease progressed to GTN was significantly greater than that of those who had spontaneous remission (34.0 ± 10.9 vs 30.2 ± 7.9; $p = 0.029$). The women who had planned their pregnancies had a higher rate of return to medical care when pregnant again than those who had not (23.3% vs 9.1%; $p = 0.027$). ►**Tables 6** and **7** show other important EA identified in the SGs, grouped according to GTD progression.

A high level of anxiety was a constant finding before admission to the RC. After admission, some actions, such as acquisition of an accurate knowledge of the natural history of GTD, personal meetings with other women experiencing the same disease and participation in specific social media platforms, such as the Facebook group in the profile of the Brazilian Association of Gestational Trophoblastic Disease, helped reduce anxiety.

Discussion

Disease progression to GTN, hysterectomy adjuvant to GTN treatment and living child were the main stressors independently associated with depressive symptoms among the women with GTD followed up in this study.

Other studies have investigated the emotional impact of disease on women with GTD using standardized questionnaires, such as the Quality of Life, Satisfaction with Life and the WHO Quality of Life scales, as well as the evaluation of depressive symptoms. However, a more detailed analysis of these symptoms and of the emotional repercussions of the disease requires an accurate evaluation using qualitative data about grief, death, anger, and delay of childbearing plans.[19]

Anxiety symptoms may also have been reported in the form of ignorance and/or fear of the disease, sexual dysfunction, low level of maternal self-efficacy, guilt for being sick and low self-esteem,[20] as showed in ►**Tables 6** and **7**.

Table 6 Emotional aspects recorded in the SG for 137 women with spontaneous remission of GTD and no additional chemotherapy

Symptoms	%
Why me?	90–95
Am I the only one with this disease?	80–95
Fear of the unknown	85–90
Hard to explain the disease to others	10–45
Fear and guilt about fertility and next pregnancy	75–80
Helplessness about family–feeling alone and sad when facing the disease	50–60
Inability to feel hurt about pregnancy loss	20–30
Powerlessness in face of future motherhood (especially women without children)	40–95
Desire to have sterilization out of fear of next pregnancy	0–50
Social shame: ashamed of facing social groups (workmates, friends, neighbors)	20–90
Emotional difficulties during a new pregnancy	50–80
Awareness of risks of a new pregnancy	90–95
Ambiguous feelings about a new pregnancy: fear and desire	5–20
Sexual dysfunction	10–30
Ambiguous feelings about the attending team	2–5
Feeling that care received out of the RC was not supportive	70–95
Feeling angry and ashamed of feelings when seeing other pregnant women	75–95

Table 7 Emotional aspects observed in the SG in 49 women whose disease progressed to GTN and who needed chemotherapy

Symptoms	%
Guilt for being ill	10–40
Fantasizing about cancer and death	60–95
Fantasizing about crying or suffering, believing they will make disease get worse	20–90
Low self-esteem because of body image (hair loss)	70–95
Helplessness about surgery (hysterectomy)	10–95
Ambiguous feelings about being ill and weak inside while looking strong outside	30–80
Fear about living with a "damaged" uterus	5–10
Feeling of inferiority and of being unable to bear children	50–70
Difficulty in interacting socially after chemotherapy	40–80
Use of disease for secondary gain and guilt relief	40–65
Fear and guilt about fertility and next pregnancy	80–95
Fear and denial of death	10–30

Several studies have reported on the relevance of the impact of communications, treatment and emotional support received from a multidisciplinary team.[6,17,18,20] The perceptions of women with GTD have also been evaluated using questionnaires, such as the Health-Related Quality Of Life and the Patient Reported Outcome Measures (PROM), which cover several domains, such as physical effects, emotional symptoms (anxiety, depression) and social relationships. Psychological interventions, participation in a SG and participation of the family, when combined with continuous education about their disease, play an important role in the context of the treatment by a multidisciplinary team.[3,7]

Ferreira et al.[11] found that the lowest scores of quality of life were associated with emotional effects, whereas physical effects due to multi-agent chemotherapy did not affect it significantly.[21] Our results showed that hysterectomy, a surgical adjuvant treatment and the most important physical intervention in our study, was significantly associated with depressive symptoms. Women whose disease progressed to GTN had more symptoms of anxiety and stress, but chemotherapy had a curative effect on patient survival and did not limit their future childbearing plans or made their reproductive future worse.[22,23]

Many studies found significant numbers of depressive symptoms in women with GTN.[6,8,24] Feelings after a molar gestation, similar to the grief felt in case of miscarriages, include depressive symptoms and reactions.[5] Several anxiety symptoms are associated with the weekly or regular measurement of the tumor marker (hCG).[8] Problems associated with relationships, marriage and reproductive future also seem to point to a greater level of sexual dysfunction in women with GTD.[24,25] No association with infertility has been found, and most women have a positive reproductive performance, confirmed by subsequent term pregnancies without complications.[8,26]

Study comparisons are limited by the difficulty in comparing heterogeneous qualitative details, although some studies have used standardized objective questionnaires. Regardless of severity of psychological effects, the emotional support of a multidisciplinary team is a unanimously effective tool to promote well being and improve women's quality of life.[27,28] The participation in SGs also strengthens adherence to follow-up and return for the visits at the recommended regular intervals. Multidisciplinary teams have an important role in detecting depressive symptoms and managing the psychological repercussions of treatment on both the women and their families during follow-up.[7]

In the future, studies about the psychosocial aspects of GTD will probably use PROM questionnaires. This instrument may be used to evaluate patient health at different time points of their follow-up, differently from other questionnaires that evaluate only disease and outcome.[22,29,30]

One of the limitations of this study is the fact that, as a retrospective study, it is difficult to characterize EA accurately, as SG records have been made along many years. Moreover, the longer time to remission and follow-up time of women whose disease progressed to GTN are confounding variables that may affect the prevalence of depressive symptoms.

Short- and long-term problems are associated with the quality of life and the psychological, social, and sexual consequences of a diagnosis of GTD, particularly when the disease progresses to GTN. Moreover, women suffering because of their experience in a hospital context, the fragility of their physical health, the constant return visits to a place marked by disease, the chances of deterioration or a prognostic change should all be taken into consideration in this analysis.

Conclusion

The main objectives of GTD-RCs, which provide multidisciplinary care to women with all types of GTD, are the recovery of physical and mental health, the preservation of fertility and the improvement of quality of life. Therefore, women

with GTD should be referred to follow-up in one of the 41 GTD-RCs in Brazil at an early stage. Follow-up in a specialized RC contributes to reducing morbidity and mortality. Moreover, it promotes positive follow-up experiences, provides understanding and mitigation of psychological stressors of treatment, and ensures that treatment approaches are comprehensive and focused on the women and their families.

Contributors

All authors were involved in the design and interpretation of the analyses, contributed to the writing of the manuscript, and read and approved the final manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

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The Role of High Concentrations of Homocysteine for the Development of Fetal Growth Restriction

O papel de altas concentrações de homocisteína para o desenvolvimento da restrição de crescimento fetal

Andrey Gaiday[1] Lazzat Balash[2] Akylbek Tussupkaliyev[1]

[1] West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan
[2] L.N.Gumilyov Eurasian National University, Nur-Sultan, Kazakhstan

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Address for correspondence Andrey Gaiday, Department of Obstetrics and Gynecology, West Kazakhstan Marat Ospanov Medical University, Maresyev str, 68, Aktobe, Republic of Kazakhstan (e-mail: a.gaiday@mail.ru).

Abstract

Objective To assess homocysteine (Hcy) levels in the three trimesters of pregnancy in women with fetal growth restriction (FGR) and to evaluate the role of Hcy as a possible predictor of FGR.

Methods A total of 315 singleton pregnant women were included in the present prospective cohort study and were monitored since the 1st trimester of pregnancy before delivery. Newborns were monitored for the first 7 days of life. Patients who had risk factors for FGR were excluded. Fetal growth restriction was defined according to uterine fundal height (< 10 percentile), ultrasound fetometry (< 5 percentile), and anthropometry of newborns (< 5 percentile). The concentrations of Hcy were detected at between 10 and 14, between 20 and 24, and between 30 and 34 weeks of pregnancy by enzyme-linked immunosorbent assay (ELISA). Receiver operating characteristics (ROC) curve test and diagnostic odds ratio (DOR) were performed to evaluate the results of ELISA.

Results The concentration of Hcy in patients with FGR was 19.65 umol/L at between 10 and 14 weeks, compared with 9.28 umol/L in patients with normal fetal growth ($p < 0.0001$). The optimal cut-off level for Hcy in the 1st trimester of pregnancy was > 13.9 umol/L with AUC 0.788, sensitivity of 75%, specificity of 83.6%, and DOR of 15.2.

Conclusion Assessment of serum Hcy concentration may be used as a predictor of FGR, with the highest diagnostic utility in the 1st trimester of pregnancy.

Keywords
- fetal growth restriction
- homocysteine
- hyperhomocysteinemia
- prediction of fetal growth restriction

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Resumo

Objetivo Avaliar os níveis de homocisteína (Hcy) em três trimestres da gravidez em mulheres com restrição de crescimento fetal (FGR, na sigla em inglês) e avaliar o papel da Hcy como possível preditor de FGR.

Métodos Um total de 315 gestantes solteiras foram incluídas no presente estudo de coorte prospectivo e monitoradas desde o 1° trimestre de gravidez antes do parto. Os recém-nascidos foram acompanhados durante os primeiros 7 dias de vida. Pacientes que apresentam fatores de risco para FGR foram excluídos. A FGR foi definida de acordo com a altura do fundo do útero (< percentil 10), ultrassonografia fetometria (< percentil 5) e antropometria dos recém-nascidos (< percentil 5). As concentrações de Hcy foram detectadas entre 10 e 14, entre 20 e 24 e entre 30 e 34 semanas de gravidez por ensaio de imunoabsorção enzimática (ELISA, na sigla em inglês). O teste da curva das características de operação do receptor (ROC, na sigla em inglês) e a razão de chances de diagnóstico (DOR, na sigla em inglês) foram realizados para avaliar os resultados do ELISA.

Resultados A concentração de Hcy em pacientes com FGR foi de 19,65 umol/L entre 10 e 14 semanas, em comparação com 9,28 umol/L em pacientes com crescimento fetal normal ($p < 0{,}0001$). O nível de corte ideal para Hcy no 1° trimestre da gravidez foi > 13,9 umol/L com AUC 0,788, sensibilidade de 75%, especificidade de 83,6%, e DOR 15,2.

Conclusão A avaliação da concentração sérica de Hcy pode ser usada como um preditor de FGR, com maior utilidade diagnóstica no 1° trimestre de gravidez.

Palavras-chave

- restrição de crescimento fetal
- homocisteína
- hiperhomocisteinemia
- predição de restrição de crescimento fetal

Introduction

Fetal growth restriction (FGR) occurs when the fetus does not reach its intrauterine potential for growth and development as a result of compromise in placental function.[1] According to various sources, the incidence of FGR is between 5 and 10% worldwide, and is the second cause of perinatal mortality.[1] The risk of death of newborns with FGR increases between 2 and 4 times, and the negative outcomes of childbirth are manifested in newborns as hypothermia, hypoglycemia, hyperglycemia, persistent pulmonary hypertension, pulmonary hemorrhage, polycythemia, stillbirth, and intranatal asphyxia.[2]

In the process of growth, the fetus produces hemodynamic and metabolic changes, in which an adequate trophoblast invasion is an important component,[3] and endothelial and subendothelial changes can contribute to their violation.[4] Today, it is known that the underlying causes of FGR are genetic, placental, fetal, and maternal factors.[2,5,6]

An important physiological process that ensures normal perfusion of the placenta is the invasion of trophoblast villi and the reshuffle of the cytotrophoblast from the epithelial to the endothelial phenotype, which is called pseudovasculogenesis.[7] Subsequently, the remodeling of the spiral arteries occurs, while the cytotrophoblast increases the expression of vascular endothelial growth factor (VEGF) and placental growth factor (PLGF).[8] Nowadays, serum biomarkers are increasingly preferred for the prediction and diagnosis of FGR, of which the most commonly used are pregnancy-associated plasma protein-A (PAPP-A), α-fetoprotein (AFP), placental growth factor (PLGF), and soluble fms-like tyrosine kinase-1 (sFlt-1).[6,9–13] Along with well-known biomarkers, in the last decade, studies indicated the possibility of using serum homocysteine (Hcy) for the prediction and diagnosis of preeclampsia (PE) and FGR;[14–18] however, there are no studies available from the Kazakhstan population. The development of FGR in hyperhomocysteinemia (HHcy) may be due to the elevation of asymmetric dimethylarginine (ADMA) levels since Hcy has an inhibitory effect on ADMA metabolism. Injury to endothelial cells is also associated with HHcy, which leads to changes in the coagulation system, platelet activation, and thrombogenesis.[19]

In this study, we hypostatized that HHcy could be considered as an additional marker for the prediction and diagnosis of FGR. The aim of our study was to assess Hcy levels in the 3 trimesters (10–14, 20–24, and 30–34 weeks) of pregnancy in women with FGR and to evaluate the role of Hcy as a possible predictor of FGR. Confirmation of the hypothesis can be used to identify groups of patients with HHcy, as well as to search for the prevention of FGR from the 1st trimester of pregnancy.

Methods

The present study was part of the scientific program "Development and scientific substantiation of new technologies for protecting the health of newborns" and was approved by the Local Ethical Committee (protocol no. 12 28/12/2015) and registered at the National Center of Science and Technology Evaluation of the Republic of Kazakhstan (0107RKI00477). All patients signed a written informed consent to participate in the study.

All patients were invited to participate in this prospective cohort study at the Aktobe city outpatient department during antenatal and postpartum periods and in the regional perinatal center (Aktobe, Kazakhstan) during the intrapartum and postpartum periods between April 2016 and February 2018. Of the 615 subjects, consent to participate in the study was obtained from 360 patients who were included in the study. A total of 45 patients did not complete the study: 7 (1.9%) had miscarriages; 6 (1.7%) changed their place of residence and were not available for observation; 8 (2.2%) refused to continue the study; and, subsequently, 24 (6.7%) had hypertensive disorders or diabetes mellitus and were excluded according to the study protocol. Finally, we studied 315 pregnancies from the 1st trimester (between 10and 14 weeks) before birth. Newborns were monitored for the first 7 days of life. The inclusion criteria were age between18 and 40 years old, singleton pregnancy, normal fetal anatomy, body mass index (BMI) between 19 and 30 kg/m^2, without preeclampsia. We excluded patients, who had confounders for FGR such as multiple pregnancies, fetuses with chromosomal anomalies, FGR in a previous pregnancy, diabetes, hematologic and autoimmune diseases, congenital disorders, lung diseases, kidney failure, history of chronic hypertension or preeclampsia, smoking, alcohol or drug abuse, and low socioeconomic status.[1,2,5,20,21]

The gestational age was determined by the date of the last menstruation by the Naegele rule, and by using a Samsung Medison RS80-A ultrasound machine (Samsung Medison, South Korea), transvaginal and transabdominal ultrasound fetometry were used, which determined the crown-rump length (CRL) and were compared with known values.[22,23] In case of difference between the gestational age (according to the date of the last menstruation) and ultrasound fetometry >5 days, the gestational age was determined according to ultrasound data.[24,25] Serial examination of the measurements of uterine fundal height and transabdominal ultrasound fetometry (abdominal circumference, head circumference, and femur length) every 4 weeks from 20 weeks of gestation were performed. Fetal growth restriction was determined as a primary <10 percentile or fetal growth arrest at initial normal rates of uterine fundal height in gravidogram[26] and/or <5 percentile by the standard curve by ultrasound fetometry,[27] which were necessarily confirmed by <5 percentile by the standard curve of the body weight, height, and BMI of the newborns regarding gestational age.[28] The diagnosis of FGR was rejected if the anthropometric parameters of newborns were >5 percentile by the standard curve and the data were not evaluated in the study. The conditions of newborns were assessed using the Apgar scale and a complete clinical examination was performed.

Homocysteine concentrations were determined at between 10 and 14, between 20 and 24, and between 30 and 34 weeks of pregnancy by enzyme-linked immunosorbent assay (ELISA). Venous blood samples (5 ml) were collected after overnight fasting and cancellation of folic acid supplements, drugs, or dietary supplements containing S–adenosyl-L-methionine intake for 14 days, into an AVATUBE vacuum container with an activator gel (Eco Pharm International, Kazakhstan), then the samples were centrifuged at 1,500 rpm no later than 30 minutes after the sample collection to split the pallets. The samples were stored at – 20°C for up to 8 weeks. Monoclonal antibodies Homocysteine EIA microtiter plate with ELISA reagents were used to detect Hcy (Axis-Shield Diagnostics Ltd, United Kingdom). The optical density was measured by photometry at 450 nm using a Dialab ELX808IU microplate reader (Dialab, Austria). Concentrations of the Hcy amino acid were obtained from the optical density data by applying a method of the standard curve.[29]

Statistical analyses were performed by using Statistica 12.0 software (Stat Soft Inc., USA). The type of distribution was evaluated by the Shapiro-Wilk test. For data with an abnormal distribution, median (Me) with 25 to 75 interquartile range (IQR) were determined. Analyses for independent two variables were performed with the Mann-Whitney U-test and the Fisher exact test (two-tailed), whereas for the dependent variables the Friedman and Tukey post-hoc tests were applied. To determine the optimal cut-off levels for the concentration of Hcy, a receiver operating characteristics (ROC) curve test was applied, performed by the statistical processing program Med Calc 19.1 (Med Calc Software Ltd). Receiver operating characteristics analyses included evaluation of the area under the curve (AUC), sensitivity (Se), specificity (Sp), Youden index (J), negative likelihood ratio (-LR), and positive likelihood ratio (+LR). The diagnostic odds ratio (DOR) was calculated and evaluated for study groups according to a previously published protocol.[30] Receiver operating characteristics curves have been compared by the DeLong et al. test.[31]

The level of statistical significance was defined as $p < 0.05$.

The present study was approved by the Local Ethical Committee protocol no. 12 of December 28, 2105, at the West Kazakhstan Marat Ospanov Medical University. The present study was conducted in accordance with the Helsinki Declaration.

Results

After the clinical manifestation of FGR, the patients were divided into 2 groups: the FGR group, with 12 (3.8%) cases, and the control group, with 305 (96.2%) cases. There were no differences between the study groups in anamnestic, clinical, and ethnic data (►**Table 1**).

The newborns had a lower median of weight, height, BMI, and Apgar score, and were more often transferred to the intensive care unit in the FGR group ($p < 0.05$) (►**Table 2**). There were no differences in stillbirth, neonatal death, and malformations between FGR and the control group ($p > 0.05$) (►**Table 2**).

The medians of Hcy concentration in the patients with FGR were 19.65 umol/L at between 10–14 weeks, 18.49 umol/L at between 20 and 24 weeks, and 15.36 umol/L at between 30 and 34 weeks, which is significantly higher when compared with the control group ($p < 0.05$) (►**Table 3**). In addition, we found that Hcy concentration was similar during the entire gestation within the FGR group, indicating

Table 1 Clinical characteristics of the patients in the FGR and Control groups

	FGR group ($n = 12$)	Control group ($n = 305$)	*p-value*
Age, years old, median (IQR)	27 (25–32)	28 (25–31)	0.883[a]
Menarche, years old, median (IQR)	14 (13–14)	13 (13–14)	0.587[a]
Abnormal menstrual function, *n*	–	6 (1.9%)	–
Nulliparous, *n*	3 (25%)	65 (21.3%)	0.999[b]
Multiparous, *n*	9 (75%)	240 (78.7%)	0.999[b]
Previous abortions, *n*	4 (33.3%)	70 (22.9%)	0.484[b]
Previous miscarriages, *n*	3 (25%)	71 (23.3%)	1.0[b]
Preterm labor, *n*	2 (16.6%)	16 (5.2%)	0.143[b]
BMI, κg/m^2, median (IQR)	21.4 (19.7–22.9)	22.4 (20.6–24.6)	0.219[a]
Gestational age at admission, weeks, median (IQR)	12.5 (10–13.5)	12 (11–13)	0.832[a]
Gestational age at delivery, weeks, median (IQR)	39 (37.5–40)	39 (38–40)	0.69[a]

Abbreviations: BMI, body mass index; FGR, fetal growth restriction; IQR, interquartile range.
[a]Mann-Whitney U-test
[b]two-tailed Fisher test

Table 2 Clinical characteristics newborns in the FGR and Control groups

	FGR group ($n = 12$)	Control group ($n = 305$)	*p-value*
Weight, grams, median (IQR)	2200 (2160–2430)	3420 (3130–3730)	< 0.0001[a]
Height, centimeters, median (IQR)	47.5 (46.5–50)	53 (52–55)	< 0.0001[a]
BMI, kg/m^2, median (IQR)	9.57 (8.8–10.77)	12 (11.46–12.57)	< 0.0001[a]
Apgar score, 1st minute, median (IQR)	7.5 (5.5–9)	9 (8–9)	< 0.0001[a]
Apgar score, 5th minute, median (IQR)	8.5 (7.5–10)	10 (9–10)	0.002[a]
Hospitalization in the intensive care unit, *n*	4 (33.3%)	14 (4.6%)	0.002[b]
Stillbirth, *n*	1 (8.3%)	1 (0.3%)	0.074[b]
Neonatal death, *n*	1 (8.3%)	1 (0.3%)	0.074[b]
Malformations, *n*	1 (8.3%)	2 (0.6%)	0.109[b]

Abbreviations: BMI, body mass index; FGR, fetal growth restriction; IQR, interquartile range.
[a]U-test Mann-Whitney
[b]two-tailed Fisher test

Table 3 Analyses of the serum homocysteine concentrations during pregnancy in the FGR and Control groups

	Hcy concentration in 10–14 weeks Median (IQR) (umol/L)	Hcy concentration in 20–24 weeks Median (IQR) (umol/L)	Hcy concentration in 30–34 weeks Median (IQR) (umol/L)	*p-value*
FGR group ($n = 12$)	19.65 (10.88–22.28)	18.49 (6.39–25.8)	15.36 (7.83–24.87)	0.558[b]
Control group ($n = 305$)	9.28[c] (5.17–12.4)	8.21[c] (4.12–10.94)	6.83[c] (2.8–9.23)	< 0.0001[b]
p-value	< 0.001[a]	< 0.012[a]	< 0.001[a]	

Abbreviations: FGR, fetal growth restriction; Hcy, homocysteine.
[a]Mann-Whitney U-test
[b]Friedman test
[c]$p < 0.0001$ post-hoc Tukey test (10–14 weeks versus 20–24 weeks versus 30–34 weeks)

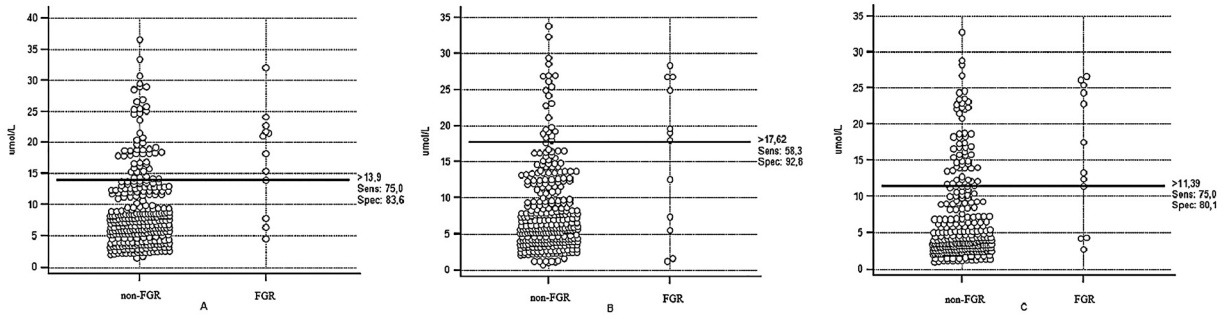

Fig. 1 Graphical characteristics of optimal cut-off levels of homocysteine concentrations in the first (**A**), second (**B**), and third (**C**) trimesters of pregnancy.

abnormal stability, compared with decreasing concentrations of Hcy during gestation in the control group (►**Table 3**).

The results of the analysis of the ROC determined optimal cut-off levels of Hcy concentrations 13.9 umol/L at between 10 and 14 weeks, 17.62 umol/L at between 20 and 24 weeks, and 11.39 umol/L at between 30 and 34 weeks (►**Fig. 1**). There were no significant differences between the AUC depending on the period of gestation (►**Fig. 2**). However, the highest DOR value (17.9) was in Hcy determined at between 20 and 24 weeks of gestation, but with a low sensitivity of 58.3%, compared with Hcy determined at between 10 and 14 weeks, with a DOR of 15.6 with sensitivity of 75% and specificity of 83.6% (►**Table 4**).

Discussion

Results of our cohort study showed that, despite the clinical homogeneity of the groups, 3.8% of the observed patients, without any risk factors, were complicated by FGR. Newborns with FGR had a lower Apgar score and were more often transferred to the intensive care unit, as confirmed by the study by Melchiorre et al.,[2] but did not present a higher frequency of stillbirth, malformations, and neonatal mortality.

In our study, the concentrations of serum Hcy in women with FGR were 19.65 umol/L at between 10 and 14 weeks, 18.49 umol/L at between 20 and 24 weeks, and 15.36 umol/L at between 30 and 34 weeks and were significantly different from those of women with normal fetal growth. These results are similar to those of studies by Bergen et al.,[32] Vollset et al.,[33] who also found significantly higher Hcy concentrations at the 1st trimester of pregnancy in women with FGR, and by Furness et al.,[34] who investigated high Hcy concentrations at the 2nd trimester of pregnancy in women with FGR. Yeter et al.,[14] Gadhok et al.,[35] and Jiang et al.[17] determined increased Hcy levels in the 3rd trimester of pregnancy in women with FGR. However, several

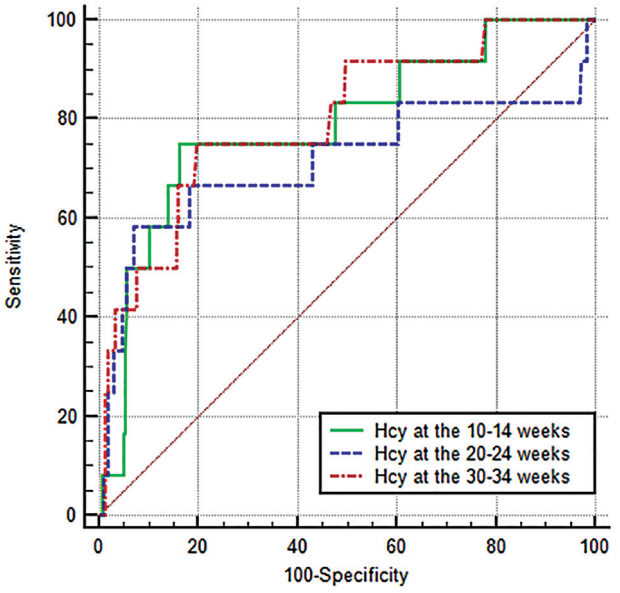

Fig. 2 Illustration of comparison of ROC curves for homocysteine (Hcy) concentrations depending on period of gestation.

Table 4 Results of ROC-analysis of homocysteine in different weeks of gestation

Gestational period of Hcy evaluation	AUC	Se (%)	Sp (%)	*p - value*	J - index	+LR (95CI)	-LR (95CI)	DOR
10–14 weeks	0.788[a]	75	83.6	< 0.001	0.586	4.58 (3.0–6.9)	0.3 (0.1–0.8)	15.2
20–24 weeks	0.712[a]	58.3	92.8	0.049	0.511	8.09 (4.3–15.1)	0.45 (0.2–0.9)	17.9
30–34 weeks	0.799[a]	75	80.1	< 0.001	0.551	3.77 (2.5–5.6)	0.31 (0.1–0.8)	12.1

AUC, area under the curve; CI, confidence interval; DOR, diagnostics odds ratio; Hcy, homocysteine; J, Youden's index; -LR, negative likelihood ratio; +LR, positive likelihood ratio; Se, sensitivity; Sp, specificity.
[a]$p > 0.05$ pairwise comparison of ROC curves.

previous studies by D'Anna et al.,[36] Hogg et al.,[37] Cawley et al.,[38] and Gomes et al.[39] demonstrated the absence of any difference in serum Hcy levels during pregnancy among women who later developed FGR and those who remained with normal fetal growth.

We also noticed high concentrations of Hcy during pregnancy in the patients who developed FGR, in contrast with pregnancies with normal fetal growth, in which Hcy significantly decreased during pregnancy.

The prognostic and diagnostic role of Hcy for FGR was confirmed by analysis of the ROC, which showed good effectiveness at the 1st and 3rd trimesters of pregnancy.

Murphy et al.[40] observed that mothers with a Hcy concentration > 8.44 umol/L at 8 weeks of gestation were 3 times more likely to give birth to an infant in the lowest birthweight tertile. In a study by Bergen et al.,[32] pregnancy was complicated by FGR at a Hcy concentration > 8.3 umol/L (OR: 1.68 [1.16–2.43]) determined at a gestational age of < 18 weeks. In another study, by Chaudhry et al.,[41] Hcy concentrations > 5.0 umol/L were significant for the development of FGR (OR: 1.69 [1.227–2.161]) at 8 weeks of gestational age. The data from previous studies differ significantly from those of our study, in which a significant Hcy concentration in the 1st trimester of pregnancy was determined at 13.9 umol/L, and are similar to those of the study by Steegers et al.,[42] which indicates that a Hcy concentration > 15 umol/L is significant for the development of FGR.

The role of Hcy assessment in the 2nd trimester of pregnancy remains unclear. Maged et al.[16] also suggested a certain role of serum Hcy determination as a prognostic and diagnostic marker for FGR, but in combination with Doppler velocimetry of the uterine artery.

As for the 3rd trimester of pregnancy, there were enough case-control studies at the time of the clinical manifestation of FGR,[17,42–45] but this does not make it possible to predict HFR, since it had already developed.

We have also identified some limitations of the present study. For example, the present study investigated patients with low risk of FGR because the well-known FGR risk factors were added to the exclusion criteria. One of the limitations of the study may also be a relatively small sample size of patients with FGR, but this is a common issue for prospective studies as judged by other publications.

Conclusion

The results of our study showed that the assessment of serum Hcy concentration at the 1st trimesters of pregnancy may be used as a predictor of FGR. Also, we hypothesize that assessment of serum Hcy concentrations in the 2nd and 3rd trimesters of pregnancy can be an additional marker of FGR.

Contributions

All authors had full access to all of the data in the present study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Akylbek Tussupkaliyev, Andrey Gaiday, Lazzat Balash. Acquisition of data: Akylbek Tussupkaliyev, Andrey Gaiday. Statistical analyses and data interpretation: Akylbek Tussupkaliyev, Andrey Gaiday, Lazzat Balash. Drafting of the manuscript: Andrey Gaiday, Lazzat Balash. Obtained funding: Akylbek Tussupkaliyev. Study supervision: Akylbek Tussupkaliyev.

Conflicts of Interests

The authors have no conflict of interests to declare.

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Exercise and Physical Activity Levels and Associated Factors Among High-Risk Pregnant Women

Fatores associados com o nível de atividade física e a prática de exercício em gestantes de alto risco

Larissa Antunes Miranda[1] Anna Caroline Ribeiro de Moura[1] Karina Tamy Kasawara[2] Fernanda Garanhani Surita[3] Mayle Andrade Moreira[1] Simony Lira do Nascimento[1]

[1] Department of Physical Therapy, Federal University Ceará, Fortaleza, CE, Brazil
[2] Department of Physical Therapy, University of Toronto, Toronto, Canada
[3] Department of Obstetrics and Gynecology, Universidade Estadual de Campinas, Campinas, SP, Brazil

Address for correspondence Simony Lira do Nascimento, PhD, Rua Major Weyne, 1440, 60430-450, Rodolfo Teófilo, Fortaleza, CE, Brazil (e-mail: simonylira@ufc.br).

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Abstract

Objective To assess the levels of physical activity and exercise practice, and examine the associated maternal characteristics; as well as the anxiety levels of high-risk pregnant women.

Methods A cross-sectional study conducted with pregnant women at a High-risk Prenatal Clinic (HRPC) in a tertiary maternity. Pregnant women of 18 to 40-years-old, with a single fetus, and with gestational age up to 38 weeks were included. The level of physical activity and exercise practice of the study's participants were investigated using the Pregnancy Physical Activity Questionnaire (PPAQ). Maternal sociodemographic, anthropometric, and medical data were investigated using a specific form. For anxiety levels, the short version of the State-Trait Anxiety Inventory (STAI) was applied. We used the Student *t*-test, chi-square test, odds ratio (OR) with 95% confidence interval (95% CI) and multiple logistic regression. The significance level was 5%.

Results Among the 109 pregnant women included, 82 (75.2%) were classified as sedentary/little active. The higher energy expenditure were for domestic activities (133.81 ± 81.84 METs), followed by work-related activities (40.77 ± 84.71 METs). Only 19.3% women exercised during pregnancy (4.76 ± 12.47 METs), with slow walking being the most reported exercise. A higher level of education was the most important factor associated with women being moderately or vigorously active (OR = 29.8; 95% CI 4.9–117.8). Nulliparity (OR = 3.1; 95% CI 1.0–9.1), low levels of anxiety (OR = 3.6; 95% CI 1.2–10.7), and unemployment (OR = 4.8; 95% CI 1.1–19.6) were associated with the practice of exercise during pregnancy.

Keywords
- pregnancy
- high-risk pregnancies
- exercise
- sedentary behavior
- motor activity

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Conclusion Most women with high-risk pregnancies exhibited a sedentary pattern, with low prevalence of physical exercise practice. Recognizing factors that hinder the adoption of a more physically active lifestyle is essential for an individualized guidance regarding exercise during pregnancy.

Resumo

Objetivo Analisar o nível de atividade física e a prática de exercício físico, examinar as características maternas associadas, assim como níveis de ansiedade de gestantes de alto risco.

Métodos Estudo observacional, transversal e quantitativo, realizado no ambulatório de Pré-Natal de Alto Risco (PNAR) de uma maternidade terciária. Foram incluídas gestantes com idade entre de 18 e 40 anos; feto único e com idade gestacional (IG) até 38 semanas. O nível de atividade física e prática de exercício físico das participantes do estudo foram investigados usando o Questionário de Atividade Física na Gestação (QAFG). Os dados sociodemográficos, antropométricos e médicos maternais foram investigados usando um formulário específico. Para níveis de ansiedade, a versão curta do Inventário de Ansiedade Traço-Estado (STAI) foi aplicado. Usamos o teste t de Student, teste qui-quadrado, razão de chances (OR) com um intervalo de confiança de 95% (IC 95%) e regressão logística multinomial. O nível de significância considerado foi 5%.

Resultados Das 109 gestantes incluídas no estudo, 82 (75,2%) foi classificada como sedentária/pouco ativa. Os maiores gastos energéticos foram em atividades domésticas (133.81 ± 81.84 METs), seguidas pelas atividades ocupacionais (40.77 ± 84.71 METs). Apenas 19.3% praticaram exercício físico durante a gravidez (4.76 ± 12.47 METs), sendo a caminhada lenta a atividade mais relatada. Maior grau de escolaridade foi o fator mais importante associado a gestante ser moderadamente ou vigorosamente ativa (OR = 29,8; IC 95% 4,9–117,8) . Nuliparidade (OR = 3,1; IC 95% 1,0–9,1), baixos níveis de ansiedade (OR = 3,6; IC 95% 1,2–10,7) e não trabalhar na gestação (OR = 4,8; IC 95% 1.1–19,6) foram associados à prática de exercício físico durante a gestação.

Conclusão A maioria das gestantes de alto risco desenvolveram um padrão sedentário, com baixa prevalência da prática de exercício físico. Reconhecer os fatores que dificultam a adoção de um estilo de vida mais ativo fisicamente é fundamental para a orientação adequada e individualizada acerca da prática de exercício físico durante a gestação.

Palavras-chave
- gravidez
- gravidez de alto risco
- exercício físico
- atividade motora
- comportamento sedentário

Introduction

In 1985, a guideline with recommendations regarding physical activity during pregnancy was published for the first time by the American College of Obstetricians and Gynecologists (ACOG), though they are now considered conservative. Since then, the practice of physical activity and exercise during pregnancy has gained notoriety, due to its potential benefits to maternal and fetal health.[1–4]

Given this context, it is essential to properly differentiate the concepts of physical activity and exercise. According to Caspersen et al.,[5] physical activity is related to any body movements performed by skeletal muscles, in which energy expenditure is above basal, such as labor, domestic, and leisure activities. On the other hand, exercise is defined as a planned, structured and repetitive physical activity, which is desired to achieve improvement or maintenance of physical fitness.

Although the numerous maternal and fetal health benefits of an active pregnancy are recognized, several studies in Brazil demonstrate alarming data on sedentary behavior among women with habitual risk pregnancies, and the restriction of physical activities is even more reinforced for high-risk pregnant women.[6–10]

The evaluation of energy expenditure and knowledge of the physical activities in which pregnant women participate allows for a better understanding of the women's profile and an adequate exercise prescription by health professionals. In this context, the application of questionnaires to measure the level of physical activity and exercise practice is a valid and useful tool, in the absence of more objective methods, such as direct or indirect calorimetry, accelerometers, and electronic movement sensors. The Pregnant Physical Activity Questionnaire (PPAQ) has been proven to be effective, since it addresses activities which are frequently present in the daily lives of pregnant women, such as domestic, sports, and work-

related activities. Thus, it can be applied to women with low and high-risk pregnancies.[9,11,12]

Several conditions can make a pregnancy high risk, including biological factors (health conditions, chronic diseases, mother's age, and nutritional and genetic aspects), psychosocial (lifestyle, emotional disturbance, and relationships), social aspects (prenatal negligence and social vulnerability), and clinical or obstetric complications that happen during pregnancy. Thus, high-risk pregnancy is defined here as any medical or obstetric conditions associated with a pregnancy with an actual or potential hazard to the health or well-being of the mother or fetus that requires specialized care.[13–15]

Chronic diseases such as diabetes mellitus and arterial hypertension, as well as overweight and obesity during pregnancy are described as contributing factors to the low adherence of women to activities with higher energy expenditure. Other reasons that also contribute to a less active lifestyle during pregnancy are: lack of infrastructure (for example, parks and places to walk), number of children at home, other occupations that limit time, little family incentive, perception of safety in public spaces. Furthermore, psychological changes, such as anxiety and depression, can be barriers capable of hindering practice of physical activities and exercise. Among sociodemographic factors, lower educational levels and income, and higher number of children at home are most frequently associated with reduced physical activity.[6,16,17]

As sedentary behaviors seem to be even more reinforced to high-risk pregnant women, we hypothesized that women with high-risk pregnancies would have a sedentary profile. Thus, this study aimed to assess the physical activity and exercise practice levels of high-risk pregnant women and to examine the maternal characteristics associated with exercising and level of physical activity during pregnancy.[7]

Methods

This is a cross-sectional study involving pregnant women attended at Maternal Fetal Medicine Service (MFMS) and High-Risk Prenatal Clinic (HRPC) of the Maternity Hospital School Assis Chateaubriand (MEAC) of the Federal University of Ceará, a reference center in maternal and childcare, in Fortaleza, Ceará, Brazil. Our facility provides care for women and newborns from the least favored segment of the population of Ceará and the Northeastern region. Data collection was performed from August 2017 to July 2019.

Eligibility criteria were pregnant women between 18 and 40 years old, single fetus, gestational age up to 38 weeks, who were attended in the service at the HRPC. High-risk pregnancy is defined as any medical or obstetric condition related to pregnancy, with an actual or potential hazard to the health or well-being of the mother or fetus, and requires specialized care.[13–15] Pregnant women with absolute contraindication to perform physical activity during pregnancy according to ACOG criteria were excluded (hemodynamically significant heart disease, restrictive lumbar disease, incompetent cervix or cerclage, multiple pregnancy at risk of premature birth, premature labor during the current pregnancy, rupture of membranes, pre-eclampsia, and severe anemia).[18]

During antenatal care (ANC) visits, women who met the eligibility criteria were invited to participate of study. Following consent, women were interviewed using standardized questionnaires: a questionnaire developed by the researchers regarding patients' socioeconomic status (age, self-reported skin color/race, marital status, educational degree, monthly family income, employment status), anthropometric data (weight, height, and pre-pregnancy body mass index [BMI]), the State-Trait Anxiety Inventory (STAI) short version, and additional data on participants' obstetric history, such as parity, gestational age, and pregnancy comorbidities were collected from medical records and prenatal care cards—independent variables. Then, all patients answered a questionnaire on physical activities, including daily amount of physical activity and exercise practice, specifically for pregnant women—dependent variables.

We assumed physical activity was any voluntary, corporal movement that increased the metabolism above its resting rate, such as labor, domestic, and leisure activities. And exercise was defined as structured, planned, and repetitive physical activity intended to promote health and maintain one or more components of physical ability.[5]

For both outcomes, this study used the PPAQ validated for Brazilian Portuguese. The PPAQ requests respondents to report the time spent participating in 31 activities including household (5 activities), caregiving (6 activities), occupational (5 activities), sports/exercise (9 activities), transportation (3 activities), and inactivity (3 activities).[17,18]

For the classification of the level of physical activity, the calculation of the energy expenditure in the metabolic equivalent of task (MET) was performed for each domain of physical activity (locomotion, leisure, domestic and occupational activities) based on the type, duration, and frequency of physical activity. The total daily energy expenditure, used to classify the pregnant woman in levels of physical activity (sedentary, little active, moderately active, and vigorously active), was calculated according to the FAO/WHO/UNU (2001) criteria.

In this calculation, it is considered that the minimum expenditure of the subjects is equal to their baseline, that is, a MET multiplied by 24 hours (MET-h). The level of physical activity is considered the total energy expenditure expressed as a multiple of the daily basal metabolic rate, based on the ratio: calculated total daily MET / 24 MET. For this reason, we categorized the level of physical activity of the pregnant woman as following: sedentary / little active ($\leq$ 1.69), moderately active (1.70–1.99) and vigorously active ($>$ 2.00). For the analysis, we categorized women in little active versus moderately and vigorously active.[19]

The prevalence of exercise was assessed using questions 18 to 26 of the PPAQ (sports/exercise), referring to different types of exercise.

To classify the level of anxiety, the short version of the State-Trait Anxiety Inventory (STAI) validated for the Brazilian Portuguese was applied. To calculate the total STAI score (range 20–80) the reverse score of the positive items (calm,

at ease, and relaxed) was added to the score of the negative items (tense, nervous, and worried), the result was then multiplied by 20/6. Following the classification established by Araújo et al.,[20] women with a score ≤ 40 were classified as having a low level of anxiety, and those with a score greater than 40 with a high level.[20–22]

To minimize information bias, all data were collected in a private environment through a standardized interview by previously trained evaluators.

The data were analyzed using the Statistical Package Social Sciences (SPSS, IBM Corp. Armonk, NY, USA) software. Continuous variables are presented as mean (M) and standard deviation (SD), and categorical outcomes in absolute and relative frequencies. To identify the factors associated with the level of physical activity (categorized in sedentary/little vs. moderately/vigorously) and the practice of exercise (sedentary vs. active), either the Chi-square or Fisher exact tests were performed, followed by a multiple logistic regression. Odds ratio (OR) with 95% confidence interval (95% CI) is present for regression. The level of significance adopted was 5%.

This study was approved by the Research Ethics Committee of the Federal University of Ceará - CEP / UFC / PROPESQ number 2.474.018 (CAAE; 62916616.0.2002.5050). All participants signed a consent form confirming their agreement to participate and received a copy of it signed by the main researcher.

Results

Of the 148 pregnant women screened at the high-risk prenatal center, 111 met the inclusion criteria, but 2 did not accept to participate in the research, thus constituting a sample of 109 participants. Of the 37 excluded pregnant women, 14 had an absolute contraindication to the practice of physical activity due to preterm labor, cervical incompetence, and vaginal bleeding, 9 were not aged between 18 and 40 years old, and the others had a gestational age greater than 38 weeks.

The analysis of participants' demographic characteristics showed an average age of 29.5 years (± 5.66), most of the participants referred to themselves as brown (87.2%), had studied up to a high school educational level (47.7%), and were residing with a partner (93.5%). More than 60% of the pregnant women did not work during pregnancy and had low monthly income of approximately a minimum wage or less. Regarding the anthropometric, obstetric, and gynecological profile of the patients, the majority was classified as overweight (32.1%) or obese (36.7%). They were also predominantly multiparous (70.6%) with a mean of 28.8 ± 6.8 weeks of pregnancy. Diabetes mellitus (38%) and hypertensive syndromes (32.4%) were the most prevalent comorbidities in the current pregnancy.

The results of the PPAQ demonstrated that the pregnant women in this study had a higher average energy expenditure in domestic activities and lower expenditure in exercise practice. Regarding the METs results related to the intensity classification of the activities performed, there is a greater predominance of energy expenditure in light and sedentary activities practiced by pregnant women, with lower average energy expenditure in moderate and vigorous activities. Thus, 75.2% of our sample were considered sedentary/not very active. The prevalence of exercise practice during pregnancy was 19.3%, with slow walking being the most reported activity (►**Table 1**).

The analysis of anxiety levels according to the STAI-6 questionnaire shows the mean level of anxiety was 47.61 ± 12.63. Most of the pregnant women ($n = 72$; 66.1%) had a total score greater than 40, showing high levels of anxiety, while only 33.9% of the women were classified as having a low level of anxiety. Among the analyzed factors related to the level of physical activity reached by patients, bivariate analysis showed that higher education level, employment, and an adequate pre-pregnancy BMI were associated with higher performance of activities with greater energy expenditure ($p < 0.05$) (►**Table 2**). However, on logistic regression only the higher education level factor remained significative (OR = 29.8; 95% CI 4.9–177.8) ($p < 0.001$) (►**Table 3**).

The bivariate analysis (►**Table 4**) and logistic regression model (►**Table 5**) for exercise as the outcome showed that not working during pregnancy (OR = 4.8; 95% CI 1.1–19.6), nulliparity (OR = 3.1; 95% CI 1.05–9.1), and low levels of anxiety (OR = 3.6; 95% CI 1.2–10.7) were associated with exercise throughout pregnancy ($p < 0.05$) (►**Table 4**).

Table 1 Description of physical activity in MET-h/week and prevalence of exercise during pregnancy, based on the PPAQ

Physical activity end exercise variables	($n = 109$)
Physical activity intensity (MET-h/week)	Mean ± SD
Sedentary	64.81 ± 34.55
Mild	127.38 ± 63.85
Moderate	37.60 ± 51.38
Vigorous	1.15 ± 5.41
Type of activity (MET-h/week)	Mean ± SD
Sports/exercise	4.76 ± 12.47
Occupational	40.77 ± 84.71
Household/caregiving	133.81 ± 81.84
Physical activity level classification	N (%)
Sedentary/Slightly active	82 (75.2%)
Moderately active	10 (9.2%)
Vigorously active	17 (15.6%)
Prevalence of physical exercise	21 (19.3%)
Type of physical exercise	
Slow walk for leisure	19 (17.4%)
Quick walk for leisure	5 (4.6%)
Other activities*	8 (7.3%)

Abbreviations: MET-h, metabolic equivalent of task per hour; SD, standard deviation. Notes: * such as dancing, stretching, and squatting.

Table 2 Bivariate analysis of association between maternal characteristics and symptoms of anxiety and the classification of the level of physical activity among high-risk pregnant women

Variables	Sedentary/little active N = 82	Moderately/ vigorously active N = 27	*p*-value
Age – n (%)			
18–34 years	63 (76.8%)	19 (70.4%)	0.5
≥ 35 years	19 (23.2%)	8 (29.6%)	
Skin color/race			
White	8 (9.8%)	6 (22.2%)	0.093
Brown or black	74 (90.2%)	21 (77.8%)	
Lives with a partner			
Yes	78 (95.1%)	24 (88.9%)	
No	4 (4.9%)	3 (11.1%)	0.252
Monthly family income[1]			
≤1	52 (65.0%)	13 (48.1%)	0.121
≥2	28 (35.0%)	14 (51.9%)	
Educational level			
Elementary school/illiterate	37 (45.1%)	4 (14.8%)	< 0.001
High school	40 (48.8%)	12 (44.4%)	
College/University	5 (6.1%)	11 (40.7%)	
Employed			
Yes	22 (26.8%)	15 (55.6%)	0.006
No	60 (73.2%)	12 (44.4%)	
Parity			
Nulliparous	24 (29.3%)	8 (29.6%)	0.971
Multiparous	58 (70.7%)	19 (70.4%)	
Gestational trimester			
2°	30 (36.6%)	9 (33.3%)	0.760
3°	52 (63.4%)	18 (66,7%)	
Hypertension[2]			
Yes	32 (39.5%)	9 (33.3%)	0.567
No	49 (60.5%)	18 (66.7%)	
Diabetes[3]			
Yes	26 (32.1%)	9 (33.3%)	0.906
No	55 (67.9%)	18 (66.6%)	
Pre-gestational BMI			
Normal	21 (25.6%)	13 (48.1%)	0.028
Overweight/Obesity	61 (74.4%)	14 (21.9%)	
Anxiety			
Low	26 (31.7%)	11 (40.7%)	0.390
Elevated	56 (68.3%)	16 (59.3%)	

Abbreviation: BMI, body mass index. Notes: [1] in minimum wages, [2] chronic or gestational hypertension, [3] type 2 or gestational diabetes

Discussion

The findings of this study show that high-risk pregnant women have a preferentially sedentary lifestyle, with a predominance of energy expenditure in domestic activities. Furthermore, the prevalence of exercise during pregnancy is quite low, with only 19.3% of this study's participants reporting some practice. Slow walking was the most common type of activity. The factors associated with higher levels of physical activity are working during pregnancy and higher level of education, whereas the factors associated with exercising during pregnancy are nulliparity, unemployment, and a low level of anxiety.

Table 3 Logistic regression model results for odds of higher level of physical activity during pregnancy according to maternal characteristics

Variable	OR	95% CI	*p*-value
Higher level of education	29.811	4.997–177.856	<**0.001**
Unemployment	0.541	0.186–1.575	0.260
Nulliparity	0.360	0.093–1.391	0.138
Adequate BMI	2.878	0.974–8.505	0.056

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; OR, odds ratio. Notes: Independent variables included in the final logistic regression model: age (18–34 vs. ≥ 35 years); employment status (employed vs. unemployed); educational level (college and university vs. elementary or high school); family income (1 vs. 2 wage); parity (nulliparity vs. multiparity); trimester of pregnancy (2° vs. 3°); BMI (adequate vs. overweight and obesity), anxiety level (low or elevated).

Studies conducted in different countries, including Brazil, reveal that women tend to reduce the level, intensity, and duration of exercise during pregnancy, corroborating the findings presented in this article. Other studies of our research group in Southern Brazil found an even lower prevalence than the one found in the present research: 14.8% of women were active before pregnancy and 12.9% during pregnancy. The prevalence decreased throughout pregnancy, and only 4.3% of the participants remained active until the end of the pregnancy.[9,23–25] To assess the physical activity levels, Silva[19] validated the PPAQ with pregnant Brazilian women and found that 80% of the women either performed mild-intensity activities or were sedentary, and that the mild-intensity activities tended to increase during pregnancy, whereas the moderate activities decreased.

It is noteworthy that we did not find studies conducted entirely with pregnant women in high-risk prenatal care. We have hypothesized that the recommendations for absolute and relative rest are further reinforced for pregnant women with comorbidities. Despite the fact that the practice of exercise plays a fundamental role in the prevention of comorbidities

Table 5 Logistic regression model results for odds of exercising during pregnancy according to maternal characteristics

Variable	OR	95% CI	*p*-valor
Unemployment	4.811	1.180–19.620	0.028
Nulliparity	3.105	1.054–9.147	0.040
Second trimester of pregnancy	0.501	0.151–1.664	0.259
Adequate BMI	1.702	0.561–5.165	0.348
Lower level of anxiety	3.641	1.233–10.748	0.019

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; OR, odds ratio. Independent variables included in the final logistic regression model: employment status (employed vs. unemployed); educational level (college and university vs. elementary or high school); family income (1 vs. 2 wage); parity (nulliparity vs. multiparity); trimester of pregnancy (2° vs. 3°); BMI (adequate vs. overweight and obesity), anxiety level (low or elevated).

Table 4 Bivariate analysis of association between maternal characteristics and anxiety symptoms, and exercise practice among high-risk pregnant women

Variables	Active N = 21	Sedentary N = 88	*p*-value
Age – n (%)			0.585
18 to 34 years	17 (81.0%)	65 (73.9%)	
≥35 years	4 (19.0%)	23 (26.1%)	
Skin color/race			0.297
White	1 (4.8%)	13 (14.8%)	
Brown or black	20 (95.2%)	75 (85.2%)	
Lives with a partner			1.0
Yes	20 (95.2%)	82 (93.2%)	
No	1 (4.8%)	6 (6.8%)	
Monthly family income[1]			0.324
≤1	15 (71.4%)	60 (58.1%)	
≥2	6 (28.6%)	36 (41.9%)	
Educational level			0.802
Elementary school/illiterate	9 (42.9%)	32 (36.4%)	
High School	10 (47.6%)	42 (47.7%)	
College/University	2 (9.5%)	14 (15.9%)	
Employed			0.027
Yes	3 (14.3%)	34 (38.6%)	
No	18 (85.7%)	54 (61.4%)	
Parity			0.041
Nulliparous	10 (47.6%)	22 (25.0%)	
Multiparous	11 (52.4%)	66 (75.0%)	
Gestational trimester			0.311
2°	5 (23.8%)	34 (38.6%)	
3°	16 (76.2%)	54 (61.4%)	
Hypertension[2]			0.457
Yes	6 (30.0%)	35 (39.8%)	
No	14 (70.0%)	53 (60.2%)	
Diabetes[3]			0.437
Yes	8 (40.0%)	27 (30.7%)	
No	12 (60.0%)	61 (69.3%)	
Pre-gestational BMI			0.565
Low weight	0 (0%)	4 (4.5%)	
Normal	8 (38.1%)	22 (25%)	
Overweight	7 (33.3%)	28 (31.8%)	
Obesity	6 (28.6%)	34 (38.6%)	
Nutritional status			0.218
Low weight	1 (4.8%)	2 (2.3%)	
Normal	7 (33.3%)	21 (23.9%)	
Overweight	7 (33.3%)	20 (22.7%)	
Obesity	6 (11.8%)	45 (88.2%)	
Anxiety			0.044
Low	11 (52.4%)	23 (29.5%)	
Elevated	10 (47.6%)	62 (70.5%)	

Abbreviation: BMI, body mass index. Notes: [1] in minimum wages; [2] chronic or gestational hypertension; [3] type 2 or gestational diabetes.

associated with a sedentary lifestyle, such as diabetes mellitus and arterial hypertension; it also prevents excess weight gain and postpartum weight retention. Recent guidelines make clear the absolute contraindication to exercise during pregnancy such as: ruptured membranes, premature labour, unexplained persistent vaginal bleeding, placenta praevia after 28 weeks' gestation, pre-eclampsia, incompetent cervix, intrauterine growth restriction, high-order multiple pregnancy (eg, triplets), uncontrolled type I diabetes, uncontrolled hypertension, uncontrolled thyroid disease, other serious cardiovascular, respiratory or systemic disorder.[1,6]

Several studies have showed walking is the most common type of physical activity practiced by pregnant women. Walking becomes the most accessible exercise, since it is easily integrated into the daily routine, and it does not require equipment or payment to be performed. Another possible reason is the traditional belief that walking during pregnancy is safe and can make delivery easier. However, in addition to aerobics, the more recent guidelines recommend the practice of strength exercises during pregnancy.[1,6,26,27]

Many studies seek to understand which are the barriers and the facilitators for the practice of exercises and for a higher level of physical activity amidst pregnant women. The present study shows that pregnant women with a higher educational level are associated with higher energy expenditure. Women with low educational level seem to have beliefs related to poor diets and physical inactivity, such as: activities associated with daily life can replace activities with greater energy expenditure.[16,26–30]

Regarding parity, a systematic literature review identified that pregnant women with at least one child tend to interrupt the practice of sports and exercises during pregnancy when compared with women who do not have children. Nevertheless, while pregnant women who already have one or more children report less time to exercise, they have a higher overall energy expenditure due to the increased activities of daily living, such as playing with children and household activities.[17] Still, some pointed out that women who work outside the house during pregnancy tend to have greater purchasing power, which reflects in healthier behaviors, such as choosing more nutritious foods and maintaining the frequency of exercise. Other studies showed that women who are not employed are more likely to comply with exercise guidelines compared with employed women. A possible explanation for this situation is the greater time availability that unemployed women have, hence including the practice of exercises into their daily routine more easily, as we found in our population.[8,18,27,29–31]

Maternal BMI has also been associated with physical activity when compared with pre-pregnancy levels. A multicenter cohort study revealed that pregnant women with a BMI greater than 25 kg/m^2 cease moderate to intense physical activity during pregnancy more frequently than women with a "normal" weight (BMI 18.5–24.99 kg/m^2), who continued with moderate to vigorous activities. A possible explanation for obese and overweight pregnant women involved in less strenuous activities is negative body image and lower self-efficacy in relation to physical activities with higher energy expenditure.[16,18,24,25,31–34]

Another factor that we studied was maternal anxiety. The study performed by Araújo et al.[20] with pregnant women in Rio de Janeiro found a similar result to the present study: 64.9% of these women had high levels of anxiety when answering the STAI questionnaire.[20,35–37] Two systematic reviews revealed low evidence about the effect of exercise on reducing anxiety symptoms during pregnancy. However, pregnant women who experience higher levels of anxiety tend to reduce self-care and have low adherence to healthy lifestyle habits, therefore, choosing more caloric foods and not exercising. Thus, anxiety symptoms should be routinely screened in pregnant women, mainly those with risk-pregnancies, to help women deal with pregnant related issues.[32,35,36,38]

Our results highlight the need for a multidisciplinary approach during pre-natal care to reinforce the adoption of health-related behaviors during pregnancy, since modifiable factors such as mental health, nutritional status and physical activity patterns have been associated with better perinatal outcomes, which is the main goal of a pre-natal service.[39]

As a limitation, the present study was carried in a single reference center with women from low socioeconomic level, which prevents us from generalizing our results for all high-risk pregnant women in Brazil. We used a questionnaire to assess the pattern of activity and exercise, which can generate an information bias. However, the questionnaire is a validated one, and it is also widely applied in national and international studies. Another limitation is the short period of time covered by the questionnaire which is, in this case, of three months; such period is insufficient to cover the entire pregnancy, leading to the need for longitudinal studies. However, this is the first study that includes only high-risk pregnant women evaluating both physical activity and exercise practice levels, and presenting a robust analysis of related factors. Thus, it brings some advance to the knowledge of this theme.[8–10,12]

Conclusion

It is observed that high-risk pregnant women adopt preferentially sedentary activities, with a predominance of energy expenditure in domestic activities. Also, the practice of exercise is greatly reduced among high-risk pregnant women. It is also noted that a higher level of education was the most important factor associated with practice of activities with greater energy expenditure. Additionally, nulliparity, unemployment, and low levels of anxiety were associated with the practice of exercise.

In view of our findings, it is plausible to acknowledge that the reduction in the practice of physical activities and exercise throughout the gestational period is a reality that involves pregnant women at habitual risk and those at high-risk. Considering the recognized benefits of exercise on maternal and fetal health, a multidisciplinary team should be engaged in prenatal care to encourage pregnant women to practice exercise properly and safely. Therefore, recognizing the factors that

facilitate and hinder the adoption of a more physically active lifestyle is fundamental for an individualized orientation, manly for high-risk pregnant women.

Contributions

LAM: Protocol/project development, data collection or management, data analysis, manuscript writing/editing. ACRM: Protocol/project development, data collection or management, manuscript writing/editing. KTK: Protocol/project development, manuscript writing/editing. FGS: data analysis, manuscript writing/editing. MAM: data analysis, manuscript, writing/editing. SLN: Protocol/project development, data analysis, manuscript writing/editing.

Conflict of Interests

The authors have no conflict of interests to declare.

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Use of Triggers on in vitro Fertilization and Evaluation of Risk Factors for Sub-Optimal Maturation Rate

Uso de gatilhos na fertilização in vitro e avaliação dos fatores de risco para taxa de maturação subótima

Larissa Matsumoto[1] Lucas Yugo Shiguerhara Yamakami[1] Edson Guimarães Lo Turco[2] Cristina Laguna Benetti-Pinto[3] Daniela Angerame Yela[3]

[1] Department of Human Reproduction, VidaBemVinda Human Reproduction Care Center, São Paulo, SP, Brazil
[2] Department of Human Reproduction, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil
[3] Department of Gynecology and Obstetrics, Faculty Medical Sciences, Universidade Estadual de Campinas, Campinas, SP, Brazil

Address for correspondence Daniela Angerame Yela, Professor, Rua Alexander Fleming, 101, Cidade Universitária, 13083-881, Campinas, SP, Brazil (e-mail: yela@unicamp.br).

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Abstract

Objective To compare the oocyte maturation rate in the treatment of in vitro fertilization (IVF) in terms of the use of human chorionic gonadotropin (hCG), agonist gonadotropin-releasing hormone (GnRH) and dual trigger and to evaluate the associated risk factors for sub-optimal maturation rates.

Methods A retrospective cohort study with 856 women who underwent IVF. They performed oocyte retrieval and were classified into 3 groups (1 - hCG, 2 - GnRH agonist, 3 - dual trigger). The primary outcome was maturation rate per trigger, and the secondary outcomes were the pregnancy rate per oocyte retrieval and the correlations between low maturation rate as well as the clinical and treatment characteristics of women.

Results The maturation rate was 77% in group 1; 76% in group 2, and 83% in group 3 ($p = 0.003$). Group 2 showed women with better ovarian reserve, greater number of oocytes collected, and more mature oocytes and embryos compared with the other groups ($p < 0.001$). The cumulative clinical pregnancy rate was no different between the groups ($p = 0.755$). Low ovarian reserve and low doses of follicle-stimulating hormone (FSH) administered during the stimulus were associated with a higher chance of null maturation rate.

Conclusion The oocyte maturation rates and IVF results were similar in all groups. Low ovarian reserve is associated with the worst treatment results.

Keywords
- dual trigger
- GnRH agonist
- HCG in vitro fertilization
- oocyte maturation

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Resumo

Objetivo Comparar a taxa de maturação oocitária no tratamento de fertilização in vitro (FIV) em relação so o uso de gonadotrofina coriônica humana (hCG), agonista de hormônio liberador de gonadotrofina (GnRH), e gatilho duplo e avaliar os fatores de risco associados a taxas de maturação subótimas.

Métodos Estudo de coorte retrospectivo com 856 mulheres submetidas à FIV. Elas foram classificadas em 3 grupos (1 - hCG, 2 - GnRH agonista, 3 - gatilho duplo). O desfecho primário foi a taxa de maturação por gatilho, e os desfechos secundários foram a taxa de gravidez por recuperação de oócitos e as correlações entre a baixa taxa de maturação bem como as características clínicas e do tratamento das mulheres.

Resultados A taxa de maturação foi de 77% no grupo 1; 76% no grupo 2, e 83% no grupo 3 ($p = 0{,}003$). O grupo 2 apresentou mulheres com melhor reserva ovariana, maior número de oócitos coletados, oócitos maduros, e embriões, em comparação aos demais grupos ($p < 0{,}001$). A taxa cumulativa de gravidez clínica não foi diferente entre os grupos ($p = 0{,}755$). Baixa reserva ovariana e baixas doses de hormônio folículo-estimulante (FSH) administradas durante o estímulo foram associadas a uma maior chance de taxa de maturação nula.

Conclusão As taxas de maturação oocitárias e os resultados de FIV foram semelhantes em todos os grupos. A baixa reserva ovariana está associada aos piores resultados do tratamento.

Palavras-chave

- gatilho duplo
- agonista de GnRH
- HCG fertilização in vitro
- maturação oocitária

Introduction

Favorable in vitro fertilization (IVF) results are related to satisfying results after ovarian stimulation, lower rates of ovarian hyperstimulation syndrome (OHSS), and lower rates of multiple pregnancies.[1] The number of mature eggs captured in in vitro fertilization is directly related to the chances of pregnancy.[2] The number of mature eggs and the risk of OHSS are directly related to the choice of the trigger. The most commonly used ovulation trigger is human chorionic gonadotropin (hCG).[3] However, the use of hCG can increase the risk of OHSS. A safer way to perform oocyte maturation is by using the gonadotropin-releasing hormone (GnRH) agonist, because it can reduce severe forms of OHSS by 50%; however, it requires intense luteal phase support.[4,5]

When maturation rates are lower than 70%, there may be impairment in the outcome of IVF.[6] There is a hypothesis that a low ovarian reserve and age are related with higher chances of inadequate response to maturation trigger.[1]

When the inadequate responses occur, there is the possibility of a new double trigger cycle that uses hCG and GnRH agonists.[7] The dual trigger presents better results regarding the number of mature oocytes collected and the oocyte quality, higher quantity of mature eggs, and better embryonic quality.[8]

Few studies compare the three types of triggers together. Thus, the present study aims to evaluate oocyte maturation rates and IVF results according to the use of the three types of triggers to decide the choice of the trigger, offering better indication with lower risk and, thus, personalizing the treatment of each woman.

Methods

A retrospective observational cohort study was performed with 856 women submitted to IVF at a private clinic in São Paulo, who performed the oocyte abstractions between October 2011 and July 2017.

The women were classified into three groups according to the type of trigger used: 1 - hCG (525 women); 2 - GnRH agonist (271 women) and 3 - dual trigger (60 women). A dosage of 5,000 IUs of hCG was used in group 1; the second group received a dose of 191.2 micrograms of triptorelin as the agonist GnRH; the last group, dual trigger, received hCG doses between 1,500 and 6,500 IUs in association with a dose of 191.2 micrograms of triptorelin as the agonist GnRH, with 36 hours before oocyte uptake.

The standard medication for egg maturation is hCG. However, the choice of medication to be used depends on the risk assessment of the patient developing ovarian hyperstimulation syndrome. The risk is identified through test results in which the patient has more than 25 developing follicles, estradiol above 3,500 pg/dl on the trigger day and when the anti-Mullerian hormone (AMH) dosage > 3.4 ng/ml, which leads to the use of agonist GnRH. For patients with a low ovarian reserve and advanced age, the dual trigger was chosen as an option seeking better results. The analyzed variables were age, body mass index (BMI), infertility time, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) dosages (hormones dosed up to 3 days of menstruation), AMH, antral follicle count (AFC: count of total ovarian follicles of size 3–9 mm, performed by ultrasound during the early follicular phase), ovarian reserve, the number of oocytes collected, the number of metaphase II (MII) oocytes, the maturation rate (ratio between a total of MII oocytes divided by the number of total oocytes $\times$ 100), the number of zygotes, fertilization rate, and biochemical pregnancy defined by the presence of positive β-hCG and clinically defined by the presence of gestational sac on ultrasound.

Serum dosages of FSH and LH were evaluated by the Immulite System kit (Diagnostic Products Corporation, DPC. Los Angeles, CA, USA) using the chemiluminescence method and expressed in IUs/ml; the AMH serum levels were obtained by the electrochemiluminescence method, and its values were expressed in nanograms per milliliters.

The ovarian reserve was evaluated according to the criteria of Bologna[9] that defines a woman with low ovarian reserve as a woman who presents at least two of the three criteria: age greater than or equal to 40 years, low count of antral follicles or low AMH, and history of poor ovarian response in previous treatments. All data were obtained from the analysis of the medical records of these women.

The exclusion criteria were women who used the long agonist protocol as a stimulus, canceling the cycle before using the trigger, women who showed no follicular growth between 7 and 10 days of stimulation, and women whose records had up to 50% of missing data and whose spermatozoa for IVF came from testicular biopsy. We calculated cumulative pregnancy rates by the stimulus; embryonic transfers were performed fresh or with a frozen embryo, but, in both cases, we performed luteal phase support.

The study was approved by the research ethics committee of the institution under the CAAE number: 80882517.0.0000.5404. The sample size was for convenience. For the calculation of sample power, the average comparison method between 3 groups was used, considering the average and standard deviation of the maturation value (transformed in ranks due to the absence of normal distribution) in each group, and setting the significance level or type I error as 5%. Thus, we obtained a sampling power of 77.7% for the maturation rate. To compare the categorical variables between the groups, the Chi-Squared or Fisher exact tests were used. The Mann-Whitney and the Kruskal-Wallis tests were used to compare the numerical variables. Analysis of variance (ANOVA) was performed to compare the variables separated by age group. To analyze the factors related to the lower maturation rate, the Poisson regression analysis, univariate and multivariate, were used, with the stepwise criterion for selecting variables and estimating the prevalence ratio and 95% confidence interval. The significance level adopted for the statistical tests was 5%.

Results

The frequency of triggers used in IVF was 61.33% hCG, 31.65% agonist GnRH, and 7.01% dual trigger. The mean age of the women was 35.83 ± 4.59 years, and the time of infertility considered was 36.43 ± 34.24 months. The women in the dual trigger group had older age and longer time of infertility in relation to the other groups ($p = 0.001$ and $p = 0.006$ respectively). About the criteria used to evaluate the ovarian reserve, the HCG group had higher FSH and lower AMH values compared with the agonist GnRH group ($p < 0.001$, $p = 0.003$ respectively) and the dual trigger group had lower AFC levels than the other two groups ($p < 0.001$) (►**Table 1**). There was a statistical difference between the variables that indicate ovarian reserve, such as AFC ($p = 0.001$), baseline FSH ($p = 0.001$), and AMH levels ($p = 0.033$) (►**Table 1**).

The agonist GnRH group had a greater number of total follicles (15.52 ± 8.80), a higher number of follicles larger than 16 mm (7.08 ± 4.46), greater number of oocytes collected (14.12 ± 9.37), and higher number of oocytes in MII (10.73 ± 7.39) comparing to the other groups ($p < 0.001$), and this result remains even after separating them by age group (►**Table 2**). The maturation rate was higher with the use of the dual trigger (0.83 ± 0.17) when compared with the other groups ($p = 0.035$), but when the groups were separated by age group, we found no difference in the rate of maturation ($p = 0.161$) (►**Table 2**).

The total cumulative pregnancy rate was 47.04%, 11.1% of which were twin pregnancies. There was no statistical difference between pregnancy rates ($p = 0.755$), the number of gestational sacs ($p = 0.648$), and the number of abortions ($p = 0.227$) among the three groups (►**Table 3**).

The null maturation rate was 3.03% and the maturation rate < 70% was 28.18%. None of the variables, such as age, infertility time, low ovarian reserve, trigger, BMI, FSH dose,

Table 1 Clinical and laboratorial characteristics of the 856 women submitted to in vitro fertilization

Variables	Total ($n = 856$)	HCG ($n = 525$)	Agonist GnRH ($n = 271$)	Double trigger ($n = 60$)	P^*	P^{**}
	Average ± *SD*	*Average* ± *SD*	*Average* ± *SD*	*Average* ± *SD*		
Age (years)[b, c]	35.93 ± 4.59	36.18 ± 4.56	34.97 ± 4.57	38.12 ± 3.83	< 0.001	—
Infertility period (months)[b]	36.43 ± 34.24	38.18 ± 35.38	32.01 ± 32.99	40.37 ± 27.55	0.006	0.016
BMI (kg/m2)[b, c]	25.33 ± 4.84	25.36 ± 4.40	25.87 ± 5.93	22.73 ± 4.80	0.029	0.028
Basal FSH (UI/L)[a]	8.76 ± 8.09	9.31 ± 9.22	7.84 ± 6.18	8.14 ± 3.73	< 0.001	0.002
Basal LH (UI/L)	6.55 ± 6.43	6.76 ± 7.24	6.43 ± 5.26	5.34 ± 2.73	0.369	0.388
AMH (ng/ml)[a]	1.39 ± 1.88	1.10 ± 1.70	2.12 ± 2.45	1.29 ± 1.00	0.033	0.042
AFC (unit)[a, b, c]	11.63 ± 7.58	10.21 ± 6.30	15.00 ± 8.91	8.63 ± 6.06	< 0.001	< 0.001

Abbreviations: AFC, count of antral follicles; AMH, anti-Mullerian hormone; BMI, body mass index; FSH, follicle stimulating hormone; LH, luteotropic hormone; SD, standard deviation.
*Kruskal-Wallis test. **Age-adjusted analysis of variance (ANOVA); **a**: difference between groups 1 and 2; **b**: difference between groups 2 and 3; **c**: difference between groups 1 and 3.

Table 2 Laboratory and characteristics of the stimulus of the three groups of triggers in women submitted to in vitro fertilization

Variables	Total ($n = 856$)	HCG ($n = 525$)	Agonist GnRH ($n = 271$)	Double trigger ($n = 60$)	P^*	P^{**}
	Average ± SD	*Average ± SD*	*Average ± SD*	*Average ± SD*		
Stimulus (days)[b, c]	10.82 ± 2.01	10.62 ± 2.00	10.94 ± 1.85	12.03 ± 2.27	< 0.001	< 0.001
FSH dosage (UI)[b, c]	2,054.30 ± 653.77	2,043.30 ± 579.43	1,936.1 ± 685.38	2,682.10 ± 768.82	< 0.001	< 0.001
LH dosage (UI)[b, c]	941.24 ± 572.44	922.20 ± 558.96	873.89 ± 503.65	1,391.10 ± 749.88	< 0.001	< 0.001
E2 trigger (pg/ml)[a, b]	2,249.90 ± 2,979.0	1,676.70 ± 1,334.30	3,310.30 ± 4,462.60	1,455.20 ± 944.10	< 0.001	< 0.001
P2 trigger (ng/ml)[b, c]	2.25 ± 6.75	1.01 ± 0.5	1.10 ± 1.80	3.66 ± 1.74	< 0.001	< 0.001
LH start (UI/L)	4.99 ± 1.65	5.12 ± 2.1	4.91 ± 5.24	4.31 ± 3.78	0.300	0.196
LH trigger (UI/L)	5.33 ± 3.28	6.2 ± 4.23	4.03V6.41	4.23 ± 5.30	0.159	0.189
Total follicles [a, b]	11.57 ± 7.23	9.71 ± 5.52	15.52 ± 8.80	9.97 ± 5.17	< 0.001	< 0.001
Follicles > 16mm [a, b]	5.16 ± 3.67	4.22 ± 2.82	7.08 ± 4.46	4.65 ± 2.83	< 0.001	< 0.001
Oocytes collected [a, b, c]	10.11 ± 7.82	8.46 ± 6.23	14.12 ± 9.37	6.72 ± 5.71	< 0.001	< 0.001
MII [a, b]	7.65 ± 5.96	6.32 ± 4.50	10.73 ± 7.39	5.43 ± 4.57	< 0.001	< 0.001
Maturation rate [b]	0.77 ± 0.22	0.77 ± 0.24	0.76 ± 0.20	0.83 ± 0.17	0.035	0.161
2PN [a, b]	5.39 ± 4,07	4.62 ± 3.45	7.11 ± 4.69	4.57 ± 3.96	< 0.001	< 0.001
D3 Embryos [a, b]	5.29 ± 4.17	4.50 ± 3.52	6.99 ± 4.82	4.37 ± 3.98	< 0.001	< 0.001
Blastocysts [a, b]	2.01 ± 2.51	1.63 ± 2.08	2.80 ± 3.08	1.80 ± 2.41	< 0.001	< 0.001

Abbreviations: 2PN, zygote with two pro nuclei; D3, total embryos on the third day; E2, estradiol dosage; LH beginning, dosage of luteotropic hormone at the beginning of the stimulus; LH trigger, dosage of luteotropic hormone on the day of the trigger; MII, ova in metaphase II; P2, dosage of progesterone; SD, standard deviation. * Kruskal-Wallis test. **Age-adjusted analysis of variance (ANOVA); **a**: difference between groups 1 and 2; **b**: difference between groups 2 and 3; **c**: difference between groups 1 and 3.

Table 3 Results obtained after the in vitro fertilization procedure in the women of the three groups of triggers ($n = 856$)

Variables	HCG ($n = 525$)	Agonist GnRH ($n = 271$)	Double trigger ($n = 60$)	P^*
	n/n total	*n/n total*	*n/n total*	
B-HCG	211/459–46%	106/217–49%	17/34–50%	0.755
Clinical pregnancy	194/456–43%	89/213–42%	16/34–47%	0.284
Twinning	50/211–24%	26/89–29%	42,401–13%	0.227
Miscarriage	39/455–09%	27/217–12%	12,510–12%	0.272

Notes: *Chi-squared test

LH dosed on the trigger day, or the LH dose administered in the stimulus, were significantly associated with the low maturation rate by univariate and multivariate analysis (►**Table 4**).

Regarding the null maturation rate when we performed the univariate analysis, the factors associated with the rate were low ovarian reserve, the LH trigger (≥ 3.80 IU), the FSH dosage (< 1,650 IUs/L) and the LH dosage (< 600 IUs/L and LH between 885–1349 IUs/L). From the results of the multivariate analysis, it was found that the low ovarian reserve and FSH dosage variables were significantly associated with the null maturation rate. The women with the highest risk of zero maturation rate were those with a low ovarian reserve (risk 4.58 times higher) and those with a low dose of FSH (< 1,650 IUs/L) (risk 16.03 times higher) (►**Table 5**).

Discussion

We observed heterogeneity among the groups: the women who used the dual trigger were older and with a longer time of infertility, and the group that used agonist GnRH had a better ovarian reserve (higher AMH and AFC values and lower values of base FSH).

Up to 37% of IVF treatments are performed in patients with advanced age. It was known that age is a prognostic factor in the results of IVF. Studies show that with increasing age there are worse results in the treatment of IVF.[10]

We separate the results by age group to avoid this bias. However, the agonist GnRH group had a greater number of total follicles, a greater number of follicles with a size larger than 16 mm, a greater number of oocytes, and a higher number of MII oocytes than the other groups. This can be

Table 4 Clinical and laboratory factors associated with the prevalence of low maturation rate ($n = 823$)

Variables	Categories	*P*-value	PR (CI 95%) *
Ages (years)	< 30 (ref.)	—	1.00 (—)
	30–39	0.847	1.04 (0.68–1.61)
	≥ 40	0.178	0.71 (0.42–1.17)
Infertility period (months)	—	0.101	1003 (0.999–1.007)
Low ovarian reserve	No (ref.)	—	1.00 (—)
	Yes	0.786	1.04 (0.80–1.34)
Group/Trigger	Double trigger (ref.)	—	1.00 (—)
	Agonist GnRH	0.499	1.23 (0.68–2.21)
	HCG	0.202	1.44 (0.82–2.54)
BMI (Kg/m2)	< 20	0.703	0.86 (0.39–1.88)
	20.0–24.9 (ref.)	—	1.00 (—)
	25.0–29.9	0.181	1.30 (0.89–1.90)
	≥ 30.0	0.053	1.53 (0.99–2.36)
LH trigger (UI)	< 1.00 (ref.)	—	1.00 (—)
	1.00–1.99	0.905	1.03 (0.66–1.59)
	2.00–3.79	0.419	0.83 (0.52–1.31)
	≥ 3.80	0.590	0.88 (0.56–1.39)
FSH dose (UI/L)	≥ 2,475 (ref.)	—	1.00 (—)
	2,025–2,474	0.390	1.16 (0.83–1.64)
	1,650–2,024	0.794	1.05 (0.72–1.53)
	< 1,650	0.096	1.35 (0.95–1.92)
LH dose (UI/L)	< 600 (ref.)	—	1.00 (—)
	600–884	0.268	0.82 (0.57–1.17)
	885–1,349	0.829	0.96 (0.67–1.38)
	≥ 1,350	0.923	0.98 (0.70–1.38)

Abbreviations: BMI, body mass index; CI, confidence interval; FSH, follicle stimulating hormone; LH, luteinizing hormone; PR, prevalence ratio; ref, reference.

* stepwise criteria for selection of variables.

explained because women in this group have the highest ovarian reserves.

The choice of the trigger is of the responsibility of the physician who conducts the treatment, and who obeys a hyperstimulation prevention protocol, in which the use of agonist GnRH and freeze all strategy are safe conducts.[11] This justifies the choice of the use of agonist GnRH for younger women those with a better ovarian reserve, as they are the ones that present a higher risk of hyperstimulation syndrome. Thus, it was expected that those were also the women with better results in the absolute number of oocytes collected and MII oocytes, as observed.

This group also showed a greater number of fertilized oocytes, and 3rd- and 5th-day embryos compared with the other two groups, which explains the use of agonist GnRH alone for oocyte maturation—as oocyte quality would not change—affecting the outcome of IVF, as shown by some.[12]

Despite the group 2 results, the dual trigger group has a higher oocyte maturation rate, though, when adjusted by age groups, we found that the three groups had similar rates of maturation.

In the other study, the randomized clinical trial showed a higher maturation rate with the agonist GnRH use over hCG use.[11] Another study comparing the dual trigger group with the hCG group found no difference in the maturation rates between them.[13]

The use of agonist GnRH is more physiologic but has a luteolytic effect, reducing the half-life of the corpus luteum, requiring more robust luteal phase support to lower implantation rates, and causing a higher risk of miscarriage in cycles transferred to fresh.[14] In our study, we did not observe a difference in the number of abortions when we compare the three groups. We also found no difference in the rate of pregnancy and twins.

A meta-analysis with 859 women shows the same pregnancy rates where fresh transfer in women who have made the use of GnRH agonist (33%) or hCG (34%). This study also found no difference in abortion rates between the groups (agonist GnRH 20%, hCG 12.5%, $p = 0.06$).[15]

In our study, we found no difference in the results of IVF treatment despite the women in the dual trigger group being older and having a worse ovarian reserve.

Table 5 Clinical and laboratory factors associated with prevalence rate of null maturation ($n = 823$)

Variables	Categories	*P*-value	Crude PR (CI 95%) *	Adjusted PR (CI 95%) *
Ages (years)	< 30 (ref.)	—	1.00 (—)	
	30–39	0.128	4.68 (0.29–76.86)	
	≥ 40	0.096	5.84 (0.34–100.90)	
Infertility period (months)	—	0.411	0.993 (0.978–1.009)	
Low ovarian reserve	No (ref.)	—	1.00 (—)	1.00(—)
	Yes	0.001	3.95 (1.70–9.15)	4.58 (1.77–11.90)
Group/Trigger	Double trigger (ref.)	—	1.00 (—)	
	Agonist	0.215	3.28 (0.19–56.54)	
	HCG	0.152	4.15 (0.25–67.97)	
BMI (Kg/m2)	< 20	0.294	0.43 (0.03–7.22)	
	20.0–24.9 (ref.)	—	1.00 (—)	
	25.0–29.9	0.496	0.63 (0.17–2.38)	
	≥ 30.0	0.857	1.13 (0.30–4.26)	
LH trigger (UI)	< 1.00 (ref.)	—	1.00 (—)	
	1.00–1.99	0.324	0.34 (0.0–8.31)	
	2.00–3.79	0.224	3.90 (0.44–34.87)	
	≥ 3.80	0.028	10.09 (1.29–78.81)	
FSH dose (UI/L)	≥ 2,475 (ref.)	—	1.00 (—)	1.00 (—)
	2,025–2,474	0.187	4.25 (0.50–36.33)	5.78 (0.67–49.85)
	1,650–2,024	0.177	4.52 (0.51–40.46)	6.36 (0.71–57.25)
	< 1,650	0.008	15.83 (2.08–120.35)	16.03 (2.07–124.32)
LH dose (UI/L)	< 600	0.049	4.74 (1.01–22.30)	
	600–884	0.257	2.58 (0.50–13.31)	
	885–1,349	0.031	5.39 (1.16–24.92)	
	≥ 1,350 (ref.)	—	1.00 (—)	

Abbreviations: BMI, body mass index; CI, confidence interval; FSH, follicle stimulating hormone; LH, luteinizing hormone; PR, prevalence ratio; ref, reference.* stepwise criteria for selection of variables.

A retrospective study comparing the dual trigger with the hCG groups in women with low ovarian reserve showed a better maturation rate with the use of the dual trigger, but found no difference in the fertilization rates, embryonic quality, and pregnancy or abortion rates.[4]

Other studies show that the dual trigger has a higher maturation rate, implantation, and pregnancy rates with hCG.[6,16] In addition to the results of IVF, we sought to identify the factors associated with the worse rates of oocyte maturation to improve the number of oocytes collected, and to help guide the expectations for treatment. According to our findings the amount of mature zygotes in treatment was directly related to the success of the IVF treatment. When we observe null maturation rates, it is usually an indicator of low ovarian reserve that was evaluated by AFC, AMH, and FSH.

A lower AFC (< 11) was related to an increased risk of cycle cancellation due to low response. A study shows 12 as a cutoff point for AFC, for low response to treatment.[17] In addition to AFC, the literature discusses the role of BMI in response to treatment; overweight and obesity were associated with a poor ovarian response, with less than three oocytes retrieved.[1] However, in our study, we found no association between BMI and worse results regarding the oocyte maturation rate.

Concerning the ovarian stimulus, lower doses of FSH administered were related to a smaller number of oocytes.[12] It is theorized that the correlation of the ratio of AMH with AFC when high, reduces ovarian sensitivity response to exogenous FSH administered, and the analysis that for women with low ovarian reserve, increasing the dose of FSH administered does not improve the ovarian response, nor the pregnancy rates.[18]

However, a multicenter study by Melo et al. with 1,515 patients, evaluating the cost-effectiveness of individual doses of FSH, concluded that individualization of the dose of FSH does not change the outcome of IVF, and is a more expensive treatment.[17]

The use of FSH at lower doses, less than 1,650 IUs per stimulus, was one of the factors correlated with the null maturation rate. Studies with mild stimulation show a greater number of cancellations cycles than those with traditional stimulus while affording the same pregnancy

rates of traditional stimulus, lead to fewer oocytes, and may present a greater risk of not finding oocytes in the oocyte retrieval in a frequency of up to 9.4%.[7,10]

The group of women with worse prognosis who followed protocols with lower doses of medication might have compromised results, with lower doses of FSH during the ovarian stimulus. Despite the differences between the groups, we had a low prevalence of zero maturation rate and the IVF results were similar between of them.

The limitations of the study are due to being a retrospective analysis, and the sample evaluated not being homogeneous. Thus, the different number of women in each group and the differences in their characteristics (such as age, infertility time, BMI, and ovarian reserve) are limiting factors for the analysis. It is noted that women who used hCG can be classified as normal responders, those who chose to use agonist GnRH presented a higher risk of OHSS and those of the dual trigger group were women with low ovarian response.

Conclusion

Despite the differences between the three evaluated groups, the rates of oocyte maturation and the IVF results were similar across the sample; this demonstrates that the adequate choice in the type of trigger used will yield good results in IVF treatments. Low ovarian reserve jeopardizes the results of IVF, increasing the chances of null maturation rates. Moreover, even on the low ovarian reserve group, the choice of the trigger is paramount to achieving greater maturation and cumulative β-hCG rates.

Contributions

All the authors participated actively in the study, as follows: D. A. Yela and C. L. Benetti-Pinto were responsible for writing the protocol and the final manuscript. L. Matsumoto, E. G. lo Turco. and L. Y. S. Yamakami collected the data and conducted the literature review.

Conflict of Interests

The authors have no conflict of interests to declare.

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Nipple-sparing Mastectomy with Immediate Implant-based Reconstruction for Patients with Pure Ductal Carcinoma in Situ

Mastectomia preservadora de mamilo com reconstrução imediata baseada em implante para pacientes com carcinoma ductal puro in situ

Antônio Luiz Frasson[2] Ana Beatriz Falcone[1,2] Isabela Miranda[2]
Alessandra Borba Anton de Souza[2] Betina Vollbrecht[2] Fernanda Barbosa[1]
Mônica Adriana Rodriguez Martinez Frasson[1] Martina Lichtenfels[2]

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

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Address for correspondence Antônio Luiz Frasson, MD, PhD, Serviço de Mastologia, Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Rua Ipiranga, 6.690, sala 714, Porto Alegre, RS, Brazil (e-mail: alfrasson.af@gmail.com).

Abstract

Objective The presence of an extensive intraductal component is associated to an increasing risk of relapse in the nipple-areola complex. The aim of the present study was to evaluate the outcomes of patients diagnosed with ductal carcinoma in situ (DCIS) who underwent nipple-sparing mastectomy (NSM) with immediate breast reconstruction using silicone implants.

Methods We retrospectively analyzed the postoperative complications and oncological safety of 67 breast cancer patients diagnosed with pure DCIS who underwent NSM with immediate breast reconstruction using silicone implants between 2004 and 2018.

Results Among the 127 NSM procedures performed, 2 hematomas (1.5%) and 1 partial nipple necrosis (0.7%) were observed. After a mean follow-up of 60 months, the local recurrence rate was of 8.9%, the disease-free survival rate was of 90%, and 1 of the patients died.

Conclusion Despite the local recurrence rate, we showed that NSM with immediate breast reconstruction using silicone implants is a feasible surgical approach, with a low rate of complications and high survival rates for patients with a diagnosis of pure DCIS when breast-conserving surgery is not an option.

Keywords
- breast cancer
- intraductal noninfiltrating carcinoma
- subcutaneous mastectomy

Resumo

Objetivo A presença de componente intraductal extenso é associada ao risco aumentado de recorrência no complexo aréolo-mamilar. O objetivo deste estudo foi avaliar os resultados de pacientes diagnosticados com carcinoma ductal *in situ* (CDIS)

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submetidas a adenomastectomia (*nipple-sparing mastectomy*, NSM, em inglês) com reconstrução mamária imediata utilizando prótese de silicone.

Métodos Restrospectivamente, foram analisadas as complicações pós-operatórias e a segurança oncológica de 67 pacientes com câncer de mama diagnosticadas com CDIS puro, e submetidas a NSM com reconstrução mamária imediata utilizando prótese de silicone, entre 2004 e 2018.

Resultados Entre os 127 procedimentos realizados, 2 hematomas (1,5%) e 1 necrose parcial de mamilo (0,7%) foram observados. Após um período médio de 60 meses de seguimento, a taxa de recorrência local foi de 8,9%, a sobrevida livre de doença, de 90%, e apenas 1 paciente foi a óbito.

Conclusão Apesar da taxa de recorrência local, demostrou-se que NSM com reconstrução mamária imediata com prótese de silicone é um procedimento viável, com baixa taxa de complicação e alta sobrevida para pacientes com diagnóstico de CDIS puro quando a cirurgia conservadora da mama não é uma opção.

Palavras-chave
- neoplasias da mama
- carcinoma ductal de mama
- mastectomia subcutânea

Introduction

Nipple-sparing mastectomy (NSM) has been successfully performed in the treatment of breast cancer, with excellent results.[1–4] The indications for NSM include invasive breast cancer and ductal carcinoma in situ (DCIS) for patients in whom breast-conserving surgery (BCS) may not be performed.[5] Some contraindications to BCS include larger tumor sizes, multifocal and multicentric tumors, contraindications to radiotherapy (RT), a potentially-poor cosmetic outcome due to the tumor/breast relationship, and patient choice.[5,6] Currently, some authors[7] suggest expanding NSM indications to include patients with large tumors who have undergone neoadjuvant chemotherapy, and patients with local recurrence after BCS followed by RT. The presence of an extensive intraductal component is strongly associated to an increasing risk of relapse in the nipple-areola complex.[8] Previous studies[3,9,10] have reported low rates of recurrence in the nipple-areola complex, ranging from 1.4% to 3.2%, in patients diagnosed with in situ tumors, and have highlighted the oncological safety of the preservation of the nipple-areola complex for patients with a negative intraoperative retroareolar frozen section. Many studies[1,3,9] evaluating the outcomes of patients who underwent NSM were performed with heterogeneous samples, including patients with invasive and intraepithelial tumors, and focusing on NSM with immediate breast reconstruction using prosthetic implants (saline-filled implants or tissue expanders) and autologous tissue flaps.[10–13] The recovery of breast reconstruction following mastectomy is a concern for surgeons. Kim et al.[14] showed that NSM with immediate breast reconstruction with implants is a safe and feasible procedure associated with good cosmetic results. In 2017, most of the NSM performed in Italy were reconstructed using prothesis and direct-to-implant reconstruction was gaining acceptance.[15] The aim of the present study was to retrospectively evaluate the oncological safety, complications and survival rates of patients diagnosed with pure DCIS who underwent NSM with immediate breast reconstruction with prostheses.

Methods

The present retrospective study was performed according to ethical guidelines, and received approval from the Ethics in Research Committee of Hospital São Lucas and Hospital Albert Einstein. Patients with complete medical records were included, and all of them had beene operated on by the main author of the present study. Informed consent was waived by the institutional review board because of the retrospective nature of the study.

Between January 2004 and December 2018, 345 NSMs with immediate breast reconstruction were performed, 77 for in situ tumors. We excluded 5 patients who underwent reconstruction with tissue expanders, 4 patients with recurrence after BCS for invasive cancer, and 2 patients due to loss to follow-up (less than 3 months of follow-up). Patients who underwent risk-reduction NSM with an accidental finding of DCIS were included in the study. The tumor-to-nipple distance and tumor size were not exclusion criteria. Sentinel lymph node biopsy (SLNB) was performed for all patients in the affected breast. All patients were operated on by the same surgeon. The data was retrospectively evaluated through the medical charts, and the follow-up of the patients was updated during the appointments.

We analyzed 67 patients diagnosed with pure DCIS who underwent NSM with immediate implant-based reconstruction. The indications for NSM were risk-reduction breast surgery with an accidental finding of DCIS ($n = 4$; 6%), multifocal disease ($n = 16$; 23.9%), compromised margins after BCS ($n = 11$; 16.4%), tumors ≥ 40 mm ($n = 16$; 23.9%), and unfavorable relationships between tumor size and breast size or patient preference ($n = 20$; 29.8%). The postoperative complications were defined as hematoma requiring drainage, infection, prolonged seroma formation, skin necrosis, partial nipple necrosis, total nipple necrosis, and prothesis extrusion.

The patients were followed by means of clinical examinations every six to twelve months for the first five years, followed by yearly exams thereafter. Imaging exams, such as

ultrasonography, magnetic resonance, or mammography, were required based on patient complaints and after a physical examination.

The recurrences were diagnosed in clinical examinations or imaging exams, and all of the breast and axillary recurrences were biopsied and sent to pathology to confirm the diagnosis. Invasive or in situ local recurrence was defined as recurrence in the same breast and/or ipsilateral axilla.

All procedures were performed under general anesthesia using a periareolar, vertical, or inframammary incision. The NSM skin incision was chosen in accordance with breast type and method of reconstruction, and the majority of them were in the inframammary fold. The glandular tissue was removed respecting the plane of the subcutaneous fascia, carefully resecting breast tissue but leaving a sufficient amount of fat tissue to preserve blood flow and avoid flap necrosis. It is important to highlight that flap thickness 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 DCIS in the retroareolar margin, and all the patients presented tumor-negative margins. No cutoffs for margin status were used, and the postoperative histopathological examination confirmed that all samples were tumor-free.

Patients with DCIS were submitted to SLNB, but not in the breast that underwent contralateral mastectomy. Immediate breast reconstruction was performed using subpectoral definitive prosthetic implants in every patient (►**Figs. 1**,**2**,**3**,**4**,**5**,**6**,**7**,**8**). None of these patients required the use of acellular dermal matrix implants.

The statistical analysis was performed with information from 67 patients. Descriptive statistics was used to summarize the characteristics of the patients. The quantitative variables were expressed as means and ranges, while the categorical variables were expressed as absolute and relative frequencies. Disease-free survival (DFS) was summarized using the Kaplan-Meier method and displayed graphically. The significance level for statistical differences was set at 0.05. The statistical analysis was performed using the SAS (SAS Institute, Inc., Cary, NC, US) statistical software, version 9.4.

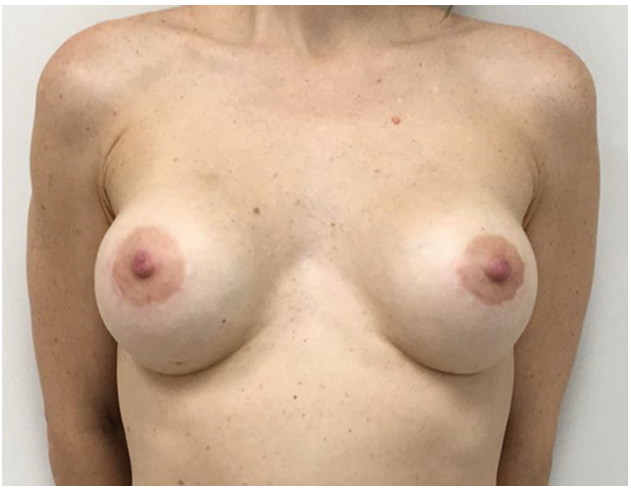

Fig. 1 Preoperative bilateral NSM.

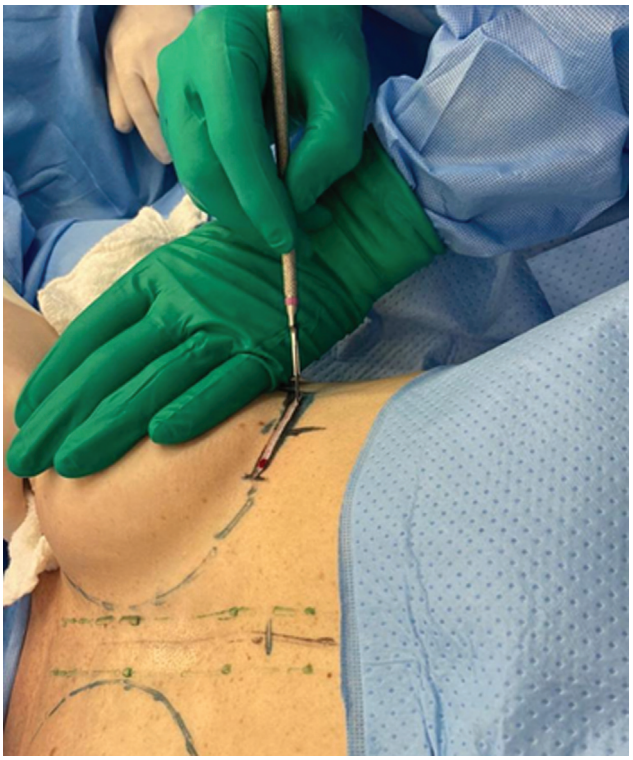

Fig. 2 Inframammary skin incision.

Results

We analyzed 67 patients who were diagnosed with pure DCIS and underwent 127 NSMs with implant-based immediate reconstruction between 2004 and 2018. The mean age of the patients was 46.8 years (range 30–75 years). The clinicopathological characteristics and treatment are listed in ►**Table 1**.

Bilateral procedures were performed in 60 (89.5%) patients, and 7 (10.5%) surgeries were unilateral. In total, 2 (3.4%) patients underwent bilateral surgery due to the diagnosis of DCIS in both breasts, 10 (16.7%) patients presented a diagnosis of atypical hyperplasia in the contralateral breast, 7 (11.7%) patients were mutation carriers with high risk of developing breast cancer, and 41 (68.2%) patients underwent bilateral NSM by choice, looking for better symmetry and a better esthetic result. All patients underwent SLNB in the affected breast, and the lymph node was free of metastasis in every case. Unifocal lesions were found in 36 (53.7%) patients, and multifocal tumors were found in 31 (46.3%) cases. Most of the tumors were high-grade; 38.9% were grade-2, and 47.8%, grade-3. Only 10.4% of the tumors were grade-1 and data was missing from from 2 (2.9%) tumors. A total of 36 (53.7%) patients presented estrogen-receptor-positive (ER+) tumors, 17 (25.4%), ER-negative (ER-) tumors, and data was missing from 14 (20.9%) tumors. Out of the 36 patients with ER+ tumors, 14 (38.9%) underwent hormone therapy (HT), and for the others patients the

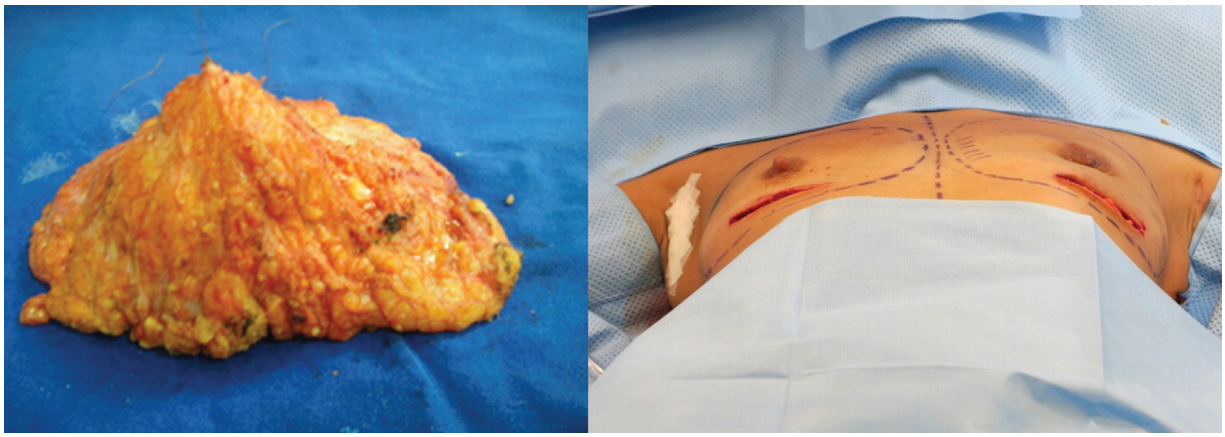

Fig. 3 All breast tissue removed.

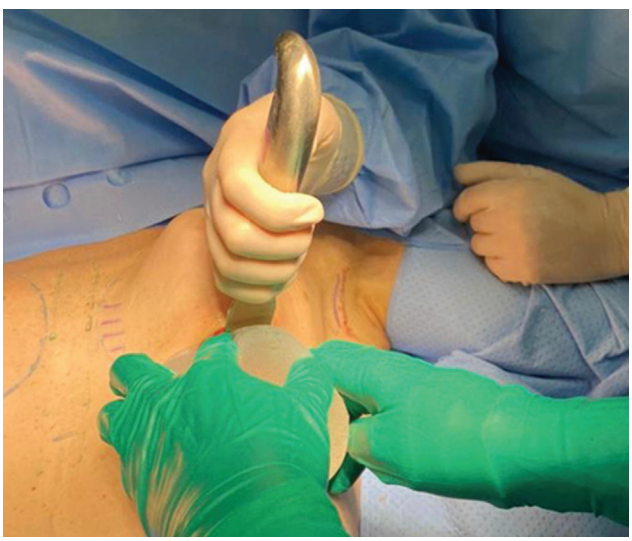

Fig. 4 Inclusion of silicone implant.

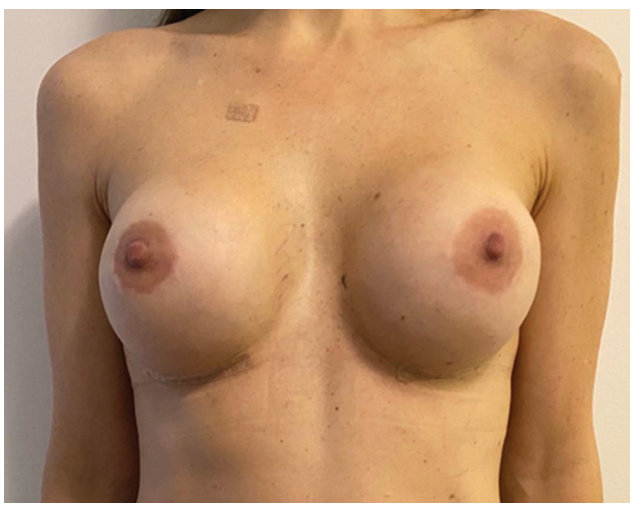

Fig. 6 Postoperative bilateral NSM with immediate breast reconstruction with permanent silicone implants.

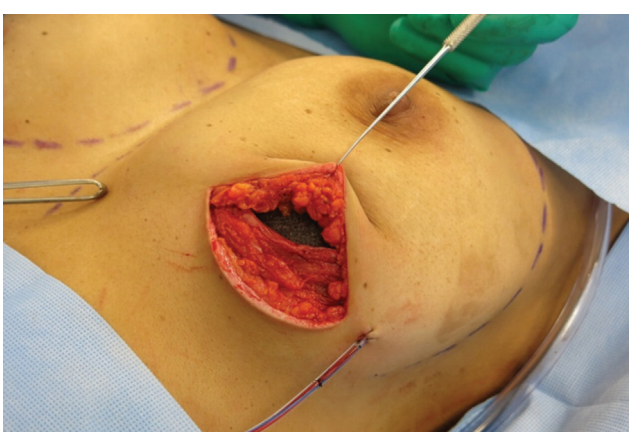

Fig. 5 Breast reconstructed with silicone implant.

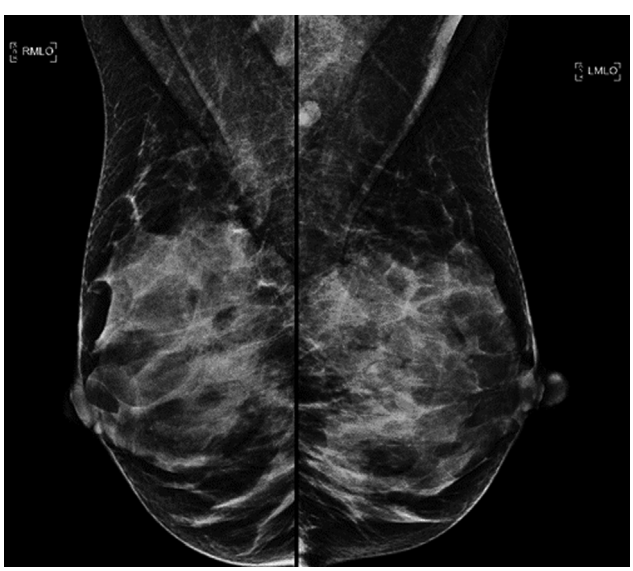

Fig. 7 Preoperative imaging exam.

treatment was not indicated based on the risk/benefit of the hormonal treatment.

Immediate breast reconstruction was performed with silicone-filled implants for all patients. Frozen sections of the areolar flap's undersurface was performed for every

Fig. 8 Postoperative imaging exam of the reconstructed breast with permanent silicone implants.

patient, and the samples were tumor-free in the final analysis.

In the 69 procedures performed for DCIS, 3 (4.3%) complications occurred, including 2 (2.9%) cases of hematomas that required drainage, and 1 (1.4%) partial nipple necrosis. Full-thickness necrosis was defined as necrosis in the entire dermis requiring surgical intervention, such as debridement, delayed repair, and skin grafting, and partial nipple necrosis was defined as injuries that heal with conservative wound care, since they do not extend to the entire thickness of the dermis.

Adjuvant hormone therapy was administered to 14 patients (20.9%), and RT was administered to 12 patients (18%): because of the large extent of the superficial distribution of the DCIS, even with free margins. For one patient, the RT data were missing, and one patient chose not to undergo it. None of the patients submitted to RT presented complications. The patient with partial nipple necrosis presented type-1 diabetes.

During the mean follow-up of 60 months (range: 3 to 183 months), 6 (8.9%) patients presented local recurrence, and 2 (2.95%) cases occurred in the nipple-areola complex. From the 6 relapses, 4 were DCIS and 2 were invasive ductal carcinoma (IDC). None of the patients who presented local recurrence underwent RT, and only 1 patient was older than 50 years old.

Details regarding local recurrence are shown in ►**Table 2** and ►**Table 3**. None of the patients presented metastasis. The DFS rate was of 90% (►**Fig. 9**), and all patients were alive at the end of the 60-month follow-up.

Table 1 Patient, tumor, and treatment characteristics ($n = 67$)

Characteristics	n	%
Age, years		
< 35	4	5.9
35–49	42	62.7
≥ 49	21	31.4
Menopause status		
Premenopausal	48	71.6
Postmenopausal	19	28.4
Previous cancer		
No previous history of breast cancer	56	83.6
Compromised margin after previous surgery	11	16.4
Genetic test		
Yes	18	26.8
Positive for mutations		
BRCA1	1	5.5
BRCA2	4	22.3
P53 4	1	5.5
ATM	1	5.5
VUS ATM e P53	2	11.2
Negative	9	50
No	49	73.2
Tumor size (mm)		
< 40	49	73.2
≥ 40	16	23.9
Unknown	2	2.9
Type of lesion		
Unifocal	36	53.7
Multifocal	31	46.3
Tumor grade		
1	7	10.4
2	26	38.9
3	32	47.8
Unknown	2	2.9
Systemic treatments		
Hormone therapy		
Yes	14	20.9
No	51	76.2
Unknown	2	2.9
Radiotherapy		
Yes	11	16.4
No	56	83.6
Reconstruction		
Implant	67	100

Abbreviations: ATM, ataxia-telangiectasia mutated; BRCA, breast cancer gene; P53, tumor protein p53.

Table 2 Local recurrence rates

Local recurrence	n	%
Same quadrant	2	2.9
Same breast in another quadrant	2	2.9
Nipple-areola complex	2	2.9

Discussion

Nipple-sparing mastectomy is a conservative approach for breast cancer with good rates of esthetic satisfaction from the patients.[16,17] The main concerns regarding the use of NSM are nipple necrosis and local and nipple recurrences. Different authors[1,3,9,11,18,19] have reported rates of local and nipple-areola-complex recurrence after NSM ranging from 0% to 11.6% and 0.7% to 4.8% respectively. The reported incidence of nipple necrosis after NSM ranges from 1.4% to 5.9%.[3,18,19] However, most of the published studies analyzed the rates of complications and recurrence after NSM in heterogeneous samples with invasive and noninvasive tumors.[1]

The increasing number of NSMs has expanded the classic indications, and the number of NSMs for patients with DCIS has been increasing. Most of the studies[10–12] available in the literature regarding the rates of nipple complications and the oncological safety of NSM for patients diagnosed with pure DCIS used different techniques of breast reconstruction, such as prosthetic implants or an autologous tissue flap. Complications related to breast reconstruction after mastectomy are still a concern. The use of immediate implant-based reconstruction after NSM seems to be safe and feasible, and has been growing worldwide.[14,15] A retrospective study[20] with 435 patients who underwent NSM for invasive and in situ tumors with primary implant reconstruction reported a rate of 5.9% of skin flap ischemia/necrosis. In the present study, we pnly analyzed patients with immediate implant-based reconstruction, and we found a rate of 1.4% of nipple necrosis, which is lower than the rates in most of the previous reports of NSM for DCIS, including a large series[13] published in 2018 that reported a rate of nipple-areola-complex necrosis of 2.2% for in situ cancer. Our cumulative complication rates were also lower than those reported in previous studies, with only 4.3% of complications in 69 NSM procedures performed for DCIS. Leclère et al.[10] reported a rate of 17% of nipple-areola-complex necrosis and 5.3% of local recurrence in the long-term follow-up of 41 patients diagnosed with DCIS who underwent NSM. Despite the high rate of nipple-areola-complex necrosis, the locoregional recurrence rate for DCIS was low; however, the loss of patients over the mean follow-up period of 7.1 years (only 46% completed the follow-up) and the subsequent small sample size were limitations of the study.[10] In 2018, Lago et al.[11] evaluated the oncological safety of NSM for DCIS in 69 patients with a 10-year follow-up. The authors reported a rate of local relapse of 11.6%, and a low rate of nipple-areola-complex recurrence (1.4%). They did not observe cases of

Table 3 Characteristics of the local recurrence

Previous cancer	Recurrence (months)	Age (years)	Surgery/ pathology	Lymph node status	Other treatments	Relapse	Survival
No	109	52	Bilateral NSM; 40 mm; multifocal; grade 3	SLNB LFN-	TMX	Nipple DCIS	Alive
No	12	47	Bilateral NSM; 17 mm; multifocal; grade 2	SLNB LFN-	None	Nipple DCIS	Alive
No	96	40	Unilateral NSM; 50 mm; unifocal; grade 2	SLNB LFN-	None	Same quadrant DCIS	Alive
No	48	38	Bilateral NSM; 45 mm; multifocal; grade 2	SLNB LFN-	None	Same quadrant DCIS	Alive
No	167	42	Unilateral NSM; 20 mm; multifocal; grade 3	SLNB LFN-	TMX	Other quadrant in same breast IDC	Alive
No	98	47	Bilateral NSM; 20 mm; multifocal; grade 3	SLNB LFN-	TMX	Other quadrant in same breast IDC	Alive

Abbreviations: DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; LFN, lymph node; NSM, nipple-sparing mastectomy; SLNB, sentinel lymph node biopsy; tMX, Tamoxifen.

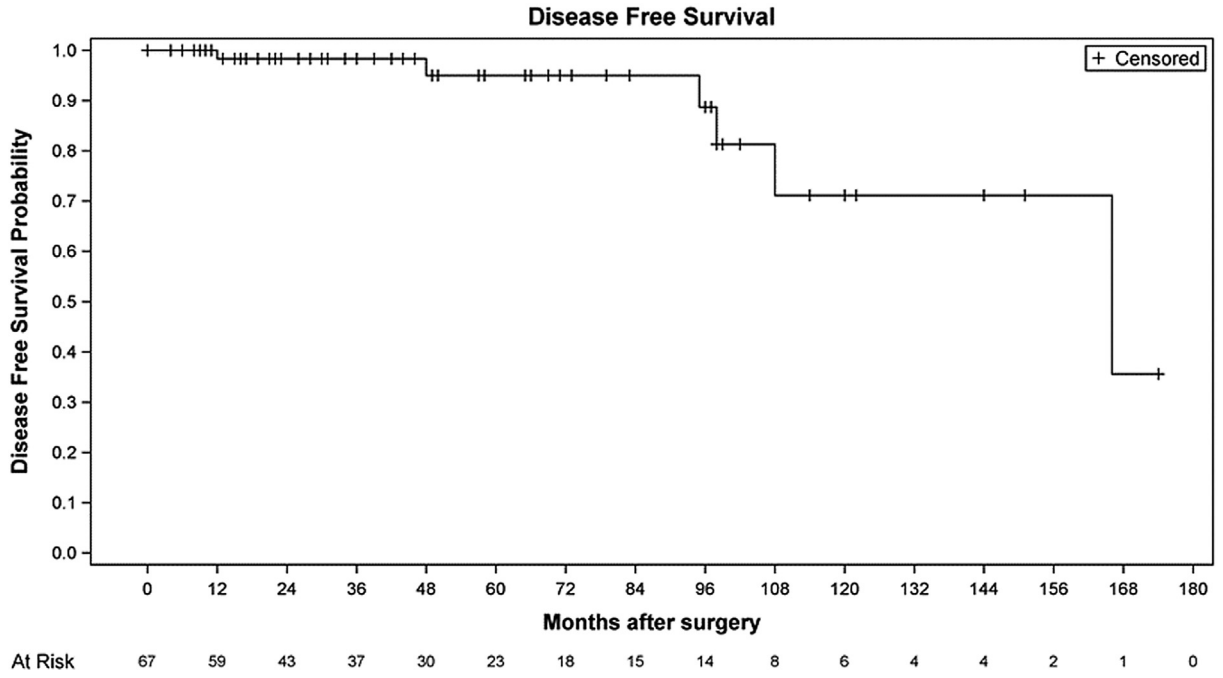

Fig. 9 Disease-free survival ($n = 67$).

nipple necrosis after surgery either.[11] The current study evidenced a rate of locoregional recurrence (LRR) of 4.5%, and a rate of nipple-areola-complex recurrence of 3% in the 10-year follow-up. The authors demonstrated that characteristics such as negative progesterone receptor status, and tumor size $\geq$ 4 cm were related to an increased risk of developing LRR. Interestingly, margin status presented no statistical significance associated with LRR.[12]

At a mean follow-up of 60 months, our local recurrence rate of 8.9%, including the nipple-areola-complex recurrence rate of 2.95%, was higher when compared with that of previous studies (**Chart 1**).

All of the relapses in the tumor bed and nipple areola complex were cases of DCIS, and the two recurrences in another quadrant in the same breast were IDCs. We consider all patients with no involvement of the skin or nipple areola complex candidates for NSM; therefore, the characteristics of our patients, such as young age, tumors larger than 40 mm, multifocal tumors, and no criteria for the distance between the lesion and the skin or the nipple areola complex (since all margins were free) might have influenced the increased rate of local relapse found in the present study. Wu et al.[12] reported that tumor size $\geq$ 4 cm was risk factor for LRR in the univariate analysis; however, in the multivariate analysis, the statistical significance was borderline ($p = 0.064$).[12] We observed a tendency of tumor multifocality to be a risk factor for local recurrence ($p = 0.061$); however, due to the small sample size of the present study, we found no statistical difference when analyzing correlations between local recurrence and the clinicopathological characteristics and treatments. No cases of distant metastasis were observed in our patients.

For patients who underwent NSM, the benefit of RT has not been confirmed yet. However, a Cochrane review[21] confirmed the benefit of RT for all patients diagnosed with DCIS and submitted to BCS. Therefore, we chose to apply RT in patients with larger tumors. None of the patients who relapsed underwent RT after the first surgery. Radiotherapy was performed after the recurrence, and only one patient presented a new recurrence after it. Radiotherapy after BCS is the gold standard treatment for cases of early breast cancer, including DCIS. We hypothesize a possible relationship between RT and a reduced risk of developing ipsilateral breast cancer recurrence after NSM for DCIS, but new studies are necessary to confirm this potential benefit.[21]

As observed in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 and B-24 randomized clinical trials for DCIS,[22] young patients with DCIS have an increased risk of developing invasive ipsilateral breast tumor recurrence; in the present study, only 1 patient who prsented relapse was older than 50 years of age. In our population, there were 48 patients aged $\leq$ 50 years, and analyzing only this population, we found a local recurrence rate of 10.4%. Approximately 19% of the young patients underwent RT; however, none of the patients who presented relapse underwent RT. The use of RT for local control in these patients might be an option.

The use of hormone receptors (ER, progesterone receptor [PR], human epidermal growth factor receptor 2 [HER2]) as prognostic biomarkers is still controversial for DCIS. Some authors have observed an association between HER2 positive and ER- DCIS with increased risk of recurrence, whereas in other studies these associations have not observed.[23–26] Endocrine therapy is indicated after BCS for patients with ER+ DCIS aiming to reduce the risk of local relapse and contralateral breast recurrence.[22] In the sample of the present study, HT was not indicated for all patients with ER+ tumors: $\sim$40% were treated with the hormone treatment. All

Chart 1 Outcomes of NSM patients in previous studies

Authors	Year	N	Nipple necrosis (%)	LR (%)	Nipple-areola-complex recurrence (%)	OS (%)	Follow-up (months)
Petit et al. (2012)[1]	2002–2007	162 in situ cases	–	4.9	2.9	95.5	Median: 50
Shimo et al. (2016)[18]	2000–2013	425 NSMs (413 patients)	1.4	5.8	2.3	96.8	Median: 46.8
Manning and Sacchini (2016)[9]	2000–2013	728 NSMs (413 patients)	0	0	0	97.3	Median: 49
Orzalesi et al. (2016)[3]	2009–2014	1,006 NSMs (913 patients)	4.8	2.9	0.7	99.3	Mean: 91.7
Headon et al. (2016)[19]	1970–2015	12,358 NSMs (10,935 patients)	5.9	2.38	–	–	Mean: 38
Leclère et al. (2014)[10]	2000–2010	41 DCIS NSM patients	17	5.3	–	–	Mean: 85
Lago et al. (2017)[11]	1984–2016	69 DCIS NSM patients	0	11.6	1.4	98.6	Mean: 142.6
Wu et al. (2020)[12]	2003–2015	199 pure DCIS NSM patients	–	4.5	3	98.5	Median: 97
Frasson et al. (2021; present study)	2004–2018	67 pure DCIS NSM patients	1.4	8.9	2.9	100	Mean: 60

Abbreviations: DCIS, ductal carcinoma in situ; LR, local recurrence; OS, overall survival; NSM, nipple-sparing mastectomy.

patients that relapsed presented ER+ tumors, and half of them underwent hormone treatment. We evaluated the risk/benefit of hormone treatment for each patient presenting ER+ DCIS, considering the side effects and the risk of recurrence based on tumor size, grade, and young age. Indeed, since of all these patients were submitted to NSM and most of them underwent bilateral procedures, we considered that the risk of local and contralateral recurrence was diminished, and did not indicate HT for all ER+ patients

In the present study, all patients were alive by the end of the follow-up, and this result is consistent with the NSM findings reported by Lago et al.,[11] 2018, and Wu et al.,[12] 2020. In the long-term follow-up, Lago et al.[11] and Wu et al.[12] indicated overall survival (OS) rates of 98.6% and 98.5% respectively in patients diagnosed with DCIS who underwent NSM. Despite the expanded NSM indications applied in the present study, such as patients with compromised margins after a previous surgery, large and high-grade tumors, and no cutoff for distance between the tumor and the nipple-areola complex, the relapses did not interfere with patient survival in 60 months of follow-up.

The present study has several limitation,s such as the retrospective design of the analysis, the small sample size, and the short follow-up. External validation is needed to confirm our results.

Conclusion

At a mean follow-up of 60 months, we demonstrated low complication rates and good survival in 67 patients who underwent NSM for pure DCIS with immediate implant-based reconstruction. The local recurrence rate was high, and characteristics such as young age, multifocal tumors, and no criteria for the distance between the lesion and the skin or the nipple-areola complex might have influenced the relapses found in the present study. We observed that the multifocality of the tumor might be a risk factor for local relapse; however further studies are needed to confirm this correlation. The present study supports that expanding the indication for NSM with immediate implant-based breast reconstruction to treat patients diagnosed with pure DCIS is acceptable when BCS is not an option and the patient wishes to preserve the nipple-areola complex.

Contributions

All the authors contributed equally to the present paper, namely to the conception and design, data collection or analysis, and interpretation of data, writing of the article, and review of the intellectual content. Therefore, all authors approved the final version to be published.

Conflict of Interests

Antônio Luiz Frasson has received a speaker honorarium from Roche. None of the other authors have conflict of interests to declare.

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Cervical Intraepithelial Neoplasia: Analyzing the Disease Present Exclusively in the Endocervical Canal

Neoplasia intraepitelial cervical: Analisando a doença presente exclusivamente no canal endocervical

Fernanda Villar Fonseca[1] Maria Victória Gutierrez Cordeiro[1] Ariadne Cristine Pozza[1] Carlos Afonso Maestri[1]

[1] Department of Gynecology and Obstetrics, Universidade Positivo, Curitiba, PR, Brazil

Address for correspondence Fernanda Villar Fonseca, PhD, R. Prof. Pedro Viriato Parigot de Souza, 5300, 81280-330, Cidade Industrial de Curitiba, Curitiba, PR, Brazil (e-mail: luifernascimento@terra.com.br).

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Abstract

Objective To evaluate the role of cervical cytology (Pap smear) in the diagnosis of cervical intraepithelial neoplasia 2 or greater (CIN2+), presented exclusively in the endocervical canal, the clinical-epidemiological characteristics of this lesion, the necessary length of canal to be removed to treat, and the rate of invasive lesion hidden in the endocervical canal.

Methods Cross-sectional study, by database analysis, of patients with abnormal cytology (high-grade squamous intraepithelial lesion [HSIL]), without visible colposcopy lesion, submitted to loop electrosurgical procedure (LEEP) to evaluate the association of cytology results with the histological product of the conization, to identify the epidemiological characteristics of endocervical lesion and clinical evolution, using a *p*-value < 0.05 and 95% CI.

Results In 444 cases, the Pap smear sensitivity for CIN2+ diagnosis was 75% (95% CI: 69.8–79.7), specificity was 40% (95% CI: 30.2–49.5), and the prevalence rate of histological lesion was 73% (95% CI: 70.1–78.7). There was a higher prevalence of CIN2+ in women over 42 years old and invasive cancer in those over 56 years old ($p < 0.001$), and it was necessary to remove 2.6 cm in length of the canal to reduce the chance of recurrence ($p < 0.006$). The rate of invasive cancer was 2.7%.

Conclusion Cytology was related to a high prevalence to histological lesion (73%) in the diagnosis of CIN2+ in the endocervical disease; older patients presented a higher relationship with histological lesions in the canal disease, and it was necessary to remove an average of 2.6 cm in length of the endocervical canal to avoid the persistence and progression of CIN. The rate of occult neoplasia in the endocervical canal was 2.7%.

Keywords
- CIN
- oncotic cytology
- cervical intraepithelial neoplasia

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Resumo

Objetivo Avaliar o papel da citologia oncótica (CO) no diagnóstico da neoplasia intraepitelial cervical 2 ou maior (NIC2+) presente exclusivamente no canal endocervical, as características clínico-epidemiológicas deste tipo de lesão, o comprimento necessário de canal a ser retirado na conização, e a taxa de lesão invasora oculta no canal endocervical.

Métodos Estudo transversal, por análise de base de dados, de pacientes com citologia alterada, sem lesão colposcópica visível, submetidas a conização por cirurgia de alta frequência (CAF), para avaliar a associação dos resultados citológicos com o produto histológico da conização, as características epidemiológicas da lesão endocervical, e evolução clínica, utilizando o valor de $p < 0.05$ e intervalo de confiança (IC) de 95%.

Resultados Nos 444 casos analisados, a sensibilidade da CO para o diagnóstico de NIC 2+ foi de 75% (IC 95%: 69.8–79.7), a especificidade foi de 40% (IC 95%: 30.2–49.5), e a taxa de prevalência de lesão histológica foi de 73% (IC 95%: 70.1–78.7). Houve maior prevalência de NIC2+ em pacientes com mais de 42 anos de idade e de neoplasia invasora naquelas com mais de 56 anos ($p < 0.001$), e foi necessário a retirada de 2.6 cm de comprimento de canal para diminuir a taxa de recidiva ($p < 0.006$). Foi identificada uma taxa de 2.7% de neoplasia invasora.

Conclusão A citologia esteve relacionada a uma alta prevalência de lesão (73%) no diagnóstico das NIC2+ na doença endocervical; quanto maior a idade, maior foi a relação da histologia com a citologia de canal, e se fez necessário retirar uma média de 2.6 cm de comprimento de canal para evitar a persistência e a progressão da NIC. A taxa de neoplasia oculta no canal endocervical foi 2.7%.

Palavras-chave

- NIC
- citologia oncótica
- neoplasia intraepiteliais cervicais

Introduction

Cervical intraepithelial neoplasia (CIN) are proliferative lesions with abnormal and atypical maturation of varying degrees, replacing part or all of the thickness of the cervical squamous epithelium, and representing the precursor lesions of cervical cancer, whose diagnosis and treatment allows for a reduction in mortality by this neoplasm.[1,2]

Cervical cancer is the third most frequent tumor in the female population, after breast and colon cancer, and the fourth leading cancer-related cause of death in women in Brazil. About 300,000 women each year die from this type of cancer, despite its high possibility of prevention and early treatment. Its incidence is concentrated in the age group from 25 to 59 years old. However, the risk increases significantly in the age group from 45 to 49 years.[1,2]

The prevention of cervical cancer consists of early diagnosis, through screening of its precursor lesions, cervical intraepithelial neoplasia (CIN), more specifically high-grade lesions (high-grade squamous intraepithelial lesion [HSIL]/CIN 2,3).[1–5]

According to data from the World Health Organization (WHO),[1] 99% of high-grade intraepithelial lesions and invasive cancers of the cervix are caused by the human papillomavirus (HPV) and can be detected early through well-organized screening programs.[1–5]

In addition to HPV, studies indicate smoking, low intake of vitamins, multiple partners, and early sexual initiation as risk factors for the development of CIN, the precursor to cervical cancer. Added to this, low socio-educational level associated with low population coverage of screening programs for precursor lesions of cervical cancer in health services increase the incidence and mortality from this neoplasm.[1–3] The diagnostic methods for these precursor lesions are morphological, such as cervical cytology (Pap smears, Pap tests), colposcopy and histology, or, in most cases, their association.[3–5]

Because it is a cheap and accessible test, cervical cytology is the preferred method of screening for cervical cancer and its precursor lesions in many countries. Despite its high specificity, it has low sensitivity. Thus, false negative results may be due to inadequate collection, inadequate fixation, or unsatisfactory material. Thus, studies point to the need for the association of another diagnostic method to increase the sensitivity in tracking precursor lesions, such as HPV-DNA research or colposcopy and/or cervical biopsy.[3–5]

The conventional periodic Pap test, or cervical cytology collected from the cervix, remains the most used strategy for tracking intraepithelial lesions in Brazil. When the patient's result shows changes with a high probability of representing cancer or preinvasive lesions, immediate referral for colposcopy is necessary.[6,7]

When CIN is detected in the uterine ectocervix, or in cases that reach the endocervical canal as far as the entire transformation zone can be seen, the treatment is performed by loop electrosurgical procedure (LEEP).[5–8] However, when the lesion is located entirely in the endocervical canal, or the transformation zone is not fully visible, colposcopy has

limitations, and it is necessary to histologically investigate the endocervical canal.[6–8]

This research aims to verify the role of cytology (Pap smears), collected exclusively from the endocervical canal of the uterine cervix, in women with an abnormal cytology (suggesting a high-grade lesion), with colposcopy disagreements (whose colposcopy does not reveal injury), and submitted to a LEEP procedure for diagnosis and relate the cytology results with those histological results of the conization product, calculating the prevalence of histological lesion in the endocervical canal. In addition, it aims to identify the clinical and epidemiological characteristics of the disease presented exclusively in the endocervical canal, and to evaluate the average length of endocervical canal excised necessary to obtain a conization product with free margins, thus ensuring an appropriate treatment to prevent progression to invasive cancer, and to identify the rate of invasive cancer hidden in these specific cases.

Methods

This is a cross-sectional study, performed by analyzing a database of patients with abnormal cytological diagnosis of the uterine cervix, suggesting CIN2 +, without visible colposcopic lesion. These patients underwent conization, for diagnosis, to evaluate the association of cytology results with the histological product of the conization, to identify the prevalence of histological lesion in the endocervical canal and the epidemiological characteristics of endocervical disease, and to determine the clinical evolution in these cases, using p-value < 0.05 and 95% CI.

The database included patients evaluated at the cervical pathology service of the gynec oncology department at Hospital Erasto Gaertner (HEG), from January 2009 to December 2016. The patients had abnormal Pap smears suggesting cervical HSIL, without visible colposcopic lesion. They underwent a second Pap test, collected exclusively from the endocervical canal, which presented a result of HSIL, atypical squamous cell, cannot rule out high-grade squamous intraepithelial lesion (ASC-H), atypical glandular cell (AGC) or adenocarcinoma in situ (AIS), invasive squamous cell carcinoma (SCC) or low-grade squamous intraepithelial lesion (LSIL) and atypical squamous cell of undetermined significance (ASC-US) (according to Bethesda terminology). Additionally, they were submitted to investigation of the endocervical canal using the LEEP procedure, because HPV test is not accessible in the public health system due to its high cost.

The exclusion criteria were all cases that presented a visible colposcopic lesion in the ectocervix and whose diagnosis was made by cervical biopsy.

The data collected from this database were transferred to an Excel spreadsheet (Microsoft Corp., Redmon, WA, USA) and analyzed using the IBM SPSS Statistics for Windows, Version 25.0 software (IBM Corp., Armonk, NY, USA), seeking a confidence interval (CI) greater than 95% and a significance level of 5% ($p \leq 0.05$). The qualitative variables were analyzed by the chi-squared test and/or Fisher exact test, with the p-value identified. And the quantitative variables were analyzed by the Student t-test, and the p-value was identified. The sensitivity and specificity of cytology collected exclusively from the endocervical canal were calculated to identify the validity of this method in diagnosing endocervical injury consistent with CIN 2 +.

A waiver of the free and informed consent form was requested, as it is not a study with living beings and whose subject are data from laboratory tests belonging to the database of the aforementioned service.

The research was approved by the research ethics committee (CAAE 61845916.6.0000.0098).

Thus, data of 4,016 patients analyzed in the period, using the inclusion and exclusion criteria, resulted in 444 cases in the sample.

The following variables were analyzed: mean age of patients, menopausal status, cytology result, histopathological result of the conization piece, length of the endocervical canal removed, margins of the conization product, percentage of invasive neoplasia found in the histological conization product, recurrence rate.

Results

Of the 444 patients evaluated, the mean age was 44 years ± 12 years (95% CI: 43–45/standard error 0.61), with a minimum age of 19 years and a maximum of 89 years. In addition, 32% (143 cases) were in climacteric and 35% of the cases were over 35 years old.

The alterations found in endocervical canal cytology (second cytology) were: HSIL and ASC-H (68%), followed by LSIL (17%), ASCUS (10%), AGC (4%), and, finally, invasion (1%). The prevalence rate of histological lesion in the conization product was 73% (324/444) of the cases with abnormal endocervical cytology, confirming endocervical disease. Of these, 64% (285 cases) were CIN2 +, 27% (120 cases) were cervicitis, 6% (26) were CIN1, and 3% (13) were invasive cancer. Added to this, 42% (175) of the cases revealed glandular extension in the histological conization product.

From the sample of 444 cases, it was possible to verify the margins in 437 patients. The result found was: 88% (383/437) had free margins. Among the 12% of compromised margins (54/437), 46% (25 cases) had compromised endocervical margin, 44% (24 cases) had ectocervical margin, and 9% (5 cases) had both compromised margins.

Regarding the length of the removed canal, the mean was 2.36 cm ± 1.04 cm (95% CI: 2.26–2.46/standard error 0.05). The minimum length of canal removed was 0.5 cm, and the maximum was 5.6 cm. Of all cases, 84% had between 1 to 3.5 cm in length of the endocervical canal removed.

Of the 444 patients, 347 patients had adequate follow-up for recurrence analysis (minimum follow-up time of 18 months), with long-term follow-up being possible. Among these cases, the recurrence rate was 23% (79/347). In relation to margins, 37% (16/43) of committed margins and 21% (63/303) of free margins relapsed, p-value = 0.021.

It was found that the mean length of the canal removed in patients with disease recurrence was 2.3 ± 0.9 cm (95% CI:

2.09–2.55), MIN 0.5, MAX 5.3cm, while the mean for cases without recurrence was 2.6 ± 0.8 cm (95% CI: 2.5–2.7, MIN 0.5, MAX 5.6 cm/p-value = 0.006, demonstrating statistical significance.

The mean age of patients without recurrence was 43 years ± 12 (95% CI: 43 ± 12 (CI: 43–45), MIN 20, MAX 89 years, and those with recurrence were: 48 ± 13 (95% CI: 45–51), MIN 23, MAX 83 years/p-value = 0.03, demonstrating statistical significance.

►**Table 1** shows the relationship between age and the histological result of the endocervical canal lesion, showing a direct relationship between increasing age and the severity of the lesion, with clinical significance.

Table 1 Relationship between the result of the pathology report of the conization product and the patient's age

Anatomopathological	Average age
Cervicitis	46 years ± 12 (95% CI: 44–49)
CIN1	38 years ± 11 (95% CI: 47–64)
CIN2	42 years ± 13 (95% CI: 34–43)
CIN3	44 years ± 11 (95% CI: 40–44)
Invasion	56 years ± 13 (95% CI: 42–46)

Abbreviations: CI, confidence interval; CIN, cervical intraepithelial neoplasia.

►**Table 2** demonstrates the correlation of cytological results collected exclusively from the endocervical canal with the definitive histological result of the piece of endocervical canal obtained from the conization product, demonstrating that cytology with a result suggestive of high-grade lesion has the highest prevalence of similar results in histology, with p-value < 0.001, demonstrating statistical significance.

The sensitivity and specificity of endocervical canal cytology for diagnosing high grade and/or invasive cervical intraepithelial neoplasia in patients with exclusive endocervical canal lesion can be seen in ►**Table 3**.

The rate of occult invasive neoplasia in the endocervical canal was 2.7% (12/444 cases).

Discussion

Cervical cancer is the fourth most prevalent cancer diagnosis in women worldwide, and, in our country, it corresponds to the third most common tumor in women and the fourth cause of death from cancer. The incidence and mortality from this type of cancer are related to prevention and screening programs. But to achieve significant results in reducing mortality, knowledge of the clinical and epidemiological characteristics of the disease and the population affected by it is necessary.[1,2,9]

The endocervical disease is not so well known, and its diagnostic limitations delay treatment and worsen

Table 2 Relationship between cytology result exclusively from the endocervical canal and the anatomopathological result of the conization product, demonstrating a greater correlation between histology and cytology with the increase in the degree of severity of the lesion/p < 0.001 (n = 444)

	CERVICITIS	CIN1	CIN2	CIN3	INVASION
ASCUS	34% (16/46)	7% (3/46)	33% (15/46)	24% (11/46)	2% (1/46)
LSIL	34% (26/76)	17% (13/76)	40% (30/76)	8% (6/76)	1% (1/76)
HSIL	25% (51/204)	3% (6/204)	41% (84/204)	30% (61/204)	2% (5/204)
ASC-H	19% (19/99)	3% (3/99)	33% (33/99)	42% (42/99)	3% (2/99)
AGC	50% (8/16)	0% (0/16)	25% (4/16)	6% (1/16)	19% (3/16)

Abbreviations: AGC, atypical glandular cell; ASC-H, atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion; ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

Table 3 Values related to the sensitivity and specificity of the endocervical cytology to diagnose high-grade squamous intraepithelial lesion and cervix invasive carcinoma

Histological lesion	Sensitivity	Specificity
CIN 2–3	74.3% (95% CI: 69–79)	40.3% (95% CI: 30–50)
Invasion SCC	50% (95% CI: 1.26–88)	90.8% (95% CI: 84.5–95.1)
CIN 2 + *	75% (95% CI: 69.8–79.7)	39.6% (95% CI: 30.2–49.5)

Abbreviations: CI, confidence interval; CIN, cervical intraepithelial neoplasia.
CIN2 + = any lesion greater than CIN 2

prognosis. Based on this, the data shown here sought to better delineate the characteristics of endocervical disease.

According to data from this research, endocervical disease was more severe and more prevalent with older age, suggesting that postmenopausal women with positive cytology and absence of colposcopic lesion should not fail to investigate the presence of endocervical canal lesion. In view of the direct relationship found between cases of invasive cancer and advancing age, the use of this method (exclusive cytology of the endocervical canal) in screening for these lesions is justified.

It also concludes that the recurrence rate is higher in women with exclusively endocervical lesions, and that it is necessary to remove a greater depth and length of the endocervical canal to ensure adequate treatment for this specific type of lesion. The prevalence rate of occult invasive cancer in the endocervical canal was 2.7%.

Cytology collected from the endocervical canal was related to a high prevalence of histological lesion in the diagnosis of CIN2+, justifying its use in the screening of suspected endocervical disease.

Although oncotic cytology is the main test for detecting changes in the cervix, it still has limitations, showing false-negative results.[3] The main factors related to low specificity are due to sampling errors, such as inadequate collection of material, inadequate fixation of the slide, and misinterpretation of the findings.[10]

The assessment of cytology quality is related directly to the assessment of the adequacy of samples, established by the Bethesda system, which advocates patient identification, relevant clinical information, technical interpretability, and cell composition. According to the literature, suitability can reach up to 99% in samples in which rapid review of negative smears, rapid prescreening, and automated review is possible.[3]

A Brazilian retrospective study found among 97 women with abnormal cytology, 88 (78.6%) also had abnormal histological examination, a result that is in accordance with the accuracy of sensitivity and lesion prevalence obtained in the present study, in which the presence of histological lesion was found in 73% of patients with cytology collected exclusively from the endocervical canal, without visible colposcopic lesion. This brings to debate the need to investigate the endocervical canal in patients with repeatedly altered cytology, due to the high prevalence of precursor lesion, which, when not identified and treated, has a high risk of progression to invasive cancer.[11]

According to an assessment performed by CICAN-Bahia/Brazil, which evaluated the accuracy of oncotic cytology, the sensitivity and specificity found were, respectively, 85% and 40%. These values agree with the results presented in this work (75% and 39%, respectively). On the other hand, Nkwabong et al.,[12] in their published article, found a sensitivity of 55.5% and a specificity of 75%.[10,12]

The literature data corroborate the findings related to relapse and compromised margins. It is notorious that compromising margins increase the chance of relapse. However, the presence of free margins is not a sufficient factor to prevent recurrences.[3,9,13–16]

However, relevant data from the research developed here demonstrate that recurrences occur in a greater proportion in disease located exclusively in the endocervical canal, when compared with the mean recurrence of ectocervical and/or CIN with visible endocervical component. Using as a parameter the literature data,[9,13,15,16] which demonstrate a recurrence rate between 8 and 15% in free margins and above 15% in compromised margins, the data produced here showed a recurrence rate in the free margins of 21%, that is, twice as many lesions located in the ectocervix.

Another piece of data in agreement with this study is in relation to the length of the canal removed. According to Rosa and Lisboa,[14] the greater the length of the excised canal, the lower the recurrence rate. However, the same study highlights that 8% of women, even with free margins, will have residual disease.[14]

Carvalho et al.,[16] in their literature review, demonstrated that excised endocervical canal lengths smaller than 1.25 cm increase recurrence rates, in agreement with the data produced here, in which, in the presence of a totally endocervical lesion, there would be a need for removal minimum 2.6 cm in length of the endocervical canal, so that the risk of recurrence and/or persistence of the disease is lower.

Another important point to be highlighted in exclusively endocervical disease is that the older the patient, the greater the relationship between the presence of a more severe histological lesion, since patients over 50 years old had a higher risk of presenting invasive carcinoma in the conization specimen, and those over 40 years of presenting a high-grade lesion (CIN 2+). In the same line of research, the mean age found in recently published articles was 43, with 5 years for the diagnosis of a precursor lesion, which corroborates the mean age found in this work (44 years).[11,12,14]

The relationship between older age and disease severity was also found by a baseline cohort study performed in the Netherlands, which indicates that women over 50 years of age diagnosed with CIN 3 are 7 times more likely to develop cervical cancer.[15]

Although the data found in this study were enlightening regarding the role of cervical cytology, the importance of early diagnosis of the disease present in the endocervical canal and the epidemiological characteristics of this specific population, this study presented a limitation: it did not carry out the HPV-DNA. The research does not allow correlating the data with the HPV typing with the severity of the endocervical lesion, which may be an influencing factor in the relationship of cytology data with the histological diagnosis. But it is important to clarify that this limitation is related to issues concerning the cost of this type of test in low-income countries such as Brazil, with this sample having been collected from patients assisted in the Brazilian Public Health System.

Conclusion

Cytology was related to a high prevalence of histological lesion (73%) in the diagnosis of CIN2+ in the endocervical

disease; the older ages present a higher relationship with histological lesions in the canal disease, and it was necessary to remove an average of 2.6 cm in length of the endocervical canal to avoid the persistence and progression of CIN. The rate of occult neoplasia in the endocervical canal was 2.7%.

Contributors

All authors collaborated with data collection and analysis as well as with the writing and conclusions of this research.

Conflict of Interests

The authors have no conflict of interests to declare.

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Knowledge, Attitude, and Practices Related to the SARS-CoV-2 Pandemic among Women Seeking Contraceptive Methods

Conhecimento, atitude e práticas relacionadas à pandemia de SARS-CoV-2 entre mulheres que buscam métodos anticoncepcionais

Elaine Aparecida Lopes Garcia[1] Jessica Mayra Ferreira[1] Nelio Veiga-Junior[1] Luis Bahamondes[1] Ilza Monteiro[1]

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

Address for correspondence Ilza Monteiro, MD, PhD, Cidade Universitária Zeferino Vaz, 13083-970, Barão Geraldo, Campinas, SP, Brazil (e-mail: ilza@unicamp.br).

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Abstract

Objective To determine knowledge, attitude, and preventive (KAP) practices towards the SARS-CoV-2 (COVID-19) pandemic among women in reproductive age seeking to use copper or hormonal intrauterine devices (IUD/LNG-IUS).

Methods We conducted a cross-sectional study in which we applied a questionnaire on 400 women about KAP practices on COVID-19 at the University of Campinas, Campinas, SP, Brazil, from May to August 2020.

Results The mean ($\pm$SD) age of the women was 30.8 $\pm$ 7.9 years, and 72.8% of them reported being pregnant at least once. Most women (95%) had heard or read about COVID-19, and their main sources of information were television (91%) and government websites (53%). However, 53% of the women had doubts about the veracity of the information accessed.

Conclusion Women without a partner and with $>$ 12 years of schooling had more information about COVID-19 and on its impact on new pregnancy, and those from high socioeconomic status had a higher chance of maintaining physical distance. Safety, effectiveness, comfort, and absence of hormone in the contraceptive method (in the case of TCu380A IUD) were the main reasons for the participants to seek the service during the pandemic, and the possibility to stop menstrual bleeding was the main reason to choose the LNG-IUS.

Keywords
- COVID-19
- knowledge
- attitudes
- practices
- copper IUD
- levonorgestrel intrauterine system
- socio demographic characteristics

Resumo

Objetivo Determinar o conhecimento, atitude e práticas preventivas (CAP) em relação à pandemia de SARS-CoV-2 (Covid-19) entre mulheres em idade reprodutiva que buscam usar dispositivo intrauterino com cobre (DIU TCu 380) ou sistema intrauterino liberador de levonorgestrel (SIU-LNG).

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Métodos Foi realizado um estudo transversal e um questionário foi aplicado a 400 mulheres para conhecer o CAP sobre o COVID-19 na Universidade Estadual de Campinas, Campinas, SP, Brasil, no período de maio a agosto de 2020.

Resultados A média ($\pm$DP) de idade das mulheres foi de 30,8 $\pm$ 7,9 anos, e 72,8% delas relataram ter engravidado pelo menos uma vez. A maioria das mulheres (95%) tinha ouvido ou lido sobre a a Covid-19, e suas principais fontes de informação foram a televisão (91%) e sites do governo (53%). Porém, 53% das mulheres tinham dúvidas a respeito da veracidade das informações acessadas.

Conclusão Mulheres sem companheiro e com mais de 12 anos de escolaridade tiveram mais informações sobre a COVID-19 e sobre o seu impacto em uma nova gravidez, e aquelas de nível socioeconômico alto tiveram maior chance de manter distância física. Segurança, eficácia, conforto e ausência de hormônio no método anticoncepcional (no caso do DIU TCu380A) foram os principais motivos para as participantes procurarem o serviço durante a pandemia, e a possibilidade de controlar o sangramento menstrual abundante foi o principal motivo para a escolha do SIU-LNG.

Palavras-chave
- COVID-19
- conhecimento
- atitudes
- práticas
- DIU de cobre
- sistema intrauterino de levonorgestrel
- características sociodemográficas

Introduction

The SARS-CoV-2, which provoked the COVID-19 pandemic by a new coronavirus, is a threatening and highly contagious infection. It was first detected in December 2019 in the province of Wuhan, China.[1–3] On March 11, 2020, the World Health Organization (WHO) declared COVID-19 as the largest and fastest-growing pandemic of the century.[3] Several actions have been taken to try to contain the spread of the virus, such as physical distancing, isolation, lockdown, and quarantine. Regarding healthcare services, many policy makers decided to maintain only essential services due to the lack of personnel, because they were allocated to provide health service related to COVID-19.[4]

Sexual and reproductive health (SRH) services, including contraceptive counseling and provision, and abortion services were considered non-essential by many policy makers, and several clinics that provide SRH services were temporarily closed.[1,2,5] For this reason and due to the interruption of chain supplies, the United Nations Population Fund reported that a shortage of contraceptive methods is expected in many settings as well as an increase in unplanned pregnancies and abortions, which could be unsafe in many settings in the near future.[6,7] This scenario shows that women and men are even more in need of contraceptive methods during the pandemic.[8,9]

Although many clinics are closed, several measures can be taken to continue the provision of contraceptives, including long-acting reversible contraceptive (LARC) methods. It is possible to implement remote consultation and counseling in particular settings to avoid unnecessary visits to the clinic, provide electronic prescriptions and more time between consultations when face-to-face appointments are needed.[1,9–11] In the family planning clinic based in the University of Campinas, Brazil, we continued to assist women during the pandemic by offering counseling and provision of contraceptive methods (mainly LARC methods) with proper authorization of local authorities. We implemented all possible safety measures to reduce the risk of COVID-19 contamination, such as telemedicine for women, when possible; reduction of daily appointments; more time between consultations; brief procedure visits; provision of open waiting spaces outside the facility, and use of appropriate personal protective equipment.[11,12]

We considered that there is a high probability that more women are trying to avoid pregnancy during the pandemic, and they have sought the family planning services looking for safe and effective contraceptive methods like LARCs. For this reason, our primary objective was to assess the knowledge, attitude, and preventive (KAP) practices towards COVID-19 among women in reproductive age. The secondary aim was to assess the reasons why these women came to the clinic seeking to use the copper-intrauterine device (Cu-IUD) or the levonorgestrel 52 mg intrauterine system (LNG-IUS).

Methods

Study Design and Participants

This was a cross-sectional study carried out at the department of obstetrics and gynecology of University of Campinas Medical School (UNICAMP), Campinas, SP, Brazil. The protocol was approved by the Ethical Committee of the university, and all women signed an informed consent before they were admitted to the study. Women between 18 and 49 years of age who visited the family planning clinic from May to August 2020 were invited to participate in the study and were included if they were willing to use the TCu380A IUD (Optima, Injeflex, São Paulo, Brazil) or the LNG-IUS (Mirena, Bayer Oy, Turku, Finland). Women who wanted to use the LNG-IUS only as a therapy for abnormal uterine bleeding were excluded. The participants filled out a 37-item questionnaire specially developed for the purpose of our study, which contained sociodemographic information and questions regarding their KAP practices towards COVID-19. The

questionnaire was based on the WHO training material for detection, prevention, and control of the disease.[13,14] It was comprised of multiple choice and open-ended questions, including 16 questions about knowledge (6 of them regarding contraceptives), 6 questions about attitude, and 6 questions about preventive practice.

Analysis of the Data

We estimated the sample size assuming that 60% of the participants would be well informed about the COVID-19 pandemic and came to a sample of 327 women in the study. The participants' sociodemographic characteristics were presented as descriptive with mean ($\pm$standard deviation [SD]), or as percentage distribution for categorical variables using the χ^2 or Fisher exact test for comparison. The univariate analysis followed by linear regression analysis (with stepwise analysis) was used to determine the relation between demographic variables and the correct answers provided by the women. Non-standardized regression coefficients (95%) were used to assess the correlation between the answers towards COVID-19. We used the SAS 9.4 software (SAS Institute, Cary, NC, USA). The level of significance was set at $p < 0.05$.

Results

Among the 410 women invited to participate in the study, 400 returned the questionnaire and were included in the analysis. The participants' mean ($\pm$SD) age was 30.8 ± 7.9 years. A rate of 56.1% of the women had a history of 1 to 2 pregnancies, 75.9% had more than 12 years of schooling, and 55.1% were living with a partner. The participants were allowed to check more than one contraceptive method in use in the questionnaire at the time of the consultation. Excluding 255 women (63.7%) that reported the use of condoms, a LARC method was used by 109 women (27.2%) followed by 100 (25.0%) users of combined oral contraceptives (►**Table 1**). All the users of LARCs who came to the clinic looking for an intrauterine device/system (IUD/IUS) were women who planned to replace the IUD after the approved labeled time of use (data not shown).

When asked about the COVID-19 pandemic, 95% of the women had heard or read information about it and 57% of them found it difficult to decide if the information about the disease was reliable (►**Table 2**). Television was the main source of information among the participants (91%), followed by government websites (53%), radio (45%), and social media (20%). In addition, the participants reported fever (89.8%), difficulty breathing (85.2%), cough (76.2%), loss of sense of smell (69.5%), headache (65.2%), and sore throat (50.0%) as the most important signs and symptoms of the COVID-19 infection. When asked how severe the virus could be to a pregnant woman and the fetus, 46% of women believed it was as serious as the Zika virus, while 22.1% and 34.0% reported not having enough information about the consequences of COVID-19 to pregnant women and the fetus, respectively.

Regarding the women's attitude towards the pandemic, 62.2% were concerned and 36.4% were afraid or very afraid of

Table 1 Sociodemographic characteristics of respondents, contraceptive methods in use at the time of interview and its length of use

Variables	n (%)
Age (years) (n = 393)	
< 20	22 (5.6)
20 a 29	164 (41.7)
30 a 40	145 (36.9)
≥ 40	62 (15.8)
Ever pregnant (n = 312)	
0	85 (27.2)
1-2	175 (56.1)
> 3	52 (16.7)
Cohabitation status (n = 390)	
With partner	215 (55.1)
Without partner	175 (44.9)
Ethnicity (n = 393)	
White	206 (52.4)
Black	141 (35.9)
Biracial	40 (10.2)
Asian	6 (1.5)
Schooling (years) (n = 378)	
< 1	3 (0.8)
1–4	2 (0.5)
5–9	12 (3.2)
10–12	74 (19.6)
≥ 13	287 (75.9)
Number of children (n = 304)	
0	92 (30.3)
1–2	186 (61.2)
≥ 3	26 (8.5)
Familiar income (US Dollar amount) (n = 390)	
R$ 403 (US$ 72)	14 (3.6)
R$ 618 (US$ 110)	18 (4.6)
R$ 933–1,391 (US$ 166–250)	161 (41.3)
R$ 2,327–4,558 (US$ 416–815)	156 (40.0)
R$ 8,099–14,366 (US$ 1,430–2,570)	41 (10.5)
Occupation (n = 376)	
Unemployed	100 (26.6)
Formal/informal job	236 (62.8)
Housewife	40 (10.6)
Number of family members at home (n = 375)	
1–3	218 (58.1)
4–6	151 (40.3)
≥ 7	6 (1.6)
Contraceptive in use (more than one answer allowed) (n = 400)	
Condom	255 (63.7)

(*Continued*)

Table 1 (*Continued*)

Variables	n (%)
Combined oral contraceptives	100 (25.0)
Injectables	33 (8.2)
Intrauterine devices/implants	109 (27.2)
Permanent contraception	7 (1.7)
No method	24 (6.0)
Fertility awareness methods	24 (6.0)

it. More than ⅓ (39.2%) of the participants considered they were capable of protecting themselves from contamination; however, the reduction of their usual income (24.9%) and difficulty of being socially isolated (62.2%) were the main reasons that interfered with the participants' actions to protect themselves. A rate of 50.0% of participants agreed that the changes in habits are important to avoid further dissemination of the COVID-19, 108 (29.3%) of the women were indifferent about it, and 12.7% disagreed with this statement. More than ⅔ (77.6%) of the participants took action to avoid an unplanned pregnancy during the pandemic. Regarding the preventative practices, 99.2% of the participants took some action to protect themselves against the contamination and spread of the virus. The most common practices to avoid COVID-19 contamination included wearing a mask when leaving home (88.7%), using alcohol gel to clean their hands (86.7%), avoiding leaving home (81%), and keeping a distance of 1 to 2 meters from other individuals (70.5%) (►**Table 3**).

The main reasons that motivated women to come to the clinic requesting the use of an IUD/IUS were to avoid pregnancy (40.7%), for personal reasons (19%), contraception and abnormal uterine bleeding (17.5%), abdominal lower pain (15.6%), and indication for medical treatment in addition to contraception (9.6%). The TCu380A IUD and the LNG-IUS were chosen by 33.9% and 66.1% of the participants, respectively. The main reason for their choice were safety (56.6%), the lack of daily attention required (38.1%), decrease or interruption of uterine bleeding in the case of the LNG-IUS (34.4%), and the absence of hormones in the case of the TCu380A IUD (21.7%). Although 72.5% of the women reported being concerned about becoming pregnant during the pandemic, the majority (82%) responded that the pandemic did not influence their choice for an IUD. After the logistic regression analysis, we observed that the women who reported having heard more information about COVID-19 and its impact on pregnancy were those

Table 3 Some practices to avoid Covid-19 and to avoid pregnancy by the respondent women (more than one option was allowed)

Practice to avoid coronavirus (n = 400)	n (%)
Wash hand for 20 seconds	268 (67.0)
Use alcohol gel for hand hygiene	347 (86.7)
Wear a mask outside home	355 (88.7))
Cleaning the house with disinfectants	254 (63.5)
Maintain 1–2 meters of social distance	282 (70.5)
Avoid touch face	218 (54.5)
Avoid leaving home	324 (81.0)
Practice to avoid pregnancy (n = 334)	**n (%)**
Use condom	89 (26.6)
Avoid sexual intercourse	65 (19.5)
Use fertility awareness method	15 (4.5)
Looking for a new contraceptive	38 (11.4)
No new attitude	127 (38.0)

Table 2 Some knowledge of the participants about Covid-19

	n (%)
Have you ever heard about covid-19? (n = 400)	
Yes	379 (94.7)
No	21 (5.3)
Have you read any message about covid-19? (n = 400)	
Yes	380 (95.0)
No	20 (5.0)
It is difficult to decide if the information about the coronavirus is true, false or rumors (n = 351)	
Disagree	65 (18.5)
Neither agree nor disagree	86 (24.5)
Agree	200 (57.0)
A person who is not sick or who does not have symptoms cannot spread the coronavirus (n = 363)	
Disagree	242 (66.7)
Neither agree nor disagree	35 (9.6)
Agree	86 (23.7)

without a partner and with more than 12 years of schooling (2.8 and 5.5 times higher than those without a partner and with < 12 years of schooling, respectively). In addition, women from low socioeconomic status were 16 times more likely to be influenced by the pandemic in their choice for an IUD when compared with women in higher socioeconomic levels. Women from high socioeconomic status and those with a partner had, respectively, 14.6 and 1.8 more chance to maintain physical distancing than the participants in the lower economic classes. Women older than 40 years of age had 15.4 times more chances to avoid leaving home than those aged under 20 years old.

Discussion

We found that most of the women who came to the clinic during the COVID-19 pandemic avoided leaving home and considered that the disease was a serious problem for the population. However, less than 30% of our sample had a job outside home making it possible for many women to stay home.

The COVID-19 pandemic raised a controversial question on whether women should consider postponing pregnancy due to the potential risk related to vertical transmission.[15,16] Since it became evident that there could be perinatal transmission with the HIV[17] epidemic, and the discussion about the subject resurfaced with the arrival of H1N1, in 2009, and the Zika virus, in 2016 and 2017, the possibility of vertical transmission of COVID-19 during pregnancy is an important consideration.[3] Although available data on risks related to COVID-19, specifically on vertical transmission of the virus, are limited, a recent study found that pregnant women with COVID-19 are 1.5 times more likely to be admitted to an intensive care unit (ICU) and 1.7 times more at risk of requiring mechanical ventilation compared to non-pregnant women of childbearing age with COVID-19. However, pregnant women were not at increased risk of death.[15,16]

However, it was reported that the risk of death by COVID-19 was higher in pregnant women in Brazil than in other countries, especially among women with comorbidities like preeclampsia and obesity, which are very common conditions in our population.[17] Although vertical transmission of COVID-19 is apparently rare, the evidence suggests that premature birth and admission to a neonatal ICU are common among babies born to women infected with COVID-19.[15,16]

The women who came to our service during the pandemic reported more years of schooling than the common population attended at the clinic, which could explain why they were well-informed about the most common symptoms of COVID-19. The knowledge about the virus was obtained mainly through television, probably because families spent more time at home during the quarantine and had more opportunities to watch television.[18,19] In addition, the fact that many healthcare facilities were closed or only dedicated to attend people with COVID-19 constituted a barrier for many women from the underprivileged portion of the society from receiving information from healthcare providers.[7,20]

Family income was associated with a polarization of our sample in the responses. Women who belonged to classes A and B questioned the information received about COVID-19, while a great rate of women in classes C, D, and E reported no opinion on the reliability of the information they received. We found that the possibility to take action to face the pandemic was directly proportional to the high income and years of schooling of the participant.[21] In Brazil, the government provided conflicting information about the pandemic. The Ministry of Health and many governors encouraged physical distance, the use of masks and lockdown. Conversely, the Brazilian president encouraged people to not practice physical distancing and to not stay home.[22] These conflicting messages from the highest level of administration created a confusing scenario for many people in the middle of the pandemic. For this reason, we believe that women with fewer years of schooling and with lower income had trouble deciding which rules to follow.

It was previously described that people in the USA who were at greater risk to be infected by the coronavirus were from the low socioeconomic portion of the society and were also African American or Hispanic.[22–25] It is important to take into account that this population was unable to discontinue the commute to their jobs, and they might have used a crowded public transportation, which did not allow physical distancing.

One quarter of the women were users of an IUD/IUS at the moment of their visit, and they came to the clinic for removal of their current device and insertion of a new one upon reaching the approved label time. Although we were aware about the recommendation of off-label extended use of the IUD/IUS made by different organizations, we decided to remove the one already in use and insert a new IUD because those women were already at the clinic.[26–28]

We consider access to IUDs important at any time as they are highly effective contraceptives; however, access to it acquired greater importance during the pandemic. Keeping contraceptive clinics open and providing SRH services is important for the population even with a limited number of consultations, with reduced number of healthcare providers, and with fewer weekly working days.[1,12,26]

Our study presents strengths and limitations. The main strength is the large sample size of women who voluntarily visited the clinic requiring an IUD. The main limitations are all respondents came from one center, one country, and most of them belonged to the middle socioeconomic class. This does not allow us to generalize our results; however, this is a group of women that received attention regularly from the Brazilian public sector.

It is important to reinforce the messages about the pandemic, especially among the underprivileged portion of the society. In addition, the COVID-19 pandemic offered new opportunities in the provision of LARC methods, focusing specifically on the needs of women with low socioeconomic status. Despite previous evidence showing that the provision of contraceptives is safe during the COVID-19 pandemic, there are many barriers worldwide. Some policy makers take advantage of the pandemic to impose restrictions and

unnecessary regulations, such as those in some countries and some USA states. We consider our practice to continue offering IUDs during the pandemic is an important service to reduce inequality and improve the safety of women trough the pandemic.[1,9,29,30]

Conclusion

In conclusion, women without partners and with over 12 years of schooling had more information about COVID-19 and its impact on pregnancy. Women with high socioeconomic status and those with partners had a higher chance to respect physical distancing. We can also conclude that it is possible to provide IUDs/IUSs during the COVID-19 pandemic.

Contributions

All authors contributed to the design of the study and were involved in the data collection, data analysis and/or interpretation. Also, all authors contributed to manuscript writing/substantive editing and review and approved the final draft of the manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

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Adequacy of Antenatal Care during the COVID-19 Pandemic: Observational Study with Postpartum Women

Adequação da assistência pré-natal durante a pandemia de covid-19: Estudo observacional com puérperas

Margot Marie Martin[1] Roxana Knobel[2] Vitor Nandi[1] Jessica Goedert Pereira[2] Alberto Trapani Junior[1,2,3] Carla Betina Andreucci[4]

[1] Divisão de Saúde da Mulher, Hospital Universitário Polydoro Ernani de São Thiago, Florianópolis, SC, Brazil
[2] Departamento de ginecologia e obstetrícia, Universidade Federal de Santa Catarina, Florianópolis, SC, Brazil
[3] Programa de residência médica em ginecologia e obstetrícia, Hospital Regional Homero de Miranda Gomes, São José, SC, Brazil
[4] Departamento de medicina, Universidade Federal de São Carlos, São Carlos, SP, Brazil

Address for correspondence Roxana Knobel, PhD, Departamento de Ginecologia e Obstetrícia, Bloco pedagógico, 2° andar, Hospital Universitário, Rua Professora Maria Flora Pausewang, s/n°, 88036-800, Campus Universitário, Trindade, Florianópolis, SC, Brazil (e-mail: rknobel@gmail.com).

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Abstract

Objective The present study aimed to evaluate the antenatal care adequacy for women who gave birth at the University Hospital of Santa Catarina in Florianopolis (Brazil) during the COVID-19 pandemic, and to evaluate the association of adequacy with sociodemographic, clinical, and access characteristics.

Methods Data were collected between October and December 2020, including 254 patients who delivered in the University Hospital from Federal University of Santa Catarina and answered our questionnaires. Additional data were obtained from patients' antenatal booklets. Antenatal care was classified as adequate, intermediate, or inadequate according to the number of appointments, gestational age at the beginning of follow-up, and tests results. We carried out a descriptive statistical analysis and a bivariate/with odds ratio analysis on maternal sociodemographic, clinical and health access variables that were compared with antenatal adequacy.

Results Antenatal care was considered adequate in 35.8% of cases, intermediate in 46.8%, and inadequate in 17.4%. The following maternal variables were associated with inadequate prenatal care (intermediate or inadequate prenatal care): having black or brown skin colour, having two or more children, being of foreign nationality, not being fluent in Portuguese, and using illicit drugs during pregnancy; the clinical variables were more than 6 weeks between appointments, and not attending high-risk antenatal care; as for access, the variables were difficulties in attending or scheduling appointments, and attending virtual appointments only.

Keywords
- prenatal care
- primary health care
- access to health services
- Covid-19

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Resumo

Conclusion In a sample of pregnant women from a teaching hospital in Florianópolis during the COVID-19 pandemic, antenatal care was considered adequate in 35.8%, intermediate in 46.8%, and inadequate in 17.4% of cases.

Objetivo O objetivo deste estudo foi avaliar a adequabilidade do pré-natal de puérperas atendidas no hospital universitário da Universidade Federal de Santa Catarina, em Florianópolis, durante a pandemia de COVID-19 e avaliar a associação de características sociodemográficas, clínicas e de acesso com essa adequabilidade.

Métodos Este estudo foi realizado de outubro a dezembro de 2020, com 254 puérperas que tiveram seus partos no hospital universitário. Os dados foram obtidos a partir de questionários respondidos pelas pacientes e dos seus cartões de pré-natal e prontuários para obter demais dados clínicos. O pré-natal foi classificado como adequado, intermediário ou inadequado segundo o número de consultas, idade gestacional ao início do pré-natal, e realização de exames. Inicialmente, se realizou uma análise estatística descritiva e, após, bivariada/com razão de chance quanto às variáveis maternas sociodemográficas, clínicas, e de acesso a saúde comparados com adequabilidade do pré-natal.

Resultados O pré-natal foi considerado adequado em 35,8%, intermediário em 46,8% e inadequado em 17,4% dos casos. Estiveram associados a uma assistência pré-natal não-adequada (pré-natal intermediário ou inadequado) as seguintes variáveis maternas: cor de pele preta, parda, ou indígena, ter dois ou mais filhos, ser de nacionalidade estrangeira, não possuir fluência em português, uso de drogas ilícitas durante a gestação; as variáveis clinicas foram: lacuna de mais de 6 semanas entre consultas e não ser atendida em pré-natal de alto risco; quanto a acesso, as variáveis foram: dificuldade de ir e de agendar as consultas e ter tido consultas virtuais.

Conclusão Em uma amostra de gestantes de um hospital universitário de Florianópolis durante a pandemia do Covid-19, a assistência pré-natal foi considerada adequada em 35,8%, intermediária em 46,8%, e inadequada em 17,4% dos casos.

Palavras-chave

- cuidado pré-natal
- atenção primária à saúde
- acesso aos serviços de saúde
- Covid-19

Introduction

Adequate antenatal care (ANC) can reduce complications during childbirth and in the postpartum period, contributing to a decrease in maternal and infant mortality/morbidity.[1–3] About 4,000 infant and neonatal deaths could have been prevented by proper antenatal care during 2014 in Brazil, corresponding to 40% of all deaths.[3] Several affections that still have high rates in the country, such as preterm birth and HIV or syphilis vertical transmission, are related with inadequacy of antenatal care.[4,5]

In the last few decades, several low- and high-risk pregnancies antenatal care protocols were proposed in Brazil. The guidelines were designed to instruct best practices, establishing the scope of primary care health professionals, therefore ensuring adequate obstetric care. Early beginning of antenatal follow-up during the first trimester of pregnancy, attendance to at least six antenatal appointments, and basic laboratory tests are among the minimum recommendations.[2–5]

Sociodemographic differences and local context should be considered for assessing and planning health policies. Antenatal care coverage is extensive in overall Brazil, with high adhesion within all country regions.[4] However, care adequacy is low, depending on pregnant women's characteristics.[2,3,6] Before the emergence of the COVID-19 pandemic, the proportion of adequate antenatal care among all Brazilian pregnant women in 2012 (at least 6 appointments) was only of 73%.[3] Additionally, only three quarters of women had early beginning of antenatal care follow-up, and care adequacy was lower for younger women, and for black women from the North and Northeast regions.[5] Pregnancy in adolescents, poverty, low literacy, parity, Brazilian region origin, living in municipalities with low HDI, and not being white are cited as possible barriers to access antenatal care.[2–4,6]

The 2020 worldwide COVID-19 pandemic caused health systems overload, as well as transportation and free movement restrictions, leading to anxiety amidst the population.[7] As soon as the pandemic hit Brazil, routine antenatal consultations were suspended, although qualified prenatal access is considered essential in health emergencies.[8] Official recommendations were vague and paradoxical, including to avoid face-to-face appointments for low-risk pregnancy, although maintaining the attendance for high-risk cases.[9] There was restriction for outpatient care during the pandemic, negatively impacting the health of pregnant women and their families.[10] Reduction of public transportation, irregular operation of health units, and fear of contagion

by women and health professionals also hampered antenatal access, causing delays in seeking and obtaining care.[7] The COVID-19 pandemic affects vulnerable populations more severely, exacerbating inequalities in health access.[11]

Quantifying access and adequacy of antenatal care during the pandemic may provide acknowledgement of barriers and risk factors associated with inadequate obstetric care. The results may allow us to recognize which women are at higher risk of inadequate care, as well as to promote inclusive care policies, improving maternal and neonatal outcomes.

The objectives of our study are to evaluate the antenatal adequacy in postpartum women who gave birth at the university hospital of Universidade Federal de Santa Catarina (HU-UFSC) during the COVID-19 pandemic, and to evaluate the association of adequacy with sociodemographic, clinical and health access characteristics.

Methods

This is a cross-sectional observational study including postpartum women admitted to Hospital Universitário Polydoro Ernani São Thiago at HU-UFSC. The facility is a public referral tertiary hospital within the *Empresa Brasileira de Serviços Hospitalares* (EBSERH) network, in Florianópolis, Santa Catarina, Brazil. The hospital is not a COVID-19 referral center.

Postpartum women who gave birth at the HU-UFSC were interviewed from October 13 to December 30, 2020, during the COVID-19 pandemic. The interview was carried out between 1 and 2 days after birth (for vaginal birth and caesarean section, respectively), just before the patient's discharge.

Women who birthed babies weighting >500 g and/or with gestational age >22 weeks were included in the study, recruited from rooming-in infirmary. The exclusion criteria were severe mental illness, home births, and refusal to participate. In case the woman was not in the infirmary or was asleep at the first interview attempt, a second approach followed. If not found or unavailable, the woman was excluded from the sample. Women who did not fulfil the variable of interest, and those for whom less than 50% of the variables were analyzed were also excluded.

Sample size was calculated with population parameter estimation approach, 95% CI, margin of error of 5%, and expected proportion in the population of 65.8%.[5] A sample of 122 women would be necessary for antenatal quality care evaluation. To assess factors associated with adequacy of care in a broader approach, we decided to include all participants who met the inclusion criteria and filled out the variable of interest.

Participants received a self-completion questionnaire specially prepared for the project containing multiple-choice and open-ended questions. The questionnaire was pretested in a similar sample and was available in Portuguese, English, Spanish, and French. The instrument could be filled out with the help of one of the researchers, if requested. Additionally, we collected information from hospital charts and from antenatal booklets. Data on antenatal consultations were obtained through antenatal booklets and information provided by the women only, since there is no means for accessing primary care follow-up through the hospital. The included variables were identification, socioeconomic status, personal morbid history, lifestyle, and information about antenatal care. From the medical chart and antenatal booklet, we obtained information on antenatal follow-up, obstetric data, and previous conditions.

The present study is part of the research "Obstetric and postpartum complications during the COVID-19 epidemic", No 5543120.7.0000.0121, and it was approved at the UFSC human research ethics committee, according to requirements for studies involving human beings at CNS Resolution 466/12 and their complementary resolutions.

Quality of antenatal care was the dependent variable. We used Kessner index[2,12] to analyze whether antenatal care was adequate, intermediate, or inadequate.[2,4,5,13] Having at least basic laboratory tests (HIV, syphilis, and routine urine) at the third trimester of pregnancy during the pandemic was considered an adequacy criterion, adapted from Silveira et al.[14] Thus, antenatal care was considered adequate if a) the first appointment happened before the 16th week of pregnancy, b) the woman attended to more than 6 consultations, and c) laboratory tests for HIV, syphilis, and routine urine were performed at the last trimester of pregnancy. Antenatal care was inadequate if presenting 1 of 2 characteristics: either less than 3 appointments, or late beginning of follow-up (after 27th week of pregnancy). Cases that did not meet adequate or inadequate criteria were considered intermediate. Patients who had no antenatal care follow-up were considered inadequate. The dependent variable "adequacy of antenatal care" was transformed into dichotomous (adequate or inadequate) to calculate associations and odds ratio.

The independent sociodemographic and health variables were maternal age, literacy, skin color, paid work engagement, social class, nationality, fluency in Portuguese, primiparity, living with a partner/with children, substance use during pregnancy (alcohol, smoking, or illicit drugs), social isolation due to pandemic measures, previous comorbidities, and suspected or diagnosed COVID-19.

We considered the following characteristics for antenatal care and health access: number of appointments and gestational age at the beginning of follow-up, more than 6 weeks of interval between appointments, high-risk pregnancy (with referral to high-risk unit-PNAR), hospitalization during pregnancy, private health insurance, antenatal care location, laboratory tests (syphilis, HIV, and routine urine during the last trimester of pregnancy), reported obstacles to schedule or attend to appointments, teleconsultations, and unexpected expenses during antenatal care.

We applied the Brazilian economic classification criterion for determining the participant's socioeconomic class.[15] The participants were classified as class A with average income of U$ 4,251.97; B1, with average income of U$ 1,951.77; B2, with average income of U$ 1,020.01; C1, with average income of U$ 569,46; C2, with average income of 338.01; D/E, with average income of U$ 152.28 (exchange rate calculated in April 2021).

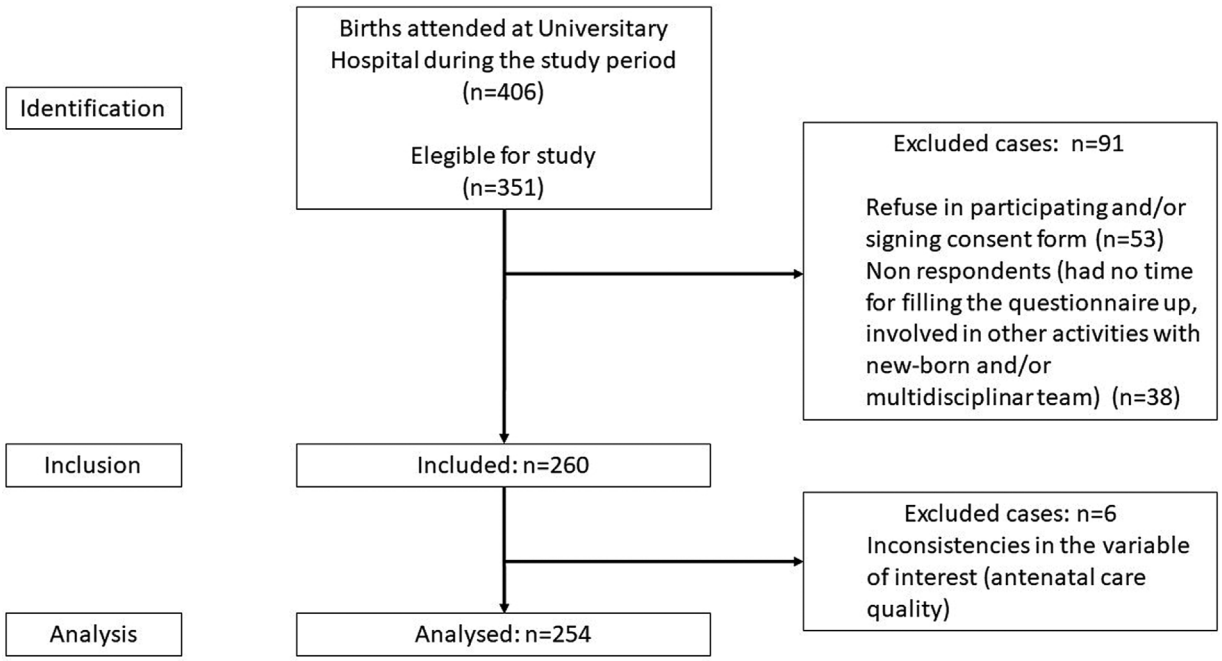

Fig. 1 Flowchart of subject's selection.

Social isolation during the COVID-19 pandemic was investigated by asking women whether they avoided crowds, worked out of home, routinely left the house, had close contacts with people with whom they do not cohabit and used public transportation. We classified social isolation as complete if the pregnant woman refrained from all aforementioned exposures, as partial when she avoided the majority, and as no social isolation if she was exposed to all situations.

The data were analyzed using the IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA). We applied descriptive statistics (absolute and relative frequency, median and standard deviation) for all variables. To compare sociodemographic characteristics and health habits to obtain antenatal care adequacy in three categories (adequate, intermediate, and inadequate), the chi-squared test and the Fisher exact test were applied. Associations and odds ratios between the dependent variable (adequate or inadequate antenatal care), as well as other variables of interest, were analyzed using binary logistic regression, with a 95% confidence interval (95% CI). For the adjusted regression analysis, we used variables that had $p < 0.250$ in the crude analysis only, in addition to possible confounding factors, such as age and social class. We adopted 5% significance level for all analyses.

Results

From October 10 to December 30, 2020, 351 women were deemed eligible for the study. Of these, 91 did not participate: 53 did not wish to answer the questionnaire, and 38 agreed, but did not complete the questionnaire for several reasons (engaged in baby care or in multidisciplinary appointments or did not have time before hospital discharge). Six questionnaires were excluded from the analysis due to inconsistencies in the variable "adequacy of antenatal care". The final sample consisted of 254 patients (►**Figure 1**).

►**Table 1** shows the distribution of participants according to sociodemographic characteristics and adequacy of antenatal care. We found 119 women with intermediate antenatal care (46.9% of the sample), 91 (35.8%) with adequate antenatal care (35.8% of the sample), and 44 with inadequate care (17.3% of the sample). Few women did not answer some items in the questionnaire, thus reducing the number of responses to the variables. However, women who did not answer any of the questions were excluded from the analysis, as they did not fulfil the variable of interest. The variables that showed significant differences were skin color, not being primiparous, and foreign nationality.

►**Table 2** shows the distribution of women according to sociodemographic characteristics and health habits, as well as having received adequate or inadequate antenatal care (intermediate and inadequate). Both crude and adjusted analyses showed that being black or brown-skinned were risk factors for inadequate antenatal care. In addition, these women are three times more likely to receive inadequate antenatal care. The variable low social class (C2/D/E) showed a borderline association in the crude analysis, which did not remain in the adjusted analysis. Regarding literacy, most of the sample was of white women who completed high school. The average age was 28 years (in full years), with a standard deviation of 6 years, with most women being in the 20 to 34 age group. No participant was from socioeconomic class A, and only five were from class B1. Thirty-six women were classified as D/E. For the entire sample, the beginning of antenatal follow-up was on average at the 12th week of

Table 1 Sociodemographic characteristics and health habits of study participants

Variables	Antenatal care follow-up			*P*-value*
	Adequate n (%)	Intermediate n (%)	Inadequate n (%)	
Age (n = 224)				
Younger than 20 years	3 (20.0)	8 (53.3)	4 (26.7)	0.686
20 to 34 years	58 (36.0)	77 (47.8)	26 (16.1)	
35 years or older	17 (35.4)	24 (50.0)	7 (14.6)	
Literacy (n = 222)				
0 to 8 education years	6 (30.0)	11 (55.0)	3 (15.0)	0.529
9 to 12 education years	45 (31.3)	72 (50.0)	27 (18.8)	
13 years or above	25 (43.1)	26 (44.8)	7 (12.1)	
Social class (n = 223)				
B1/B2/C1	49 (40.2)	56 (45.9)	17 (13.9)	0.133
C2/D/E	28 (27.7)	53 (52.5)	20 (19.8)	
Skin color (n = 222)				
White/Asian	60 (42.9)	55 (39.3)	25 (17.9)	0.001
Black/brown	17 (20.7)	53 (64.6)	12 (14.6)	
Primiparous (n = 254)				
Yes	38 (34.9)	59 (54.1)	12 (11.0)	0.037
No	53 (36.6)	60 (41.4)	32 (22.1)	
Paid work (n = 206)				
Formal	35 (38.0)	46 (50.0)	11 (12.0)	0.489
Informal	18 (41.9)	19 (44.2)	6 (14.0)	
No paid work	22 (31.0)	34 (47.9)	15 (21.1)	
Lives with partner (n = 210)				
Yes	67 (38.1)	85 (48.3)	24 (13.6)	0.473
No	10 (29.4)	17 (50.0)	7 (20.6)	

gestation (standard deviation of 7 weeks), and women had an average of 7 appointments (standard deviation of 3 consultations). A total of 63% of women started antenatal care follow-up before the 16th week of gestation, 48.4% before the 12th week, and 34.3% had 6 or more appointments (not tabulated data).

The variables of antenatal care characteristics are distributed according to adequacy in **table 3**. The number of appointments and gestational age at the beginning of antenatal follow-up were used to classify the studied variable (adequacy of antenatal care); therefore, statistically significant differences were expected. The variables were maintained in the regression model, and the result showed that an increase by one appointment decreased in 34% the chance of inadequate antenatal care (0.66; 95% CI: 0.55–0.79). In the same way, each delay of one week in starting antenatal follow-up increased in 1.17 times the chance of inadequate antenatal care (95% CI: 1.06–1.29). In addition, an interval longer than 6 weeks between appointments, not attending high-risk unit, obstacles to schedule or to attend to appointments, and having virtual consultations were risk factors for not receiving adequate antenatal care, while exclusively private health insurance was a protective factor. In the adjusted analysis, only obstacles to schedule and to attend appointments and virtual consultations remained significant (both increasing the chance of inadequate antenatal by three times). Seventy-two women did not have third trimester laboratory tests (HIV, syphilis, and routine urine); thus, 50 of them were classified as intermediate, and 22 as inadequate (data not shown). Out of 254 women, 95 reported unexpected expenses (they paid for appointments, laboratory, and imaging tests), corresponding to 45% of the sample. Among six women who had no antenatal follow-up (included in the inadequate antenatal group), three claimed they were unable to schedule appointments at a primary health facility in Florianópolis, and others claimed as reasons for abandoning antenatal care follow-up unwanted pregnancies, late diagnosis, and moving out of the country (data not shown).

In the pandemic context, more than half of postpartum women reported partial social isolation, and less than 5% of them reported complete social isolation (►**Table 4**). In total, 31 women were suspected or diagnosed with COVID-19, with confirmed etiology in 9 patients (the remainder had not been diagnosed through laboratory tests, but through

Table 2 Distribution of women according to sociodemographic characteristics and health habits by adequacy of antenatal care

Variables	Antenatal follow-up		Crude OR (CI95%)	Adjusted OR (CI95%)
	Adequate n (%)	Inadequate n (%)		
Age				
Younger than 20 years	3 (20.0)	12 (80.0)	2.25 (0.61-8.31)	
20–34 years	58 (36.0)	103 (64.0)	1	
35 years or older	17 (35.4)	31 (64.6)	1.03 (0.52-2.01)	
Literacy				
0–8 education years	6 (30.0)	14 (70.0)	1.06 (0.38-2.94)	
9–12 education years	45 (31.3)	99 (68.8)	1	
13 years or above	25 (43.1)	33 (56.9)	0.60 (0.32-1.12)	
Skin color				
White/Asiatic	60 (42.9)	80 (57.1)	1	1
Black/brown	17 (20.7)	65 (79.3)	2.87 (1.53-5.39)*	2.99 (1.49-6.00)*
Primiparous				
Yes	38 (34.9)	71 (65.1)	1.08 (0.64-1.81)	
No	53 (36.6)	92 (63.4)	1	
Paid work				
Yes	57 (37.7)	94 (62.3)	1	
No	20 (31.7)	43 (68.3)	1.30 (0.70-2.43)	
Lives with partner				
Yes	67 (38.1)	109 (61.9)	0.68 (0.31-1.51)	
No	10 (29.4)	24 (70.6)	1	
Lives with own children				
Yes	42 (35.3)	77 (64.7)	1.15 (0.65-2.02)	
No	35 (38.5)	56 (61.5)	1	
Foreign				
Yes	2 (18.2)	9 (81.8)	2.60 (0.55-12.31)	2.47 (0.26-23.94)
No	89 (36.6)	154 (63.4)	1	1
Speaks Portuguese				
Yes	89 (36.2)	157 (63.8)	1	
No	2 (25.0)	6 (75.0)	1.70 (0.34-8.61)	
Social class				
B1/B2/C1	49 (40.2)	73 (59.8)	1	1
C2/D/E	28 (27.7)	73 (72.3)	1.75 (0.99-3.08)	1.23 (0.64-2.35)
Previous comorbidities				
Yes	26 (34.7)	49 (65.3)	1.04 (0.58-1.86)	
No	54 (35.5)	98 (64.5)	1	
Alcohol abuse				
Yes	9 (26.5)	25 (73.5)	1.71 (0.76-3.88)	1.89 (0.75-4.75)
No	69 (38.1)	112 (61.9)	1	1
Smoking				
Yes	7 (27.0)	21 (75.0)	1.84 (0.74-4.54)	1.31 (0.49-3.49)
No	71 (38.0)	116 (62.0)	1	1
Illicit drugs				
Yes	5 (33.3)	10 (66.7)	1.15 (0.38-3.49)	
No	73 (36.5)	127 (63.5)	1	

Abbreviation: OR, odds ratio.
* $p < 0.05$; Hosmer-Lemeshow = 0.452.

Table 3 Antenatal characteristics according to adequacy of offered care

Variables	Antenatal care follow-up		Crude OR (CI95%)	Adjusted OR** (CI95%)
	Adequate median (SD)	Inadequate median (SD)		
Number of appointments	9 (1.99)	6 (2.99)	0.66 (0.58–0.75)[&]	0.66 (0.55–0.79)[&]
Gestational age at beginning of follow-up	9 (3.03)	12 (8.56)	1.13 (1.07–1.20)[&]	1.17 (1.06–1.29)[*]
	Adequate n (%)	Inadequate n (%)		
Over 6 weeks interval between appointments				
Yes	35 (25.9)	100 (74.1)	2.92 (1.68–5.07)[&]	1.84 (0.66–5.16)
No	49 (50.5)	48 (49.5)	1	1
Referral to high-risk unit				
Yes	32 (43.2)	42 (56.8)	1	
No	59 (32.8)	121 (67.2)	1.56 (0.90–2.72)	
High-risk unit attendance				
Yes	30 (50.8)	29 (49.2)	1	1
No	61 (31.3)	134 (68.7)	2.27 (1.26–4.11)[*]	2.07 (0.77–5.60)
Hospital admission during pregnancy				
Yes	7 (25.9)	20 (74.1)	1	
No	84 (37.0)	143 (63.0)	0.60 (0.24–1.47)	
Private health insurance				
Yes	11 (52.4)	10 (47.6)	1	
No	68 (34.0)	132 (66.0)	2.14 (0.86–5.28)	
Exclusively public health follow-up				
Yes	72 (53.3)	132 (64.7)	1.12 (0.59–2.13)	
No	19 (38.0)	31 (62.0)	1	
Exclusively private health follow-up				
Yes	10 (62.5)	6 (37.5)	0.31 (0.11–0.88)[*]	0.57 (0.13–2.50)
No	81 (34.0)	157 (66.0)	1	1
Difficulty in attending to appointments				
Yes	12 (20.7)	46 (79.3)	2.78 (1.37–5.66)[*]	0.71 (0.24–2.06)
No	66 (42.0)	91 (58.0)	1	
Difficulty in scheduling appointments				
Yes	22 (23.4)	72 (76.6)	2.91 (1.60–5.29)[&]	2.87 (1.18–6.99)[*]
No	56 (47.1)	63 (52.9)	1	1
Virtual consultations				
Yes	32 (25.4)	94 (74.6)	2.82 (1.59–4.98)[&]	3.08 (1.28–7.40)[*]
No	46 (48.9)	48 (51.1)	1	1

Abbreviations: OR, odds ratio; SD, standard deviation.
[*] $p < 0.05$; [&] $p < 0.001$; [**]Adjusted analysis for confounding factors (age, social class, and isolation during the COVID-19 pandemic); Hosmer-Lemeshow = 0.494.

clinical and/or epidemiological course), and 2 were hospitalized during pregnancy (data not shown). The COVID-19 pandemic and its association with the adequacy of antenatal care is displayed in ►**Table 4**. We found no association of any variable with adequacy of antenatal care, even in the adjusted model. The model was considered highly suitable by the Hosmer-Lemenshow test (0.991).

Discussion

In our sample, 35.8% of pregnant women received adequate antenatal care during the COVID-19 pandemic. According to official 2019 data, the percentage of women who had adequate or more than adequate antenatal care was 77.5% in Florianopolis, 79.3% in the South region, and 70.7% in overall

Table 4 COVID-19 pandemic and adequacy of antenatal care

Variables	Antenatal		Crude OR (CI95%)	Adjusted OR** (CI95%)
	Adequate n (%)	Inadequate n (%)		
Avoided crowds				
Yes	76 (36.9)	130 (63.1)	1	1
No	4 (19.0)	17 (81.0)	2.49 (0.81-7.66)	2.38 (0.45-12.67)
Avoided close contacts				
Yes	74 (37.2)	125 (62.8)	1	1
No	6 (21.4)	22 (78.6)	2.17 (0.84-5.60)	1.52 (0.44-5.26)
Public transportation				
Yes	17 (26.6)	47 (73.4)	1.74 (0.92-3.30)	1.68 (0.81-3.49)
No	63 (38.7)	100 (61.3)	1	1
Worked				
Yes	45 (37.5)	75 (62.5)	1	
No	32 (34.0)	62 (66.0)	1.16 (0.66-2.04)	
Work outside of home				
Yes	23 (30.7)	52 (69.3)	1.36 (0.75-2.45)	
No	57 (37.5)	95 (62.5)	1	
Avoided leaving home				
Yes	66 (35.9)	118 (64.1)	1	
No	14 (32.6)	29 (67.4)	1.16 (0.57-2.35)	
Behavior during the pandemic				
Total isolation	2 (20.0)	8 (80.0)	2.40 (0.45-12.83)	0.25 (0.02-3.64)
Partial isolation	63 (35.6)	114 (64.4)	1.09 (0.53-2.21)	0.88 (0.39-1.98)
No isolation	15 (37.5)	25 (62.5)	1	1
Had COVID-19				
Yes	8 (25.8)	23 (74.2)	1.69 ((0.72-3.98)	1.30 (0.53-3.22)
No	73 (37.1)	124 (62.9)	1	1

Abbreviation: OR, odds ratio.
**Adjusted analysis for confounding factors (age, social class, and paid work); Hosmer-Lemeshow = 0.991.

Brazil.[16] The Southern region of Brazil has a significantly higher chance of offering adequate antenatal care.[12] We found a percentage of inadequate antenatal care of 17.4%, higher than the 14.8% official data for 2019 in Florianópolis.[16] Notwithstanding, the 2019 data were based on first antenatal care appointment up to 12 weeks as a criterion for adequacy, rather than up to 16 weeks, as in our study. Even applying a less rigid standard, our findings suggest that fewer women had adequate or more than adequate antenatal care during the COVID-19 pandemic in Florianopolis when compared with the previous year in the same state, and in the overall country. Thus, we concluded that a decrease in the adequacy of antenatal care occurred in Florianopolis during the 2020 COVID-19 pandemic.

Skin color, nationality and primiparity were significant for antenatal care adequacy, with only skin color remaining in the adjusted analysis. Women with black or brown skin were 2.99 times more likely to have inadequate antenatal care, as already described in the literature.[2–4] Non-white skin color is a known risk for delayed first antenatal care appointment as well as lower rates of complementary exams during pregnancy follow-up.[3] This is especially relevant, considering that black women have the highest maternal mortality within the obstetric population in Brazil, along with more barriers to health access during the COVID-19 pandemic.[17]

Foreign women had less access than adequate antenatal care and a higher chance of inadequate care in our sample, though the association was not maintained in the logistic regression. Previously, pregnant Haitians living in Brazil had fewer antenatal consultations when compared to Brazilian women, due to language barriers, prejudice or intolerance, and irregular/illegal documentation.[18] However, studies on the topic are scarce.

Primiparous women had a lower proportion of inadequate antenatal care. Multiparous women may be less assiduous to antenatal consultations because they have been pregnant before. Additionally, barriers to health access, adversity of maternal social context, or previous negative experiences with the health system may play a role favoring primiparity over multiparity on antenatal care adherence.[2]

We also hypothesized that the closing of schools and day-care centers during the pandemic posed further difficulties for pregnant women with older children.

Several aspects that have been previously associated with the adequacy of antenatal care were not observed in our sample, that is, maternal age, literacy, income, and comorbidities. Previous findings showed higher antenatal adequacy associated with older maternal age,[6,19] and in women with longer formal education.[13,19] Low income and unemployment are risk factors for antenatal care inadequacy, before and during the pandemic.[13,20] Women with comorbidities or previous in-hospital treatment appear to have higher antenatal care adequacy rates.[4]

We found 13.8% of reported alcohol consumption during pregnancy among participants, 11% of cigarette consumption, and 6% of drug use, higher rates than previously reported data from Brazil.[21] The COVID-19 pandemic may have intensified psychoactive substances utilization, such as alcohol, tobacco, and others.[22] The consumption of substances was not associated with adequacy of antenatal care.

In our sample, 63% of women began antenatal follow-up before 16 weeks, and 48.4% before 12 weeks. In comparison, before the pandemic, 75.8% and 50% of women had early antenatal care attendance at 16 and 12 weeks of pregnancy, respectively.[12,14] In our sample, 34.3% of women had at least 6 appointments, lower numbers than the 75% reported in previous years.[6,12] Early beginning of antenatal follow-up was delayed, but the number of appointments suffered a more severe decrease, maybe due to health system organization during the pandemic in Brazil.

After evidence of coronavirus community transmission in the country, the Brazilian Ministry of Health released recommended (not mandatory) COVID-19 contention measures, subsequently locally regimented as quarantine regimens.[23] Officially, women's health care should not be discontinued. However, non-emergency appointments have been postponed or cancelled in Florianópolis. Regarding antenatal care, high-risk pregnancy follow-up, first consultations, and follow-up after the 36th week of pregnancy were maintained, and the remainder offered through virtual appointments.[24]

Approximately 72% of participants were routinely tested for HIV, syphilis, and urine at the third trimester of pregnancy. Nationally, the percentage varies from 21.6 to 25.4%.[12,25] In our sample, one third or more of the women reported extra expenses during pregnancy, a common fact in Brazilian obstetric care. Previously, many pregnant women claimed to have paid for appointments and complementary tests in Fortaleza,[26] and for obstetric ultrasound in São Paulo.[27] Such unexpected expenditures suggest lower access to health care.

Women who attended high-risk antenatal units had higher antenatal care adequacy. For 15 participants referred to high-risk units without receiving the care (reasons obscured due to study design), the association with better adequacy was not observed. Before the pandemic, the percentage of high-risk pregnancies in Brazil was 15%, and many pregnant women reported delays in accessing their referral units.[26] Amidst the COVID-19 pandemic, the number of antenatal care appointments may have been reduced for women with comorbidities also.[19]

We estimated access to antenatal care during the COVID-19 pandemic by identifying obstacles on receiving or scheduling appointments, as well having virtual consultations. One quarter of postpartum women reported difficulties in reaching scheduled consultations, which did not remain after the adjusted analysis. Approximately half of the women (44%) reported troubles in scheduling appointments, increasing the risk of inadequate antenatal care by 3 times. Three participants declared that the difficulty in scheduling was the reason for abandoning antenatal follow-up.

Even though virtual consultations were significantly associated with inadequate antenatal care, it is not possible to distinguish whether they were the cause or consequence of the association. Remote consultations are described as a viable socioeconomic alternative during the COVID-19 pandemic.[28] Thus, some guidelines state that they should be encouraged when physical examination is not necessary, and when pregnancy does not have risk factors. However, there are concerns about the lack of light technologies that depend on human contact, such as physical examination, blood pressure assessment, edema evaluation, and uterine fundal height measurement.[20,28] Virtual consultations may be a valid and necessary alternative and can assure access under special circumstances. Evidently, when health access is impaired, it is more appropriate to have virtual appointments than to have none. However, there is a need to develop validated protocols and systems for assessing virtual consultations quality, as well as guidelines identifying situations of necessary face-to-face assistance.

Only a few women adopted social isolation in our sample. Although Brazil appears as the country with the highest number of maternal deaths related to COVID-19,[29] the government failed in adopting or encouraging social isolation measures. Horizontal social isolation was not encouraged in Brazil. Isolation of contacts was also compromised due to limited tests availability at the time of data collection, corroborated by the small number of women tested to confirm COVID-19 diagnosis, as well as low adherence to social isolation in our sample. Our finding of few hospital admissions could be explained due to the fact that the chosen facility was not a local reference for COVID-19 cases. Access to primary care in Brazil faces adversity since long before the incoming pandemic.[30] Once antenatal care adequacy was not associated with social isolation, COVID-19 contamination, or difficulties in scheduling appointments, barriers to access health care emerge as the bottom line. Some authors have suggested COVID-19 suspicion or diagnosis might be associated with antenatal care adequacy,[7,8] which was not evidenced in our sample. Our study has limitations. First, it is difficult to compare studies on the subject, due to lack of criteria to analyze antenatal care adequacy, and the wide differences within the findings.[1,12,13,31] Usually, authors assess adequacy through quantitative and restricted criteria, and quality of care is not evaluated.[3,12] Secondly, it was not possible to determine sample selection bias, which could

have significantly altered the results. However, according to the sample size calculation, the number of completed questionnaires was more than double needed to assess the outcome, and the results were in agreement with the published data.[1,4,12] Our findings suggest the need for further studies on the subject for better evaluation and qualification of obstetric care in Brazil.

Our study showed a decrease in the number of women who had access to adequate antenatal care during the COVID-19 pandemic in Florianopolis, a location with broad coverage of a primary care access initiative in Brazil (the Family Health Program).[32] It is estimated that little as 10% decrease in health care access for pregnant women during the COVID-19 pandemic in low-income countries may cause a considerable increase in obstetric complications and maternal deaths, affecting more than one million people worldwide.[19]

Universal and qualitative health care is achievable by providing continuous professional training, compliance with technical standards, and adequate management of available health resources, prioritizing vulnerable women.[13] Access to qualified antenatal care should be favored, despite challenges of lack of resources and the pandemic pressure over the already weakened Brazilian health system.[20]

Conclusion

In a sample of pregnant women from a teaching hospital in Florianópolis during the COVID-19 pandemic, antenatal care was considered adequate for 35.8%, intermediate for 46.8%, and inadequate for 17.4% of the public. There were significant differences on adequacy of antenatal care regarding skin color: white and Asian women had a higher proportion of adequate antenatal care, while black and brown-skinned women had higher proportions of intermediate antenatal care ($p = 0.001$). As for parity, the majority of both primiparous and multiparous women had intermediate antenatal care, though a higher number of multiparous women had inadequate care ($p = 0.037$). Women with foreign nationality had inadequate antenatal care more frequently ($p = 0.044$). The following variables were significantly associated with inadequate antenatal care: black or brown skin color (odds ratio [OR] 2.99 (95% confidence interval [CI] 1.49–6.00), difficulty in scheduling appointments (OR 2, 87 (CI 1.18–6.99), and virtual consultations (OR 3.08- CI 1.28–7.40). The increase of at least 1 appointment in the total number of antenatal consultations increased the chance of adequate antenatal care by 34% (OR 0.66; 95% CI: 0.55–0.79), and each delay in one week before the beginning of antenatal follow-up increased the chance of inadequate prenatal care by 1.17 times (95% CI: 1.06–1.29). Only 4.4% of women consistently practiced social isolation during pregnancy, and 31 women were diagnosed with COVID-19 during pregnancy. None of those variables were associated with the adequacy of antenatal care.

Contributors
Margot Marie Martins worked on study conceptualization, design, data collection, data analysis, drafted, critically reviewed, and revised the manuscript as well as approved its final version as submitted. Roxana Knobel worked on study conceptualization, design, data collection, data analysis, drafted, critically reviewed, and revised the manuscript as well as approved its final version as submitted. Victor Nandi worked on study conceptualization, design, data collection, critically reviewed and revised the manuscript, and approved finalist final version as submitted. Jessica G Pereira worked on study conceptualization, design, data collection, critically reviewed and revised the manuscript, and approved its final version as submitted. Alberto Trapani Junior worked on analysis and interpretation of data, as well as in writing the manuscript, critical review of the intellectual content, and final approval of the version to be published. Carla Betina Andreucci worked on analysis and interpretation of data, as well as in writing the manuscript, critical review of the intellectual content, and final approval of the version to be published.

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

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Deficiency and Insufficiency of Vitamin D in Women of Childbearing Age: A Systematic Review and Meta-analysis

Deficiência e insuficiência de vitamina D em mulheres na idade reprodutiva: Uma revisão sistemática e meta-análise

Rosa Camila Lucchetta[1] Isabele Held Lemos[1] Ana Luísa Rodriguez Gini[1]
Sophia de Andrade Cavicchioli[2] Marcela Forgerini[1] Fabiana Rossi Varallo[3]
Mariane Nunes de Nadai[4] Fernando Fernandez-Llimos[5] Patricia de Carvalho Mastroianni[1]

[1] Department of Drugs and Medicines, School of Pharmaceutical Sciences, Universidade Estadual de São Paulo, São Paulo, SP, Brazil
[2] Universidade de Araraquara, Araraquara, São Paulo, SP, Brazil
[3] Department of Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences of Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, SP, Brazil
[4] Department of Dentistry, Pediatric Dentistry and Public Health, Bauru School of Dentistry, Universidade de São Paulo, Bauru, SP, Brazil
[5] Department of Drug Sciences, Laboratory of Pharmacology, Faculty of Pharmacy, Universidade do Porto, Porto, Portugal

Address for correspondence Patricia de Carvalho Mastroianni, PhD, Department of Drugs and Medicines, School of Pharmaceutical Sciences, São Paulo State University (UNESP) Highway Jaú, Km 01 s/n, 14800-901, Campus Vile, Araraquara, SP, Brazil (e-mail: patricia.mastroianni@unesp.br).

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Abstract

Objective To estimate the prevalence of inadequate vitamin D level and its associated factors for women of childbearing age in Brazil.

Methods A systematic review was conducted (last updated May 2020). Meta-analyses were performed using the inverse-variance for fixed models with summary proportion calculation by Freeman-Tukey double arcsine. Reporting and methodological quality were assessed using the Joanna Briggs Institute tool for prevalence studies.

Results Our review identified 31 studies, comprising 4,006 participants. All the studies had at least one weakness, mainly due to the use of convenience sampling and small sample size. The overall prevalence of vitamin D deficiency, insufficiency, and both deficiency and insufficiency were 35% (confidence interval, 95%CI: 34–37%), 42% (95%CI: 41–44%), and 72% (95%CI: 71–74%), respectively.

Conclusion Although the magnitude of the prevalence of inadequate levels of vitamin D is uncertain, the evidence suggests that presence of vitamin D deficiency or insufficiency in women of reproductive age can cause moderate to severe problems.

Keywords
- cholecalciferol
- vitamin D deficiency
- nutritional epidemiology
- maternal nutrition
- women's health

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Resumo

Objetivo Estimar a prevalência de níveis inadequados de vitamina D e seus fatores associados para mulheres em idade fértil no Brasil.

Métodos Uma revisão sistemática foi realizada (última atualização em maio de 2020). As meta-análises foram realizadas usando o inverso da variância para o modelo fixo com cálculo de proporção sumarizada por transformação arco-seno duplo de Freeman-Tukey. A qualidade metodológica e de reporte foi avaliada usando a ferramenta do Joanna Briggs Institute para estudos de prevalência.

Resultados Nossa revisão identificou 31 estudos, compreendendo 4.006 participantes. Todos os estudos apresentaram pelo menos uma limitação, principalmente devido ao uso de amostra de conveniência e tamanho amostral pequeno. As prevalências gerais de deficiência, insuficiência e deficiência de vitamina D foram 35% (intervalo de confiança, IC 95%: 34–37%), 42% (IC 95%: 41–44%) e 72% (IC 95%: 71–74%), respectivamente.

Conclusão Embora a magnitude da prevalência de níveis inadequados de vitamina D seja incerta, a evidência sugere que presença de deficiência ou insuficiência de vitamina D em mulheres em idade reprodutiva pode causar problemas moderados a graves.

Palavras-chave

- colecalciferol
- deficiência de vitamina D
- epidemiologia nutricional
- nutrição materna
- saúde da mulher

Introduction

The deficiency and insufficiency of 25-hydroxyvitamin D, also known as 25(OH)D or vitamin D, is a worldwide issue: less than 50% of the world population has an adequate level of vitamin D, but in older people, pregnant women, and non-Western immigrants the proportion is smaller.[1] In pregnant women, for instance, the prevalence of insufficiency (25(OH) D < 50 nmol/L) and deficiency (25(OH)D < 25 nmol/L) ranged from 46% to 87% and 9% to 79%, respectively.[2] Even in warmer countries, such as Brazil, there is an alarming prevalence of vitamin D deficiency (28%) and insufficiency (45%), reaching 85% in pregnant women.[3,4]

Recent studies suggested that vitamin D homeostasis may be important for several nonskeletal outcomes, including cardiovascular and respiratory diseases, neuromuscular function, psoriasis, falls, obesity, type 2 diabetes mellitus, multiple sclerosis, colorectal cancer, and coronavirus disease 19 (COVID-19).[5–12] Vitamin D deficiency also causes a series of poor gestational outcomes,[13] increasing the risk of pre-eclampsia and gestational diabetes mellitus, as well as the production of maternal inflammatory cytokines,[13,14] insulin resistance,[13,15] and postpartum depression.[13,16]

In Brazil, there is a great variability in studies assessing insufficiency and deficiency of vitamin D in women of childbearing age (12–68%),[17–19] but there is also a lack of evidence that systematically summarizes their prevalence. A systematic review (2019) evaluated the deficiency and insufficiency of vitamin D in Brazil, with no specific analysis for women of childbearing age.[4] The present systematic review aimed to identify the prevalence and factors associated with inadequate levels of vitamin D in women of childbearing age in Brazil.

Methods

Study Design, Protocol, and Registration

A systematic review was performed in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group,[20] and Joanna Briggs Institute recommendations,[21] and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[22] The protocol of this review is available at Center for Open Science[23] and PROSPERO (CRD42020221605). This study is part of a larger project that evaluated vitamins A, B, C, D, and E, calcium, iodine, iron, and zinc deficiencies in women of childbearing age in Brazil.

Information Sources, Search Strategy, and Eligibility Criteria

Electronic searches were conducted in the following databases: PubMed, Scopus, LILACS, World Health Organization (WHO), and CAPES' dissertations and theses (gray literature). The selection of these sources ensured including EMBASE, Medline, open access sources, scientific websites, and gray literature,[24] through a predefined search strategy (available in the protocol)[23] from their inception to May 2020. An additional manual search was performed using reference lists of reviews and included studies.

Studies that fulfilled the following criteria according to the CoCoPop acronym were included[25]: i) Condition: vitamin D deficiency or insufficiency; ii) Context: Brazil, without restriction of setting; iii) Population: women of childbearing age (15–49 years old) without any restriction of diseases or physiological status (e.g., nonpregnant, pregnant, postpartum). Data from studies that reported the deficiencies of interest, using a different population classification (e.g., premenopausal women), or different laboratory parameters were separated for appropriate subgroup analyses. All types of articles were included, except for reviews, letters, comments, case reports, and case series. No language restriction was applied.

Study Selection and Data Extraction

Two researchers screened the titles and abstracts and evaluated the full-text articles independently. Discrepancies were

solved in consensus meetings using another researcher as a referee.

Five researchers independently extracted the following data:

(i) Study characteristics (e.g., type of study, analysis period, state, region, funding, micronutrient assessed, and sampling method);
(ii) Participant characteristics (e.g., pregnant women, ethnicity, comorbidities, drug therapy or supplement in use, body mass index, age, education, per capita income);
(iii) Prevalence estimate, according to cutoff values used (n/N [%]) to total population and subgroups, when the information was available. When the studies reported vitamin D deficiency and insufficiency separately, we deduced the estimates considering the sum of participants.

Synthesis of Results

Although predefined cutoffs for the assessment of deficiencies and insufficiencies of vitamin D were not considered inclusion criteria in the present review, only studies that considered identical cutoffs were grouped.

The data synthesis was primarily done by meta-analysis. Transitivity assessment was performed by comparing the CoCoPop acronym for each study.[25] Once important discrepancies were identified, sensitivity analyses with the exclusion of the study in question were performed (i.e., leave-one-out method). Proportion meta-analyses were conducted in the RStudio IDE (RStudio, PBC. Boston, MA, USA) software, version 3.6.3, 1.2.5033,[26] using the READR (RStudio, PBC.)[27] and META packages (RStudio, PBC.).[28]

In the base-case, direct proportion meta-analyses were conducted using the inverse variance method.[28] To calculate the weighted summary proportion, the Freeman-Tukey double arcsine (PFT) was considered in the fixed effects model.[22,28] Although high heterogeneity is expected and, therefore, a random effects model could be considered appropriate, a fixed effects model is preferred for the assessment of prevalence, because otherwise the weighting will not properly consider the weight of the studies.[29] The result of the meta-analysis was given by the proportion combined with 95% confidence interval (95% CI), as well as the list of proportions (presented as a percentages), with their respective 95%CIs found in the individual studies. A Higgins inconsistency test (I^2) with an estimator for tau^2 was considered using the DerSimonian-Laird method.

Cumulative meta-analyses were also performed to assess changes and trends over time, and to highlight emerging or decreasing deficiency or insufficiency. Potential publication bias was assessed using rank tests with at least ten studies by meta-analysis.[28]

Sensitivity analyses were performed by the leave-one-out method. Subgroup and meta-regression analyses, considering the publication year, state and region of Brazil, comorbidities, age, or status (i.e., not pregnant, pregnant, postpartum) were planned for meta-analyses with at least ten studies. Alternative statistical methods were also conducted to validate the conclusions (i.e., GLMM, Logit transformation, random effects, and Hartung and Knapp for random models).

Methodological Quality in Individual Studies

An assessment of methodological and reporting quality based on the JBI Critical Appraisal Checklist for studies reporting prevalence data was conducted.[30,31] Two reviewers performed the assessment, independently. In the absence of consensus, points of disagreement were resolved by a third investigator.

Data Sharing and Data Accessibility

The data that support the findings of this study are openly available in OSF at http:doi.org/10.17605/OSF.IO/J9QMH.[23]

Results

Our systematic review identified 1,977 records in the electronic databases after duplicate removal (PubMed, LILACS, and Scopus) and 91 additional records identified through other sources (manual search, WHO, and CAPES' dissertations and theses databases). After selection process, 31 studies were included, published between 2008 and 2020, reporting deficiency or insufficiency of vitamin D. The list of included and excluded studies, as well as a PRISMA flowchart, are available in the OSF.[23] Of the 31 studies selected, 23 were cross-sectional, 4 prospective, 2 retrospective cohorts, and 2 were case-control studies. The studies were conducted between 1995 and 2017 (six studies did not report inclusion period), in cities in the Southeast ($n = 18$), South ($n = 7$), Northeast ($n = 5$), and Center-west ($n = 2$) Brazilian regions, with women selected mainly from outpatient care ($n = 20$). Araújo et al.,[32] Queiroz,[33] Queiroz et al.,[34] de Oliveira et al.,[35] and dos Santos et al.[36] used a random probabilistic sampling, while Martins et al.[37] used convenience sampling (►**Chart 1**).[3,17–19,32–68]

Most studies assessed women of childbearing age ($n = 13$), followed by pregnant women ($n = 10$), adolescents ($n = 6$), and postpartum women ($n = 4$). Two studies assessed pregnant and nonpregnant women, concomitantly. Therefore, 4,006 participants were included, mainly women of childbearing age ($n = 1,239$), with a mean age ranged from 13 to 46 years old, and mean body mass index ranged from 22 to 46 kg/m^2. The majority of studies included women with a medical condition (e.g., HIV +, gestational diabetes mellitus, hypertension) or post Roux-en-Y gastric bypass surgery (RYGB, $n = 18$). Although drug therapy use was not reported is most studies, nutrient supplementation ($n = 11$) or no supplementation ($n = 11$) use were reported. The main characteristics of the participants are described in ►**Chart 2**.[3,17–19,32–35,37–66]

In the quality assessment, all studies had at least one 'No' answer, which suggests an overall poor reporting or methodological quality. The main questions with 'No' answers were regarding sample size ($n = 30$) and sampling method ($n = 29$). Questions with 'Yes' answers were about sample frame and valid methods used for the identification of the

Chart 1 Description of the characteristics of the included studies

Study	Inclusion period	State/ region	Setting	Cutoff values	Funding
Cross-sectional studies					
Araújo et al. (2017),[32] Queiroz (2016),[33] and Queiroz et al. (2019)[34]	Jun–Aug 2015	PB/NE	School	< 75 nmol/L	NR
Chrisostomo et al. (2018)[38]	Jan–Mar or Jul–Aug 2016	PR/S	Obstetrical care	< 75 nmol/L 50–75 nmol/L < 50 nmol/L	NR
Duran de Campos et al. (2008)[39]	Oct 1995–Jan 1999	SP/SE	Outpatient	25–50 nmol/L 12.5–25 nmol/L	NR
de Oliveira et al. (2020)[35]	Feb 2013–Nov 2014	DF, RJ, RS, SC/S, SE, CW	School	< 75 nmol/L 50–75 nmol/L < 50 nmol/L	Brazilian Funding Authority for Studies and Projects, and CNPq
Souza et al. (2019)[40]	Jan–Feb 2017	MA/NE	Outpatient	< 75 nmol/L 50–75 nmol/L < 50 nmol/L	NR
Delmonico et al. (2018)[41]	2008–2016	RJ/SE	Outpatient	< 75 nmol/L	CAPES
Prado et al. (2015)[3]	Dec 2011–Nov 2012	MG/SE	Obstetrical care	< 50 nmol/L	FAPEMIG
Ferreira et al. (2015)[42]	NR	RJ/SE	Outpatient	< 50 nmol/L	FAPERJ
Flauzino et al. (2017)[43]	Jul 2010–Mar 2011	PR/S	Outpatient	< 75 nmol/L	CAPES, CNPq, and UEL
Lopes et al. (2015)[44]	2011–2013	SP/SE	Outpatient	< 75 nmol/L	FAPESP
Lopes et al. (2016)[45]	Jan–May 2012	DF/CW	Outpatient	< 75 nmol/L 50–75 nmol/L < 50 nmol/L	NR
Machado et al. (2013)[46]	May 2010–Dec 2011	SP/SE	University	< 75 nmol/L 50–80 nmol/L < 50 nmol/L	UNIFESP
Martins et al. (2018)[37]	Oct–Dec 2016	CE/NE	Obstetrical care	< 75 nmol/L 50–75 nmol/L < 50 nmol/L	NR
Mendes et al. (2019)[47]	NR	NR	NR	25–50 nmol/L	CNPq
Pena et al. (2015)[48]	Nov 2012–Mar 2013	PE/NE	Obstetrical care	< 75 nmol/L 50–75 nmol/L < 50 nmol/L	CNPq
Pereira-Santos (2014)[49] and Pereira-Santos et al. (2018)[50]	NR	BA/NE	Obstetrical care	< 75 nmol/L 50–75 nmol/L < 50 nmol/L	CNPq and CAPES
Peters et al. (2009)[51]	Apr–May 2006	SP/SE	Outpatient/ Rural	25–75 nmol/L	FAPESP
Santos et al. (2013)[52]	Apr 2008–Sep 2010	PR/S	School	< 75 nmol/L 50–75 nmol/L < 50 nmol/L	CNPq
Santos et al. (2017)[53]	NR	RS/S	Outpatient	< 75 nmol/L 50–75 nmol/L < 50 nmol/L	CNPq and CAPES
Santos et al. (2019)[54]	2005–2012	RS/S	NR	< 50 nmol/L	CNPq, FAPERGS, and CAPES
Schtscherbyna et al. (2016)[55]	Apr 2008–May 2011	RJ/SE	Outpatient	< 75 nmol/L	CAPES, FAPERJ, and CNPq
Shinjo et al. (2011)[56]	NR	SP/SE	Outpatient	< 50 nmol/L	CNPq and Federico Foundation
Simões et al. (2016)[57]	Apr 2013–Jun 2013	SP/SE	Obstetrical care		FAPESP and CAPES

Chart 1 (*Continued*)

Study	Inclusion period	State/ region	Setting	Cutoff values	Funding
				< 75 nmol/L 50–75 nmol/L < 50 nmol/L	
Case-control					
Dutra et al. (2019)[58]	Sep 2016–Dec 2017	SP/SE	Obstetrical care	< 75 nmol/L 50–75 nmol/L < 50 nmol/L	CAPES, CNPq, and FAPESP
Menegati et al. (2016)[17]	2006–2010	RJ/SE	Outpatient	< 75 nmol/L 50–75 nmol/L < 50 nmol/L	CAPES
Prospective cohorts					
Benaim et al. (2019)[59]	Nov 2009–Oct 2011	RJ/SE	Outpatient	< 75 nmol/L 50–75 nmol/L < 50 nmol/L	CNPq and FAPERJ
Lepsch et al. (2017)[60] and Figueiredo et al. (2017, 2018, 2020)[61–63]	Nov 2009–Oct 2011	RJ/SE	Obstetrical care	< 75 nmol/L 50–75 nmol/L < 50 nmol/L	CNPq and FAPERJ
Medeiros et al. (2016)[64]	Mar 2010–Jul 2013	RJ/SE	Outpatient	< 75 nmol/L 50–75 nmol/L < 50 nmol/L	NR
Weinert et al. (2014, 2016)[65,66]	Nov 2009–May 2012	RS/S	Obstetrical care	< 75 nmol/L 50–75 nmol/L < 50 nmol/L	Hospital de Clínicas de Porto Alegre
Retrospective studies					
Cruz et al. (2018, 2020)[18,19,67]	Jan 2011–Jul 2015	RJ/SE	Outpatient	< 75 nmol/L 50–75 nmol/L < 50 nmol/L	FAPERJ
Rosa et al. (2013)[68]	NR	RJ/SE	NR	38–225 nmol/L	NR

Abbreviations: NR, not reported; SD, standard deviation.
State/Region: BA, Bahia; CE, Ceará; CW, Center-west; DF, Distrito Federal; MA, Maranhão; MG, Minas Gerais; NE, Northeast; PB, Paraíba; PE, Pernambuco; PR, Paraná; RJ, Rio de Janeiro; RS, Rio Grande do Sul; S, South; SC, Santa Catarina; SE, Southeast; SP, São Paulo. **Funding/Institutions**: CAPES, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; CNPq, Conselho Nacional de Desenvolvimento Científico e Tecnológico; FAPEMIG, Fundação de Amparo à Pesquisa do Estado de Minas Gerais; FAPERGS, Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul; FAPERJ, Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro; FAPESP, Fundação de Amparo à Pesquisa do Estado de São Paulo; UEL, Universidade Estadual de Londrina; UNIFESP, Universidade Federal de São Paulo.

deficiencies. The detailed assessment of the methodological quality of the included studies is presented in **Chart 3**.[3,17–19,32–35,37–66]

Most studies ($n = 26$) used common cutoff values (vitamin D deficiency: < 50 nmol/L or < 20 ng/mL; vitamin D insufficiency: 50–75 nmol/L or 20–30 ng/mL; and vitamin D deficiency or insufficiency: < 75 nmol/L or 30 ng/mL) (**Chart 1**) and were included in meta-analyses.

The prevalence of vitamin D deficiency ranged from 3 to 85%, insufficiency from 15% to 68%, and deficiency or insufficiency from 34 to 94%. In the meta-analysis for the base-case, an overall prevalence of vitamin D deficiency of 35% (95%CI: 34–37%), insufficiency of 42% (95%CI: 41–44%) (►**Fig. 1**), and deficiency or insufficiency of 72% (95%CI: 71–74%) (►**Appendix A, supplementary material**) were obtained.[23] When the population subgroups were considered, lower and higher prevalence of vitamin D deficiency were identified in pregnant (27%) and postpartum women (48%), respectively; and lower and higher prevalence of vitamin D insufficiency were associated with adolescents (37%) and women of childbearing age (50%) (►**Fig. 1**).

Some studies reported subgroup analyses: higher deficiency or insufficiency prevalence values were found in adolescence (p-value = 0.02),[40] first pregnancy ($p = 0.01$),[40] ≥ 11 years of schooling ($p = 0.03$),[49,50] first gestational trimester ($p = 0.01$),[49,50] face and hands exposed to the sun ($p = 0.01$),[49,50] methods of commuting by motor vehicles ($p = 0.01$),[49,50] and winter ($p < 0.001$).[49,50,60–63] Except for gestational trimester, no meta-analyses for these subgroups were possible due to the small number of studies in each subgroup, or different categorization for the same subgroup. Four studies assessed vitamin D status throughout gestational trimesters, with little variation among trimesters of vitamin D deficiency (15–20%) or insufficiency (34–49%) and wide confidence intervals (►**Fig. 2**).

Five studies assessed vitamin D in women post-RYGB, and two of them analyzed pregnant women after RYGB. No meta-analysis was possible due to the different cutoff values and categories used. The deficiency, insufficiency, and deficiency

Chart 2 Description of the characteristics of the included participants

Study	Main characteristic (N)	Ethnicity	Comorbidities	Medicine/ supplement	Body mass index, kg/m^2	Mean age, years
Araújo et al. (2017),[32] Queiroz (2016),[33] and Queiroz et al. (2019)[34]	Adolescents (136)	Brown (62%)	NR (Excluded some conditions) [a]	NR/None	Normal weight (72%)	17 (±SD 1) [b]
Benaim et al. (2019)[59]	Pregnant women (181)	Mixed (47%)	NR (Excluded some conditions) [c]	NR/Yes	Median: 24 (IQR 22–27)	Median: 26 (IQR 22–31)
Chrisostomo et al. (2018)[38]	Pregnant women (520)	Euro-descendant (52%)	Preeclampsia; GDM; HIV+	Antiretroviral/ None	Median 31 (IQR: 27; 35)	Median: 30 (IQR: 25–35)
Cruz et al. (2018, 2020)[18,19,67]	Pregnant and nonpregnant women (121)	NR	RYGB (Excluded some conditions) [d]	NR/Yes [e]	43 (±SD 3) to 44 (±SD 6)	30 (±SD 4) to 32 (±SD 4)
Rosa et al. (2013)[68]	Women of childbearing age (56)	NR	RYGB	NR/Yes [f]	46 (±SD 8)	35 (±SD 9)
Duran de Campos et al. (2008)[39]	Women of childbearing age (30)	NR (excluded nonwhite)	RYGB	NR	29 (±SD 2.3) to 47 (±SD 8.6)	46 (±SD 3)
de Oliveira et al. (2020)[35]	Adolescents (100)	Nonwhite (54%)	NR	NR	Normal weight (71%)	15–17 (59%)
Souza et al. (2019)[40]	Pregnant women (71)	Dart (62%)	Healthy	NR/None	NR	26 (±SD 6)
Delmonico et al. (2018)[41]	Women of childbearing age (20)	NR	Malignant breast lesions	NR	NR	37
Prado et al. (2015)[3]	Postpartum women (226)	White (52%)	NR	NR/Yes (97%)	NR	28 (range 20–44)
Dutra et al. (2019)[58]	Postpartum women (126) [g]	NR	Hypertension (23%)	NR/Yes	26 (±SD 6) to 27 (±SD 5)	25 (±SD 7) to 26 (±SD 7)
Ferreira et al. (2015)[42]	Women of childbearing age (73)	White (68%)	NR (Excluded some conditions) [h]	NR/None	26 (±SD 1)	32 (±SD 1)
Flauzino et al. (2017)[43]	Women of childbearing age (205)	Caucasian (71–78%) [b]	HIV+	Antiretroviral/ None	25 (±SD 0) to 26 (±SD 0) [b]	40 (±SD 1) [b]
Lepsch et al. (2017)[60] and Figueiredo et al. (2017, 2018, 2020)[61–63]	Pregnant women (199)	Mixed (46%)	NR (Excluded some conditions)	None/None	< 25 (60%)	27 (±SD 6)
Lopes et al. (2015)[44]	Adolescents (97)	NR	NR	NR	26 (±SD 9)	16 (±SD 1)
Lopes et al. (2016)[45]	Women of childbearing age (369)	NR	Infertility and control	NR/None	NR	36 (±SD 4) to 37 (±SD 4)
Machado et al. (2013)[46]	Pregnant women (49)	NR	HIV+	Antiretroviral/ None	Excessive gestational weight (35%)	30 (±SD 7)
Martins et al. (2018)[37]	Postpartum women (225)	Dark (79%)	Urinary tract infection (32%), hypertension (9%), GDM (1%), and bleeding (8%)	NR/Yes (64%)	Overweight or obesity (34%)	26 (±SD 7)
Medeiros et al. (2016)[64]	Pregnant women (46)	NR	RYGB	NR/Yes [i]	28 to 44 (±SD 6)	31 (±SD 5)
Mendes et al. (2019)[47]	Women of childbearing age (79)	White (63%)	NR	NR/None	24 (±SD 5)	Median: 27 (IQR 24–31)
Menegati et al. (2016)[17]	Women of childbearing age (58)	NR	RYGB and control (obesity) (Excluded some conditions) [j]	NR/Yes (calcium)	35 (CI 95% 33–37) to 52 (CI 95% 40–73)	39 (CI 95% 36–42) to 40 (CI 95% 38–42)
Pena et al. (2015)[48]		Nonwhite (82%)		NR	IQR: 21–37	IQR: 19–33

Chart 2 (*Continued*)

Study	Main characteristic (N)	Ethnicity	Comorbidities	Medicine/ supplement	Body mass index, kg/m^2	Mean age, years
	Pregnant and nonpregnant (179)		Preeclampsia and gestational obesity			
Pereira-Santos (2014)[49] and Pereira-Santos et al. (2018)[50]	Pregnant women (190)	Nonblack (68%)	NR (Excluded some conditions) [k]	NR/Yes (5%)	Overweight (43%)	18–29 (63%)
Peters et al. (2009)[51]	Adolescents (71)	NR (excluded nonwhite)	NR (Excluded some conditions) [l]	NR	22 (±SD 0)	18 (±SD 1)
Santos et al. (2013)[52]	Adolescents (198)	NR	Healthy	NR/None	Normal weight (76%)	13 (±SD 2)
Santos et al. (2017)[53]	Women of childbearing age (102)	White (94%)	Polycystic ovary syndrome and controls	NR	27 (±SD 6) to 30 (±SD 6)	23 (±SD 7) to 25 (±SD 8)
Santos et al. (2019)[54]	Women of childbearing age (61)	Caucasian (80%)	Healthy	NR/Yes (calcium and vitamin D)	29 (±SD 8)	37 (±SD 11)
Schtscherbyna et al. (2016)[55]	Adolescents and young adults (35)	White (35%) [b]	HIV+	Antiretroviral/ NR	Normal (62%) [b]	Around 18 (±SD 2) [b]
Shinjo et al. (2011)[56]	Women of childbearing age (20)	White (75%)	Juvenile onset of systemic sclerosis and controls	NR	NR	21 (±SD 2) to 21 (±SD 2)
Simões et al. (2016)[57]	Postpartum women (99)	Blacks or mulatto (58%)	NR (Excluded some conditions) [m]	NR/Yes (9%)	Overweight or obese (69%)	26 (±SD 5)
Weinert et al. (2014, 2016)[65,66]	Pregnant women (184)	White (74%)	GDM (100%); Hypertension (22%)	NR/None	27 (±SD 5) to 30 (±SD 7)	32 (±SD 6)

Abbreviations: CI, confidence interval; GDM, gestational diabetes mellitus; HIV, human immunodeficiency virus; IQR, interquartile range; NR, not reported; RYGB, Roux-en-Y gastric bypass; SD, standard deviation. Notes: **A -** Pregnant, breastfed, carriers of chronic diseases (diabetes, hypertension, chronic kidney disease), chronic alcoholics, and chronic smokers were excluded. **B -** Both genders. **C -** Without any known infectious or chronic noncommunicable diseases (except obesity). **D -** Disabsorptive and restrictive surgeries prior to RYGB, disabsorptive syndromes, cancer and liver and/or kidney diseases (except hepatic steatosis), hypolipidemic or hypoglycemic use, active thyroid disorders, metabolic bone diseases, chronic use of diuretics or calcium channel blockers, female smokers, and presence of gestational diabetes were excluded. **E -** 850 mg of calcium carbonate and 600 IU of vitamin D3; when inadequacy of vitamin D was found in the preoperative period, all participants consumed 1500 IU of vitamin D; in addition, in case of pregnancy after RYGB, supplementation was adjusted from 1500 to 2000 IU vitamin D and 1200 mg after the immediate confirmation. **F -** Daily dietary supplementation of 500 mg of calcium carbonate and 400UI of vitamin D for an undetermined length of time. **G –** Mothers' full-term births, and mothers' preterm births. **H -** Women with smoking; eating disorders; major depression; any metabolic disease, such as diabetes mellitus or hypothyroidism; any chronic diseases severely affecting the CV, gastrointestinal, and renal systems; and pregnancy or lactation were excluded; **I -** 850 mg of calcium carbonate and 600 IU of vitamin D3. **J -** Women with malignant tumors or infectious diseases; were postmenopausal; were taking drugs that affect bone metabolism (bisphosphonates, estrogens, anticonvulsants, glucocorticoids); were pregnant; had malabsorption syndrome, primary hyperparathyroidism, renal, or liver failure; or weighed $>$ 120 kg were excluded. **K -** Women with multiple pregnancies, preeclampsia, kidney problems, HIV and women who had not fasted for the blood collection were excluded. **L -** Chronic illness, pregnancy, and obesity were excluded. **M -** Alcohol use, hyperglycemia, hypertension, preterm/post-term deliveries and adolescent pregnancy, were excluded.

or insufficiency ranged from 12 to 39%, 41 to 54%, and 60 to 91%, respectively.

Cumulative meta-analyses were performed considering the year of publication, showing a trend toward a lower prevalence of vitamin D deficiency, and higher prevalence of vitamin D insufficiency and vitamin D deficiency or insufficiency, with a slight join point in 2017 (►**Appendix B, supplementary material**).[23] Meta-regression analyses were conducted for publication year, and a moderator effect was not identified ($p > 0.05$) (►**Appendix C, supplementary material**).[23] Meta-regression or subgroup analyses for other variables were not possible, and neither were cumulative meta-analyses regarding gestational trimesters, because the minimum number of studies required was not met.

Sensitivity analyses by the leave-one-out method were not able to reduce heterogeneity (93–96%) and the overall prevalence ranged from 32 to 37% for vitamin D deficiency, 41 to 44% for vitamin D insufficiency, and 71 to 73% for vitamin D deficiency or insufficiency (►**Appendix D, supplementary material**).[23] The study with more influence in the variations was Prado et al.,[3] conducted in Minas Gerais, in 2012, with postpartum women taking supplements (97%). Sensitivity analyses with alternative statistical methods identified values of prevalence ranging from 35 to 37% for vitamin D deficiency, 41 to 43% for vitamin D insufficiency, and 69 to 72% for vitamin D deficiency or insufficiency (►**Appendix A, supplementary material**).[23] It was not possible to conduct sensitivity analyses regarding gestational trimesters.

Potential publication biases were not identified in vitamin D deficiency ($p = 0.84$), insufficiency ($p = 0.60$), or deficiency or insufficiency ($p = 0.54$) in statistical or visual analyses (►**Appendix E, supplementary material**).[23] It was also not

Chart 3 Methodological and reporting quality assessment, considering the Joanna Briggs Institute tool for prevalence studies

	Question								
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Araújo et al. (2017),[32] Queiroz (2016),[33] and Queiroz et al. (2019)[34]	Yes	Yes	No[c]	Yes	Yes	N/A	Yes	Yes	No[h]
Benaim et al. (2019)[59]	Yes	No[a]	No[d]	No[e]	Unclear	N/A	Yes	Yes	Unclear[i]
Chrisostomo et al. (2018)[38]	Yes	No[a]	No[d]	Yes	Yes	N/A	Yes	Yes	Yes[j]
Cruz et al. (2018, 2020)[18,19,67]	Yes	No[a]	No[d]	No[e]	Unclear	N/A	Yes	No[g]	No[h]
Rosa et al. (2013)[68]	Yes	No[a]	No[d]	No[e]	Unclear	N/A	No[f]	No[g]	No[h]
Duran de Campos et al. (2008)[39]	Yes	No[a]	No[d]	No[e]	Unclear	N/A	No[f]	Yes	No[h]
de Oliveira et al. (2020)[35]	Yes	Yes	Yes	No[e]	Unclear	N/A	Yes	Yes	No[h]
Souza et al. (2019)[40]	Yes	No[a]	No[d]	No[e]	Unclear	N/A	Yes	Yes	No[h]
Delmonico et al. (2018)[41]	Yes	No[a]	No[c]	No[e]	Unclear	N/A	Yes	Yes	No[h]
Prado et al. (2015)[3]	Yes	No[a]	No[d]	No[e]	Unclear	N/A	Yes	Yes	Unclear[i]
Dutra et al. (2019)[58]	Yes	No[a]	No[d]	No[e]	Unclear	N/A	Yes	No[g]	No[h]
Ferreira et al. (2015)[42]	Yes	No[a]	No[d]	No[e]	Unclear	N/A	Yes	Yes	No[h]
Flauzino et al. (2017)[43]	Yes	No[a]	No[d]	Yes	Yes	N/A	Yes	No[g]	Unclear[i]
Lepsch et al. (2017)[60] and Figueiredo et al. (2017, 2018, 2020)[61–63]	Yes	No[a]	No[d]	Yes	Yes	N/A	Yes	No[g]	Unclear[i]
Lopes et al. (2015)[44]	Yes	No[a]	No[d]	No[e]	Unclear	N/A	Yes	Yes	No[h]
Lopes et al. (2016)[45]	Yes	No[a]	No[d]	No[e]	Unclear	N/A	Yes	Yes	Yes[j]
Machado et al. (2013)[46]	Yes	No[a]	No[d]	Yes	Yes	N/A	Yes	Yes	No[h]
Martins et al. (2018)[37]	Yes	No[b]	No[d]	Yes	Yes	N/A	Yes	Yes	Unclear[i]
Medeiros et al. (2016)[64]	Yes	No[a]	No[d]	No[e]	Unclear	N/A	Yes	Yes	No[h]
Mendes et al. (2019)[47]	Yes	No[a]	No[d]	No[e]	Unclear	N/A	No[f]	Yes	No[h]
Menegati et al. (2016)[17]	Yes	No[a]	No[d]	No[e]	Unclear	N/A	Yes	Yes	No[h]
Pena et al. (2015)[48]	Yes	No[a]	No[d]	Yes	Yes	N/A	Yes	Yes	No[h]
Pereira-Santos (2014)[49] and Pereira-Santos et al. (2018)[50]	Yes	No[a]	No[d]	No[e]	Unclear	N/A	Yes	Yes	Unclear[i]
Peters et al. (2009)[51]	Yes	No[a]	No[d]	No[e]	Unclear	N/A	No[f]	No[g]	No[h]
Santos et al. (2013)[52]	Yes	No[a]	No[c]	No[e]	Unclear	N/A	Yes	No[g]	Unclear[i]
Santos et al. (2017)[53]	Yes	No[a]	No[d]	Yes	Yes	N/A	Yes	No[g]	No[h]
Santos et al. (2019)[54]	Yes	No[a]	No[d]	Yes	Yes	N/A	Yes	Yes	No[h]
Schtscherbyna et al. (2016)[55]	Yes	No[a]	No[d]	Yes	Yes	N/A	Yes	Yes	No[h]
Shinjo et al. (2011)[56]	Yes	No[a]	No[d]	No[e]	Unclear	N/A	Yes	Yes	No[h]
Simões et al. (2016)[57]	Yes	No[a]	No[d]	No[e]	Unclear	N/A	Yes	Yes	No[h]
Weinert et al. (2014, 2016)[65,66]	Yes	No[a]	No[d]	Yes	Yes	N/A	Yes	Yes	Unclear[i]

Abbreviation: N/A, not applicable. Notes: **1.** Was the sample frame appropriate to address the target population? **2.** Were study participants recruited in an appropriate way? **3.** Was the sample size adequate? **4.** Were the study's subjects and setting described in detail? **5.** Was data analysis conducted with sufficient coverage of the identified sample? **6.** Were valid methods used for the identification of the condition? **7.** Was the condition measured in a standard, reliable way for all participants? **8.** Was there appropriate statistical analysis? **9.** Was the response rate adequate, and if not, was the low response rate managed appropriately? **a** – Not reported, convenience sampling was considered. **b** – Reported convenience sampling. **c** – The target sample size reported was low. **d** – A target sample size was not reported. **e** – Did not report at least two of the following information: ethnicity, comorbidities, medicines/supplementation, body mass index, age, educational level, or income per capita. **f** – Vitamin D cutoff different than usual. **g** – Not reported numerator (n) or denominator (N) of prevalence). **h** - Not reported numerator (n) or denominator (N) of prevalence. **i** – The studies presented a response rate below 176 participants to vitamin D assessment. **j** – The studies presented a response rate between 176 and 345 (vitamin D), therefore is unclear if the sample size is appropriate, since a reliable estimate was not possible. **k** – The studies presented a response rate higher than 345, therefore, high confidence about good response was achieved.

possible to conduct statistical and visual analyses of publication bias for meta-analysis along gestational trimesters.

Four studies reported different cutoff values and were not included in any meta-analysis. They identified prevalence values ranging from 11% to 75%: Duran de Campos et al.[39] identified serum 25(OH)D levels between 12.5 and 25 nmol/L (5–10 ng/mL) in 50% of the participants, and between 25 and 50 nmol/L (10–20 ng/mL) in 40% of the participants; Mendes et al.[47] identified 11% of the participants with values between 25 and 50 nmol/L; Peters et al.[51] identified 61% of the participants with values between 25 and 75 nmol/L (11–30 ng/mL); and Rosa et al.[68] identified 55% and 75% of the participants with values between 15 and 90 ng/mL in pre- and postoperative RYGB, respectively.

Discussion

In this systematic review, 31 studies assessing prevalence of inadequate levels of vitamin D in women of childbearing age were found, reporting vitamin D deficiency (3–85%), insufficiency (15–68%), and deficiency or insufficiency (34–94%), with a mean prevalence of 35%, 42%, and 72% identified through the meta-analysis, respectively.

Redundant evidence of vitamin D levels was identified, especially for women of childbearing age in Brazil, to the detriment of population subgroups such as pregnant women, women who have recently given birth, and adolescents. In 2019, Pereira-Santos et al.[4] identified 72 studies that reported prevalence of vitamin D deficiency (28%) and insufficiency (45%) in the general population, and five studies that reported prevalence of 33% and 49%, respectively, in pregnant women. Although our systematic review identified the double of studies in pregnant women and 22 studies with women of childbearing age, our prevalence is similar to the Pereira-Santos' et al.[4] study, confirming the findings of our cumulative meta-analysis that new studies (published after 2017) had little impact on the prevalence estimates. At the same time, all the included studies showed weaknesses and

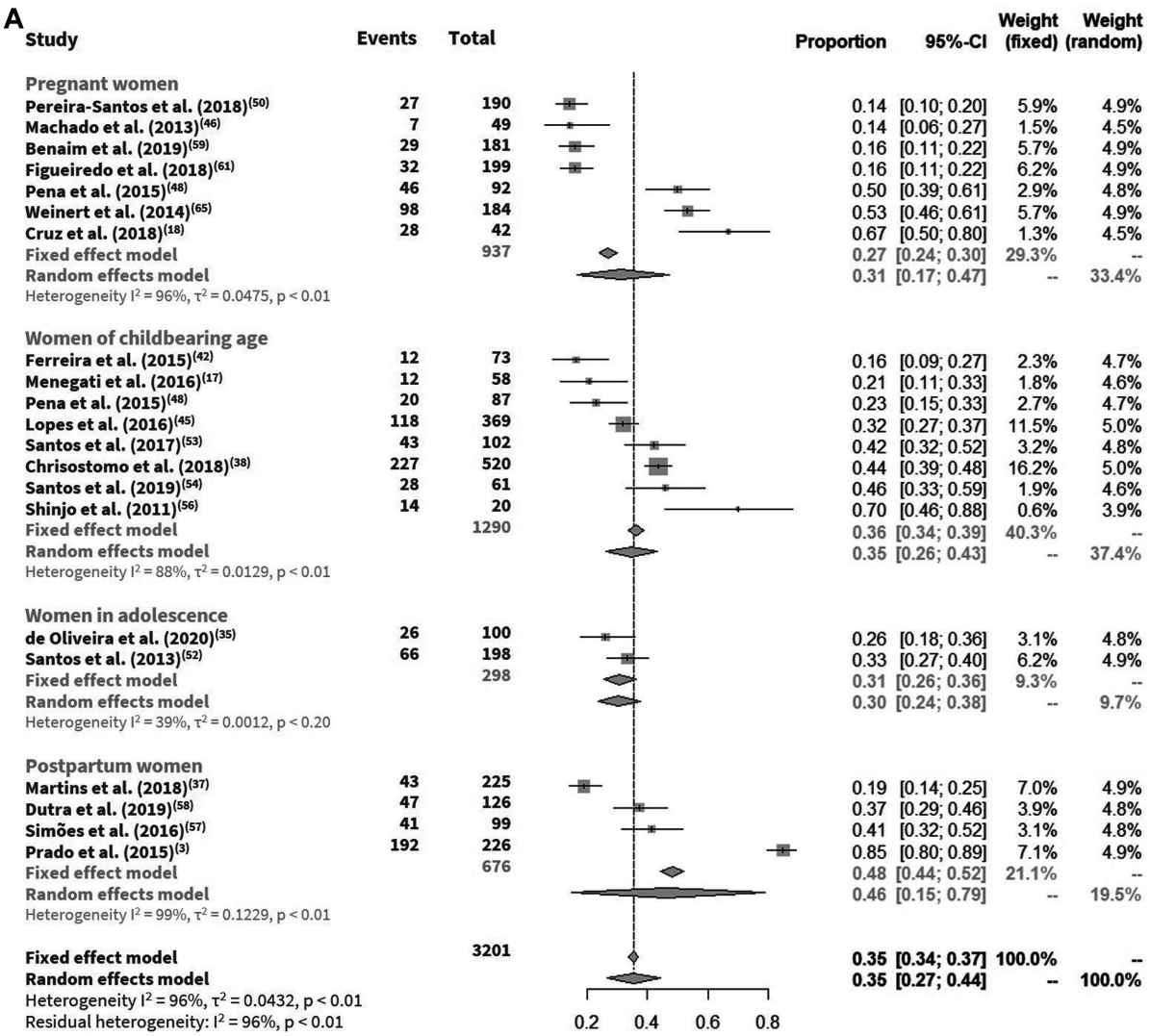

Fig. 1 (A) Vitamin D deficiency in pregnant women, women of childbearing age, women in adolescence, and postpartum women; (B) Vitamin D insufficiency in pregnant women, women of childbearing age, women in adolescence, and postpartum women.

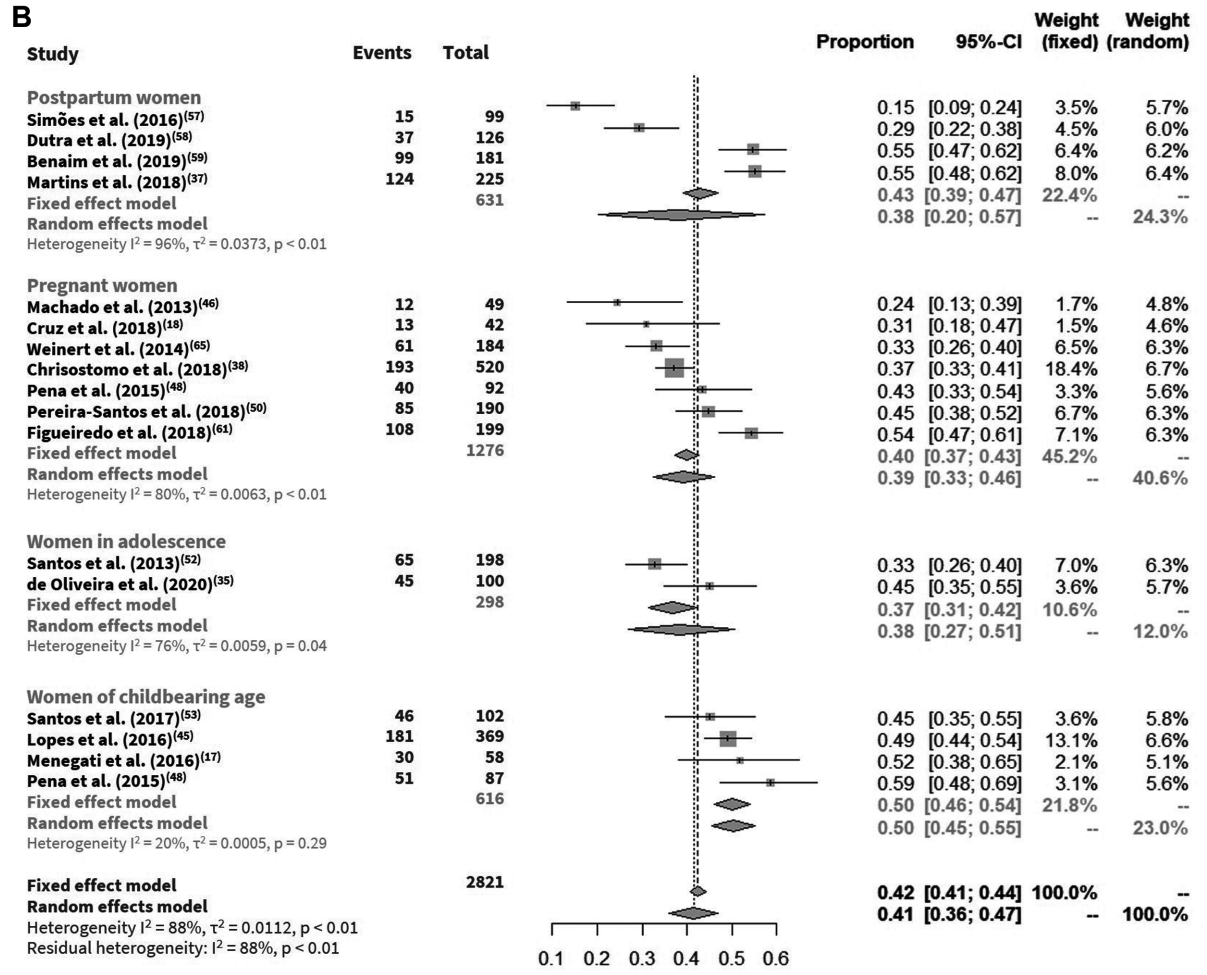

Fig. 1 (*Continued*)

high heterogeneity, which reduced the confidence on the prevalence rates reported.

Although little variation on the estimates has been added in the last years for women of childbearing age, when considering population subgroups (e.g., adolescents, pregnant women, postpartum women) the uncertainty still exists. For instance, when considered vitamin D deficiency in postpartum women (48%, 95% CI 44–52%, I^2 99%), Martins et al.[37] identified prevalence of 19%, whereas Prado et al.[3] described it as 85%. While Martins et al.[37] included 79% of dark-skin women (variable associated with deficiency), 64% using supplement (variable associated with sufficiency), and during spring and summer (variable associated with sufficiency); Prado et al.[3] included 52% of white women (variable associated with sufficiency), 97% using supplement (variable associated with sufficiency), and throughout the year.

Moreover, it was not possible to conduct a robust subgroup analysis to explore the heterogeneity, as well as to identify possible associated factors to deficiency or insufficiency of vitamin D, since most studies did not report the characteristics of the participants, nor population subgroup analysis using common categories. Primary studies should appropriately report the findings according to common subgroups, and minimally, season, skin pigmentation, WHO standardized age group,[69] and supplement use.

In comparison with international data for inadequate vitamin D levels, our prevalence estimates are lower than estimates for women in Iran (44% deficiency),[70] and for women of childbearing age in in Saudi Arabia (77% deficiency or insufficiency),[71] but higher than estimates for adolescent girls in India (26% deficiency).[72] Several factors can explain the differences between the estimates, such as age, latitude, skin pigmentation, dietary habits, fortification of foods with vitamin D, use of vitamin D supplements, sunlight exposure, and cultural factors.[1,73–75] To exemplify, Gomes et al.[76] identified a seriously inadequate intake of vitamin D among Brazilian pregnant women in the primary healthcare network.

It is important to highlight that our systematic review identified several studies evaluating nonpregnant and nonlactating women, which were grouped as women of childbearing age. Notwithstanding, it was noted that many of these women had conditions associated with inadequate levels of vitamin D, such as overweight or obesity,[77–79] gestational diabetes mellitus,[80] preeclampsia,[81,82] cardiovascular disease,[83] breast cancer,[84] polycystic ovarian

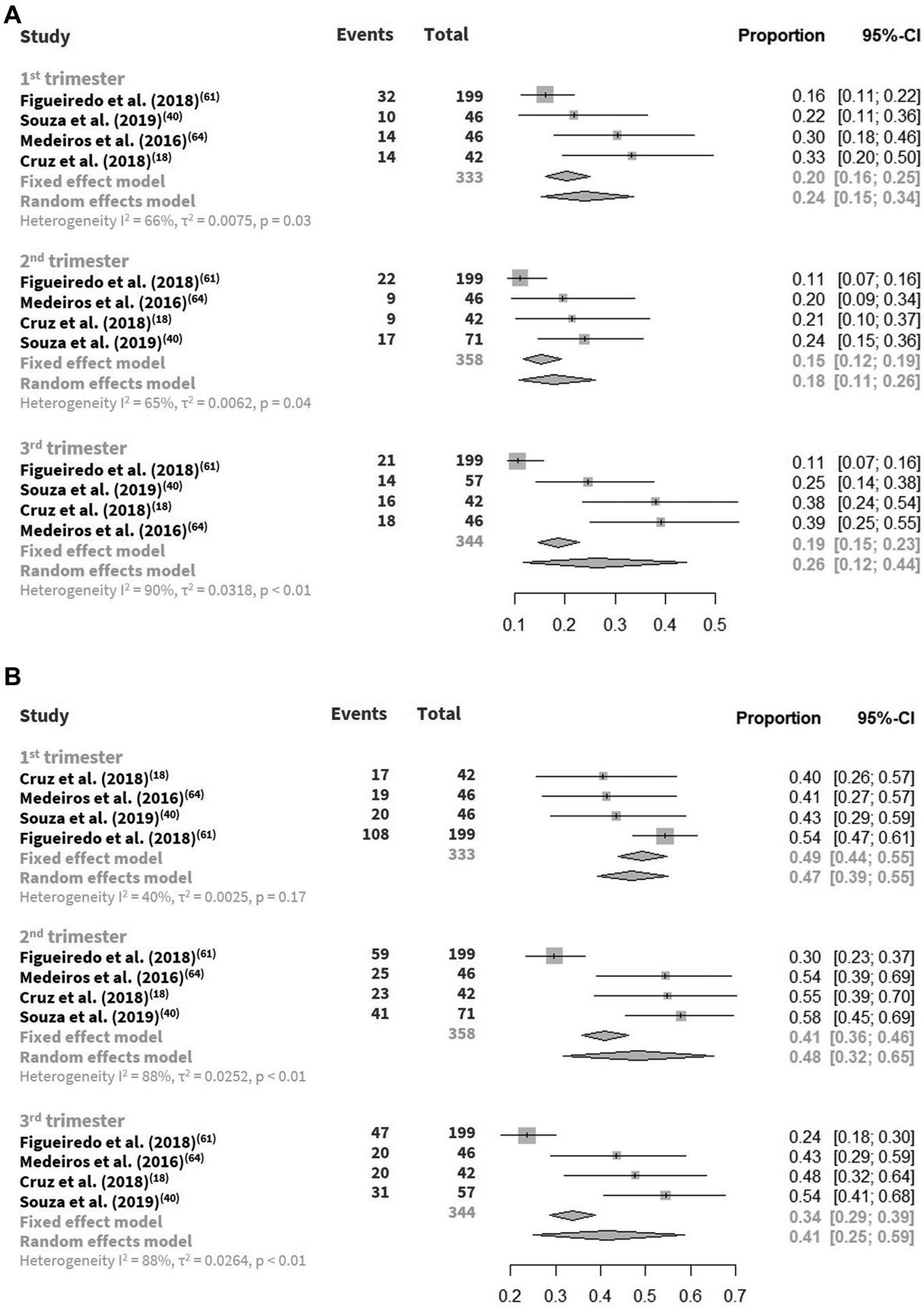

Fig. 2 (A) Vitamin D deficiency along gestational trimesters; (B) Vitamin D insufficiency along gestational trimesters.

syndrome,[85] and infertility,[86] among others, which may overestimate the identified prevalence.

Another important consideration is that despite the variation in cutoff values used by studies to define vitamin D deficiency, most studies included in this meta-analysis considered the threshold recommended by the US Institute of Medicine (< 50 nmol/L of 25 (OH)D) as opposed to the threshold recommended by the Endocrine Society Practice Guidelines (< 75 nmol/L of 25(OH)D). The generally accepted cutoff levels consider the values necessary to ensure optimal effects in the calcium economy and skeletal health,[87] and studies designed to assess the correlation of clinical responses with clinically relevant vitamin D deficiency suggest that depending on the physiological parameters considered (e.g., pregnancy outcomes, cardiometabolic risk) the results may differ and be even greater than those mentioned above,[88–90] resulting in the identification of larger populations with vitamin D deficiency. Although it is not possible to be sure about the magnitude of deficiency/insufficiency of vitamin D in some subgroups among Brazilian women, current evidence suggests that this is a public health problem, given the Institute of Medicine's (US) recommended cutoff values.[91] In this sense, some preventive strategies for adequate vitamin D levels include fish consumption, food fortification,[92] and advice on moderate sunlight exposure.[1,93]

Among the few countries with specific policies, the United Kingdom and Finland stand out with the recommendation of 10 µg of vitamin D daily intake for general population, and the mandatory food fortification programs, respectively.[94] In pregnant women, conflicting evidence suggests the benefit of supplementation, despite the documented negative clinical, humanistic, and economic impact of the deficiency or insufficiency of vitamin D, mainly, during the first trimester of pregnancy.[95] The hesitation about the recommendation of supplement intake may be justified by the limited evidence on the safety of vitamin D supplements, which could explain the reason why WHO does not recommend the supplementation during pregnancy as part of routine antenatal care.[96] Conversely to WHO, the Brazilian consensus recommends supplementation in pregnant women at risk of deficiency.[11] However, the Brazilian consensus does not recommend generalized vitamin D supplementation for the entire population, while it recommends the assessment of serum levels in obese patients.[11]

Despite several options of vitamin supplements containing vitamin D being available in Brazil, with some of them included in Brazilian National List of Essential Medicines (Rename),[97] no national policy to prevent vitamin D insufficiency or deficiency in any women subgroup exists. In addition to funding studies to estimate the prevalence of micronutrient deficiencies in women of childbearing age,[98] a government policy is needed to avoid vitamin D inadequate levels, as well as excessive intake by self-medication or inappropriate prescription.[99]

As any systematic review, one limitation of this study is that missing studies could exist. To overcome this limitation, extensive gray literature and manual searches to find unpublished and published studies were conducted, having found a few studies not retrieved by electronic searches. Although a high number of studies were identified through manual search, which could be seen as a limitation of the search strategy, one hypothesis is that many studies may not have properly written titles and abstracts, or are not correctly indexed, hindering the automatic search algorithm's ability to retrieve them. Finally, another limitation was the absence of a robust analysis about potential associated factors of inadequate levels of vitamin D, due to the poor reporting of the compiled studies.

Conclusion

Although the magnitude of the prevalence of inadequate levels of vitamin D is uncertain, the evidence found in the literature suggests a moderate to severe problem with a prevalence of vitamin D deficiency (35%), insufficiency (42%), and deficiency or insufficiency (72%) in women of reproductive age. Future studies about vitamin D levels should consider random probabilistic sampling, appropriate sample sizes and reporting of findings. Furthermore, vitamin D studies should consider estimates according to the season, skin pigmentation, age range standardized by WHO, and use of supplements, to better inform potential health policies.

Contributions

Lucchetta RC: Conceptualization, Methodology, Writing, Investigation, Visualization, Supervision, Validation; Lemos IH: Writing- Reviewing and Editing, and Investigation; Gini ALR: Writing- Reviewing and Editing, and Investigation; Cavicchioli SA: Writing- Reviewing and Editing, and Investigation; Forgerini M: Visualization, Writing- Reviewing and Editing; Varallo FR: Visualization, Writing- Reviewing and Editing; de Nadai MN: Visualization, Writing- Reviewing and Editing; Fernando Fernandez-Llimós: Visualization, Writing- Reviewing and Editing; Mastroianni P: Conceptualization, Visualization, Validation, Writing- Reviewing and Editing, Project administration.

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Conflict to Interests

The authors have no conflict of interests to declare.

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Polycystic Ovary Syndrome in Adolescence: Challenges in Diagnosis and Management

Síndrome do ovário policístico na adolescência: Desafios no diagnóstico e tratamento

Mariana Enxuto Santos Manique[1] Ana Margarida Antunes Póvoa Ferreira[2,3,4]

[1] Department of Ginecology and Obstetrics, Faculty of Medicine, Universidade do Porto, Porto, Portugal
[2] Department of Gynecology, Unit of Reproductive Medicine, Centro Hospitalar Universitário São João, Porto, Portugal
[3] Department of Gynecology, Obstetrics and Pediatrics, Faculty of Medicine, Universidade do Porto, Porto, Portugal
[4] Institute for Investigation and Innovation in Health, Universidade do Porto, Porto, Portugal

Address for correspondence Mariana Enxuto Santos Manique, MD, Faculty of Medicine, Universidade do Porto, Alameda Professor Hernâni Monteiro 4200-319 Porto, Portugal (e-mail: mariana.smanique@gmail.com).

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Abstract

Diagnosing polycystic ovary syndrome (PCOS) during adolescence is challenging since normal pubertal development overlap typical features of this syndrome. The authors aim to summarize the existing evidence concerning PCOS in adolescence, particularly its diagnostic criteria and therapeutic options. A search throughout medical databases such as PubMed and MedScape was performed. Diagnostic criteria include irregular menstrual cycles according to time postmenarche and evidence of clinical hyperandrogenism and/or biochemical hyperandrogenism, provided other causes have been excluded. Polycystic ovarian morphology ought not to be used as a diagnostic criterion. Treatment should target manifestations and/or comorbidities, even in the absence of a definite diagnosis. Lifestyle interventions are the first-line treatment. Combined oral contraceptives, metformin or antiandrogens may also be considered as adjuvants. Screening for PCOS in adolescence is crucial as it allows an early intervention on the symptoms and comorbidities presented leading to better long-term reproductive and metabolic outcomes.

Keywords

- polycystic ovary syndrome
- adolescence
- diagnosis
- management

Resumo

Diagnosticar a síndrome do ovário policístico (SOP) durante a adolescência é um desafio, uma vez que o desenvolvimento puberal normal se sobrepõe às características típicas desta síndrome. Os autores têm por objetivo resumir as evidências existentes sobre a SOP na adolescência, particularmente seus critérios diagnósticos e opções terapêuticas. Uma pesquisa em bases de dados médicas como PubMed e MedScape foi realizada. Os critérios de diagnóstico incluem ciclos menstruais irregulares de acordo com o tempo pós-menarca e evidência de hiperandrogenismo clínico e/ou hiperandrogenismo bioquímico, após exclusão de outras causas. A morfologia policística dos

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Palavras-chave
- síndrome do ovário policístico
- adolescência
- diagnóstico
- gestão

ovários não deve ser usada como um critério diagnóstico. O tratamento deve ser direcionado às manifestações e/ou comorbilidades, mesmo na ausência de um diagnóstico definitivo. As intervenções no estilo de vida são o tratamento de primeira linha. Contraceptivos orais combinados, metformina ou antiandrogênios também podem ser considerados como adjuvantes. O rastreamento da SOP na adolescência é fundamental, pois permite uma intervenção precoce ao nível dos sintomas e comorbilidades presentes levando a melhores resultados reprodutivos e metabólicos a longo prazo.

Introduction

Polycystic ovary syndrome (PCOS) is the most frequent reproductive endocrine disorder affecting reproductive-aged women, being also the major cause of both chronic hyperandrogenic anovulation and infertility. Its estimated prevalence ranges from 6 to 15% depending on the populations studied and their ethnicity. Nevertheless, in adolescents, data concerning both incidence and prevalence is insufficient.[1,2] This syndrome has two main characteristic features: hyperandrogenism and ovulatory dysfunction. Clinical manifestations of hyperandrogenism include hirsutism and moderate to severe inflammatory acne. Ovulatory dysfunction may present as oligomenorrhoea or amenorrhea (primary or secondary). Among the main reproductive comorbidities are chronic anovulation, infertility, and pregnancy complications. Metabolic comorbidities include insulin resistance (IR), hyperinsulinemia, impaired glucose tolerance, type 2 diabetes mellitus (T2DM), gestational diabetes, hypertension, nonalcoholic fatty liver disease (NAFLD), dyslipidemias, metabolic syndrome, and an increased cardiovascular risk. Regarding psychological comorbidities, depression and anxiety are the most common, but eating disorders, negative body image, and sexual dysfunction may also be present.[2] Although the pathophysiology of PCOS remains unclear, it may result from multiple interactions (►**Fig. 1**) leading to heterogeneous manifestations among patients.[2,3] Even though it seems to mimic an autosomal dominant trait with variable penetrance, no single gene has yet been identified as responsible for all manifestations.[4]

Under normal circumstances, there is a balance between growing and dormant follicles. In adolescent PCOS, several components of the hypothalamic-pituitary-ovarian axis are dysfunctional (►**Fig. 2**).[2–5] Insulin resistance with consequent hyperinsulinemia may play a role in its pathogenesis. It directly stimulates ovarian and adrenal androgen secretion and inhibits hepatic production of sex hormone binding-globulin (SHBG) with consequent increase of free testosterone concentrations. Insulin resistance together with parameters of oxidative stress also play a significant role in the development of metabolic comorbidities. Hyperandrogenemia per se might increase the production of free radicals, thereby disturbing redox balance toward the pro-oxidant state leading to early subtle clinical manifestations.[4,6]

Potential risk factors for PCOS include low birthweight, *in uterus* exposure to androgens, postnatal rapid weight gain,

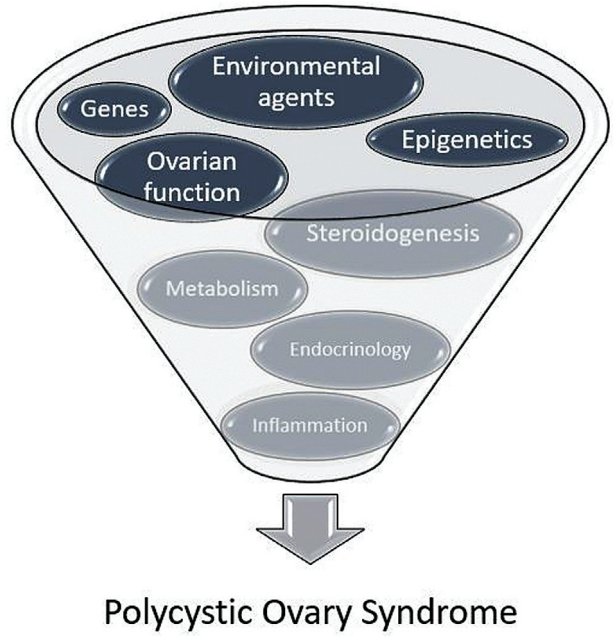

Fig. 1 PCOS pathophysiology. Environmental agents comprise lifestyle factors such as food, exercise, stress, and endocrine-disrupting chemicals (estrogens, antiandrogens, bisphenol A, and other nutritional toxins). Endocrine factors include IR, hyperinsulinemia, nutrient excess, and ectopic fat storage. **Source:** Witchel et al.[2] and Ibáñez et al.[3]

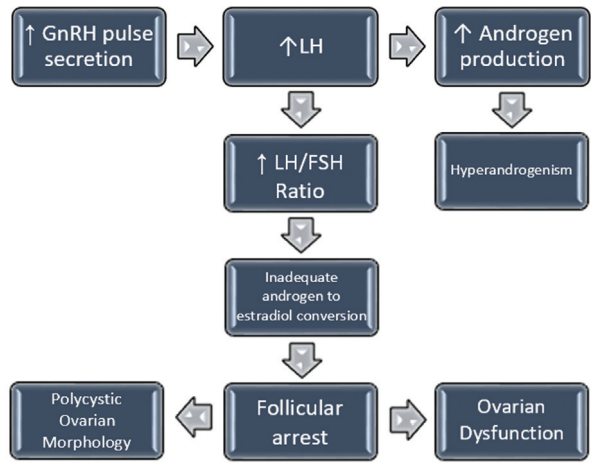

Fig. 2 Hypothalamic-pituitary-ovarian axis dysfunction in PCOS. Abbreviations: FSH: follicle-stimulating hormone; GnRH: Gonadotropin-releasing hormone; LH: luteinizing hormone. **Source:** Witchel et al.,[2] Ibáñez et al.,[3] Fitzgerald et al.[4] and Trent and Gordon.[5]

adiposity rebounds at younger ages, early pubertal development with either premature menarche or pubarche, and adult weight gain with higher body mass index (BMI) values.[2,3] Interestingly, girls whose mothers have PCOS present with metabolic features even before the onset of hyperandrogenism.[7]

Diagnosis

Several diagnostic criteria have been proposed throughout the years. Notably, all require the exclusion of other potential causes of hyperandrogenism and ovulatory dysfunction.[8] In fact, conditions such as nonclassical congenital adrenal hyperplasia (NCCAH) – main differential diagnosis –, hypo or hyperthyroidism, pituitary disorders (hyperprolactinemia), hypothalamic amenorrhea, premature ovarian insufficiency, endogenous Cushing syndrome, and virilizing tumors, among others, must be ruled out.[9–11] Also, and since the main cause of amenorrhea in sexually active adolescents is pregnancy, the diagnostic workup should always include a pregnancy test.[10]

The initial evaluation of a girl with signs and symptoms suggestive of PCOS begins with a precise medical history (including family history) and complete physical examination followed by appropriate laboratory assessment.[8,12] According to the most recent recommendations, this initial laboratory panel ought to include a pregnancy test, serum LH and FHS, as well as a complete blood count, comprehensive metabolic profile, and erythrocyte sedimentation rate.[9] It may also comprise thyroid function, prolactin, total testosterone, androstenedione, SHBG, dehydroepiandrosterone sulfate (DHEAS), and 17-hydroxyprogesterone concentration. Fasting glucose, glycated hemoglobin (HbA1c), and lipid concentrations are also typically requested.[12,13]

The first criteria by the National Institute of Health (NIH) in 1990 established a PCOS diagnosis based on the presence of both clinical and/or biochemical hyperandrogenism and menstrual irregularity.[7] The Rotterdam criteria were developed in 2003 and further reformulated in 2004.[7,13] In 2006, the Androgen Excess Society (AES) came up with refined criteria.[7]

Since there is a considerable convergence between normal pubertal milestones (such as acne, irregular menses, and polycystic ovaries) and PCOS phenotypes, experts considered the ahead criteria (NIH, Rotterdam and AES criteria) led to an overdiagnosis within this age group.[1] Therefore, several societies started including adolescents as a specific group within their guidelines for the diagnosis of PCOS.[7,10,13]

The Amsterdam criteria, in 2012, was the first official consensus directed toward the specificities of adolescents,[13,14] followed by the Endocrine Society (ES) guidelines in 2013[13] and by an adolescent-specific expert consensus by the Pediatric Endocrine Society (PES) in 2015.[13,15]

Also in 2015, the American Association of Clinical Endocrinologists (AACE), together with the American College of Endocrinology (ACE), the AES, and other PCOS societies created a practical guideline for evaluation and work-up of PCOS in this age group. They considered biochemical and/or clinical hyperandrogenism manifested as hirsutism and oligomenorrhoea for 2 to 3 years postmenarche as the basis of the diagnosis. Ultrasound should be excluded from the diagnostic criteria until the age of 17 years old.[14]

Strong efforts have been made within recent years to overcome controversies from previous criteria resulting in three international consensuses for PCOS during adolescence (2015–2018). According to Rosenfield,[9] there are no discrepancies concerning the core diagnostic criteria (►**Chart 1**). Confusion emerges around their fulfilment. For instance, there is no agreement on the clinical manifestations of hyperandrogenemia or the time interval menstrual irregularities must persist until a definite diagnosis can be made.[9]

Therefore, all guidelines advocate for an evaluation 2 to 3 years after menarche whenever PCOS is a possible diagnosis. These girls should remain with a provisional diagnosis of "at risk" for PCOS. Definite diagnosis could be made afterwards in a retrospective way as long as the irregular menstrual cycles criteria persist according to time postmenarche.[12,17]

Current recommendations reinforce the importance of establishing a balance: underdiagnosing this condition

Chart 1 Polycystic ovary syndrome diagnostic criteria in adolescence

Polycystic ovary syndrome diagnostic criteria in adolescence	
Hyperandrogenism*	- Evidence of clinical hyperandrogenism (moderate to severe hirsutism and/or severe acne) and/or - Evidence of biochemical hyperandrogenism
Ovulatory dysfunction*	- Irregular menstrual cycles according to time postmenarche: • 1st year postmenarche: normal pubertal transition • From 1 to 3 years postmenarche: < 21 days or > 45 days • From 3 years postmenarche: < 21 or > 35 days or < 8 cycles per year • > 1 year postmenarche: > 90 days for any cycle • Primary amenorrhea: absence of menstruation by 15 years old or > 3 years postmenarche
Polycystic ovarian morphology	- Ought not to be used as a diagnostic criterion within this age group - Pelvic ultrasound should not be performed in adolescents < 8 years postmenarche.
Metabolic factors	- Metabolic criteria are not accepted - Metabolic factors should be considered as a warning sign to look for associated comorbidities

*Provided other causes are excluded.
Source: Rosenfield,[9] Akgül et al.,[13] Peña et al.[16] and Witchel et al.[17]

compromises early treatment and prevention of future complications; overdiagnosis has a great impact on both the physical and psychological health and on the well-being of the adolescent, with unnecessary exposure to side effects of certain medications.[2,4] As such, experts consider starting treatment targeted to the main manifestations and/or comorbidities presented by each patient, even in the absence of a definite diagnosis, which could be protruded to an older age as far as follow-up with careful monitoring is provided. In fact, recommendations do not require a definite diagnosis to effectively treat and manage young women presenting with typical features.[18]

Hyperandrogenism

DiVall et al.[10] defined hyperandrogenism as cutaneous evidence of excess androgens (excessive acne and/or hirsutism) or hyperandrogenemia (excess androgen levels in serum). It is the most common abnormality in PCOS, being present in between $\sim$ 60 and 80% of patients.[3] Although excessive ovarian androgen production represents most cases, increased adrenal androgen production can also occur.[3]

Hirsutism, the primary and most reliable clinical marker for hyperandrogenemia, is the presence of excessive terminal hair growth with a male pattern. Due to the difficulties bellow presented in the biochemical evaluation of hyperandrogenemia (such as lack of a clear cuff point and the usage of male gender dosage callibration curves), its clinical evaluation is undoubtedly relevant, even with its inherent disadvantages.[6] Its main evaluation tool for diagnosis and follow-up is the modified Ferriman Gallwey (FG) score, whose cutoff depends both on the age and ethnicity of the girl.[6,16] In fact, it is expected that girls with Mediterranean, Hispanic or Middle Eastern origins develop a more severe hirsutism, whereas adolescents from East Asia tend to have milder forms.[19] The classical cutoff point of ≥ 8 is widely found in the literature to establish clinical hyperandrogenism. Nevertheless, and taking ethnical variations into consideration, Teede et al.[19] proposed a cutoff stratification. Accordingly, a score $\geq$ 8 should be restricted to those girls whose origins, as mentioned above, tend to developed a more severe hirsutism, whereas a score ≥ 6 should be applied in Caucasian and Afro descendant women, and $\geq$ 4 should be considered instead in Oriental/Asian girls.[6,19] In fact, and as defended by Soares-Jr et al.,[6] the excess of body hair in women is a frequent problem at the clinic that interferes with their femininity and self-esteem and, therefore, should be appropriately diagnosed and managed. Nevertheless, using this score in females without complaints is controversial since a diagnosis of hirsutism may create a stigma and a strong emotional burden, especially within this age group, not to mention the exposure to unnecessary side effects of treatments.[6] In fact, milder forms of hirsutism may be considered normal within the Mediterranean, Middle Eastern or Latin American areas.[6] Furthermore, it does not take into consideration pubertal stages, has high interevaluator discrepancy, and is influenced by previous cosmetic treatments.[3,16,17] Finally, care must be taken to make a correct differential diagnosis between clinical hyperandrogenism and other forms of excessive hair growth, namely hypertrichosis and lanugo to avoid unnecessary treatments.[6]

Hirsutism does not correlate directly with androgen circulating levels.[12,17] Therefore, whenever clinical hyperandrogenism is undetected, biochemical hyperandrogenism should be evaluated by high-quality assays, measuring total serum testosterone and SHBG.[3,16] Conversely, and since this conventional dosage calibration curve is the same used for the male gender, it is quite inaccurate for females, being unable to detect analytical evidence of hyperandrogenism in less severe forms of hirsutism. In fact, 30 to 50% of women with mild symptoms do not have corresponding elevated androgen levels. Another possible explanation for this finding relies on an exacerbated action of the androgens in effector organs (hair follicle) rather than on a significant elevation of its circulating levels.[6] Also, one must not forget that combined oral contraceptives affect SHBG and alter gonadotrophin-dependent androgen production. Thus, a reliable assessment of biochemical hyperandrogenism requires withdrawal of these therapeutic agents at least 3 months before measurement, providing another mean of contraception for sexually active adolescents.[18,19]

Even though no clear cutoff points have been established, available guidelines recommend total testosterone concentrations $>$ 55 ng/dl (1.91 nmol/l) for probable hyperandrogenism.[20] Ramezani Tehrani et al.[8] considered persistent elevation of serum total and/or free testosterone levels by $>$2 standard deviation (SD) above the mean of adult norms, determined by a reliable reference laboratory, as valid criterion.

Androstenedione and DHEAS provide limited additional information and are not recommended for the initial biochemical evaluation. They might be useful when testosterone levels are within the normal range for exclusion of other causes of hyperandrogenism, especially if an androgen-secreting tumor is suspected.[16]

New highly specific and sensitive diagnostic tools are under investigation. One of these is anti-Müllerian hormone (AMH), which is produced by the granulosa cells of the ovaries, being involved both in the development and maturation of follicles. Anti-Müllerian hormone correlates with ovarian reserve, the number of developing follicles, and is a potential marker of ovarian aging.[17] Its concentration is frequently elevated in females with PCOS. Advantageously, it is not affected by the phase of the menstrual cycle.[4,21] However, there is still no cutoff validated for PCOS diagnosis in adolescent girls and its use is still controversial.[4] Khashchenko et al.[22] concluded that AMH as a sole marker for PCOS diagnosis in adolescents was insufficiently accurate. Accordingly, the consensus of opinion between pediatric endocrinologists and adolescent medicine experts considered that serum AMH concentration in adolescents should not be used to characterize polycystic ovarian morphology (PCOM) or to predict a diagnosis of PCOS.[18]

Nevertheless, Dursun et al.[21] demonstrated that treatment with COC with or without metformin reduced AMH levels, independently of hyperandrogenism. Similarly, Asanidze et al.[23] showed AMH levels were reduced after

treatment with combined oral contraceptives (COCs) or with COCs plus inositols. Hence, AMH might be a good marker for monitorization.[21,23]

Finally, moderate to severe comedonal acne (that is, ≥ 10 facial lesions) or moderate to severe persistent inflammatory acne unresponsive to topical therapy is uncommon even within this age group and should prompt biochemical evaluation for hyperandrogenemia prior to medical treatment.[16,24]

Ovulatory Dysfunction

Whenever irregular menstrual cycles are present, a diagnosis of PCOS should be considered.[16] According to Peña et al.,[16] irregular menstrual cycles are normal pubertal transition during the 1st year postmenarche. After that, the following definitions of irregular menstrual cycles were reached by consensus, since there was insufficient data to formulate evidence-based ones: from 1 to 3 years postmenarche < 21 days or > 45 days; from 3 years postmenarche < 21 or > 35 days or < 8 cycles per year; and > 1 year postmenarche > 90 days for any cycle.[16] Primary amenorrhea is the absence of menstruation by the age of 15 years old or > 3 years post-thelarche[16] and, according to Javed et al.,[25] it is associated with increased metabolic risk. Importantly, early menstrual patterns are predictive of the future ones and ovulation can occur even with irregular menstrual cycles.[12] In contrast, ovarian dysfunction may be present in females with regular menstrual cycles.[16]

Ovarian Morphology

In PCOS, ovarian cycles include the development of several primordial follicles but no dominant one is selected, leading to anovulation, atresia, and to PCOM.[26] Various parameters have been suggested to study ovarian morphology using ultrasonography (gold standard) in adults; however, no consensus concerning their diagnostic value in adolescents has yet been established.[27] Pelvic ultrasound might be used to better evaluate ovarian morphology and to exclude or investigate other possible uterine or ovarian abnormalities (functional cysts, ovarian masses, and endometrial alterations, among others).[16] However, it should not be used in females < 8 years postmenarche.[16,18] Polycystic ovarian morphology can be defined based on ovarian size and volume, stromal volume, and follicle size and number. The Rotterdam criterion defines ultrasonographic PCOM as a thickened capsule and enlarged ovary ($> 10\,cm^3$ in volume), with multiple small cysts or ≥ 12 follicles that are 2 to 9 mm in diameter.[26] However, since ovaries reach their maximum volume and follicle count during puberty, this recommendation is not widely accepted and different sources suggest alternative dimensions specific for this age group.[26,27] The PES, for example, established a cutoff value of $> 12\,cm^3$ rather than $> 10\,cm^3$ for ovarian volume.[26] The AES guidelines, in turn, considered follicle number per ovary (FNPO) $\geq$ 25 could define PCOM.[26] Importantly, ultrasonographic findings are not specific for PCOS.[26] Furthermore, a high prevalence of girls has PCOM without an underlying pathology. Therefore, current recommendations advocate PCOM should not be considered as a diagnostic criterion of PCOS in this population.[16,18]

Metabolic Factors

Classically, PCOS is described as a primary ovarian disease. However, growing evidence shows neuroendocrine factors also play a role. In fact, in the presence of obesity, metabolic syndrome or IR, PCOS should be considered.[8] Polycystic ovary syndrome and metabolic syndrome have several common features such as obesity, IR, T2DM, hyperlipidemia, and hypertension. The prevalence of this syndrome is almost three times higher in women with PCOS.[1,12] However, data concerning its prevalence in adolescents with PCOS is discrepant.[15] First, the choice of diagnostic criteria for PCOS resulted in a great disparity in terms of the prevalence of metabolic syndrome ranging from 4.9 to 43.9%, being the highest when the PES criteria were used. This reinforces the importance of adolescent-specific definitions.[15] Second, there is still no consensus definition of metabolic syndrome in adolescents and published pediatric criteria are based on adult ones.[11,12] Nevertheless, metabolic syndrome is more prevalent among obese girls compared with lean adolescents when both are diagnosed with PCOS. During puberty, due to the increase in growth hormone (GH) levels, there is a physiological decrease in insulin sensitivity, which is also one of the reasons why PCOS may become clinically evident at this age.[1,3,12] However, IR is not necessarily present. Therefore, it should not be considered a diagnostic feature but rather a warning sign to look for associated comorbidities.[13] Even though there is data supporting a chronic low-grade inflammatory basis for PCOS, research concerning cytokine profiles within this syndrome turned out to be controversial. In fact, obesity itself is responsible for a proinflammatory state and, according to Barcellos et al.,[28] independently of the presence of PCOS, circulating levels of interleukin 6 and high sensitive C-reactive protein are higher in obese females when compared with normal-weight ones. Therefore, the authors concluded that obesity, but not PCOS, affects circulating markers of low-grade inflammation in young women without major CV risk factors.[28] Also, higher levels of cystatin C (a proinflammatory marker related to low-grade inflammation) were found in girls with PCOS. This might be a promising early predictor of adverse cardiovascular outcomes, having a prognostic value and helping in risk stratification.[29] Similarly, progranulin levels are higher in these girls, being inversely correlated with HDL-C. Considering low HDL-C levels are a strong predictor of future cardiac events, progranulin might be used as a cardiovascular risk biomarker.[30]

Treatment

Usually, adult women with PCOS seek medical advice and/or treatment either due to menstrual dysfunction or to unsuccessful reproduction. However, the main concerns of adolescents are different and most often include irregular menstruation, acne, and hirsutism.[3] Treatment aims to

Chart 2 Classical treatment options (nonpharmacological and pharmacological) for polycystic ovary syndrome

Lifestyle interventions (weight loss and physical activity)	
Indications	- 1st line nonpharmacological treatment - Recommended to all adolescents with polycystic ovary syndrome
Advantages	Weight loss: ↙ ↓ BMI ↙ ↓ FG score Physical Activity: ↙ Menstrual cycle regulation (↓ LH and ↓ AMH)
Disadvantages	✗ Suboptimal adherence ✗ High relapse rate
Combined Oral Contraception (estrogen and progestin combinations)	
Indications	- 1st line pharmacological treatment - Menstrual irregularities and hirsutism - Contraception
Advantages	↙ Menstrual cycle regulation (↓ LH) ↙ ↓ Hyperandrogenemia ↙ ↓ Clinical manifestations of hyperandrogenism (seborrhea, acne, and hirsutism)
Disadvantages	✗ IR remains unchanged ✗ At least 6 to 9 months for measurable effects on hirsutism
Antiandrogens (Spironolactone/Finasteride)	
Indications	- Adjuvant to COC in severe hirsutism cases - COC contra-indication or not tolerated
Advantages	↙ ↓ FG score
Disadvantages	✗ Less effective for pre-existing hair ✗ Teratogenic
Eflornithine (topical)	
Indications	- Adjuvant to photoepilation in patients with laser-resistant facial hirsutism - Monotherapy whenever photoepilation is not recommended
Advantages	↙ ↓ Hirsutism
Disadvantages	✗ Relapse after discontinuation
Metformin	
Indications	- 2nd line pharmacological treatment - Ineffective lifestyle interventions - COC contraindication or not tolerated
Advantages	↙ ↓ IR and hyperinsulinemia ↙ Menstrual cycle regulation ↙ ↓ Hyperandrogenemia ↙ ↓ Cardiovascular risk
Disadvantages	✗ Most symptoms relapse after discontinuation ✗ Side effects: gastrointestinal symptoms; lactic acidosis (extremely rare).

Abbreviations: BMI, body mass index; COC, combined oral contraceptive; FG, Ferriman Gallwey; IR, insulin resistance.
Source: Le et al.,[1] Ibáñez et al.,[3] Fitzgerald et al.,[4] Trent and Gordon,[5] DiVall and Merjaneh,[10] Kostopoulou et al.,[11] Peña et al.,[16] Morin-Papunen,[18] Pal Singh Kochar et al.,[31] Pkhaladze et al.,[32] Abdolahian et al.[33] and Wong et al.[34]

improve both hormonal and metabolic status, quality of life, and long-term health status, preventing comorbid complications.[3] It should be started with education and lifestyle interventions. Classical pharmacological options include metformin, COCs, spironolactone, and topical drugs for hirsutism and acne (►**Chart 2**).[1,3–5,8,10,11,16,18,31–34]

Lifestyles changes including weight loss and physical activity in obese or overweight adolescents remain the first-line treatment. According to Wong et al.,[34] these are beneficial for weight control but have no effect on biochemical hirsutism. However, more recent results advocate lifestyle interventions may also improve clinical, hormonal, and metabolic features (such as IR), decreasing androgen levels and improving menstrual cycle patterns.[33] Nevertheless, there is a high degree of relapse and a suboptimal adherence.[1,32,34]

As for therapeutic interventions, COCs with 20 to 35 µg of ethinylestradiol combined with a progestin are widely recommended as first-line pharmacological treatment. These agents target both menstrual dysfunction and clinical manifestations of hyperandrogenism, further providing hormonal contraception. In fact, COCs are considered the most

effective treatment for hirsutism, with up to 70% improvement in unwanted hair growth.[5,10] Nevertheless, insulin sensitivity does not change.[5,10] It is essential to screen adolescents for possible contraindications prior to starting this treatment.[11,12]

There are insufficient trials in adolescents with PCOS evaluating different COCs and the literature shows no significantly different hyperandrogenism outcomes either with an antiandrogenic progestin or a nonantiandrogenic one. Therefore, no COC is clearly superior to help decision-making.[3] Combined transdermal paths and vaginal rings might be adequate methods, but, once again, there is no superiority evidence.[5] Progestin-only contraception (such as intrauterine devices) may be an alternative first-line treatment given its low systemic side effects and high contraceptive effectiveness. However, it does not raise SHBG and may cause weight gain.[3]

There are several other treatment options for hirsutism, including mechanical hair removal techniques, topical medications (eflornithine), light-based strategies, and antiandrogens, apart from the ahead mentioned COC. Light-based strategies (photoepilation by laser or electrolysis) should be considered as first-line treatment for localized hirsutism in PCOS.[3,5,11]

Topical eflornithine is indicated as an adjuvant to photoepilation in patients with laser-resistant facial hirsutism or as monotherapy whenever these light-based strategies are not recommended. Even though promising, the duration of treatment is not clear yet.[3,5,11] Nevertheless, clinical results might take up to 8 weeks and a relapse is expected after discontinuation.[4]

Antiandrogens are an adjuvant option to COC in severe cases of hirsutism to inhibit the development of new terminal hair. Spironolactone, the most commonly prescribed androgen receptor blocker, effectively reduces the FG score. However, this option should mainly be considered if hirsutism has not improved after 6 months of COC monotherapy and only if the patient clearly considers it a manifestation that makes her uncomfortable. Once again, limited evidence is available regarding its use in adolescents.[4–6,8,16]

Finasteride, an 5α-redutase inhibitor, also plays an antiandrogen role, reducing dihydrotestosterone levels by between 50 and 60% with a consequent significant reduction in FG scores after 6 months of treatment. This agent should be considered mainly when prior therapy with COC and spironolactone were not effective for severe forms of hirsutism. Nevertheless, there is a paucity of literature concerning the use of antiandrogens within this population, namely in terms of safety and security. Furthermore, we must not forget that this therapy in adolescence could affect bone mineral density.[35]

There are several pharmacological approaches available for acne, including topical retinoic acid and antibiotics (clindamycin, erythromycin, …) as well as oral antibiotics, hormonal therapy, and antiandrogens. However, retinoids are considered the most effective treatment.[5,8]

Although insulin-sensitizing medications may have a positive impact on PCOS treatment, their use in adolescents is still controversial. Metformin reduces IR and, therefore, improves menstrual regularity and decreases hyperandrogenemia. Also, a decrease in cardiovascular risk is expected. However, conflicting results on weight loss remain among studies and effects on hirsutism are barely observed.[4,8,11,18] Nevertheless, Pal Singh Kochar et al.,[31] for instance, advocated for its positive effects on hirsutism and, hence, this point remains controversial. Unfortunately, most symptoms relapse after discontinuation. Even though the severity, duration, and persistence of side effects can be highly variable, the dropout rate due to these is minimum and this medication could be considered safe in this age group.[31]

Some authors do not recommend other insulin sensitizers, such as thiazolidinediones, for the treatment of PCOS in adolescents due to safety concerns, but this is also controversial.[1,11]

Since adolescent girls with PCOS require long-term treatments, alternative therapies with less unwanted effects are under investigation (►**Chart 3**).[1,4,5,23,32] Even though data in adolescents is still very limited and further studies are needed, the following seem to be the most promising options.

A recent study cited in an article by Trent et al.[5] published in 2020 compared N-acetylcysteine with metformin. It had very positive results in terms of BMI, waist-to-hip ratio, and waist circumference reductions. N-acetylcysteine also increased insulin sensitivity and decreased testosterone levels, thereby improving metabolic and hormonal profiles. Overall, this agent seems promising especially due to lesser side effects.[5]

Inositols (myo-inositol and D-chiro-inositol) may also have a role in the treatment of adolescents with promising

Chart 3 New therapeutic options under investigations for polycystic ovary syndrome

N-acetylcysteine	- ↓ BMI, ↓ waist-to-hip ratio and ↓ waist circumference - ↑ Insulin sensitivity - ↓ Testosterone levels - Lesser side effects
Inositols (myo-inositol and D-chiro-inositol)	- ↓ Weight - Menstrual cycle regulation - ↑ Insulin sensitivity - ↓ Hirsutism - Virtual absence of side effects
Vitamin D supplementation	- ↓ Total testosterone - ↑ Insulin sensitivity - Menstrual cycle regulation
Chromium supplementation	- Menstrual cycle regulation - ↓ Free testosterone - ↓ IR (?) - No side effects
Orlistat	- ↓ Weight - ↓ Cardiovascular risk - Improved ovulation rates - Lesser side effects

Abbreviations: BMI, body mass index; IR, insulin resistance.
Source: Le et al.,[1] Fitzgerald et al.,[4] Trent and Gordon,[5] Amr and Abdel-Rahim[24] and Pkhaladze et al.[32]

results regarding weight reduction, menstrual regularity, and improvement of insulin, androgen levels, and hirsutism. These may rise as new agents in this age group given their virtual absence of side effects.[1] Moreover, with the association of myo-inositol and COCs, positive results both in metabolic and androgen profiles are enhanced, and weight gain associated with COCs is balanced.[32] Also, the combination of myo-inositol with α-lipoic-acid reduces both IR and inflammation.[33–36]

Vitamin D supplementation in PCOS may reduce total testosterone concentration but it has no effect on free testosterone nor on SHBG levels. A favorable effect on insulin sensitivity and on menstrual regularity has also been described.[4] Additionally, it seems to improve both acne and hirsutism.[5] However, controversies remain as some authors came up with opposing conclusions.

According to Amr et al.,[24] chromium supplementation may reduce IR and improve both mean ovarian volume and total follicular count, with consequent better menstrual regularity in adolescents. It also decreased free testosterone levels, with no side effects being reported.

Finally, orlistat has been suggested for the long-term management of PCOS due to its potential to promote weight loss and improve metabolism, diminishing cardiovascular risk. It may also improve ovulation rates, with less side effects than metformin, for instance.[5]

Unfortunately, due to insufficient interventional studies, it is not yet possible to determine which could be the most effective treatment and management approach for PCOS in adolescents.[18]

Conclusion

According to the most recent recommendations, the diagnostic criteria for PCOS during adolescence include irregular menstrual cycles according to time postmenarche and evidence of clinical hyperandrogenism and/or biochemical hyperandrogenism, provided other causes have been excluded. Polycystic ovarian morphology ought not to be used as a diagnostic criterion. Girls who have features of PCOS but do not meet diagnostic criteria should be labeled as “at risk” of PCOS and monitored carefully. Therefore, if the symptoms persist, a retrospective diagnosis could be made. Lifestyle interventions are the first-line treatment for most adolescents with PCOS. Pharmacological agents such as COCs, metformin or antiandrogens may also be considered as adjuvants.

Conflict of Interests

The authors have no conflict of interests to declare.

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Imaging Assessment of Prognostic Parameters in Cases of Isolated Congenital Diaphragmatic Hernia: Integrative Review

Avaliação de fatores prognósticos por métodos de imagem em casos de hérnia diafragmática congênita isolada: Revisão integrativa

Juliana da-Costa-Santos[1] João Renato Bennini[1]

[1] Department of Maternal-Fetal Medicine, Universidade Estadual de Campinas, Campinas, SP, Brazil

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Address for correspondence João Renato Bennini, MD, PhD, Cidade Universitária Zeferino Vaz, 13083-970, Barão Geraldo, Campinas, SP, Brazil (e-mail: bennini@unicamp.br).

Abstract

Objective Antenatal recognition of severe cases of congenital diaphragmatic hernia (CDH) by ultrasound (US) and magnetic resonance imaging (MRI) may aid decisions regarding the indication of fetal endoscopic tracheal occlusion.

Methods An integrative review was performed. Searches in MEDLINE and EMBASE used terms related to CDH, diagnosis, MRI, and US. The inclusion criteria were reviews and guidelines approaching US and MRI markers of severity of CDH published in English in the past 10 years.

Results The search retrieved 712 studies, out of which 17 publications were included. The US parameters were stomach and liver positions, lung-to-head ratio (LHR), observed/expected LHR (o/e LHR), and quantitative lung index. The MRI parameters were total fetal lung volume (TFLV), observed/expected TFLV, relative fetal or percent predicted lung volumes, liver intrathoracic ratio, and modified McGoon index. None of the parameters was reported to be superior to the others.

Conclusion The most mentioned parameters were o/e LHR, LHR, liver position, o/e TFLV, and TFLV.

Keywords
- hernias diaphragmatic congenital
- ultrasonography prenatal
- magnetic resonance imaging
- patient selection
- reference standards

Resumo

Objetivo A identificação pré-natal de casos graves de hérnia diafragmática congênita (HDC) por ultrassonografia (US) e ressonância magnética (RM) pode ajudar a decidir sobre a indicação de oclusão traqueal endoscópica fetal.

Métodos Uma revisão integrativa foi realizada pesquisando nas bases MEDLINE e EMBASE com termos relativos a HDC, diagnóstico, RM, e US. Os critérios de inclusão foram revisões e diretrizes abordando marcadores ultrassonográficos e de ressonância para a gravidade de HDC publicados em inglês nos últimos 10 anos.

Resultados Foram obtidos 712 estudos, dos quais 17 foram incluídos. Os parâmetros de US foram posições do estômago e do fígado, relação pulmão-cabeça (LHR, na sigla em inglês), LHR observada/esperada (o/e LHR), e índice pulmonar quantitativo (QLI, na sigla em

Palavras-chave
- hérnias diafragmáticas congênitas
- ultrassonografia pré-natal
- imagem por ressonância magnética
- seleção de pacientes
- padrões de referência

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inglês). Os parâmetros de RM foram volume pulmonar fetal total (TFLV, na sigla em inglês), o/e TFLV, volume pulmonar fetal relativo e porcentagem predita, razão do fígado intratorácico (LiTR, na sigla em inglês) e índice de McGoon modificado. Nenhum dos parâmetros foi mencionado como superior aos demais.

Conclusão Os parâmetros mais citados foram o/e LHR, LHR, posição do fígado, o/e TFLV, e TFLV.

Introduction

Congenital diaphragmatic hernia (CDH) is a rare disease,[1] with a reported frequency of 1 to 4 per 10,000 live births.[2–6]

Congenital diaphragmatic hernia is an embryological defect derived from the incomplete fusion of the septum transversum, pleuroperitoneal folds, esophageal mesentery, and muscles from the body wall.[3] The defect may be located anywhere in the diaphragm, but it is usually located in the posterolateral region: Bochdalek hernia, corresponding to up to 95% of cases.[3] Also, left-sided hernias constitute the majority of cases (85%).[1]

Congenital diaphragmatic hernia results in the displacement of abdominal organs, which mainly includes different combinations of herniated intestines, stomach, and/or liver.[3,4] Thus, a mass effect is created in the thoracic cavity, reducing lung growth and resulting in variable degrees of pulmonary hypoplasia and pulmonary hypertension, which are the main causes of postnatal severe morbidity and mortality.[4,6] In addition, considering the need for postnatal definitive surgical intervention for CDH and for neonatal intensive care, delivery should occur in a tertiary center.[4]

Since the 1980s, it is possible to recognize cases of CDH with antenatal ultrasound.[7] The ability to identify CDH antenatally, and the frequency of neonatal complications of these infants led to the development of an intrauterine intervention: fetal endoscopic tracheal occlusion (FETO). This procedure cannot substitute the postnatal intervention, for it does not repair the diaphragmatic defect, but it enhances lung development by preventing lung fluid escape, thus increasing intrapulmonary pressure, cellular proliferation, and allowing maturation of the pulmonary vasculature.[2]

Fetal endoscopic tracheal occlusion is a surgical intervention. Therefore, patient selection is of utmost importance. Currently, FETO is reserved for cases with poor prognosis,[5] but there is no consensus on which parameters should be used for prognostic assessment. Ultrasound (US) and magnetic resonance imaging (MRI) criteria have been used heterogeneously in the literature to classify cases of CDH, with numerous techniques and cutoff points. Therefore, the present study aimed to review the antenatal US and MRI criteria to assess the severity of the disease (CDH), their cutoff points, and postnatal prognosis according to the literature.

Methods

An integrative review was performed according to Whittemore and Knafl.[8]

A search was conducted in the MEDLINE and EMBASE databases, using the following strategies:

- MEDLINE: [*Hernias*, *Diaphragmatic*, *Congenital* AND *Diagnosis* AND (*Ultrasonography*, *Prenatal*" OR *Magnetic Resonance Imaging*)]. Filter: past 10 years.
- EMBASE: *congenital diaphragm hernia* AND *diagnosis* AND (*ecography* OR *nuclear magnetic resonance*) AND [2011–2021]/py.

The inclusion criteria were reviews and protocols approaching US and MRI prognostic markers of severity of disease published in English in the past 10 years. Clinical studies of any design and reviews and/or protocols that did not address antenatal imaging prognostic tools were excluded. Studies published in other languages were excluded. Data was collected in an online form specifically developed for this review.

Study selection was performed independently by the authors (J. C. S. and J. R. B.) using Rayyan software (Rayyan Systems Inc., Cambridge, MA, USA).[9] Conflicting selections were resolved by consensus. The first step of study selection was screening by title and abstract. The publications included were further screened by full text assessment. For each parameter, the severity of disease was defined according to the reported outcome in each review, such as mortality and pulmonary hypertension.

Results

The search retrieved 712 studies. After the exclusion of duplicates ($n = 112$), 600 studies were independently screened by J. C. S. and J. R. B. by title and abstract. The first step of study selection resulted in inclusion of 22 studies. There were 49 conflicting selections, which were resolved by consensus, and resulted in the inclusion of 6 of these publications. The second stage of study selection was full text assessment of the 28 studies included. In this step, 16 studies were included, and there were 2 conflicting selections, which were resolved by consensus, and 1 article was included, totaling 17 studies for this review. The main reasons for exclusion are described in ►**Figure 1**. The final selection included 17 studies, which analyzed prenatal US and MRI parameters for prediction of severity of the disease. They included 14 narrative reviews (of these, 1 was a narrative review and clinical protocol),[1–5,7,10–17] 2 systematic reviews with metanalyses,[18,19] and 1 clinical protocol.[6] Regarding the imaging method, one of the studies

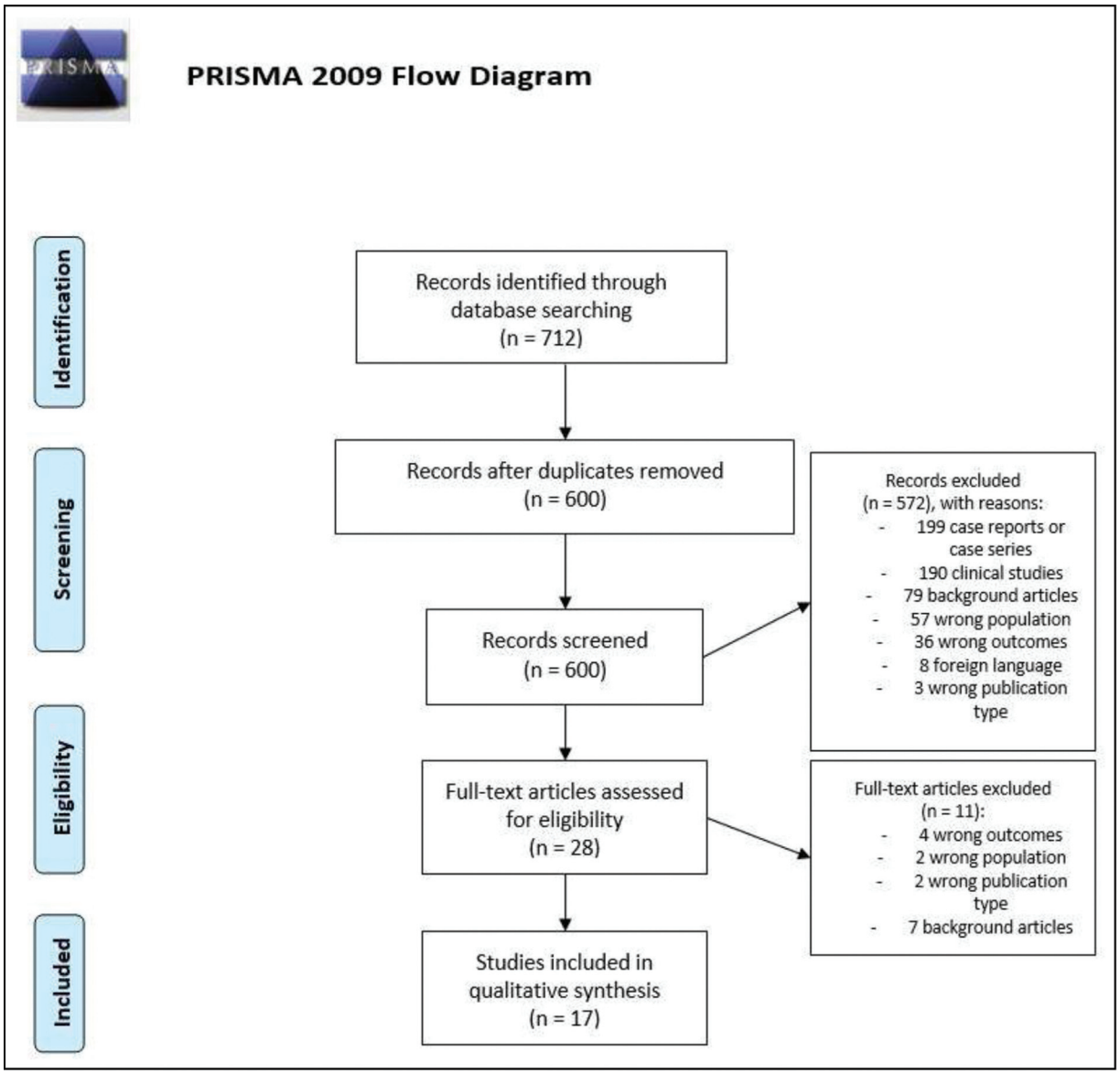

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection.

approached MRI exclusively,[19] 7 analyzed exclusively US,[1–4,6,13,14] and 9 studies reported MRI and US parameters.[5,7,10–12,15–18] Although the imaging modality varied throughout the selected studies, it is important to note that the severity of disease definitions and reference cutoff points for each parameter were similar; this is probably due to the use of the same source of information. There was a notable heterogeneity of gestational ages (GAs) at the time of the evaluation: 6 studies did not report GA at the imaging evaluation,[3,10,13,14,17,18] and the other 11 studies reported GA that ranged from 18 to 39 weeks.[1,2,4–7,11,12,15,16,19] There were five US and six MRI parameters described in the reviews. The US parameters were stomach position, liver position, lung-to-head ratio (LHR), observed/expected LHR (o/e LHR), and quantitative lung index (QLI). The MRI parameters were total fetal lung volume (TFLV), observed/expected TFLV (o/e TFLV), relative fetal lung volume (relative FLV), percent predicted lung volume (PPLV), liver intrathoracic ratio (LiTR), and modified McGoon index. The findings of this review are summarized in ►**Tables 1** and **2**.

Stomach Position

There were five reviews describing this criterion.[1,5,7,10,12] The parameter was mostly reported in the context of left sided hernias and evaluated at 22 weeks of gestational age (GA) or more. There were two different descriptions of severity: the first one considered two possibilities of stomach position (abdominal — "stomach down"— or thoracic — "stomach up"), and the second one considered grades of stomach herniation. Stomach up was associated with survival rates of 29 to 35%, whereas stomach down was associated with survival rates of 90 to 100%. Stomach herniation grades evaluate stomach position in relation to thoracic organs: grade 1 is characterized by stomach in the normal position; grade 2 is characterized by stomach anteriorly at the apex of

Table 1 Summary of ultrasound parameters for antenatal evaluation of severity of disease in CDH

US parameter	Number of reviews that mentioned the parameter	Lesion side	GA at evaluation (weeks)	Cutoff point for severe CDH	Definition of severity
Stomach position	4	Left	$\geq$ 22	Stomach up	Survival: stomach up: 29–35%; stomach down: 90–100%
					Survival according to grade of herniation: grade 1 and grade 2: around 90%; grade 3: around 70%; grade 4: around 10%
Liver position	8	Left	Not mentioned	Liver up	Mortality liver up: 44–100% Liver down: 0–45.4%
					Need for ECMO Liver up: 42–80% Liver down: 0–25%
LHR	8	Left	< 25	LHR < 0.6 and liver up	Survival rates of liver up and LHR: < 0.6: 0 0.6–1.35: 61% > 1.4: 100%
		Not mentioned	20–26	< 1.0	Survival: < 0.6: 0 > 1.35: 100%
o/e LHR	16	Left	18–38	< 25%	Survival: o/e LHR > 55%: 85% (liver up)–100% (liver down)
					46–55%: 90% (liver up) to 100% (liver down)
					36–45%: 65% (liver up) to 75% (liver down)
					26–35%: 55% (liver up) to 65% (liver down)
					$\leq$ 25%: 15% (liver up)–30% (liver down)
		Right	18–38	< 45%	Survival rate: < 45%: up to 17%
					> 45%: at least 60%
QLI	1	Not mentioned	Not mentioned	QLI < 0.6 (or centile 1)	Values correlate with lung hypoplasia

Abbreviations: CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; LHR, lung-to-head ratio; o/e, observed/expected; QLI, quantitative lung index; US, ultrasound.

the heart and in contact with the chest wall; grade 3 has the larger part of the stomach anteriorly, but it reaches the level of the atrioventricular valves; and grade 4 has most of the stomach in the posterior thorax, in a retrocardiac position. According to this classification, survival rates are around 90% for grades 1 and 2, around 70% for grade 3, and around 10% for grade 4.

Liver Position

There were eight studies describing this parameter.[1,4,5,7,10,11,17,18] Liver position could be abdominal ("liver down") or thoracic ("liver up"). None of the reviews mentioned the GA for this assessment. Liver up was associated with greater mortality rates (44–100%), contrasting with liver down (0–45.4%). Furthermore, liver herniation is associated with the need for extracorporeal membrane oxygenation (ECMO); in liver-down cases, the need for ECMO ranged from 0 to 25%, whereas liver-up cases needed ECMO in 42 to 80% of cases.

Lung-to-head Ratio: LHR

The search retrieved eight reviews.[1,3–5,10,11,15,18] Lung-to-head ratio is obtained by dividing the area of the lung contralateral to the hernia at the level of the four chambers view by the head circumference. Lung area measurement can be performed by obtaining the greatest orthogonal diameters at the level of the mid-clavicle line or at the level of the atrioventricular valves, or tracing the contours of the lung.[1,2,10,16,17] The tracing method is the most reproducible and accurate method for this parameter.[1,2,6,12,16,17] Reviews approaching left sided CDH with LHR used this ratio before 25 weeks of gestation and found that, if the LHR is less than 0.6 and there is liver herniation, there are no survivors; if LHR is 0.6 to 1.35, survival rate is 61%, and, when LHR is > 1.4,

Table 2 Summary of magnetic resonance imaging parameters for antenatal evaluation of severity of disease in CDH

MRI parameter	Number of reviews that mentioned the parameter	Lesion side	GA at evaluation (weeks)	Cutoff point for severe CDH	Definition of severity
TFLV	5	Right and left	18–38	$< 20cm^3$	Survival: TFLV $< 20\,cm^3$: 35% TFLV $> 40\,cm^3$: 90% Need for ECMO: TFLV $< 20\,cm^3$: 86% TFLV $> 40\,cm^3$: 10%
o/e TFLV	10	Right and left	≥ 22	25%	Survival: o/e TFLV $< 25\%$: 25% or less o/e TFLV 25–35%: 25–69% o/e TFLV $> 35\%$: 75 - 89%
Relative FLV	1	Not mentioned	Not mentioned	40%	Values correlate with poor outcomes
PPLV	3	Not mentioned	Not mentioned	15%	Survival: PPLV $< 15\%$: 40% PPLV $> 40\%$: survival 100%
LiTR	2	Not mentioned	Not mentioned	Liver herniation of 14% or more:	Values correlate with mortality
Modified McGoon index	1	Not mentioned	Not mentioned	1.0	Values correlate with severe pulmonary hypertension at 3 weeks of life

Abbreviations: CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; FLV, fetal lung volume; GA, gestational age; LiTR, liver intrathoracic ratio; MRI, magnetic resonance imaging; o/e, observed/expected; PPLV, percent predicted lung volume; TFLV, total fetal lung volume.
US parameters.

survival rate is 100%. When the side of the lesion is not mentioned, the most common cutoff point was less than 1.0 for poor outcomes such as mortality, need for ECMO, and lung hypoplasia.

Observed/Expected LHR: O/E LHR

Observed/expected LHR was mentioned in 16 studies.[1–7,10–18] Regardless of the side of the lesion, the o/e LHR was evaluated between 18 and 38 weeks. Observed/expected LHR is obtained by dividing the LHR of the examined fetus by the expected LHR for that GA. For left sided lesions, there are multiple ways of classifying the disease. The general concept is that there are subgroups of o/e LHR which correlate with mortality and, given the same subgroup of o/e LHR, liver herniation could enhance mortality. The most used cutoff point for severe disease was o/e LHR less than 25%. When o/e LHR is $\leq$ 25% and the liver is herniated (liver up), the estimated survival rate is 15%. For the same o/e LHR, if the liver is down, survival could reach 30%. If the o/e LHR is between 26 and 35% and the liver is up, survival rate is 55%; if the liver is down, survival rate is 65%. For o/e LHR between 36 and 45% and liver up, estimated survival rate is 65%. In the same subgroup, if the liver is down, survival is estimated to be 75%. When the o/e LHR is between 46 and 55%, survival rates are estimated to be 90% if the liver is up, and 100% if the liver is down. Finally, if the o/e LHR is greater than 55%, survival rates are estimated to be 85% if the liver is up and 100% if the liver is down. For right sided lesions, the reported cutoff point for severe disease is 45%. For o/e LHR greater than 45%, survival rate is at least 60%. For o/e LHR less than 45%, survival rate is up to 17%. Liver herniation, in this case, is not a prognostic factor because this type of hernia usually presents with liver up.

Quantitative Lung Index: QLI

The search retrieved one study that presented QLI as a parameter for evaluation of severity of the disease.[5] The present study did not report GA at evaluation or side of the lesion. Quantitative lung index is obtained by the division of the contralateral lung area by a tenth of the head circumference. Values below the 1st percentile, which corresponds to QLI 0.6, are predictive of lung hypoplasia.

MRI Parameters

Total Fetal Lung Volume: TFLV

Total fetal lung volume is the sum of both lung volumes obtained by MRI, which was mentioned as a severity of disease marker by 5 studies.[5,6,11,18,19] Total fetal lung volume was used to evaluate both left- and right-sided lesions. The GA at evaluation was variable, from 18 to 38 weeks. The cutoff point of TFLV less than 20 cm^3 was suggested. When the TFLV is greater than 40 cm^3, survival is estimated to be 90%, and the need for ECMO is around 10% of cases. When the

TFLV is below 20 cm^3, survival is up to 35% and 86% of these infants need ECMO. The TFLV was evaluated in some studies, with different populations, at variable GAs, aiming to elaborate reference values.[11,19] This topic was previously addressed,[20] and it was observed that normal and abnormal lung volumes at a certain GA could overlap. Furthermore, the range of normality widens throughout gestation. For example, at 25 weeks of gestation, the normal range varies from 20 to 35 cm^3, and, at 35 weeks of gestation, it varies from 58 to 95 cm^3. Therefore, the TFLV is generally used to obtain the o/e TFLV.

Observed/Expected TFLV: o/e TFLV

This criterion was reported in 10 studies.[5,7,10–12,15–19] This parameter is the MRI analog of o/e LHR. The suggested cutoff point is 25%: below this threshold, survival rate is 25% or less. When o/e TFLV is between 25 and 35%, survival is reported as 25 to 69%. Survival of 75 to 89% is obtained when o/e TFLV is greater than 35%. Evaluation of the o/e TFLV is feasible for right- and left-sided lesions at a GA of 22 weeks or more.

Relative Fetal Lung Volume: Relative FLV

Relative FLV was cited in one study.[10] A relative FLV of 40% or less correlates with poor outcomes. Gestational age at the evaluation and side of the lesion were not mentioned.

Percent Predicted Lung Volume: PPLV

Percent predicted lung volume was reported by 3 studies.[5,10,18] The suggested cutoff point for severe disease was less than 15%. Below this threshold, survival rates are estimated to be 40%, and above this threshold, the survival rate is 100%. There was no mention of GA at evaluation or side of the lesion.

Liver Intrathoracic Ratio: LiTR

The search retrieved two studies that mentioned LiTR.[5,18] None of the studies mentioned either the GA for assessment or the side of the lesion. This parameter is a ratio between herniated liver volume and fetal thoracic volume. Liver intrathoracic ratio of 14% or greater correlates with neonatal mortality.

Modified McGoon Index

The modified McGoon index is a mathematical relation involving the sum of the diameters of the right and left pulmonary arteries, which are then divided by the diameter of the aorta. This parameter was assessed by one study.[10] Values lower than 1.0 correlate with severe pulmonary hypertension at 3 weeks of life. Side of the lesion and GA at evaluation were not mentioned.

Conclusion

Several parameters were evaluated for severity of CDH assessment throughout the past 10 years. Although none of the parameters was reported to be superior to the others, the most mentioned ones were o/e LHR, LHR, liver position, o/e TFLV, and TFLV. This information may be used as the background for other studies comparing the performance of different diagnostic techniques.

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

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FEBRASGO POSITION STATEMENT

Progestogen-only oral contraceptives

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The National Specialized Commission on Contraception of the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo) endorses this document. The content production is based on scientific studies on a thematic proposal and the findings presented contribute to clinical practice.

Key points

- Progestogen-only oral contraceptives comprise pills composed of progestogens with distinct contraceptive properties, including central or peripheral effects.
- Norethisterone acetate 0.35 mg, desogestrel 75 mcg and drospirenone 4 mg are the progestogen pills available in Brazil. The main mechanism of contraceptive action of desogestrel and drospirenone is the inhibition of the ovulation. The main effect of norethisterone is the alteration of cervical mucus.
- Progestogens used alone for contraception that promote inhibition of the ovulation have greater contraceptive efficacy.
- The bleeding profile of progestogen-only oral contraceptives is regimen dependent. Desogestrel and norethisterone taken continuously have a variable bleeding pattern, ranging from amenorrhea to spotting or even irregular bleeding. Drospirenone alone in a 24/4 regimen has a predictable bleeding pattern in most cases.
- As progestogen pills have a lower risk of cardiovascular events, they are particularly indicated for women with contraindications to combined contraceptives, given the absence of estrogen in their formulations.

Recommendations

- Progestogen pills containing desogestrel or drospirenone have lower failure rates due to the antiovulatory effect and should be considered for women who require highly effective contraceptives.
- The use of oral desogestrel alone, as well as of norethisterone, should be continuous. Drospirenone alone should be used for 24 days actively followed by a four-day interval.
- All progestogen-only pills are indicated and safe for use in nursing mothers.
- Counseling about the irregular bleeding pattern that may occur when a progestogen pill is prescribed is essential. Prior guidance leads to greater continuity and adherence to this contraceptive modality.
- Progestogen pills may be indicated for obese women, smokers, hypertensive or those with risk factors for cardiovascular disease.
- Progestogen-only oral contraceptives are not associated with a higher risk of venous thromboembolism and may even be indicated for women with a personal history of deep venous thrombosis or pulmonary embolism.
- There is no restriction on the use of progestogen pills by women with a history of cardiovascular disease, including myocardial infarction or stroke.
- Progestogen pills are not associated with reduced bone mineral density.

Background

Approximately 100 million women worldwide currently use a combined oral contraceptive (COC) containing an estrogen-progestogen combination.[1] Combined oral contraceptives are associated with a higher risk of venous thromboembolism (VTE) and cardiovascular disease.[2,3] The World Health Organization (WHO) attests that progestogen-only oral contraceptives, also known as POPs (progestin-only pills), do not offer a higher risk for VTE, myocardial infarction, and stroke.[4] In this sense, aspects related to safety may result in a greater prescription of POPs for a greater number of women eligible for this contraceptive modality. In Brazil, an analysis of 1,113 women from the supplementary health system showed that the use of a single POP, desogestrel, was reported by 18% of users of contraceptive methods.[5] The most relevant aspects of POPs should be observed in view of the option or medical indication, since all methods containing only progestogens have different biochemical and pharmacological characteristics, in addition to the contraceptive

effect itself. The first question that may generate doubt refers to the "progestogen pills" term, which is widespread in the gynecological setting. This group includes compounds previously called minipills, which contained norethisterone, lynestrenol and levonorgestrel (the last two no longer available in Brazil), in addition to desogestrel alone. Recently, drospirenone alone has been incorporated into the group of POPs.[6] The contraceptive mechanism of action is different among POPs. The main mechanism of action of minipills is the alteration of the cervical mucus and secondarily, the endometrial activity hostile to implantation.[7] On the other hand, desogestrel and drospirenone alone have gonadotropic blockade as their main mechanism of action, which offers greater contraceptive efficacy for women who are not breastfeeding.[8,9] Thus, although "progestogen pills" represent the different isolated progestogens used orally, the mechanisms of action are distinct and ultimately, reveal the main characteristic of a contraceptive: effectiveness. The aim of this document is to critically analyze the main characteristics of POPs available in Brazil, with emphasis on frequently asked questions in the practice of professionals involved with the subject.

What are the main differences between POPs? What are the effectiveness rates of these compounds?

Norethisterone 0.35 mg, desogestrel 75 mcg and drospirenone 4 mg constitute the isolated oral progestogens used in contraception in Brazil. Norethisterone and desogestrel correspond to progestogens structurally related to 19-nortestosterone, synthesized from modifications in the testosterone molecule. Drospirenone, in turn, is a progestogen structurally related to 17α -spironolactone.[10] Although norethisterone and desogestrel interact with the androgen receptor based on their structural conformation, androgenic effects such as acne and hirsutism are rarely observed clinically. This is explained by the small dose of norethisterone used for contraception (0.35 mg) and the antiovulatory action by suppressing the luteinizing hormone levels of desogestrel at a dose of 75 mcg. The dose of norethisterone used in contraception is insufficient for expressive androgenic stimulation of terminal effectors in the pilosebaceous unit. Desogestrel provides less androgenic activity as a result of gonadotropic blockade and consequent reduction in ovarian testosterone production.[10] Isolated drospirenone, in turn, in addition to gonadotropic blockade, has an antiandrogenic effect, which may promote improvement in acne.[11] Other relevant aspect refers to the way POPs are used. Norethisterone and desogestrel are used continuously, while drospirenone is used in a cyclic regimen, with 24 active pills followed by four days of placebo.[10,11] The effectiveness of POPs depends on the mechanism of action. As norethisterone alone has the main effect on cervical mucus, it depends on high motivation for daily use at the same time (with a maximum delay of three hours). As a result, contraceptive failure rates range from 4 to 7.9 pregnancies per 100 women per year.[12,13] Among POPs that provide gonadotropic blockade, desogestrel alone has a failure rate of 0.14/100 women per year,[14] while drospirenone shows a failure rate of 0.72/100 women per year[15] so, these are classified as highly effective methods.

How should the optimal use of POPs be and what factors can influence their effectiveness?

The main mechanisms of action of POPs must be considered to obtain greater effectiveness. As norethisterone acts by promoting changes in the cervical mucus, its use demands care: must be continuous and at the same time, with a maximum variation of three hours. Studies show that minipills have a lower failure rate in women over 40 years of age, probably as a result of the natural decline in fertility in this age group.[16] As most women under 40 years of age maintain ovulatory cycles, the effect of norethisterone on cervical mucus should be intense, aiming at greater effectiveness. The effect on cervical mucus, reducing sperm penetration, occurs from 4 to 22 hours after the first dose of progestogen, and the repetition of doses causes difficulty in sperm ascent in the subsequent 24 hours, provided there is no interruption or forgetting of doses. There is no evidence that other factors, such as weight or smoking can interfere with the antisperm activity of small doses of norethisterone.[16] On the other hand, desogestrel and drospirenone alone have an antiovulatory effect, showing greater efficacy regardless of age, and are currently more appropriate choices of a POP. Studies with intentional delays or omission of active pills were performed to attest the antiovulatory effect of progestogens alone. Desogestrel used continuously was evaluated after three 12-hour delays in taking the dose, showing an escape ovulation rate of 1% generally occurring after seven days.[17] Thus, guidance in case of forgetting the dose of this contraceptive formulation is to respect the 12-hour period. Drospirenone alone at a dose of 4 mg is used in a cyclic regimen of 24 active pills, followed by four placebo pills. A study with four intentional 24-hour delays in the administration of active pills showed an escape ovulation rate of 0.8%.[18] The difference can be explained by the properties of drospirenone, which has plasma half-life of approximately 33 hours. In fact, mean rates of escape ovulation with combined oral contraceptives are around 2%.[19] Factors that could negatively influence the antiovulatory activity of drospirenone and desogestrel alone, such as obesity or smoking, have not been identified.

Drug interactions, particularly with anticonvulsants, should be considered.[20]

What are the effects of progestogens alone on lactation?

The importance of contraception in the puerperal period is widely known, and the use of effective contraceptive methods is recommended as early as possible. Most contraceptives, except for combined hormonal contraceptives, can be indicated in the immediate postpartum period both for lactating and non-lactating women.[20] Progestogens alone are traditionally indicated in contraception for breastfeeding women, as they do not present adverse effects on lactation.[21] Classically, the WHO recommends starting progestogens from the sixth week after delivery for breastfeeding women, and it can be started immediately by non-lactating women.[22] However, for patients at high cardiovascular or thromboembolic risk, progestogens can be prescribed in the immediate postpartum period, even for breastfeeding women, since the method does not add risk of thrombosis.[23] Furthermore, desogestrel doses higher than 75 mcg do not cause any difference in the composition or amount of milk, nor in the development and growth of children, compared to women who used postpartum copper IUDs.[24] An important aspect discussed recently, during the pandemic, refers to the clotting disorder involving the infection by SARS-CoV-2.[25] As puerperal women can be contaminated and the hormonal condition of this period itself increases the thromboembolic risk, concerns about the contraceptive method used have been considered, reinforcing the indication of methods containing progestogen-only.[26] Drospirenone alone at a dose of 4 mg was evaluated in a subgroup of lactating women, calculating the passage of the hormone into maternal milk in 24 hours and the consequent exposure of the newborn to drospirenone. Considering a daily intake of 800 mL of breast milk, in which the drospirenone concentration reached 4478 ng, 0.11% of the progestogen was transferred to the newborn, attesting the safety of the method during breastfeeding. Thus, drospirenone can also be indicated in the postpartum period to lactating women.[27]

How is the bleeding profile characterized with the different progestogens in contraception?

The bleeding pattern with the use of POPs is variable, ranging from amenorrhea to frequent and irregular bleeding. In general, women exposed to minipills such as norethisterone will continue to ovulate and have regular cycles, while those who experience ovarian suppression will have irregular and unpredictable bleeding. The mechanisms involved in bleeding during the use of progestogen-only pills are not well established. Possible explanations for the bleeding alterations when using contraceptives include more changes in tissue perfusion in combination with local angiogenic factors, together with the permeability of superficial vessels and the change of receptor functions for endometrial steroid hormones.[28] In fact, irregular bleeding is the most commonly cited reason for discontinuing POPs, and occurs in up to 25% of users.[14,29] The WHO recommends using the analysis by "reference period" (RP),[30] defined as periods of time measured in number of days to analyze the bleeding pattern with different contraceptives. In most current studies, the 90-day RP is used to characterize the bleeding pattern with hormonal contraceptives, particularly with progestogens alone. In a one year follow-up study, two progestogen-only contraceptives, desogestrel 75 mcg and levonorgestrel 30 mcg, were compared.[14] The analysis of the bleeding pattern followed the WHO nomenclature. In the RP, about 50% of women on desogestrel 75 mcg experienced amenorrhea or infrequent bleeding compared to 10% of levonorgestrel users. Only 4% of women on desogestrel experienced frequent bleeding, in contrast to 10% of women in the levonorgestrel group. The incidence of prolonged bleeding decreased with time in both treatment groups. As the regimen of drospirenone alone has a four-day break between active pills, the bleeding profile is distinct, and evaluated in 30-day RPs. In a phase 3 double-blind, randomized, controlled clinical trial study involving healthy women aged 18-45 years, the bleeding profile of the contraceptive containing drospirenone only (4 mg) on a 24/4 cyclic regimen was compared to the contraceptive containing desogestrel (75 mcg) used continuously over nine cycles.[31] Scheduled bleeding was defined as any bleeding or spotting that occurred during the hormone-free intervals (between days 25 and 28, ± one day), lasting up to eight consecutive days for women using drospirenone. For this group, unscheduled bleeding was defined as any blood loss or spotting occurring between days 2 and 23 of each cycle, corresponding to the period of intake of active pills. For the group of desogestrel users, definitions for scheduled bleeding were not considered, and all days of bleeding or spotting during the use of active pills were recorded. Women who used desogestrel experienced a percentage decrease in bleeding/spotting rates from 74% to 45.3% between cycles 2 and 9, respectively. When considering only unscheduled bleeding/spotting, the percentage for drospirenone users was significantly lower compared to desogestrel users, particularly between cycles 2-6 and 2-9. The mean number of days of unscheduled bleeding during cycles 2-9 was significantly lower for drospirenone (21.5 days) compared to desogestrel (34.7 days). There was also a trend towards fewer bleeding/spotting days over time for drospirenone users (mean 13.1 days between cycles 2-4 to 9.7 days between cycles 7-9). The desogestrel group experienced a mean reduction from 16.9 days to 10.8 days, between cycles 2-4 and 7-9, respectively.

The number of bleeding/spotting days was lower in the group of women who used drospirenone at all defined treatment periods.

What is the impact of progestogen-only contraceptives on bone mass?

The effects of estrogens as antiresorptive agents on bone mass are widely known.[32] Low estrogen levels are associated with inadequate bone remodeling, with increased bone resorption activity.[33] The use of estrogen-free contraceptives with antigonadotropic effects may raise doubts about bone metabolism. Studies show that mean estradiol concentrations in users of intramuscular depot progestagen (medroxyprogesterone acetate – MPA) are lower than those observed with use of oral desogestrel or drospirenone. In fact, estradiol rates measured with the use of MPA, desogestrel 75 mcg and drospirenone 4 mg, were 26.6 pg/mL,[34] 54.4 pg/mL[35] and 48.4 pg/mL,[36] respectively. Note that according to the hierarchy of tissue-specific estrogenic response, levels below 20 pg/mL are associated with substantial bone loss.[37] Studies on the subject are focused especially on the use of intramuscular depot MPA, due to the pronounced gonadotropic blockade and the consequent hypoestrogenic effect. In a systematic review, Curtis et al.[38] observed that a study reported a higher number of stress fractures in users of MPA compared to non-users of the contraceptive. However, this finding was not significant after checking baseline BMD in both groups. The authors also found that cross-sectional studies demonstrate a decrease in BMD with variations within one standard deviation for women who used MPA versus non-users and, according to longitudinal studies, there was a recovery of BMD after discontinuation of use. Thus, they concluded that, except for depot MPA, other progestogen-only contraceptives would not affect BMD.

What is the risk of having cardiovascular disease with progestogen-only contraceptives?

The association between POPs and the risk of various cardiovascular outcomes, including VTE, myocardial infarction, stroke, hypertension, and diabetes by route of administration was also studied. In a review of 19 studies[39] based on the random effects model, the pooled adjusted relative risks (RRs) for VTE, myocardial infarction and stroke for POP users versus non-users were 1.06 (95% confidence interval [CI]: 0.70-1.62), 0.98 (95%CI: 0.66-1.47) and 1.02 (95% CI: 0.72- 1.44), respectively. No effect of POP use on blood pressure was found. Hence the assumption that the oral use of POPs is not associated with a higher risk of developing various cardiometabolic outcomes. On the other hand, women with past medical conditions that offer higher risk of thrombosis should also not use estrogen-containing contraceptives. Little is known about POPs in this situation. In the systematic review by Tepper et al.,[40] most evidence do not suggest a higher risk of venous or arterial events with the use of POPs. Thus, hypertensive or smoker women can still benefit from using POPs to prevent pregnancy.

According to eligibility criteria, under which conditions should oral progestogen-only methods be prioritized?

Progestogen-only methods have few contraindications. They are also highly indicated in clinical situations in which there is an absolute contraindication to the use of hormonal contraceptives containing estrogens (combined hormonal contraceptives).

The unrestricted indications (categories 1 and 2) for progestogen-only methods, when estrogen-associated methods are generally contraindicated, are summarized in chart 1.[22]

Chart 1. Indications for progestogen-only methods, particularly when the use of combined hormonal contraceptives is contraindicated

Patient choice, regardless of age
Lactation, including the period from 6 weeks to 6 months after delivery
Smokers aged over 35 years
Obesity (BMI > 30 kg/m^2)
Multiple risk factors for cardiovascular disease
Controlled high blood pressure or levels of 140-159/90-99 mmHg
Known thrombophilia, history of DVT or PTE, thromboembolism on anticoagulant use
Major surgeries with immobilization
Dyslipidemia
Valvular heart disease, even complicated
Systemic lupus erythematosus, except in the presence of antiphospholipid antibodies or severe thrombocytopenia
Headaches, including migraine with aura
Epilepsy, depression
Menstrual irregularities, endometriosis, benign ovarian cysts, cervical ectopia, gestational trophoblastic neoplasia, cervical intraepithelial neoplasia
Benign breast diseases
Endometrial and ovarian cancer
Uterine fibroids, pelvic inflammatory disease, STIs
High risk for HIV, HIV positive, AIDS
Diabetes mellitus
Thyroid diseases
Gallbladder diseases, hepatitis, compensated cirrhosis, benign liver tumors
Anemias (including thalassemia and sickle cell anemia)
Concomitant use of antiretrovirals, antifungals, broad-spectrum antibiotics, and antiparasitics

BMI: body mass index; DVT: deep vein thrombosis; PTE: pulmonary thromboembolism; STIs: sexually transmitted infections; AIDS: acquired immunodeficiency syndrome; HIV: human immunodeficiency virus
Source: World Health Organization. Medical eligibility criteria for contraceptive use [Internet]. 5th ed. Geneva: WHO; 2015 [cited 2021 Oct 24]. Available from: https://www.who.int/publications/i/item/9789241549158.[22]

Final considerations

The class of progestogen-only oral contraceptives combine efficacy with very broad indications, including critical clinical situations, particularly when combined hormonal methods are not recommended. Although they are described together, progestogen contraceptive methods must be analyzed individually. The specific characteristics of each compound require a critical analysis focused on the clinical condition where the method is intended to be instituted. Note that the unpredictable bleeding pattern is the main element responsible for the abandonment of POPs. In this sense, desogestrel and drospirenone alone are different; drospirenone showed better cycle control in phase 3 studies, allowing greater contraceptive coverage in situations where estrogen is contraindicated.

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Rogério Bonassi Machado
Faculdade de Medicina de Jundiaí, Jundiaí, SP, Brazil.
Rogério: https://orcid.org/0000-0001-9361-0905

Carlos Alberto Politano
Universidade Estadual de Campinas, Campinas, SP, Brazil.
Carlos: https://orcid.org/0000-0001-8054-1621

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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:

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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;

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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.

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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?

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Abstract: Does the abstract contain the proper article synthesis?

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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

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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.

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*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.***

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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
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