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Editorial

Placenta Accreta Spectrum Disorders: Current Recommendations from the Perspective of Antenatal Imaging

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The Burden of a Previous Uterine Scar

Cesarean section (CS) is the most commonly performed surgical procedure in the United States (more than a million surgeries per year) and one of the most frequently performed procedures worldwide.[1] Although CS is a potentially life-saving procedure when correctly indicated, its worldwide use has steadily increased over the last decades (currently 21.1% globally, ranging from 5% in sub-Saharan Africa to 42.8% in Latin America and the Caribbean). Moreover, it will continue increasing worldwide (2030 projection: 28.5% globally, ranging from 7.1% in sub-Saharan Africa to 63.4% in Eastern Asia).[2] Dominican Republic, Brazil, Cyprus, Egypt and Turkey are the worldwide leaders, with CS rates ranging from 58.1% to 50.8%, respectively, which points to a worrying trend towards overmedicalization of childbirth and overuse of CS.[2] Other surgical procedures such as dilation, curettage, myomectomy, and surgical hysteroscopy are less frequent than CS. Still, due to the trend towards more advanced maternal age, the number of pregnant women previously submitted to these procedures also tends to increase. These data point to a growing number of pregnancies in surgically manipulated uteruses.

Pregnant women with previous uterine scars are at risk for increased morbimortality. Complications such as placenta previa, spontaneous uterine rupture, uterine dehiscence (with or without placental intrusion), cesarean scar pregnancy (CSP) and placenta accreta spectrum disorders (PAS) are associated with potentially life-threatening uterine bleeding, extra-uterine lesions and preterm delivery (►**Figure 1**).[3]

A previous CS increases up to 60% the risk for placenta previa at delivery (approximate incidence: 0.3-2%), with a dose-response pattern based on the number of previous surgeries.[4] The incidence of uterine rupture was estimated as being 5.1 per 10,000 in scarred and 0.8 per 10,000 in unscarred uteruses, with 72% occurring during spontaneous labor.[5] A retrospective cohort of 169,356 pregnancies in a high-risk tertiary hospital reported 0.1% cases of uterine disruption - 83% dehiscence and 17% complete uterine ruptures - the latter significantly more associated with adverse perinatal outcomes. All these pregnancies had previous CS, mainly by low transverse incisions (60%).[6] CSP was estimated to range from 1:1,800 to 1:2,216 pregnancies, 52% in women with only one previous CS.[7] A systematic review and meta-analysis reported that the median prevalence of placenta previa with PAS was 0.07%, with an incidence of PAS in women with placenta previa of 11.1%. More than 90% of PAS cases occurred in women with a previous CS and low-lying/placenta previa.[8] Based on its mounting incidence and potential impact on maternal-fetal mortality, current strategies for mitigating the risks of CSP/PAS must be discussed.

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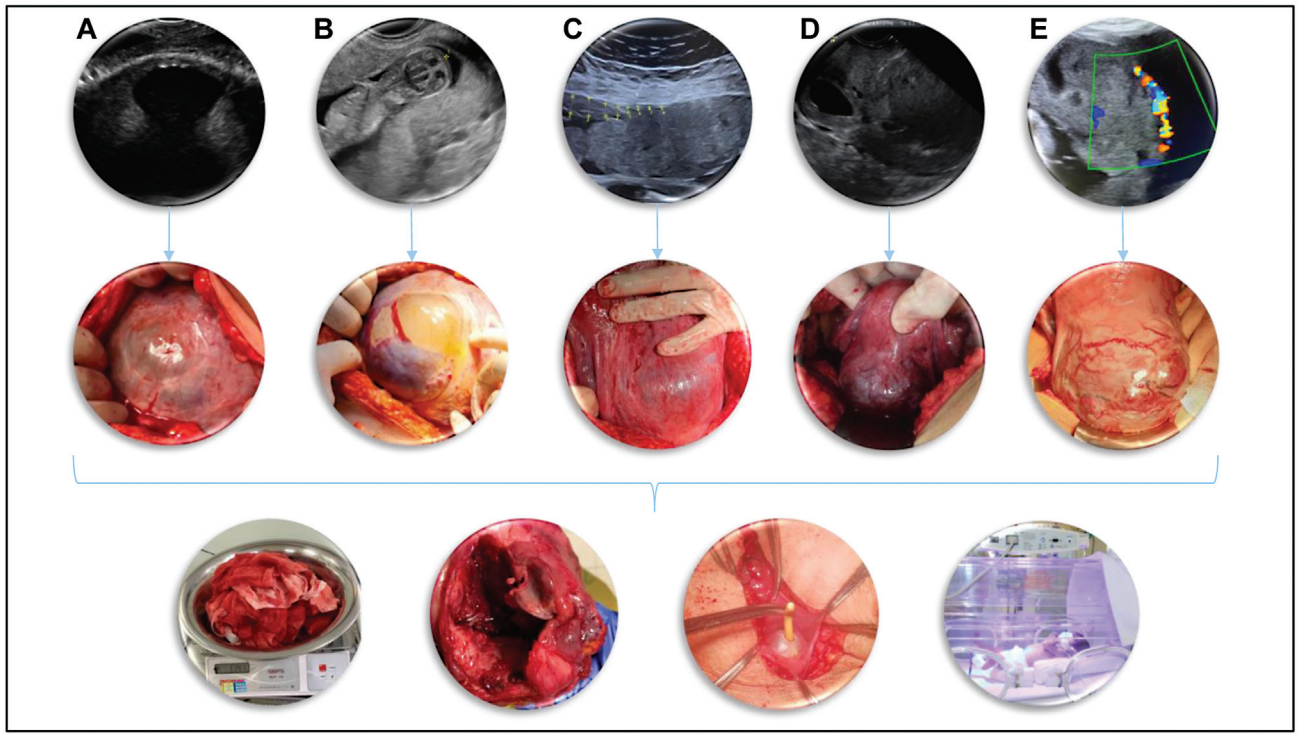

Fig. 1 The broader spectrum of potential complications in pregnancies with prior uterine scars. On first and second lines, the respective ultrasound and surgical appearances of the following potential pregnancy abnormalities: **A**- myometrial dehiscence without overlying placenta; **B**- myometrial dehiscence with partial placental intrusion; **C**- myometrial dehiscence with complete placental intrusion; **D**- cesarean scar pregnancy; **E**- placenta accreta spectrum. Apart from case A, placenta previa is present on all other cases. On the lower line, potential perinatal adverse outcomes: major uterine bleeding, uterine rupture, unintentional bladder lesion, and neonatal complications of prematurity.

Updates on CSP/PAS Pathophysiology

Although the pathophysiological reasons for some women having abnormal uterine healing after uterine surgical procedures are still not fully understood, this might be mainly related to individual factors leading to remodeling of a previously healthy myometrium and its substitution for uterine niches with defective decidua basalis and low residual myometrial thickness. When implantation occurs over or into these defective scars, the closer proximity of the placenta with larger superficial arteries, increased fibrinoid deposition between placental villi and the myometrial layer, and adhesions from previous surgical procedures are directly associate with the occurrence of adverse outcomes.[9,10]

Then, it is essential to emphasize contemporary pathophysiological concepts with important practical applicability regarding pregnancies in a scarred uterus. Current evidence does not support the role of placental "cancer-like invasion" on the pathophysiology of CSP/PAS[9]; Instead, the shared histopathology between CSP and PAS has been already demonstrated,[11] and recent prospective studies[12,13] support the primary role of an abnormal implantation into a previously scarred myometrium, its progressive dehiscence and uterine remodeling as the proxy for the continuum between CSP and PAS. Therefore, the existence of extrauterine placental "invasion" (invasive percreta[14] or the International Federation of Gynecology and Obstetrics - FIGO 3b[15]) is being currently challenged. In reality, the challenging surgical dissection of dense adhesive disease seems to produce the lesions disrupting the serosa/scar shell observed on gross anatomy, which can lead the pathologist to an incorrect diagnosis of placental "invasion".[12,13] Also, the absence of placental "invasion" does not lessen the severity of PAS, as the surgical difficulty generated by the hypervascularization and anatomical distortion from dense adhesions that involves adjacent organs are associated with potential life-threatening complications. More importantly, increase production of vascular growth factor induces the formation of a rich anastomotic pattern between vaginal, uterine, and vesical arteries, which represents a surgical challenge and constitutes the basis for the massive hemorrhagic risk of women affected by PAS. Whether the placenta reaches the deeper layers of the uterine wall is less important than the size and topography of the lesion in the uterus, which are related to the severity and the type of treatment required.[16–18]

The Importance of Antenatal Screening/Diagnosis for PAS and Surgical Planning

Antenatal recognition of CSP/PAS is crucial, because timely referral of suspected cases to specialized referral centers with multidisciplinary teams that manage these complex

cases continuously is the key to reducing perinatal morbimortality.[19] A retrospective Latin American study reported that among 52 maternal deaths related to PAS, 40% did not have antenatal diagnosis and almost 46% were not evaluated in a PAS referral hospital before delivery. According to the authors, all maternal deaths were potentially preventable, 77% by low- to moderate-complexity interventions.[20] Therefore, regional PAS care pathways should be set up to ensure every pregnant women has access to qualified primary care ultrasound and, in case of a positive screening for CSP/PAS, prompt referral for a specialized diagnostic center should be made. Fetal medicine providers specialized in PAS will be responsible for defining whether the patient should be managed in a specially funded PAS referral center or a low-complexity hospital.[21] Regional PAS referral centers should be carefully identified by stakeholders based on quality markers in care, such as application of comprehensive care models, human and technological resources, surgical expertise, self-assessment and research output.[22–24]

For screening purposes, all sonographers responsible for obstetrical ultrasounds should always ask themselves two questions: (1) is the placenta low-lying? (2) did the patient have a previous uterine surgery? If the answer is positive to both questions, the patient should be considered at risk for CSP/PAS at any gestational age and referred to a PAS specialized diagnostic center.[25] Screening for CSP should ideally be performed for all patients with previous CS between 6-9 gestational weeks, when the gestational sac is more related to the uterine scar niche than to the uterine cavity, resulting in better accuracy.[26] The reason for the higher accuracy of ultrasound in detecting CSP in the early compared to the late first trimester relies on the fact that with advancing gestation, the upper pole of the gestational sac grows towards the uterine fundus, thus making assessment of the relationship between the sac and the area of the prior CS scar more difficult to assess. If the patient is first seen for the 11-14 week scan, positive answers to both questions should trigger a referral to the specialized center.[27] CSP/PAS detection at the time of 11-14 weeks scan has been also reported in several large studies with good sensitivity and specificity.[28] Despite that, the role of first trimester ultrasound in the detection of CSP/PAS in terms of clinical and economic effects is far from established. For locations with more restricted access to ultrasound, a contingent screening strategy for placenta previa on the 18-24 week scan, with a reassessment of persistent low-lying/placenta previa between 32-34 weeks and referral of patients to referral centers with positive answers for both questions at this moment seems to be more cost-effective and very accurate.[25,29] The disadvantage of this last strategy is the loss of opportunity for counselling and early treatment of CSP cases, which are associated with fewer complications.[30]

Diagnostic accuracy for CSP/PAS in specialized diagnostic centers, mainly using ultrasound but relying on nuclear magnetic resonance for specific cases, is usually higher than 90%.[31–33] Recently, one expert consensus by modified Delphi procedure was published regarding definitions and sonographic reporting systems for CSP[34] and another for assessing the recommended ultrasound signs for evaluation of PAS.[35] According to the latter, ultrasound signs more helpful in predicting surgical outcomes in patients at high risk for PAS are (1) loss of clear zone, (2) bladder wall interruption, (3) placental lacunae and (4) placenta previa involving the cervix. These recommendations should ideally be used to standardize diagnostic features across all centers.

Most importantly, previous PAS classifications are not helpful for diagnostic or treatment purposes since there are many false positives and false negatives when trying to distinguish between accreta/increta/percreta or FIGO 1/2/3 cases[12,36] as well as between uterine dehiscence with placental intrusion and PAS cases, both by imaging studies and intraoperative assessment.[37] Based on current pathophysiological concepts, it seems much more appropriate that imaging specialists should focus on features that would help counsel patients regarding the risks of worse perinatal outcomes, such as those described on the modified Delphi consensus, and help the surgeons regarding the necessary interventions. Fetal medicine specialists should do their best to describe the topography of the uterine dehiscence(s), its size, proximity to other pelvic structures (such as the bladder, cervix, parametria, uterine arteries), degree and location of sub placental vascularity, and lower and upper limits of the placenta. A face-to-face debriefing between the diagnostic and the surgical team before the surgery or a preoperative/intraoperative scan would be highly recommended to help the multidisciplinary team prepare for more challenging cases and define essential strategies, such as type of skin incision, location of hysterotomy, use of ureteral stenting or invasive radiology and the possibility of a sub-total hysterectomy.

Instead of trying to describe the "depth of invasion/protrusion/involvement", fetal medicine specialists should do their best to anticipate, as much as possible, uterine, and placental features targeted on the PAS topography classification and surgical staging, which will eventually impact on the management decision,[17,18] as shown in ►**Figure 2**. Intraoperatively, surgeons will analyze three essential aspects: (1) Is it possible to separate the bladder from the uterus? (2) Is there at least 2 cm of healthy myometrium caudal to the PAS area and above the cervix? (3) Is there healthy myometrium in over 50% of the uterine circumference? Positive answers to these 3 questions would direct the surgical team to a more conservative approach, achievable in almost 80% of cases.[18,38] From the point of view of imaging studies, there is lack of evidence to support prediction of bladder-uterus adhesive disease (question 1). However, placental implantation above/below the superior bladder reflection, the thickness of the myometrial layer, the vascularity of the myometrium/bladder interface, and the sliding sign between the bladder and the gravid uterus should be further explored in future studies and might be helpful to predict surgically challenging cases. In addition, the transvaginal scan can accurately define the characteristics of the placenta and the distance of its lower border from the internal cervical os, as well as cervical remodeling (question 2). Finally, the size and location of the uterine

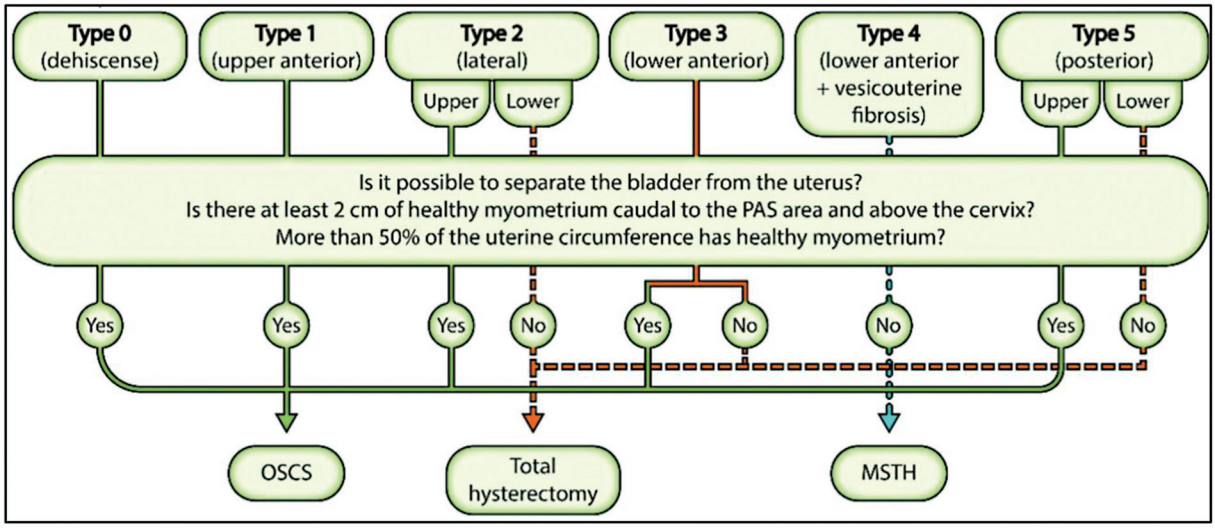

Fig. 2 Intraoperative topographical classification for placenta accreta spectrum and management protocol. MSTH, Modified subtotal hysterectomy; OSCS, One-step conservative surgery; PAS, Placenta accreta spectrum. **Source:** Adapted from Nieto-Calvache AJ, Aguilera LR. Simulation, a fundamental component of training to treat placenta accreta spectrum. Rev Bras Ginecol Obstet. 2022;44(12):1159-60. doi: 10.1055/s-0042-1760216.[38]

dehiscence/PAS should be clearly described, helping to answer question 3.

As previously cited, it may be challenging to differentiate a large uterine dehiscence with overlying placenta from an anterior lower uterine PAS. But does it matter? The definitive diagnosis between PAS vs. non-PAS is the role of a targeted histopathological diagnosis. More than that, even extensive uterine dehiscence might lead to increased bleeding and the need for a hysterectomy, outcomes that could eventually be more severe than in minor PAS cases.[37]

Another major issue is that the previously published literature does not report the diagnostic accuracy of prenatal imaging in predicting complex cases of PAS. Most studies reported the prediction of maternal outcome, including need for transfusion or hysterectomy. However, these measures are not entirely associated with difficulty at surgery and are largely affected by several factors, such as operator's experience or type of intervention, and do not necessary reflect the difficulty at surgery. Studies exploring the diagnostic performance of ultrasound in predicting complex case are needed to improve prenatal counselling and management of pregnancies complicated by PAS.

Potential PAS diagnoses issued by expert sonographers must be always confirmed by intraoperative staging and before carrying out potentially morbid interventions.[17] The presence of imaging specialist on the surgical theater is recommended and feedback from the surgical team to the prenatal diagnosis team are essential to ascertain diagnostic quality control and improve the whole team performance.

Antenatal diagnosis of PAS is not easy and most obstetricians do not receive comprehensive training during their residence to diagnose or treat this disease. It is essential to join efforts at the regional and international level to provide women with the best possible care. Telehealth emerges as a strategy to accelerate the set-up of regionalization of care. Telemedicine support can be directed to both primary and specialized services, improving timely diagnosis, promoting individualized and accurate treatment, and strengthening local interdisciplinary groups.[39,40]

To conclude, qualified ultrasound screening for CSP/PAS should be widely available, focusing on risk factors and placental position on ultrasound. Referral pathways to PAS specialized centers should be set up to ensure prompt assessment and confirmation of a high-risk PAS situation. Trained providers should assess these pregnant women. All efforts should be made to start the topographical classification of PAS antenatally and assist in the surgical planning, which must be carried out in the specialized referral center to manage PAS.

Conflicts to Interest
None to declare.

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Impact of Obesity and Hyperglycemia on Pregnancy-specific Urinary Incontinence

Impacto da obesidade e hiperglicemia na incontinência urinária específica da gravidez

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Abstract

Objective The lack of data on the impact of hyperglycemia and obesity on the prevalence of pregnancy-specific urinary incontinence (PSUI) led us to conduct a cross-sectional study on the prevalence and characteristics of PSUI using validated questionnaires and clinical data.

Methods This cross-sectional study included 539 women with a gestational age of 34 weeks who visited a tertiary university hospital between 2015 and 2018. The main outcome measures were the prevalence of PSUI, the International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF), and the Incontinence Severity Index (ISI) questionnaires. The women were classified into four groups: normoglycemic lean, normoglycemic obese, hyperglycemic lean, and hyperglycemic obese. The differences between groups were tested using descriptive statistics. Associations were estimated using logistic regression analysis and presented as unadjusted and adjusted odds ratios.

Results Prevalence rates of PSUI were no different between groups. However, significant difference in hyperglycemic groups worse scores for severe and very severe PSUI. When adjusted data for confound factors was compared with normoglycemic lean group, the hyperglycemic obese group had significantly higher odds for severe and very severe forms of UI using ICIQ-SF (aOR 3.157; 95% CI 1.308 to 7.263) and ISI (aOR 20.324; 95% CI 2.265 to 182.329) questionnaires and highest perceived impact of PSUI (aOR 4.449; 95% CI 1.591 to 12.442).

Conclusion Our data indicate that obesity and hyperglycemia during pregnancy significantly increase the odds of severe forms and perceived impact of PSUI. Therefore, further effective preventive and curative treatments are greatly needed.

Keywords
- urinary incontinence
- pregnancy
- diabetes *mellitus*
- maternal obesity

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Resumo

Objetivo A falta de dados sobre o impacto da hiperglicemia e obesidade na prevalência de incontinência urinária específica da gravidez (IAPS) nos levou a realizar um estudo transversal sobre a prevalência e características da IAPS usando questionários validados e dados clínicos.

Métodos Este estudo transversal incluiu 539 mulheres com idade gestacional de 34 semanas que visitaram um hospital universitário terciário entre 2015 e 2018. As principais medidas de desfecho foram a prevalência de PSUI, o formulário curto do International Consultation on Incontinence Questionnaire (ICIQ-SF) e os questionários do Incontinence Severity Index (ISI). As mulheres foram classificadas em quatro grupos: magras normoglicêmicas, obesas normoglicêmicas, magras hiperglicêmicas e obesas hiperglicêmicas. As diferenças entre os grupos foram testadas por meio de estatística descritiva. As associações foram estimadas usando análise de regressão logística e apresentadas como odds ratio não ajustadas e ajustadas.

Resultados As taxas de prevalência de PSUI não foram diferentes entre os grupos. No entanto, houve diferença significativa nos grupos hiperglicêmicos com piores escores para PSUI grave e muito grave. Quando os dados ajustados para fatores de confusão foram comparados ao grupo magro normoglicêmico, o grupo obeso hiperglicêmico teve chances significativamente maiores de formas graves e muito graves de IU usando ICIQ-SF (aOR 3,157; IC 95% 1,308 a 7,263) e ISI (aOR 20,324; 95% CI 2,265 a 182,329) questionários e maior impacto percebido de PSUI (aOR 4,449; 95% CI 1,591 a 12,442).

Conclusão Nossos dados indicam que a obesidade e a hiperglicemia durante a gravidez aumentam significativamente as chances de formas graves e o impacto percebido da PSUI. Portanto, tratamentos preventivos e curativos mais eficazes são extremamente necessários.

Palavras-chave

- incontinencia urinaria
- gravidez
- diabetes *mellitus*
- obesidade materna

Introduction

Urinary incontinence (UI) may be a very common experience during a woman's lifetime,[1] with a robust influence on well-being and quality of life, as well as an immense economic burden for health services.[2] Estimates of the prevalence and incidence of UI depend on the definitions of the study type and population. Previous epidemiological data showed that the prevalence of UI in women older than 20 years was 23.4–26.4% in the United States.[3] In Brazil, it is considered a common health problem, with an estimated prevalence rate of 27%.[4] Therefore, UI is an important public health concern.

Pregnancy appears to be a major risk factor, particularly during late gestation.[5] In general population, the risk of UI during pregnancy is 18–75%.[6] The term pregnancy-specific UI (PSUI) is used to define any urinary leakage onset during pregnancy.[7] The risk of UI increases as pregnancy progresses due to anatomical and hormonal changes.[6,8] Despite certain risk factors being established for PSUI, some risk factors, such as gestational diabetes mellitus (GDM), are still under consideration. Although some perinatal morbidities related to GDM are associated with UI, GDM alone is considered an independent risk factor for all UI types on post-partum.[9] Taken together, these studies provide compelling evidence for an association between GDM and post-partum UI. Likewise, women with a previous diagnosis of GDM have a well-known increased risk to develop type 2 diabetes mellitus (20–50%) by 10 years postpartum.[10] Obesity (body mass index [BMI] $> 30\,kg/m^2$) and weight gain during pregnancy are some of the main modifiable risk factors for the development of postpartum diabetes.[11] In the United States, from 1999 to 2010, obesity increased from 28.4% to 34% in women aged 20–39 years.[12] Moreover, 15–20% of mothers have pre-pregnancy obesity[13] and 20–40% experience excessive weight gain during pregnancy.[14] Increased BMI has consistently been reported to play a role in the occurrence of clinical UI.[15]

Given that the prevalence of obesity has increased in recent decades, and it is one of the most common medical conditions in women of reproductive age,[16] the premise that obesity and diabetes are linked and are considered a prominent risk factor for developing UI is concerning. Despite compelling epidemiologic data supporting the association of GDM and post-partum UI,[9] as well as obesity and UI,[17] little is known about how hyperglycemia and concurrent obesity might affect the severity of PSUI. Furthermore, current international clinical practice guidelines for UI management fail to present specific recommendations for pregnant women with comorbid conditions, including GDM and obesity, and the treatment of such patients remains a neglected aspect of care.[18,19] Therefore, we hypothesized that GDM and obesity are associated with higher odds of PSUI severity.

The present study aimed to investigate the prevalence of PSUI in a population using questionnaires and clinical data to assess the possible associations between PSUI severity, GDM, and obesity.

Methods

This cross-sectional study focuses on the relationship between UI, obesity, and GDM. All pregnant women were recruited at the time of prenatal care follow-up at the University Hospital from the Perinatal Diabetes Research Centre (PDRC) of Botucatu Medical School/UNESP/Brazil between 2015 and 2018 and were screened for GDM.

We identified four groups of patients categorized as normoglycemic lean (NL), normoglycemic obese (NO), hyperglycemic lean (HL), and hyperglycemic obese (HO). The diagnosis of GDM was established between the 24th and 28th gestational weeks, using the 75-g oral glucose tolerance test (OGTT) according to the American Diabetes Association criteria[20] and glycemic profile.[21,22] All women with positive screening results for GDM or altered glycemic profiles were classified as hyperglycemic. Glycemic control of women following a diagnosis of hyperglycemia followed the protocol in PDRC. The protocol includes a team of healthcare professionals that encourage adequate nutrition, exercise, and insulin administration.[21] The cut-off for obesity was a BMI of $> 30\ kg/m^2$ (calculated using the participant's height and weight).[23] The inclusion criteria were restricted to women with singleton pregnancies who underwent an OGTT between 24 and 28 weeks of pregnancy with a new onset of urinary leakage during pregnancy. Pre-pregnancy UI, known type 1 or type 2 diabetes mellitus, preterm delivery (< 37 weeks of gestation), multiple pregnancies, known fetal anomaly, or any clinical condition that may have jeopardized the health status of the woman were considered as the exclusion criteria.

Data on baseline information (age, parity, pre-pregnancy and current BMI, weight gain during pregnancy, educational level, marital status, fasting glucose, and glycosylated hemoglobin) were collected during the interview at of 34 weeks of gestation and medical records assessment. The Brazilian version of the Incontinence Severity Index (ISI) was used to categorize incontinence severity.[24] The multiplicative score is based on two questions assessing the frequency and volume of incontinence.[25] Women were also asked to complete the Brazilian version of the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF).[26] The ICIQ-UI SF comprises three scored items and one non-scored item, making it possible to assess the prevalence, severity, interference in daily life, and type of UI.[26] The ICIQ-UI SF score ranges from 0 to 21. Scores on the perceived impact of those reporting UI are set from '0' as not at all to '10' as a great deal. One non-scored item of the ICIQ-UI SF includes eight answers and is a self-diagnostic item to understand the participant's perception of the cause and type of leakage. A form completed immediately after birth was used to record the labor process, mode of delivery, and neonatal birth profile.

The primary outcome was the PSUI prevalence among the groups. UI was classified according to the International Continence Society guidelines for stress UI (SUI) (involuntary leakage on effort or exertion, sneezing, or coughing), urge UI (UUI) (involuntary leakage accompanied by or immediately preceded by urgency), and mixed UI (MUI) (involuntary leakage associated with urgency and exertion, effort, sneezing, or coughing).[27] Secondary outcomes were the prevalence of SUI, UUI, and MUI, as well as the frequency of UI, amount of leakage, the ISI score, the ICIQ-UI score, and perceived impact of UI.

SAS version 9.4 for Windows (Statistical Analysis System Institute Inc., USA) was used for statistical analyses. Clinical features are presented as frequencies and percentages or as means with standard deviations. Differences between groups were tested using chi-square or analysis of variance followed by the Tukey–Kramer analysis. A logistic regression model was used to assess the association between GDM and obesity and UI. Only clinical features with a p-value < 0.05 were included in the adjusted logistic regression analysis (age, gestational age, parity, previous newborn weight, hypertension, newborn weight, and classification).

This study was approved by the Research Ethics Committee of the institution (CAAE: 41570815.0.0000.5411). All patients were informed about the purpose of the study, and those who agreed to participate signed a consent form before recruitment.

Results

Among the 563 women eligible for recruitment, 539 (95.7%) agreed to participate in the present study. Among these patients, 172 participants were included in the NL group (31.91%), 113 in the NO group (20.97%), 109 in the HL group (20.22%), and 145 in the HO group (26.90%). Baseline characteristics differed between groups, including clinical features such as age, gestational age, parity, previous newborn weight, hypertension, newborn weight, and classification. The background variables of the study population are shown in ►**Table 1**.

The overall prevalence of PSUI was 70.87% ($n = 382$), with no difference in the prevalence or type of UI between groups (►**Table 2**). However, the HO group had more frequent ($p < 0.0001$) and more abundant ($p = 0.0009$) higher scores for the perceived impact of UI ($p < 0.0001$), ICIQ-UI SF ($p < 0.0001$), and ISI ($p < 0.0001$) questionnaires (►**Table 3**).

►**Table 4** shows the logistic regression analysis with unadjusted and adjusted UI. Surprisingly, when adjusted for age, gestational age, parity, previous newborn weight, hypertension, newborn weight, and classification, the hyperglycemic group had significantly higher odds of UI severity than the other groups in the study. Furthermore, these groups presented a higher perceived impact of UI, ISI, and ICIQ-UI SF severe scores.

Discussion

To the best of our knowledge, this is the first study to assess the influence of obesity and hyperglycemia on the odds of PSUI severity. This cross-sectional study assessed the

Table 1 Clinical features of the study population

	Total population ($n = 539$)	Normoglycemic Lean ($n = 172$) 31.91%	Normoglycemic Obese ($n = 113$) 20.97%	Hiperglycemic Lean ($n = 109$) 20.22%	Hiperglycemic Obese ($n = 145$) 26.90%	*p*-value between groups
Age (years)	29.12 (6.44)	27.20 (6.15)	28.12 (6.47)	29.73 (7.15)[a]	31.68 (5.25)[a,b]	
Gestational age (weeks)	36.85 (1.58)	37.01 (1.57)	37.30 (1.63)	36.54 (1.51)[a]	36.54 (1.52)[a,b]	
Parity	1.11 (1.02)	1.02 (0.99)	0.97 (1.03)	1.06 (0.98)	1.37 (1.04) [a,b,c]	
Previous newborn (g)	2237.27 (1601.06)	1950.31 (1590.17)	2221.50 (1590.23)	2188.87 (1655.11)	2627.24 (1518.14)[a]	
Weight gain during pregnancy (kg)	10.34 (7.59)	13.15 (6.57)	9.16 (9.05)[a]	11.8 (6.52)b	6.74 (6.57)[a,b,c]	
Prepregnancy BMI (kg/m^2)	30.46 (7.46)	24.34 (3.27)	36.44 (5.12)[a]	25.49 (3.24)[b]	36.77 (5.93) [a,c]	
Pregnancy BMI (kg/m^2)	34.52 (7.21)	29.53 (3.97)	40.37 (7.01)[a]	30.18 (4.13)[b]	39.16 (5.70)[a,c]	
OGTT (mg/dL)						
Fasting	82.86 (16.42)	72.24 (7.65)	76.27 (7.59)	89.69 (17.06)[a,b]	94.74 (17.07)[a,b,c]	
1 hour	134.77 (40.78)	107.50 (23.88)	115.58 (26.64)	159.72 (37.04)[a,b]	166.65 (36.28)[a,b]	
2 hours	117.39 (56.78)	96.27 (20.10)	110.63 (98.77)[a]	136.59 (39.41)[a,b]	135.22 (38.69)[a,b]	
Glycemic mean (mg/dL)	90.31 (13.54)	82.28 (8.46)	84.33 (7.98)	96.24 (10.36)[a,b]	99.43 (15.67)[a,b]	
HbA1c	5.24 (0.55)	4.91 (0.42)	5.12 (0.47)[a]	5.33 (0.41)[a,b]	5.59 (0.59)[a,b,c]	
Hypertension	161 (29.87%)	29 (16.86%)	56 (49.56%)	18 (16.51%)	47 (40%)	<.0001
Race						
White	361 (66.98%)	127 (73.84%)	79 (69.91%)	67 (61.47%)	88 (60.69%)	0.0605
Non-white	178 (33.02%)	45 (26.16%)	34 (30.09%)	42 (38.53%)	57 (39.31%)	
Smoker	53 (9.83%)	17 (9.88%)	9 (7.96%)	13 (11.93%)	14 (9.66%)	0.8038
Vaginal	202 (40.89%)	78 (53.42%)	44 (40.74%)	38 (36.89%)	42 (30.66%)	0.0011
C-section	292 (59.11%)	68 (46.58%)	64 (59.26%)	65 (63.11%)	95 (69.34%)	
Newborn weight (g)	3367.28 (511.25)	3287.11 (493.22)	3350.09 (480.12)	3337.70 (506.14)	3496.01 (535.51)a	
Newborn weight classification						
SGA	31 (6.39%)	16 (11.19%)	5 (4.72%)	7 (6.86%)	3 (2.24%)	0.0058
AGA	403 (83.09%)	114 (79.72%)	94 (88.68%)	87 (85.29%)	108 (80.60%)	
LGA	51 (10.52%)	13 (9.09%)	7 (6.60%)	8 (7.84%)	23 (17.16%)	

Abbreviations: AGA, appropriate for gestational age; BMI, Body Mass Index; HbA1c, Glycated Hemoglobin; LGA, large for gestational age; OGTT, Oral Glucose Tolerance Test; SGA, small for gestational age.
[a]$p < 0.05$–indicate significant difference compared with normoglycemic lean group (Tukey-Kramer).
[b]$p < 0.05$ - indicate significant difference compared with normoglycemic obese group (Tukey-Kramer).
[c]$p < 0.05$ - indicate significant difference compared with hiperglycemic lean group (Tukey-Kramer).

Table 2 Prevalence of Pregnancy-Specific Urinary Incontinence (PSUI), stress urinary incontinence (SUI), urge urinary incontinence (UUI) and mixed urinary incontinence (MUI)

		Total population ($n = 539$)	Normoglycemic Lean ($n = 172$)	Normoglycemic Obese ($n = 113$)	Hiperglycemic Lean ($n = 109$)	Hiperglycemic Obese ($n = 145$)	*p*-value between groups
PSUI	Yes	382 (70.87%)	115 (66.86%)	85 (75.22%)	73 (66.97%)	109 (75.17%)	0.2143
	No	157 (29.13%)	57 (33.14%)	28 (24.78%)	36 (33.03%)	36 (24.83%)	
PSUI ($n = 382$)	UI	1 (0.26%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0.1224
	SUI	152 (39.79%)	51 (44.35%)	26 (30.59%)	35 (47.95%)	40 (36.70%)	
	MUI	201 (52.62%)	57 (49.57%)	50 (58.82%)	30 (41.10%)	64 (58.72%)	
	UUI	28 (7.33%)	7 (6.09%)	8 (9.41%)	8 (10.96%)	5 (4.59%)	

PSUI: Pregnancy-Specific Urinary Incontinence; UI: Urinary incontinence; SUI: stress urinary incontinence; UUI: urge urinary incontinence; MUI: mixed urinary incontinence

Table 3 Frequency, duration, amount of leakage, scores for the perceived impact of those reporting UI, ICIQ UI-SF and ISI scores

			Total population ($n = 539$)	Normoglycemic Lean ($n = 172$) 31.91%	Normoglycemic Obese ($n = 113$) 20.97%	Hiperglycemic Lean ($n = 109$) 20.22%	Hiperglycemic Obese ($n = 145$) 26.90%	*p*-value between groups[§]
ICIQ UI-SF	Frequency of incontinence episodes	No leakage	157 (29.13%)	57 (33.14%)	28 (24.78%)	36 (33.03%)	36 (24.83%)	<0.0001
		≤Once/week	146 (27.09%)	63 (36.63%)	38 (33.63%)	22 (20.18%)	23 (15.86%)	
		2–3 times/week	83 (15.40%)	25 (14.53%)	12 (10.62%)	20 (18.35%)	26 (17.93%)	
		Once/day	60 (11.13%)	13 (7.56%)	17 (15.04%)	8 (7.34%)	22 (15.17%)	
		>Once/day	78 (14.47%)	11 (6.40%)	12 (10.62%)	22 (20.18%)	33 (22.76%)	
		All the time	15 (2.78%)	3 (1.74%)	6 (5.31%)	1 (0.92%)	5 (3.45%)	
	Amount of leakage	None	157 (29.13%)	57 (33.14%)	28 (24.78%)	36 (33.03%)	36 (24.83%)	0.0009
		Small	217 (40.26%)	78 (45.35%)	56 (49.55%)	41 (37.61%)	42 (28.97%)	
		Moderate	121 (22.45%)	31 (18.02%)	20 (17.70%)	22 (20.18%)	48 (33.10%)	
		Severe	44 (8.16%)	6 (3.49%)	9 (7.96%)	10 (9.17%)	19 (13.10%)	
		Score perceived impact of those reporting UI ($n = 382$)	4.16 (3.72)	5.12 (3.01)	5.12 (3.17)	5.26 (3.61)	6.69 (3.11)*#‡	
		ICIQ UI-SF score ($n = 539$)	7.76 (6.41)	6.49 (5.78)	7.47 (5.93)	7.27 (6.51)	9.64 (6.97) abc	
	Perceived impact of those reporting UI ($n = 382$)	Not at all	39 (10.21%)	11 (9.57%)	9 (10.59%)	13 (17.81%)	6 (5.50%)	<0.0001
		Mildly	76 (19.9%)	26 (22.61%)	21 (24.71%)	13 (17.81%)	16 (14.68%)	
		Moderately	97 (25.39%)	40 (34.78%)	27 (31.76%)	14 (19.18%)	16 (14.68%)	
		Severely	112 (29.32%)	22 (19.13%)	15 (17.65%)	26 (35.62%)	49 (44.95%)	
		To a great extent	58 (15.18%)	16 (13.91%)	13 (15.29%)	7 (9.59%)	22 (20.18%)	
	ICIQ UI-SF ($n = 539$)	None	157 (29.13%)	57 (33.14%)	28 (24.78%)	36 (33.03%)	36 (24.83%)	<0.0001
		Slight	61 (11.32%)	20 (11.63%)	15 (13.27%)	15 (13.76%)	11 (7.59%)	
		Moderate	167 (30.98%)	65 (37.79%)	45 (39.82%)	27 (24.77%)	30 (20.69%)	
		Severe	132 (24.49%)	26 (15.12%)	19 (16.81%)	30 (27.52%)	57 (39.31%)	
		Very Severe	22 (4.08%)	4 (2.33%)	6 (5.31%)	1 (0.92%)	11 (7.59%)	
	ISI ($n = 382$)	Slight	123 (32.20%)	53 (46.09%)	33 (38.82%)	22 (30.14%)	15 (13.76%)	<0.0001
		Moderate	135 (35.34%)	42 (36.52%)	33 (38.82%)	25 (34.25%)	35 (32.11%)	
		Severe	86 (22.51%)	15 (13.04%)	11 (12.94%)	19 (26.03%)	41 (37.61%)	
		Very Severe	38 (9.95%)	5 (4.35%)	8 (9.41%)	7 (9.59%)	18 (16.51%)	

Abbreviations: ICIQ-SF, International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form; ISI, Incontinence Severity Index; UI, Urinary incontinence.
[a]$p < 0.05$–indicate significant difference compared with normoglycemic lean group (Tukey-Kramer).
[b]$p < 0.05$ - indicate significant difference compared with normoglycemic obese group (Tukey-Kramer).
[c]$p < 0.05$ - indicate significant difference compared with hiperglycemic lean group (Tukey-Kramer).
* $p < 0.05$–indicate significant difference compared with normoglycemic lean group (Poisson).
[#]$p < 0.05$ - indicate significant difference compared with normoglycemic obese group (Poisson).
[‡]$p < 0.05$ - indicate significant difference compared with hiperglycemic lean group (Poisson).
[§]Chi-square test.

Table 4 Unadjusted and adjusted odds ratio in the four groups

		Normoglycemic Lean ($n = 172$)	Normoglycemic Obese ($n = 113$)	Hiperglycemic Lean ($n = 109$)	Hiperglycemic Obese ($n = 145$)	
Unadjusted			**OR with 95% CI**	**OR with 95% CI**	**OR with 95% CI**	***p*-value between groups**
	PSUI	1	1.505 (0.884 - 2.562)	1.005 (0.604 - 1.674)	1.501 (0.917 - 2.456)	0.2164
PSUI	SUI	1	0.563 (0.312 - 1.016)	1.156 (0.642 - 2.082)	0.727 (0.426 - 1.243)	0.1056
	MUI	1	1.496 (0.847 - 2.643)	0.710 (0.393 - 1.284)	1.447 (0.853 - 2.454)	0.0586
	UUI	1	1.624 (0.565 - 4.669)	1.899 (0.658 - 5.481)	0.742 (0.228 - 2.411)	0.3427
Perceived impact of those reporting UI	Not at all	1	0.745 (0.453 - 1.225)	1.249 (0.769 - 2.030)	0.624 (0.389 - 0.999)	0.0419
	Mildly	1	1.123 (0.581 - 2.170)	0.742 (0.353 - 1.557)	0.589 (0.296 - 1.171)	0.2871
	Moderately	1	0.873 (0.481 - 1.585)	0.445 (0.221 - 0.894)	0.323 (0.168 - 0.621)	0.0021
	Severely	1	0.906 (0.438 - 1.872)	2.338 (1.200 - 4.558)	3.452 (1.897 - 6.282)	<0.0001
	To a great extent	1	1.117 (0.506 - 2.467)	0.656 (0.256 - 1.682)	1.565 (0.773 - 3.168)	0.2690
ICIQ UI-SF	None	1	0.665 (0.390 - 1.132)	0.995 (0.597 - 1.657)	0.666 (0.407 - 1.091)	0.0419
	Slight	1	1.163 (0.568 - 2.380)	1.213 (0.596 - 2.484)	0.624 (0.288 - 1.349)	0.3856
	Moderate	1	1.089 (0.670 - 1.772)	0.542 (0.318 - 0.924)	0.429 (0.259 - 0.713)	0.0008
	Severe	1	1.135 (0.595 - 2.165)	2.132 (1.179 - 3.855)	3.637 (2.132 - 6.204)	<0.0001
	Very Severe	1	2.355 (0.649 - 8.540)	0.389 (0.043 - 3.526)	3.448 (1.074 - 11.072)	0.0580
ISI	Slight	1	0.742 (0.420 - 1.313)	0.505 (0.271 - 0.938)	0.187 (0.097 - 0.360)	<0.0001
	Moderate	1	1.103 (0.619 - 1.967)	0.905 (0.490 - 1.674)	0.822 (0.473 - 1.429)	0.7878
	Severe	1	0.991 (0.430 - 2.282)	2.346 (1.104 - 4.983)	4.020 (2.063 - 7.831)	<0.0001
	Very Severe	1	2.285 (0.720 - 7.249)	2.332 (0.711 - 7.647)	4.350 (1.555 - 12.171)	0.0372
adjusted						
	PSUI	1	0.760 (0.297 - 1.949)	2.439 (1.016 - 5.855)	0.631 (0.256 - 1.557)	0.0238
PSUI	SUI	1	0.567 (0.220 - 1.462)	2.012 (0.664 - 6.099)	0.637 (0.261 - 1.551)	0.1220
	MUI	1	1.241 (0.498 - 3.095)	0.490 (0.158 - 1.513)	1.820 (0.766 - 4.328)	0.1138
	UUI	1	2.372 (0.500 - 11.257)	0.927 (0.135 - 6.352)	0.420 (0.063 - 2.784)	0.3238
Perceived impact of those reporting UI	Not at all	1	0.687 (0.281 - 1.680)	2.066 (0.874 - 4.885)	0.511 (0.214 - 1.216)	0.2222
	Mildly	1	2.221 (0.770 - 6.407)	0.822 (0.212 - 3.182)	0.805 (0.270 - 2.400)	0.2564
	Moderately	1	1.156 (0.445 - 3.001)	0.301 (0.087 - 1.039)	0.300 (0.111 - 0.809)	0.0271
	Severely	1	0.468 (0.126 - 1.737)	3.810 (1.134 - 12.801)	4.449 (1.591 - 12.442)	0.0005
	To a great extent	1	0.920 (0.239 - 3.537)	0.962 (0.195 - 4.747)	1.198 (0.361 - 3.977)	0.9752
ICIQ UI-SF	None	1	0.760 (0.297 - 1.949)	2.439 (0.516 - 5.855)	0.631 (0.256 - 1.557)	0.2381
	Slight	1	0.677 (0.181 - 2.539)	0.600 (0.145 - 2.474)	0.631 (0.180 - 2.217)	0.8412
	Moderate	1	2.081 (0.903 - 4.793)	0.204 (0.071 - 0.584)	0.415 (0.178 - 0.964)	0.0001
	Severe	1	0.438 (0.141 - 1.357)	2.244 (0.885 - 5.691)	3.157 (1.308 - 7.623)	0.0012
	Very Severe	1	3.852 (0.357 - 41.511)	3.389 (0.443 - 33.526)	6.496 (0.662 - 63.742)	0.4536
ISI	Slight	1	0.759 (0.297 - 1.939)	0.214 (0.059 - 0.774)	0.194 (0.072 - 0.527)	0.0042
	Moderate	1	1.739 (0.683 - 4.427)	1.106 (0.377 - 3.242)	0.587 (0.234 - 1.472)	0.1660
	Severe	1	0.208 (0.037 - 1.188)	2.297 (0.617 - 8.547)	3.130 (1.070 - 9.153)	0.0059
	Very Severe	1	6.092 (0.603 - 61.538)	11.709 (1.027 - 133.489)	20.324 (2.265 - 182.392)	0.0381

Abbreviations: ICIQ-SF, International Consultation on Incontinence Questionnaire-Urinary Incontinence-Short Form; ISI, Incontinence Severity Index; MUI, mixed urinary incontinence; PSUI, Pregnancy-Specific Urinary Incontinence; SUI, stress urinary incontinence; UI, Urinary incontinence; UUI, urge urinary incontinence.

prevalence, frequency, amount, perceived impact, and severity of PSUI in women as of 34 weeks of gestation. Overall, a high prevalence (70.87%) of PSUI among the 539 participants. We found the highest odds of PSUI severity and the perceived impact of UI in women with hyperglycemia. Even after adjustment for various confounders, including age, gestational age, parity, previous newborn weight, hypertension, newborn weight and classification, women with hyperglycemia without obesity presented the highest odds of PSUI (adjusted odds ratio [aOR]: 2.43; 95% confidence interval [CI]: 1.01–5.85). We observed a substantial increase in the odds of extremely severe PSUI in the HL (aOR: 11.70; 95% CI: 1.02–133.48) and HO groups (aOR: 20.32; 95% CI: 2.26–182.39). Our logistic regression model found that hyperglycemia alone and hyperglycemia linked to obesity were also associated with severe perceived impact of UI in daily life (aOR: 3.81; 95% CI: 1.13–12.80; aOR: 4.44; 95% CI: 1.59–12.44). The persistence, progression and severity of pelvic floor dysfunction can have a significant impact on women's quality of life.[28]

With respect to the baseline characteristics of the present study, this cohort represented the underlying population characteristics of women with hyperglycemia during pregnancy. Advancing maternal age has been recognized as a major risk factor for the development of hyperglycemia during pregnancy.[29] The other risk factors greater parity, increased BMI, and hypertension.[30,31] Our data indicate these risk factors in the present cohort of the hyperglycemic groups. Such risk factors are also associated with an increased risk of developing UI.[6,32] In our study, although women in the HO group presented lower weight gain during pregnancy, which may be related to the fact that they received the treatment at PDRC, the symptoms related to UI appeared to be more severe than those in the other groups.

According to Daly et al.,[33] 21.7% of the population studied presented women with new-onset leakage who were continent in the 12 months before pregnancy. Brown et al.,[34] found that the most common PSUI is SUI, characterized by unintentional loss of urine during physical movement or activity (e.g., sneezing, coughing, running, or heavy lifting). The pathophysiology of PSUI is multifactorial and yet to be understood. It has been implicated that hormonal and mechanical changes may play an important role.[35] In our sample, there was no difference in the prevalence of the UI types between the groups. Studies showed that irrespective of the type, UI has detrimental effects on the quality of life in ~54.3% of all pregnant women[36] and the quality of life of pregnant women with incontinence worsens with increasing gestational age to term.[37] Our sample presented higher prevalence of PSUI rates (70.87%) when compared the general literature. However, this corresponds with a similar study with smaller sample size, in the same gestational period (i.e., 34–38 weeks of gestation) the prevalence rate was 60.5%.[38] Further research is needed to explore the differences in prevalence of PSUI in multicentric and multi-ethnic groups.

Our findings show that women with a BMI of $\geq 30\,kg/m^2$ are significantly more likely to report less frequent incontinence episodes and amount of leakage, moderately perceived impact of UI, and slight to moderate UI severity. A large longitudinal study that enrolled 10,098 women who were followed up as of 28 weeks of gestation found that high prenatal BMI increased the risk of SUI in late pregnancy (OR: 1.037; 95% CI: 1.020–1.054).[39] Overweight and obesity are considered major modifiable risk factors for UI in young and middle-aged women.[40] Previous studies have shown that middle-aged women with obesity are 3.1 times more likely to have severe UI than women with BMI in the normal range.[41] These differences might be related to the different types of inquiries used to address UI symptoms and study designs. Anatomical changes in patients with obesity assessed by ultrasonography showed that bladder neck descent was more evident in women with obesity than in women with normal weight.[42] A high BMI increases intra-abdominal pressure, resulting in an imbalance between vesical pressure and urethral closure, triggering urine leakage.[15,43]

The first study to report the prevalence of UI in women with GDM was conducted by Kim et al.[44] They recruited 228 women with GDM; 49% reported weekly or more episodes of incontinence during pregnancy and 50% after delivery.[44] Another cross-sectional study found that GDM was an independent risk factor (OR: 2.26; 95% CI: 1.116–4.579) for PSUI, and PSUI was a risk factor 2 years post cesarean section UI (OR: 4.992; 95% CI: 1.383–18.023).[45] A large study[9] recruited 6653 women who were followed up for 2 years postpartum to investigate the association between GDM and postpartum UI. They demonstrated that women with GDM were more likely to report SUI (OR: 1.97; 95% CI: 1.56–2.51), UUI (OR: 3.11; 95% CI: 2.18–4.43), and MUI (OR, 2.73; 95% CI: 1.70–4.40).[9] Furthermore, another study showed that the occurrence of PSUI, the severity of UI, and the negative impact of UI on the quality of life are increased in women with hyperglycemia during pregnancy.[38] Recent studies[46,47] conducted in animal models and pregnant women have aimed to identify and quantify the morphological changes in the rectus abdominis muscles due to hyperglycemia during pregnancy. Changes in the fiber type, fiber area, and collagen content have been reported and may be related to diabetic myopathy.

The strengths of this study include the use of validated questionnaires that enable the identification of the type, frequency, severity, and perceived impact of UI. The International Consultation on Incontinence recognized that ICIQ questionnaires are grade A (high-quality) measurement instruments for assessing UI.[48] Another strength of our study is the use of a database with the glycemic values of the participants and the established diagnostic criteria for GDM and obesity. An important limitation is the limited number of participants that could have powered our results and the lack of an objective measure of UI assessment, such as bladder diaries, pad test, and/or urodynamic test, to compare with our subjective measures.

Conclusion

The results of the present study show that hyperglycemia during pregnancy is an independent risk factor for PSUI. The

logistic regression models showed that when compared with the normoglycemic lean women, women who are obese and have hyperglycemia during pregnancy are more likely to experience severe and very severe PSUI with important perceived impact on daily life. The findings from our study provide information on PSUI in volunteers at the third trimester of pregnancy screened for hyperglycemia, and such findings are directly relevant to clinical practice. Such risk factors are preventable, manageable, and even curable, and healthcare professionals should perform evidence-based treatment.

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.

Conflicts to Interest

The authors have no conflicts of interest to declare.

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Cardiovascular Risk Factors in Premature Ovarian Insufficiency using Hormonal Therapy

Fatores de risco cardiovascular na insuficiência ovariana prematura em uso de terapia hormonal

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Abstract

Objective Premature ovarian insufficiency (POI) is characterized by early hypoestrogenism. An increased risk of cardiovascular (CV) disease is a long-term consequence of POI. A challenge of hormone therapy (HT) is to reduce the CV risk.

Methods Cross-sectional study with lipid profile analysis (total cholesterol, LDL-C, HDL-C, VLDL-C and triglycerides), blood glucose levels and arterial blood pressure of women with POI using HT, compared with age and BMI-matched women with normal ovarian function (controls).

Results The mean age and BMI of 102 POI patients using HT and 102 controls were 37.2 ± 6.0 and 37.3 ± 5.9 years, respectively; 27.0 ± 5.2 and $27.1 \pm 5.4\,kg/m^2$. There wasn't difference between groups in arterial systolic and diastolic blood pressure, blood glucose levels, total cholesterol, LDL-C, VLDL-C and triglycerides. HDL-C levels were significantly higher in the POI group (56.3 ± 14.6 and 52 ± 13.9mg/dL; $p = 0.03$). Arterial hypertension was the most prevalent chronic disease (12% in the POI group, 19% in the control group, p = ns), followed by dyslipidemia (6 and 5%, in POI and control women).

Conclusion Women with POI using HT have blood pressure levels, lipid and glycemic profile and prevalence of hypertension and dyslipidemia similar to women of the same age and BMI with preserved gonadal function, in addition to better HDL levels.

Palavras-chave
- insuficiência ovariana prematura
- doença cardiovascular
- amenorreia secundária
- terapia hormonal
- fatores de risco cardiometabólicos

Introduction

Premature ovarian insufficiency (POI) is an unusual but important cause of sex steroid deficiency and infertility in women under 40. It is characterized by high FSH levels (>25 UI/L) and irregular menstrual cycles or lack of menstrual bleeding. POI affects 1% of women before the age of 40.[1–4] Many health complications associated with POI are directly related to ovarian hormone deficiency, particularly estrogen deficiency.[1] Presenting symptoms and health complications related to hypoestrogenism include menopausal symptoms, decreased bone mineral density, infertility, mood disorders, cognitive decline, a higher risk of developing type 2 diabetes mellitus (T2DM) or prediabetes, cardiovascular (CV) disease, decreased sexual function and impaired quality of life.[5–8] There is also some evidence of reduced life expectancy.[9,10]

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Resumo

Objetivo A insuficiência ovariana prematura (IOP) é caracterizada pelo hipoestrogenismo precoce. Risco aumentado de doença cardiovascular (CV) é uma consequência a longo prazo da IOP e um desafio da terapia hormonal (TH) é reduzir o risco CV.

Métodos Estudo transversal com análise do perfil lipídico (colesterol total, LDL-C, HDL-C, VLDL-C e triglicerídeos), glicemia e pressão arterial de mulheres com IOP em uso de TH, em comparação a mulheres com função ovariana normal (controles) pareadas por idade e IMC.

Resultados A média de idade e IMC de 102 pacientes com IOP em uso de TH e 102 controles foi de $37,2 \pm 6,0$ e $37,3 \pm 5,9$ anos, respectivamente; $27,0 \pm 5,2$ e $27,1 \pm 5,4$ kg/m^2. Não houve diferença entre os grupos na pressão arterial sistólica e diastólica, glicemia, colesterol total, LDL-C, VLDL-C e triglicerídeos. Os níveis de HDL-C foram significativamente maiores no grupo IOP ($56,3 \pm 14,6$ e $52 \pm 13,9$mg/dL; $p = 0,03$). A hipertensão arterial foi a doença crônica mais prevalente (12% no grupo POI, 19% no grupo controle, p = ns), seguida da dislipidemia (6 e 5%, no grupo POI e controle).

Conclusão Mulheres com IOP em uso de TH apresentam níveis pressóricos, perfil lipídico e glicêmico e prevalência de hipertensão e dislipidemia semelhantes às mulheres da mesma idade e IMC com função gonadal preservada, além de melhores níveis de HDL.

Keywords

- premature ovarian insufficiency
- cardiovascular disease
- secondary amenorrhea
- hormonal therapy
- cardiometabolic risk factors

Estrogen has several regulatory cardiometabolic functions that reduce oxidative stress, vasoconstriction, atherosclerosis and ischemia. Furthermore, it modifies the hepatic metabolism of lipoproteins, reducing LDL-cholesterol (LDL-C) and increasing HDL-cholesterol (HDL-C) levels.[11,12] Compared with age-matched women with normal ovarian function, women with POI have diminished endothelial function and early signs of atherosclerosis.[13–15] The increased risk of CV disease and stroke underscore the role of hypoestrogenic status. In addition, POI women had higher levels of blood glucose, insulin resistance, systemic arterial blood pressure, along with increased inflammatory factors.[2,16–20] These data show that POI can be an independent risk factor for ischemic heart disease, and CV disease is possibly the main reason for a shorter life expectancy.[8,15]

Unless a strong contraindication exists, HT is recommended for women with POI until the natural age of menopause for protection against the negative effects of hypoestrogenism.[2] In women after natural menopause, the use of HT has been associated with reduced levels of LDL-C, triglycerides (TG) and insulin resistance, in addition to increased levels of HDL-C.[21–24] Due to the complexity of estrogen and progestogen receptor systems, the benefits should be weighed and may differ in younger and healthier women. In POI, it is believed that HT can restore endothelial function usually within 6 months of treatment.[25,26] Nevertheless, there is insufficient data confirming other effects of the long-term use of HT to reduce cardiovascular risk in this specific population.

The current study was conducted to assess clinical and metabolic cardiovascular risk profile in women using HT diagnosed with POI, compared with a population of age-matched and BMI-matched women with preserved ovarian function.

Methods

A cross-sectional study was conducted at the Endocrinological Gynecology Outpatient Clinic of the Department of Obstetrics and Gynecology of the University of Campinas. A convenience sample size was used, including women diagnosed with POI who were managed during a 24-month period. POI was diagnosed in women aged 40 or younger, without any menstrual periods or who had irregular menstrual cycles and at least two FSH values measuring higher than 25mUI/L, taken at least 4 weeks apart. Only women with secondary amenorrhea, normal karyotype and no history of oncology treatment, chemotherapy or radiotherapy were included. Furthermore, women belonging to the POI group should have been adequately using hormone therapy for at least 6 months to be included. Each woman from the POI group was matched for age (± 2 years) and BMI class ($<$20kg/m^2; 20 to 24.9kg/m^2; 25 to 29.9 kg/m^2; 30 to 34.9 kg/m^2; 35 to 40kgm^2; $>$ 40kg/m^2) to women with preserved gonadal function (control group), and follow-up visits in the Family Planning Unit at the same institution. Women from the control group were required to have spontaneous and regular menstrual cycles (between 24 and 38 days), a negative history of hormone use or at least in the preceding 6 months and serum FSH levels within the normal range.[27]

In both groups, clinical parameters such as age, medical history (chronic hypertension, diabetes mellitus, dyslipidemia diagnosis), obstetric history, weight (kg), height (meters), BMI (kg/m^2), systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg) were evaluated. Metabolic parameters were also studied by laboratory measurements, after a 12-hour fast, blood glucose levels (mg/ dL), total cholesterol (mg/ dL), HDL-C (mg/dL), LDL-C (mg/dL), VLDL-cholesterol (mg/dL), TG (ml/dL), TSH

Table 1 Characteristics of premature ovarian insufficiency (POI) and women with preserved gonadal function (control group)

	POI Group ($n = 102$)	Control Group($n = 102$)	p-value (*)
Age (Years)	37.2 ± 6.0	37.3 ± 5.9	0.210
Weight (kg)	66.2 ± 15.1	70.0 ± 14.7	0.002
Height (m)	1.5 ± 0.2	1.6 ± 0.1	0.010
BMI (kg/m2)	27.0 ± 5.2	27.1 ± 5.4	0.490
Pregnancies	1.7 ± 1.6	2.3 ± 1.7	0.007
Deliveries	1.4 ± 1.3	1.9 ± 1.3	0.004
Miscarriage	0.3 ± 0.9	0.3 ± 0.9	0.880
FSH (mUI/mL)	85.3 ± 38.2	6.7 ± 8.9	<0.0001

Abbreviations: BMI, Body Mass Index; FSH, Follicle-stimulating hormone.
*Student *t*-test.

(mUI/L), free T4 (ng/dL). Women under treatment for previously diagnosed chronic disease were not excluded (chronic hypertension, dyslipidemia, hypothyroidism, diabetes).

The analyzed variables were considered altered when: SBP $\geq$ 140mmHg; DBP $\geq$ 90mmHg; fasting glucose $\geq$ 100-mg/dL; total cholesterol $\geq$ 200mg/dL; LDL-C $\geq$ 130mg/dL; HDL-C $<$ 45 mg/dL; triglycerides $\geq$150ml/dL; TSH $\geq$ 5mU/L.

In the POI group, only age was evaluated at the time of POI diagnosis (in years) and duration of POI (calculated as years from the last period until study entry).

The HT of choice was: conjugated estrogen (0.625 mcg or 1.25 mcg, associated with medroxyprogesterone acetate); estradiol (1mg or 2mg, associated with norethisterone); combined oral contraceptive (30mcg of ethinylestradiol associated with levonorgestrel), and tibolone (2.5mg).

Categorical variables were described as the absolute frequency (n) and percentage (%), and numerical variables were described as mean and standard deviation values. To compare categorical variables between groups (POI and control), the Chi-square or Fisher's exact tests were used. The *t*-test or Mann-Whitney test was used to compare numerical variables. To compare categorical variables, a paired analysis was performed using the McNemar test. A paired *t*-test was used to compare quantitative variables. A 5% significance level was adopted. The computer program used was SAS (Statistical Analysis System), version 9.4 for Windows.

This study was approved by the Ethics Review Board of the institution (CAAE n° 08623412.7.0000.5404).

Results

A total of 204 women were included in the study. Of these women, 102 had POI and were taking HT and 102 women belonged to the control group (with preserved gonadal function). The mean age and mean BMI, for POI and controls, were 37.2 ± 6.0 and 37.3 ± 5.9 years, respectively; 27.0 ± 5.2 kg/m^2 and 27.1 ± 5.4 kg/m^2, with no difference between groups. Ovarian insufficiency was established at age 31.9 ± 7.8 years on average and the time between diagnosis and study inclusion was 5.3 ± 5.6 years. HT containing conjugated estrogen was used by 63 women, estradiol by 33 women, combined oral contraceptives by 3 women, as well tibolone (3 women). Women with POI conceived less often and gave fewer births than women in the control group, and there was no difference in the number of miscarriages (►**Table 1**). The groups did not differ in mean levels of SBP (111.1 ± 11.7 of the POI group; 113.5 ± 16 mm Hg of the control group), DBP (71.5 ± 9.3 and 70.8 ± 9.4 mm Hg), blood glucose levels (86.8 ± 18.4 and 85.2 ± 14.1 mg/dL), total cholesterol (198.1 ± 44.6 and 187.3 ± 39.7 mg/dL), HDL-C (56.3 ± 14.6 and 52.0 ± 13.9 mg/dL), LDL-C (119.3 ± 39.6 and 111.8 ± 38.8 mg/dL), VLDL-C (23.0 ± 19.1 and 23.5 ± 15.7 mg/dL), triglycerides (126 ± 115 and 112.9 ± 67.7 mg/dL) and thyroid function (TSH 2.1 ± 1.4 and 2.2 ± 1.2 mU/L, respectively; p= NS; ►**Table 2**). There were also no differences between the mean metabolic parameters evaluated, fasting blood glucose, total cholesterol, LDL-C and triglycerides. Serum HDL-C levels were

Table 2 Clinical parameters of women with POI and control group

	POI Group ($n = 102$)	Control Group ($n = 102$)	p-value
Systolic blood pressure levels (mmHg)	111.1 ± 11.7	113.5 ± 16	ns
Total cholesterol (mg/dL)	198.1 ± 44.6	187.3 ± 39.7	ns
HDL-cholesterol (mg/dL)	56.3 ± 14.6	52.0 ± 13.9	ns
LDL-cholesterol (mg/dL)	119.3 ± 39.6	111.8 ± 38.8	ns
Thyroid function (mU/L)	2.1 ± 1.4	2.2 ± 1.2	ns

ns, not significant.

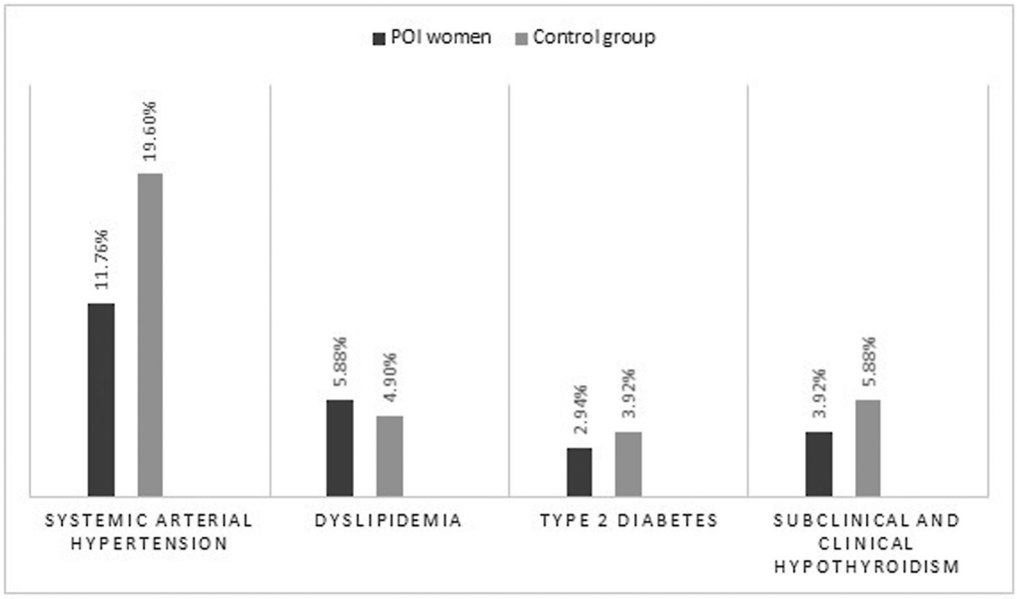

Fig. 1 Prevalence of Chronic Diseases in women with POI and control group.

significantly higher in the POI group (56.3 ± 14.6 and 52 ± 13.9; $p = 0.03$). Thyroid function parameters were similar in both groups (►**Fig. 1** and **2**).

Among chronic diseases, systemic arterial hypertension was the most prevalent condition in both groups (11.76% in the POI group; 19.6% in the control group), followed by dyslipidemia, diagnosed in 5.88% of women with POI and 4.90% of women with preserved gonadal function, without any statistical difference (►**Fig. 1**). T2DM was diagnosed in 2.94% of women with POI and in 3.92% of controls, while subclinical and clinical hypothyroidism was present in 3.92% of women with POI and 5.88% in the control group, without any difference between groups (►**Fig. 2**). Adequate disease control, assessed by measurements of blood pressure, blood glucose levels, cholesterol, triglycerides and TSH within the normal range, also showed no statistical difference between groups, with the exception of diastolic blood pressure, where levels above normal were more commonly found in women with POI (►**Fig. 3**).

Discussion

This study evaluated parameters associated with increased cardiovascular risk in predominantly overweight women (mean age, 37 years) with POI taking hormone therapy, in relation to age-matched and BMI-matched women with preserved ovarian function. The groups were similar in the majority of evaluated parameters. However, serum HDL-C levels were significantly higher in the POI group. Chronic arterial hypertension and dyslipidemia were the most prevalent diseases in both groups. BMI averages close to $27 kg/m^2$ revealed a high prevalence of overweight and obese women, in agreement with values found among the female population in the world and in Brazil.[28]

Cardiovascular disease is currently the main cause of morbidity and mortality among women.[29] POI is considered an independent albeit modest cardiovascular risk factor, especially for ischemic heart disease and overall CV disease, with the exclusion of stroke.[16] Epidemiological data suggest that life expectancy in women with POI is 2 years shorter than in women with natural menopause (at the usual age). Although many gaps remain in the current knowledge of the long-term consequences of hypoestrogenism for young women, as well as the control of the effects of estrogen replacement therapy, the available literature suggests that hormone therapy can reduce morbidity and mortality in this population.[30,31] There is evidence showing similar levels of glucose, insulin, HOMA-IR, LDL-C and TG among women with POI using HT, compared with controls with preserved ovarian function.[17,18] However, despite substantial evidence that treatment with estrogen improves vascular endothelial function in postmenopausal women, studies on the impact of HT on the cardiovascular system of women with POI are limited.[26,31]

Since early hypoestrogenism seems to be associated with a higher mortality rate due to cardiac ischemia, this risk is known to increase in association with uncontrolled blood pressure levels.[10,23,29] Results have shown that women diagnosed with previous hypertension that experience menopause at a physiological age and initiate HT in the first 10 years of amenorrhea or before the age of 60 may have improved blood pressure levels. However, the effect of hormone replacement therapy on blood pressure control in women with POI is less widely known.[12] Some data show a similar effect, especially in those using formulations containing natural estrogen.[32] In our study, systemic arterial hypertension was the most prevalent chronic disease among all women evaluated (12 women in the POI group, 20 in the control group). There was no statistical difference between the two groups, and both groups were adequately controlled.

Dyslipidemia was the second most prevalent condition found in both groups studied. However, in women with POI,

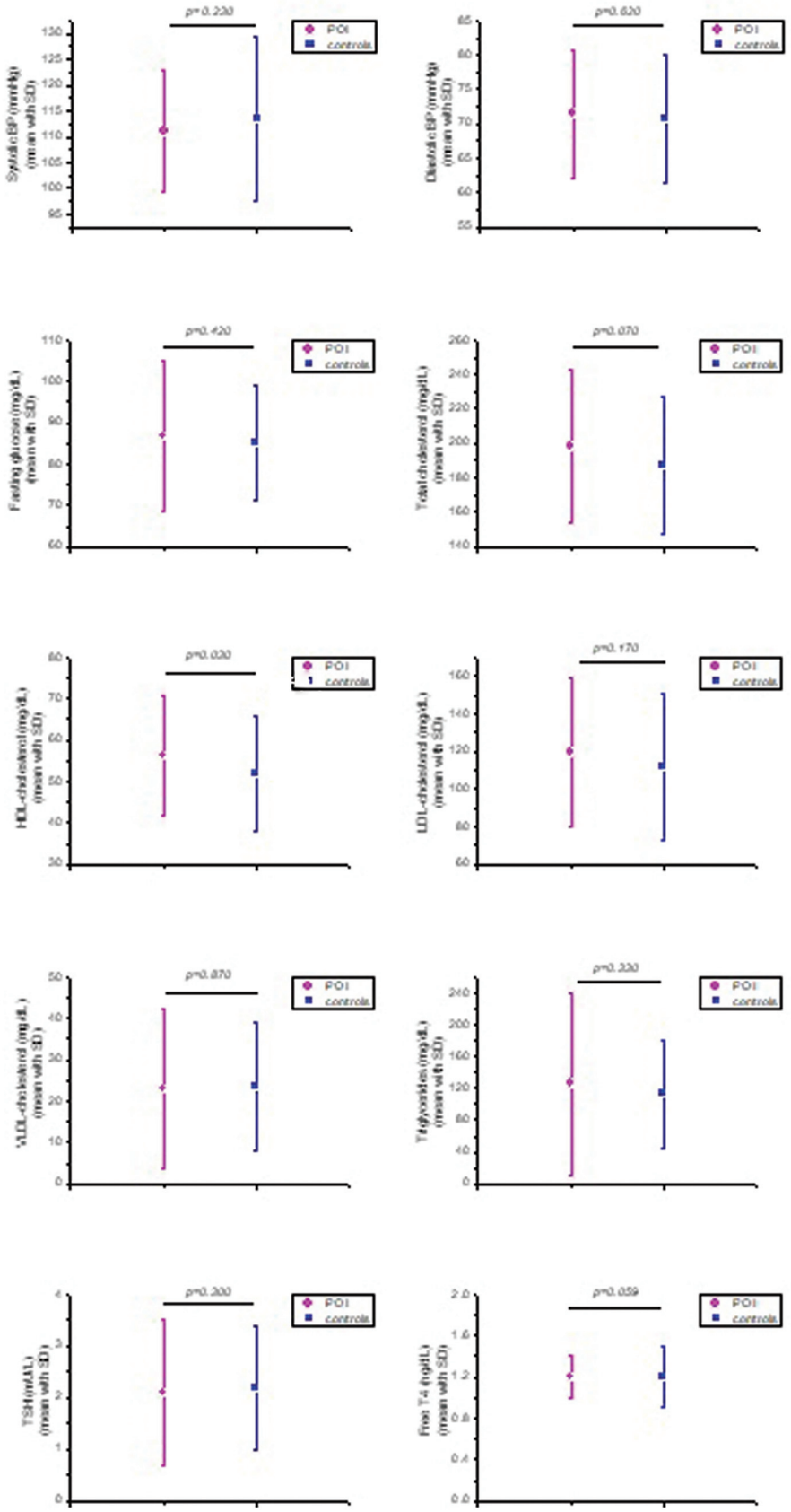

Fig. 2 Comparative analysis of clinical and laboratory parameters between women with POI ($N = 102$) and those with preserved gonadal function ($n = 102$). *Student 's *t*-test.

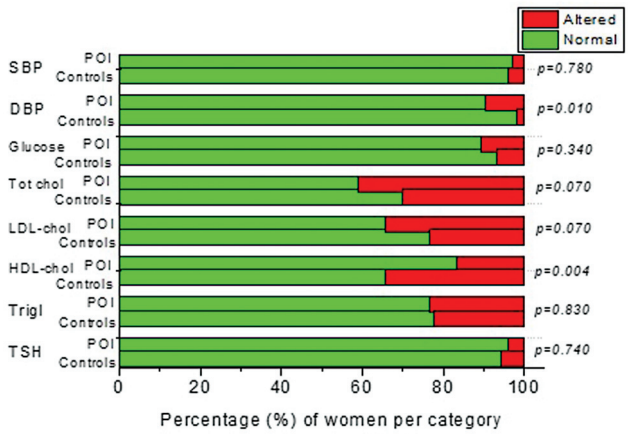

Fig. 3 Parameters associated with the most prevalent chronic diseases (Chronic hypertension: $n = 12$ and 20 in the POI and control groups; Diabetes Mellitus: $n = 3$ and 4 in the POI and control group; Dyslipidemia: $n = 6$ and 5 in the POI and control group), classified as normal or altered. *Mann-Whitney test for a mean comparison between groups; POI (premature ovarian insufficiency).

HDL-C levels were significantly higher, which is in agreement with the available literature on the subject.[17,20] Oral HT containing estrogen in postmenopausal women is associated with a reduction in total cholesterol and LDL-C and an increased HDL-C level, an effect that was not observed in transdermal hormone therapy.[24–26] Regarding POI, the data are scarce, but studies conducted with women undergoing surgical menopause and transdermal hormone replacement demonstrated an improvement in HDL-C levels, compared with those undergoing oophorectomy who did not use HT.[33,34] There is also evidence that endothelial function is established within six months of hormone replacement in women with POI. In addition to an improvement in lipid profile, a decrease in cardiovascular risk may also be associated.[15,22,34]

There is controversy in the literature surrounding other metabolic parameters. Regarding TG levels, evidence suggests that women with POI who do not use HT more commonly have higher triglyceride levels than women with preserved gonadal function, while divergent results were obtained by other authors.[10,14,16,33] In women with natural menopause, oral HT can increase triglyceride levels.[25] Our results did not show any difference in lipid metabolism between the two groups, although the oral route was chosen for the administration of HT.

Glucose metabolism is also influenced by hypoestrogenism. There is evidence that a higher prevalence of insulin-dependent diabetes mellitus occurs among women with POI. In women who develop T2DM during the period of hypoestrogenism, HT is associated with a greater insulin sensitivity.[26,29,30] In the current study, the prevalence of T2DM was similar between both groups analyzed, just like fasting glucose levels.

Our results showed that women with POI who had been using HT did not present worse cardiometabolic markers or comorbidities, in comparison to age-matched and BMI-matched women with preserved ovarian function. These results point toward the same direction as the available literature, although most studies were conducted with very small sample sizes (less than 20 women). Thus, the strength of our study is the expressive sample included, especially considering that the prevalence of POI is low. A recent meta-analysis was performed with a total of 21 studies involving 1573 women with POI. Most of the included studies have around 30–80 subjects. However, most studies do not differentiate between women with POI using and not using HT. According to these authors, analysis between POI women using and not using hormone therapy was not available because most included studies didn't mention whether the women used hormone therapy, which reinforce that our results can collaborate to reduce the gap in the evidences.[35] All women were using HT and were matched by age and BMI to control group women, which are confounding factors that can influence the variables that were analyzed. Furthermore, women diagnosed with previous comorbidities that have a potential cardiovascular risk were not excluded to avoid an important selection bias. Limitations of the study were the characteristics of design (cross-sectional) that do not allow a cause-and-effect relationship, in addition to the lack of a control POI group that does not use HT. Nevertheless, there are ethical restrictions on with holding hormone treatment from these women, unless they refuse to take it.

Conclusion

Women with POI using HT had levels of blood pressure, lipid profile and blood glucose, similar to those of age-matched and BMI-matched women with preserved gonadal function. Comorbidities such as systemic arterial hypertension, diabetes and thyroid dysfunction were similar between both groups. Overweight and obesity should be viewed as comorbid conditions. These risk factors were equally prevalent in both groups.

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.

Conflicts to Interest

The authors have no conflicts of interest to declare.

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Treatment and Management Experience of Idiopathic Granulomatous Mastitis in a Low-income Country

Experiência de tratamento e manejo da mastite granulomatosa idiopática em um país de baixa renda

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Abstract

Objective Reporting our experience of the management and treatment of Idiopathic granulomatous mastitis (IGM) in a low-income country by describing patients characteristics and therapy with emphasis on conservative surgical excision and postoperative care as the cornerstone of treatment.

Methods A retrospective cohort of women with histopathological diagnosis of IGM from 2014 to 2018 at Instituto Nacional Materno Perinatal in Lima, Peru. Patients' characteristics, clinical presentation, treatment, management, postoperative care, and follow-up were analyzed.

Results Thirty-eight patients with histopathological diagnosis of IGM were identified. Their average age was 35.9 years and 23 (60.5%) reported previous use of hormonal contraceptives. Nine (23.7%) patients had chronic mastitis with previous treatment. The time from the onset of symptoms to the first clinic consult was 5.1 months on average. Twenty-one (55.3%) patients had the lesion in the right breast, with a mean size of 6.9 cm. Conservative surgical excision was performed in all patients. Additionally, 86.8% required corticosteroids and 78.9% were treated with antibiotics. Complete remission was obtained at 141 days on average (range 44 to 292 days). Six (15.8%) women reported ipsilateral recurrence and 5 (13.2%), contralateral. The latency time was 25.5 months on average.

Conclusion The conservative surgical treatment demonstrated and close follow-up made for a high cure rate, but with recurrence similar to that reported in the literature. Use of gloves is an alternative to manage post operative wounds in a low-income country. The most frequent adverse effect was breast surgical scar.

Keywords
- idiopathic granulomatous mastitis
- breast
- surgery
- corticosteroid
- recurrence

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Introduction

Granulomatous mastitis (IGM) is a benign inflammation of the breast, of unknown etiology.[1] Several possible causes have been proposed, including immune reactions, infectious disease, and hormonal disturbances, though none has been fully tested.[2] This entity is a diagnosis of exclusion[3]; thus, malignancy, infections such as tubercular mastitis (in countries with a high incidence of tuberculosis),[4] and systemic diseases that can induce its appearance must be ruled out. It occurs mainly in young multiparous women on average 35 years old, shortly after pregnancy.[5] There is no additional risk of subsequent breast cancer in these patients.[6]

IGM is a therapeutic challenge, since more than 50% of reported cases are initially confused with other pathologies including breast cancer,[7] and a lot of patients have several courses of antibiotic and other treatments unnecessarily. Surgical treatment is not a widely accepted therapeutic option, although previous studies report it as an alternative in recurrent cases that did not respond to more conservative treatments.[8] Currently, there is no consensus to describe conservative surgical excision as a cornerstone intervention for idiopathic granulomatous mastitis as the best treatment for this pathology, and the frequency of recurrence is high.[1,7] Other studies have reported it as a successful alternative, with partial or total mastectomy offering a high percentage of cure compared with medical treatment options such as corticosteroids.[9,10] Accordingly, more effective and efficient therapeutic options should be sought in this pathology.

We report our experience of the management and treatment of IGM in a low-income country by describing patients characteristics and therapy with emphasis on conservative surgical excision and postoperative care as the cornerstone of treatment.

Methods

This retrospective study was conducted at Instituto Nacional Materno Perinatal in Lima, Peru, one of the largest tertiary hospitals in South America fully dedicated to providing health care to women with gynecological and oncological problems and high-risk pregnancy and to their infants. Our institution is a reference center for all of Peru.

This cohort included all women with a histopathological diagnosis of IGM during the period from January 2014 to January 2018 who received treatment in our Gynecology, Oncology and Breast Unit. The data collection was performed by the study investigators through a review of the clinical history of the registered patients with histopathological diagnosis of IGM and later telephone communication with them.

A histological diagnosis of IGM was required on core needle biopsy or open surgical biopsy. Patients with the following characteristics were excluded: positive laboratory study for mammary tuberculosis, histopathological study with diagnosis of breast cancer or other associated breast pathology, immune disorders, mainly HIV-AIDS, pregnancy during the course of the disease. We collected data on sociodemographic characteristics, clinical presentation, different combinations of medical (use of antibiotics and/or steroids) and surgical management, postoperative care, follow-up, and outcomes. All patients had undergone a conservative surgical excision of the lesion for inflammatory granulomatous tissue.

Specific location of the lesion clinically and sonographically (avoiding further resection). Regional anesthesia is administered. A small incision is made, with drainage and removal of granulomatous tissue respecting the structure of the breast with ectoscopic negative margins with the aim of preserving the maximum volume of healthy tissue. After the excision, the cavity is washed with sodium chloride and surgical gloves are inserted whose function is to facilitate the exit as multiple lamellar drains, avoiding the accumulation of dead tissue, hemostasis, and premature adhesions. The open wound is subjected to daily dressing to achieve wound retraction, and surgical closure is performed in the outpatient consult as soon as the drainage of secretions is reduced to a minimum.

The antibiotics given were cephalosporins, quinolones, tetracyclines, or trimethoprim-sulfamethoxazole, for 7 to 21 days. Prednisone was given at a dose of 0.5 mg/kg a day for 2–3 weeks. After this, a tapering protocol began according to the clinical response, at the rate of 5 mg per week until it was reduced to the lowest dose, until 7 weeks approximately. We uses steroids depending on the dimensions of the lesion, the severity of the symptoms, and the patient's general health and personal treatment preferences. No patient received immunosuppressant therapy during the time of management in our institution.

The database was cleaned to eliminate repeated values, assign lost values, and recategorize variables for the final analysis. We performed a descriptive analysis to summarize the characteristics of the patients. The distribution of the absolute, relative, and accumulated frequencies of categorical variables was calculated. For numerical variables, summary measures were applied as averages and ranges. Statistical analysis was performed using Stata Statistical Software 14.0 (Stata Corp. 2015, College Station, TX, USA). We obtained ethical approval from the local Ethical Institutional Board (reference number: 169–2019-CIEI/INMP).

Results

While 41 patients were identified with a histopathological diagnosis of IGM, three of them were excluded. Two patients had pregnancy of 10 and 18 weeks and one had a PCR positive for tuberculosis. We describe the characteristics of the 38 included patients in ►**Table 1**. The average age of the women was 35.9 years. Twenty-three patients (60.5%) reported using hormonal contraceptives for at least six months, the most common being the injection (52.6%). Only 2 women reported a history of tuberculosis, one of them pulmonary and the other in the left breast. No patient reported smoking. A history of chronic mastitis was present in 9 patients (23.7%); 7 of them had it in the contralateral breast while 2 patients reported bilateral mastitis; all of them had

Table 1 Characteristics of patients with idiopathic granulomatous mastitis ($n = 38$)

Characteristics	n(%)
Mean age in years (range)	35.9 (20 - 59)
Contraceptive methods	
Injection	20 (52.6)
Intrauterine device	2 (5.3)
Implant	1 (2.6)
None	15 (39.5)
Smoking	0 (0.0)
Previous tuberculosis	2 (5.26)
Previus mastitis	9 (23.7)
Previus treatment	9 (23.7)
Duration of symptoms in months (range)	5.1 (1–36)
Disease Laterality	
Right	21 (55.3)
Left	13 (34.2)
Bilateral	4 (10.5)
Size, cm (range)	6.9 (3–12)
Breast manifestations	
Mass	38 (100.0)
Swelling	34 (89.5)
Fistula	31 (81.6)
Nipple discharge	20 (55.6)
Imaging evaluation	
Ultrasaund	37 (97.4)
Mammogram	22 (57.9)

received previous treatment, of whom four women had surgical treatment.

The time from the onset of symptoms to the first clinical visit was on average 5.1 months. Most of the patients (55.3%) had the lesion in the right breast, with average size of 6.9 cm. In the clinical evaluation, 34 (89.5%) patients had swelling; 31 (81.6%) presented fistulous trajectories, and 20 (55.6%) discharge from the nipple (►**Fig. 1**).

Among the 21 patients who had radiographic evaluation, the most frequent classification was BIRADS 0, in 16 patients.

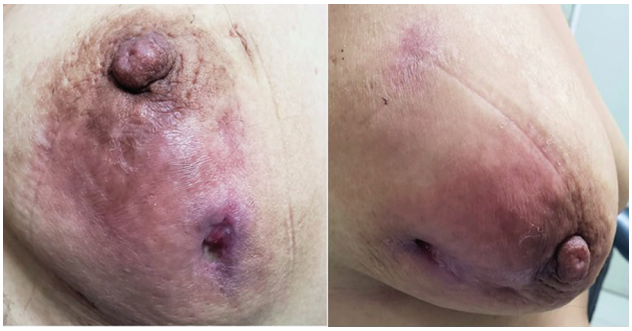

Fig. 1 Erythema, phlogosis and ulceration with active suppuration in the lower quadrante. Gynecology Oncology and Breast Unit. INMP.

Table 2 Treatment of mastitis granulomatous mastitis

Features	Patient (n)	Percent
Type of treatment		
Surgery + steroids + antibiotics	28	73.68
Surgery + steroids	5	13.16
Surgery	3	7.89
Surgery + antibiotics	2	5.26
Time from open surgical wound (days)	38	24.7 (13–50)
Time from diagnosis to resolution (days)	141	44 - 292
Recurrence		
Ipsilateral	6	15.8
Contralateral	5	13.2
Time of recurrence (months)	6	25.5 (3–84)

One patient was classified as BIRADS 4C, with subsequent confirmation of benignity of the lesion. Ultrasonography diagnosed chronic mastitis existed in 17 patients (44.7%), and signs of acute mastitis with abscesses and collections in 12 patients (31.6%). Only 21% of the patients had a biopsy before the start of treatment. The type of treatment is described in ►**Table 2**. All the patients had conservative surgical excision of the lesion for IGM (►**Fig. 2**). Additional treatment was used in different combinations: corticosteroids and antibiotics were applied in 28 patients (73.7%), corticosteroids in 5 patients (13.2%), and only antibiotics in 2 patients (5.3%). While 86.8% of the patients received corticosteroids, 78.9% were administered an antibiotic cycle. The average number of healings during the open wound period among the patients was twenty.

The resolution time for granulomatous mastitis was an average of 141 days, with a minimum of 44 days and a maximum of 292. Six (15.8%) women reported ipsilateral recurrence and 5 (13.2%), contralateral. The latency time was 25.5 months on average. The most frequent adverse effect

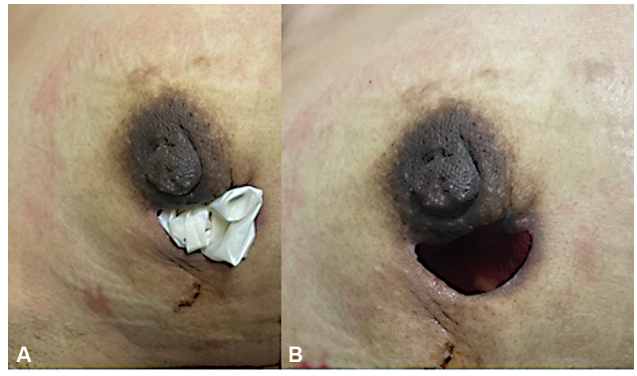

Fig. 2 (**A**) Surgical Gloves after surgery. (**B**) No adhesions or dischargue. Gynecology Oncology and Breast Unit. Instituto Nacional Materno Perinatal.

reported was breast scar distortion. No side effects of corticosteroid, antibiotic, or NSAID therapy were reported.

Discussion

This retrospective study showed the characteristics and type of treatment of 38 women with granulomatous mastitis treated in our Breast Unit. The conservative surgery treatment was performed in all patients and was associated with corticosteroids in 86.8%. Additionally, 78.9% received an antibiotic cycle. The resolution time was 141 days on average. Eleven patients (28.9%) had recurrence in 25.5 months on average.

Childbearing age between the 3rd and 4th decenniums is the most common in IGM diagnosis. In our study, the mean age of patients was 35.9 years. However, the literature reports 11 years as the youngest patient[11] and 83 years old as the oldest.[7] Contraceptive users are at increased risk of developing IGM. We reported 60% of patients with a history of using some hormonal contraceptive.

The pathogenesis and etiology of IGM is a not clear issue, but this disorder is characterized by granulomatous inflammation like many others diseases.[12] There are many agents and diseases related, such as local irritants, viruses, bacteria, mycotic and parasitic infections, diabetes mellitus, smoking, and systemic immune abnormalities.[10,13] Any etiological factors could permit damage to the ductal epithelium, allowing luminal secretion to leak into the lobular connective tissue, and an autoimmune reaction to these extravasated secretions was hypothesized.[11] However, the trigger in the development of this epithelial damage remains unknown.[2]

Mastitis tuberculosis should be a differential diagnosis for IGM, even more so in Peru that has 14% of the estimated cases of tuberculosis in the America Region.[14] Mammary tuberculosis has been estimated to be 0.1% of breast lesions examined histologically. Breast tuberculosis is paucibacillary, and routine diagnostic tests such as microscopy and culture and nucleic acid amplification tests such as PCR techniques do not have the same diagnostic utility as they do in pulmonary tuberculosis.[15] We reported only 2 patients with previous lung tuberculosis infection, but in none of them was TB found. Pinto et al reported 28 patients with chronic tuberculous granulomatous mastitis in a Peruvian hospital; however, only 3 patients in that cohort had PCR positive, and 2 of them, BK culture.[16]

The most described clinical presentation was mass (80 -100%),[17,18] fistula (16–52%),[19] and inflammation of erythema (11%).[10,20] In this study all patients had a breast mass associated with phlogosis, nipple discharge, or fistulas. Although bilateral involvement has rarely been reported, 4 (10%) patients had this characteristic. In the other patients, there was predominance in the right breast. IGM remains a diagnostic challenge for clinicians. The delay in diagnosis is around 5.1 months on average, similar to what a systematic review of 70 articles with 3060 patients found.[21]

The diagnosis of IGM is one of exclusion and should be based on a multidisciplinary approach. Thus, all infectious and noninfectious causes of granulomatous inflammation must be excluded.[11] The gold standard for definitive diagnosis is core breast biopsy.[22] Image studies could help differentiate malignant lesions and thus avoid adverse effects of aggressive treatments when cancer is suspected.[23] Thus, ultrasound may show the number of masses and the heterogeneity with diffuse parenchymal edema, fluid in fat planes, and abscess.[8] Mammography is used to identify suspicious for malignancy with ill-defined focal densities and spiculated pattern. Another technique is Magnetic Resonance Imaging (MRI), whose findings include parenchymal enhancement, with asymmetrical signal intensity changes. However, the heterogeneous spectrum of presentation of IGM results in all images' findings being inconclusive for differentiating benign from malignant disease.[24] In our patients, only 21% had core breast biopsy previous to surgical management and almost 100% had ultrasound as the study protocol. However, only 55% had access to mammography, and no patient had MRI. These data reflect that the diagnosis in low-income countries such as Peru has such difficulties. Thus, we trust in clinic presentation and keeping a high index of clinical suspicion in cases of mastitis not responsive to antibiotics or a lot of other failed treatments.

Therapies for IGM included surgery (mastectomy, excision, and drainage), drug therapies (antibiotics, corticosteroids, immunosuppressive drugs, anti-inflammatory drugs, and others), and simple observation. However, the optimal treatment of IGM is still controversial due to varying degrees of success, and recurrence rates remain as high as 50%.[7,21,25] Moreover, the management of this pathology is based on observational studies, most of which were retrospective, with only a few prospective ones.[7,20] No clinical trials of treatment of this pathology are reported, and therefore the quality of the data are not optimal.

Bouton in 2015 followed up 37 cases of IGM, of which 27 cases resolved spontaneously without treatment; but the authors takes into account that the evolution of the disease is long and the quality of life was affected.[26] There are reports of up to 59% women who received single or multiple courses of antibiotics without any response.[8] Corticosteroids are usually used in IGM; methylprednisolone,[17] prednisolone, and prednisone[27] have been used with different schemes. Although Pandey et al reported 80% complete resolution of the disease, the median time was 159 days.[8] Methotrexate is an alternative treatment; it is an immunosuppressor agent used in IGM patients with favorable results, and it is usually combined with corticosteroids when the patient does not consider a surgical option at first.[28–30] Haddad et al reported complete remission of moderate to severe IGM after treatment with methotrexate. However, almost half of these patients received prednisone as a combinate regimen, and 17.6% experienced relapse of the disease.[28]

Surgery is the most widely used technique to reduce symptoms quickly[17]; moreover, recurrence, fistula formation (4.7 to 30%), and infection are documented complications after these procedures.[2,20,31] Lai et al consider that surgical treatment should be applied only for patients with refractory or recurrent mastitis. Thus, the frequency of recurrence is high in all types of surgery except for total

mastectomy.[9,32] Wang et al in 2020 reported a novel technique to avoid bigger scars, of using indwelling hoses and surgical inlets.[17] A systematic review reported in 2017 that treatment with corticosteroids provides significant regression of inflammatory lesions, allowing the possibility of conservative surgery that could decrease the healing time as well as the frequency of recurrence in the patient and improve her quality of life.[33]

In our Breast Unit, aggressive and definitive treatment of mastitis was performed by conservative surgical excision associated with corticosteroids, with some complementary treatments such as antibiotic therapy and analgesics. The resolution time reported in our study was an average of 141 days. In the literature, it is reported as approximately up to 159 days[8] with various treatment options, and a total cure for between 42 to 93% of patients using a combination of only conservative surgery and corticosteroids.[8,32] Recurrence is variable, at 16 to 50% among patients with strict follow-up and without treatment[7]; however, we report a recurrence of 29%. It is a suitable option for treatment and management of IGM in our low-income country scenario. However, as the sample size of this cohort was limited and a longer follow-up period is necessary, we should be more cautious when making recommendations.

It is a retrospective cohort study, based on review of medical records and phone calls; the analysis could have biases of memory or information bias. The main form of diagnosis was based on clinic manifestation and ultrasound features; some patients had biopsy before surgery, but all patients had mastitis histology confirmation. There is no protocol for management in our country, so there are several ways to approach management. This analysis is the largest Peruvian case series of patients with granulomatous mastitis with a combination of conservative surgical treatment and corticosteroids. All our patients had histopathological diagnosis of granulomatous mastitis, and all of them had very close follow-up until resolution. This study allowed building a local management protocol for this pathology because our institution is a national reference center. Larger observational studies and clinical trials are required to allow statistical comparison of the types of treatment.

Conclusion

Granulomatous mastitis is a rare, benign breast disease but locally aggressive, which decreases the quality of life of the patient and that still does not have a standardized treatment. Conservative surgical treatment associated with corticosteroids and close follow-up until resolution are demonstrated to be a highly effective cure, but with recurrence rates similar to those reported in the literature. The most important adverse effect of the type of treatment applied in the study was breast scarring.

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.

Conflicts to Interest

The authors have no conflict of interest to declare.

Acknowledgments

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Efficacy of Embolization in Acquired Uterine Vascular Malformations: An Experience in Tertiary Care Centre in India

Eficácia da embolização em malformações vasculares uterinas adquiridas: uma experiência em centro de atendimento terciário na Índia

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Abstract

Objective: To determine the efficacy of Uterine Artery Embolization in patients with bleeding acquired uterine arteriovenous malformations (AVMs).

Methods: A prospective review of all patients who underwent Uterine Artery Embolization at our institution between July 2015 and April 2022 was performed. 225 patients were diagnosed with a uterine vascular malformation on doppler and corresponding MRI imaging. All patients underwent transcatheter embolization of the uterine arteries. Embolic agents in the 375 procedures included Histoacryl glue only (n = 326), polyvinyl alcohol (PVA) particles and Histoacryl glue (n = 29), PVA particles (n = 5), Gelfoam (n = 5), coils (n = 4), PVA particles and coils (n = 3), Histoacryl glue and Gelfoam (n = 2), and Histoacryl glue and coils (n = 1).

Results: A total of 375 embolization procedures were performed in 225 patients. 90 patients required repeat embolization for recurrence of bleeding. The technical success rate of embolization was 100%. The clinical success rate was 92%: bleeding was controlled in 222 of 225 patients and three patients underwent a hysterectomy. 60 of the 225 patients had uneventful intrauterine pregnancies carried to term. The 210 patients who underwent successful embolization had no recurrence of bleeding at a median follow-up of 53 months (range, 5-122 months) after treatment. 15 patients were eventually lost to follow-up. One minor complication (0.4%) of non-flow-limiting dissection of the internal iliac artery occurred.

Conclusion: Uterine Artery Embolization is a safe, effective, minimally invasive method to treat uterine AVMs with long-term efficacy, which can provide the preservation of fertility.

Keywords

- Uterine arteriovenous malformations
- Uterine artery embolization
- Uterus
- Endovascular
- Histoacryl glue

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Introduction

Arteriovenous malformations (AVMs) can be found anywhere in the vascular system, including the uterus. Uterine AVMs consisting of an abnormal connection between an artery and a vein. They usually occur in women of reproductive age, but are very rare after menopause. Uterine AVM is a rare but potentially severe cause of genital haemorrhage that can be life-threatening.[1] Unlike other conditions, curettage is not therapeutic and may aggravate the bleeding.[2,3] Uterine AVMs are most commonly observed after pregnancy that occurs in women with a past history of induced abortion, curettage, uterine surgery, caesarean section, or diethylstilbestrol exposure.[4–8] The clinical diagnosis of uterine AVM is often difficult. However, correct diagnosis can be reliably made using imaging by doppler ultrasonography (USG). It is a low cost and non-invasive procedure. Other imaging methods including computed tomography (CT) and magnetic resonance imaging (MRI) may be used to complement the diagnosis in difficult cases and are used to determine its size, extent and vascularity, and the involvement of adjacent organs. Traditionally uterine AVMs have been surgically treated with hysterectomy or uterine artery ligation. More recently, endovascular treatment has proven to be an effective alternative.[9] Because most uterine AVMs are diagnosed in women of childbearing age, the recent development of curative embolization therapy should reduce the indications for hysterectomy and preserve fertility.[10] For uterine AVM embolization several embolic agents have been used including Histoacryl glue, polyvinyl alcohol particles (PVA), Gelfoam and coils. The objective of this study was to determine the efficacy of Uterine Artery Embolization in patients with bleeding acquired AVMs.

Methods

This was a Prospective study where 225 patients referred to the department of Interventional Radiology for uterine artery embolization between July 2015 - April 2022 and 375 embolization procedures were done. The average age was 35.8 years. Serial β-human chorionic gonadotropin (hCG) levels were measured to exclude gestational trophoblastic neoplasia. Uterine artery embolizations were performed with use of standard 5F Robertson Uterine Curve catheter (RUC) and 2.7F Progreat microcatheter when necessary. Embolic agents used in the 375 procedures included Histoacryl glue only (n = 326), PVA particles and glue (n = 29), PVA particles (n = 5), Gelfoam (n = 5), coils (n = 4), PVA particles and coils (n = 3), glue and Gelfoam (n = 2), and glue and coils (n = 1) (►**Table 1**). Outcomes assessed were cessation of bleeding, persistence or resolution of the AVM, complications and pregnancy after embolization. These were assessed by chart, laboratory and imaging reviews. For all patients, clinical assessment was performed and informed consent was obtained before the procedure. Diagnosis was made based on clinical, imaging findings on Doppler and MRI examinations. Method of collection of data includes Brief clinical history and examination, fluoroscopic guided uterine artery embolization interventions, relevant biochemical investigations, and post procedural follow up. All the participants provided written informed consent.

Table 1 Embolic agents used

Embolic agents used	Number (n)	%
Histoacryl glue	326	86.9
PVA, Histoacryl glue	29	7.7
PVA	5	1.3
Gelfoam	5	1.3
Coils	4	1.0
PVA, Coils	3	0.8
Histoacryl glue, Gelfoam	2	0.5
Histoacryl glue, Coils	1	0.2
Total	375	

Abbreviation: PVA, Polyvinyl Alcohol.

Embolization Technique

Procedure done under strict aseptic conditions, local anaesthesia (2% lignocaine). Anaesthetist was involved throughout the procedure. The Right Common Femoral Artery was accessed using 20G puncture needle and 5F Radifocus Introducer Sheath (Terumo) was placed by seldinger single puncture technique. Under fluoroscopic guidance using 5F 90cm RUC catheter (Merit Medical) and 0.032 150cm angled tip guide wire (Terumo) combination, the 0.032 guide wire was negotiated into contralateral external iliac artery (left). The RUC catheter was pushed into left external iliac artery. The guide wire is withdrawn into the RUC catheter. The RUC catheter was pushed up into abdominal aorta there by forming the curve. Left internal iliac artery was accessed using RUC catheter and 0.032 guide wire combination and angiogram demonstrated tortuous vessels supplying the AVM arising from the left uterine artery. The left uterine artery was selectively catheterized using 5F RUC catheter or by 2.7F 130cm Progreat Microcatheter (Terumo). The angiogram showed tortuous vessels supplying the AVM arising from the left uterine artery with drainage into a large venous channel. The AVM was embolized using Histoacryl glue (Braun) or PVA particles (Merit Medical 500-710 microns) and Histoacryl glue or PVA particles or Gelfoam (Spongostan Ethicon) or coils (Cook MicroNester Embolization coil) or PVA particles and coils or Histoacryl glue and Gelfoam or Histoacryl glue and coils. Post embolization angiogram showed Histoacryl glue cast within the branches of left uterine artery with no significant flow into the AVM. Similarly, the right uterine artery was accessed using a 5F RUC catheter or by 2.7F Progreat Microcatheter and the AVM was embolized. Check angiogram showed significant reduction of flow or stasis into the AVM. The introducer sheath was removed and compression bandage was applied. Post uterine AVM embolization all patients are advised bedrest with lower limb movement restriction and were treated with antibiotics (Ciprofloxacin, Amoxycillin + Clavulanic acid), analgesics,

Table 2

Associated clinical history	Number	%
D&C	143	63
Delivery	53	24
Abortion	29	13
Total	225	

Abbreviations: D&C, dilation and curettage.

Table 3

No. of Patients	No. of Repeat Embolizations	Median Period (months)
76	2	21
6	3	35
3	6	44

intravenous fluids and with supportive care. Patients were advised post procedural four weeks follow up with USG Abdomen, MRI Pelvis and relevant biochemical investigations.

Results

A total of 225 patients are included in our study (mean age, 35.8 years; age range, 22-43 years). Fourth decade individuals are most commonly effected. All 225 patients had previously undergone gynaecological procedures or obstetric events, such as dilatation and curettage (D&C) (n = 143) or delivery (n = 53) or abortion (n = 29) (►**Table 2**). Presenting symptoms were intermittent or progressive vaginal bleeding. The mean time interval between these obstetric events and symptom presentation was 7 weeks. A total of 375 embolization procedures were performed in 225 patients. Early venous drainage from the AVM to pelvic veins was demonstrated in all patients (►**Fig. 1**). 90 patients required repeat embolization for recurrence of bleeding (►**Table 3**). 3 of these patients underwent embolization six times over a median period of 44 months (range, 3-88 months), 6 of these patients underwent embolization thrice over a median period of 35 months (range, 4-74 months), 76 of these patients underwent embolization twice where the median time to second embolization was 21 months (range, 3–36 months). The embolic material used most often was Histoacryl glue in 358 procedures (►**Fig. 2**). 240 procedures were performed on an elective basis and 35 were performed on an emergent basis. Technical success was defined as the complete disappearance of angiographic staining of the AVM on post-embolization angiography and the absence of any procedure related complications (►**Fig. 3**). Clinical success was defined as immediate resolution of vaginal bleeding without symptom recurrence and resolution of the AVM on subsequent imaging studies. Technical success was achieved

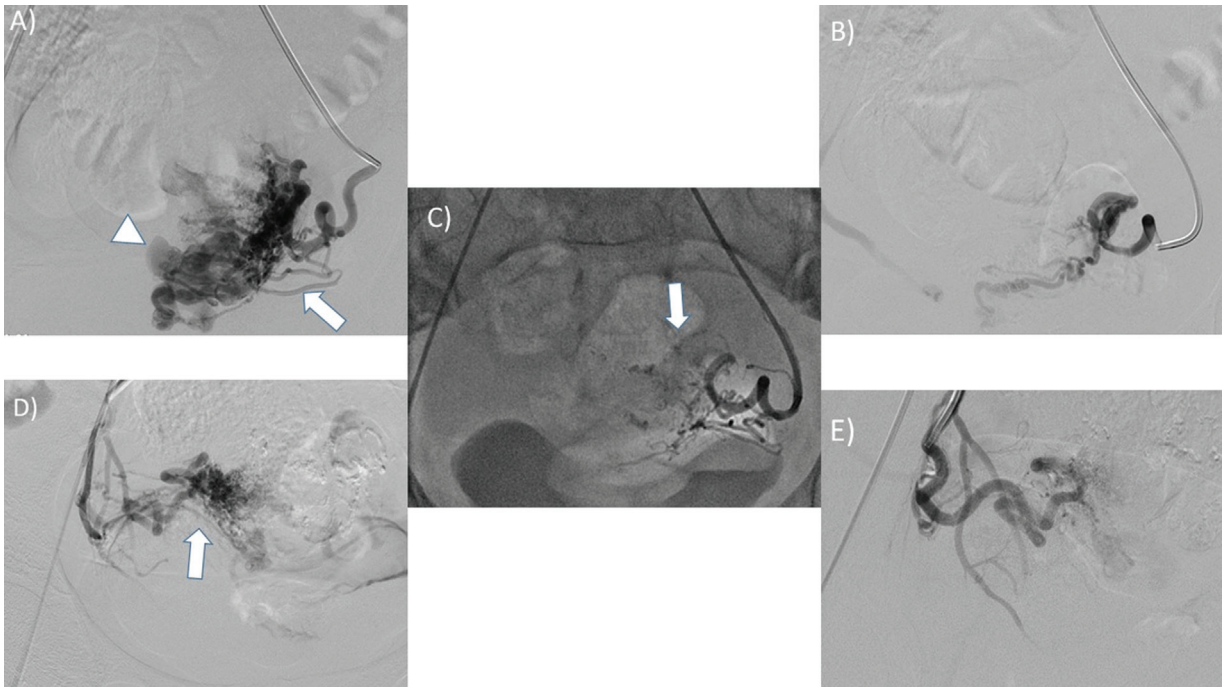

Fig. 1 A 22 year young female patient with history of previous caesarian section presenting with recurrent per vaginal bleeding following D&C. (A and D) Bilateral uterine arteries were accessed using a 5F RUC catheter. The angiogram demonstrated tortuous vessels supplying the AVM (arrow) arising from the bilateral uterine arteries with drainage into a large venous channel (arrow head). (C) The AVM was embolized using PVA particles (500-710micron), followed by histoacryl glue which formed casts (arrow) within the network of arteries arising from the bilateral uterine arteries. (B and E) Repeat angiogram showed significant reduction of flow into the AVM. D&C: Dilatation and Curettage, AVM: Arteriovenous Malformation, RUC: Robertson Uterine Curve, PVA: Polyvinyl Alcohol.

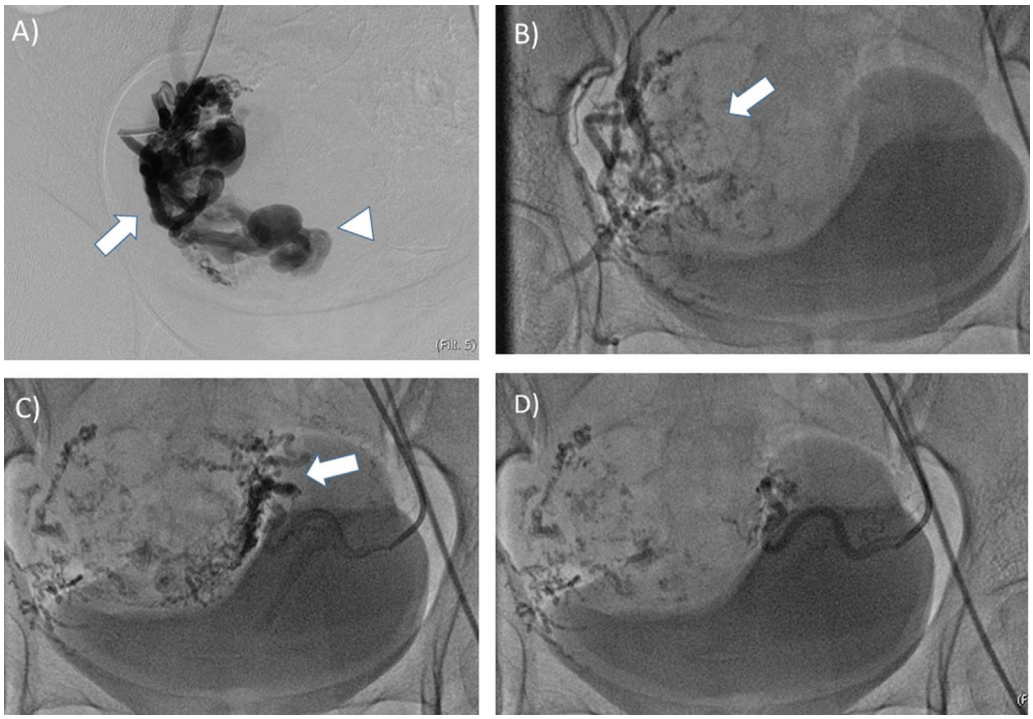

Fig. 2 A 25 year young female patient presenting with menorrhagia and urinary incontinence, diagnosed with uterine AVM. (A) Using a 5F RUC catheter and 0.032 guide wire combination, right uterine artery was selectively catheterized and angiogram showed a large AVM (arrow) with drainage into a large venous channel (arrow head). (B) The AVM was embolized using histoacryl glue which formed casts (arrow) within the network of arteries. This was followed by embolization using 500-710micron PVA particles till it achieved stasis. (C) Similarly the left uterine artery was accessed using a 5F RUC catheter. The angiogram demonstrated tortuous vessels supplying the AVM (arrow). (D) The capillary network was embolized using 500-710micron PVA particles till the artery showed stasis in flow. AVM: Arteriovenous Malformation, RUC: Robertson Uterine Curve, PVA: Polyvinyl Alcohol.

in 100% of cases. The clinical success rate was 92%. Vaginal bleeding was controlled in 222 of 225 patients and three patients underwent a hysterectomy. Recovery to normal menstrual cycle was seen in all 222 patients with clinical success within one or two months. Duplex ultrasound evaluation performed three days after embolization showed ultrasonographic success in all patients. 84 of the 225 patients conceived following embolization. 60 patients had uneventful intrauterine pregnancies carried to term. 15 woman had an induced abortions. Nine woman went into premature labor and in that four newborns died 1 week later. The longest delay between embolization and pregnancy was 3 years and the shortest was seven weeks. The mean time period between embolization and delivery was 21.3 months. The 210 patients who underwent successful embolization had no recurrence of bleeding at a median follow-up of 53 months (range, 5-122 months) after treatment. 15 patients were eventually lost to follow-up. One minor complication (0.4%) of non-flow-limiting dissection of the internal iliac artery occurred. There were no cases with uterine necrosis, non target embolization. No other side effects, either early or delayed, were documented as a result of the embolization procedure.

Discussion

Vascular malformations of the uterus are rare and potentially life threatening lesions. AVMs have been described in women of all ages, but predominantly among women of childbearing age. Uterine AVM can be congenital or acquired. Congenital uterine AVMs have multiple feeding arteries, a central tangle of vessels, and numerous large draining veins; these result from abnormal embryologic development of primitive vascular structures and tend to invade the surrounding structures.[11–14] Most congenital uterine AVMs are isolated anomalies, but can occur in association with AVMs at other sites.[15,16] Acquired uterine AVM is the predominant type of uterine AVM. It consists of multiple small arteriovenous fistulas between intramural arterial branches and the myometrial venous plexus, tends to have single or bilateral uterine artery feeders without an extrauterine arterial supply, and does not have a characteristic nidus.[17–20] Acquired Uterine AVM has been reported after abortion, caesarean section, direct uterine trauma like D&C and gestational trophoblastic disease etc.

During a normal pregnancy, utero-placental arteries are invaded by the trophoblast during the first two trimesters, which results artery enlargement and decreased resistance followed by re-endothelialisation during the third trimester. In subinvolution of placental bed vessels, uteroplacental arteries maintain characteristics similar to those of the first two trimesters. Some authors suggest that low flow uterine AVMs may be caused by subinvolution of placental bed vessels.[21,22] For normal pregnancies, there is an arteriovenous network in the myometrium that remains about 48 hours after delivery,[23] which may be a cause of uterine

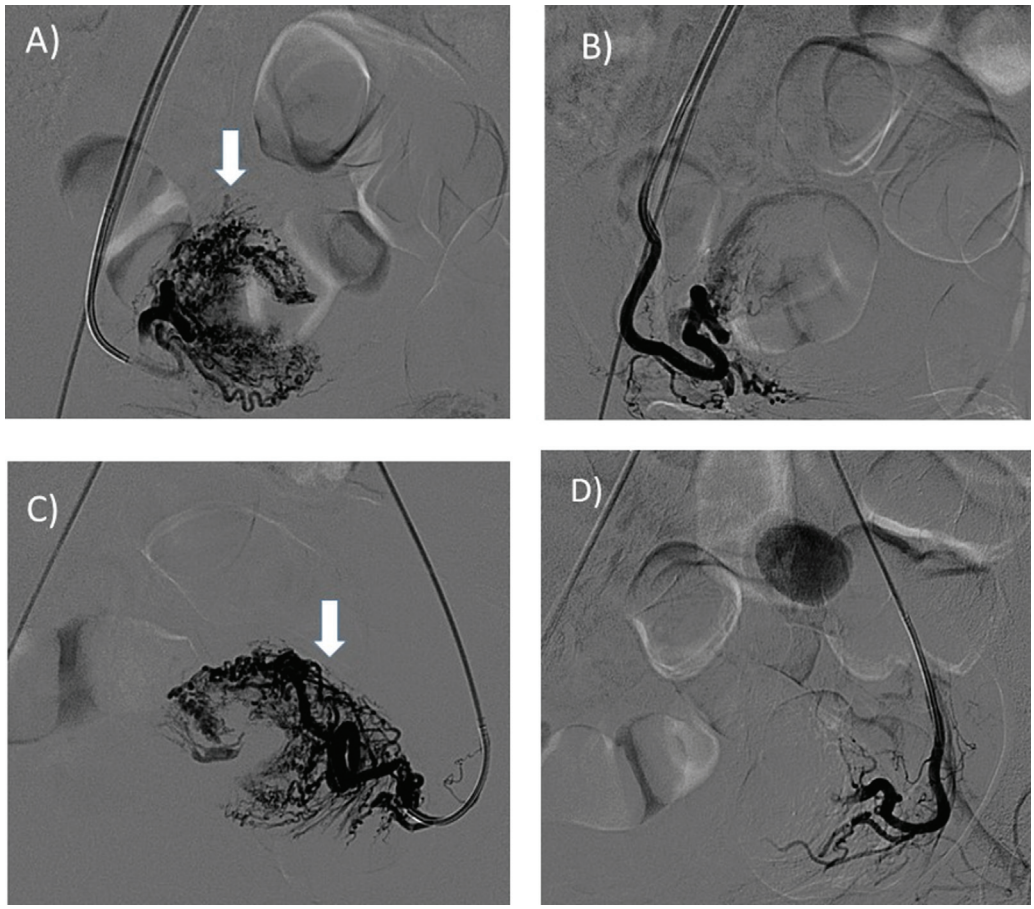

Fig. 3 A 19-year-young woman with intermittent vaginal bleeding due to uterine AVM. (A and C) Selective catheterization of bilateral uterine arteries with 5F RUC catheter and angiogram shows tangle of blood vessels fed by Uterine Arteries (arrow). (B and D) Post Embolization angiogram with histoacryl glue shows significant reduction in Arterio-Venous shunting. AVM: Arteriovenous Malformation, RUC: Robertson Uterine Curve.

AVMs, specifically for high-flow AVMs. Patients with Uterine AVM can present with the following symptoms like menorrhagia, throbbing discomfort in the lower abdomen, urinary frequency or incontinence, dyspareunia, strong pelvic pulsations after exercise, systemic hypotension caused by blood pooling within the AVM, and even cardiac failure.

Clinical diagnosis of uterine AVM is often difficult and requires a high index of suspicion. Currently, transvaginal USG with doppler is the imaging modality of choice. Typical findings includes tortuous anechoic spaces in the myometrium which on colour doppler shows high-flow velocity with low resistance and mixing of arterial, venous waveforms where AVM drains into a large low-pressure venous pool**.**

Transcatheter arterial embolization is a minimally invasive treatment option with potential to preserve fertility because it does not seem to interfere with the menstrual cycle or pregnancy.[2,24,25] The typical finding of Uterine AVM by angiography is a high arterial flow with early venous filling. A single direct fistulous communication to the venous structures may be identified. Compared with surgical procedures, transcatheter arterial embolization is a safe and effective treatment option which includes low procedure related complication rates and shorter hospitalization. We have reported that treatment of uterine AVMs with arterial embolization has a high technical and clinical success rate. Our results demonstrate that this is effective and safe for the treatment of haemorrhagic complications of uterine AVM and may further preserve future fertility**.** Once the diagnosis of uterine AVM is made, embolization can be considered for anaemic or hemodynamically unstable patients.[26] Conversely, women who present with only one episode of metrorrhagia and who are hemodynamically stable should be monitored.[27] This is based on the hypothesis that uterine AVMs caused by subinvolution of the placental bed can have spontaneous involution. Curettage does not convey any risk for hemodynamically stable patients. On the opposite, hemodynamically unstable women should have an arteriogram and further embolization because curettage is at high risk in women with uterine AVMs. Embolization of the uterine arteries has not been associated with uterine infarction because of the presence of a rich collateral vascular network within the pelvis.[28]

Although repeat embolization for recurrent bleeding may be required, hysterectomy can be avoided and fertility preserved, which is extremely important for this group of patient**s.** In our study 90 patients required repeat embolization for recurrence of bleeding. 3 of these patients

underwent embolization six times, 6 of these patients underwent embolization thrice, 76 of these patients underwent embolization twice.

Our results demonstrate that Histoacryl glue is effective, safe and most commonly used embolic agent for the treatment of haemorrhagic complications due to uterine AVM and further preserves future fertility**.** It is an embolic agent that enables controlled and permanent obliteration of the AVM. It is a liquid ester that polymerizes rapidly in the presence of ionic substances like blood or saline. Histoacryl glue is mixed with lipiodol at a ratio ranging from 1:1 or 1:2. 0.1ml of this embolic agent mixture is injected followed by 25% w/v dextrose per injection. Other agents such as PVA particles, Gelfoam, coils are also used for embolization, especially when the target of embolization is more distal and further catheter advancement is difficult or impossible.

Failure of embolization therapy can be managed with hysterectomy[19,29] or with uterine artery and ovarian ligament ligation when uterine preservation is desired.[30] In our study three patients underwent hysterectomy as vaginal bleeding is not controlled after uterine artery embolization.

After successful embolization of a uterine AVM, hypovascularity of involved areas could, in theory, affect placentation and foetal growth; yet, several successful intrauterine pregnancies after transcatheter arterial embolization of uterine AVMs have been reported[20,31,32] including a successful twin pregnancy,[33] which suggests that adequate collateral blood supply can develop to support a full-term pregnancy. Normal placental blood flow has been documented after previous transcatheter arterial embolization to treat uterine AVM.[20] In the study by O'Brien et al.,[34] normal menstrual cycles returned 2 months after transcatheter arterial embolization, and 5 patients became pregnant. In our study, we observed 84 patients conceived following embolization. 60 patients had uneventful full term pregnancy. Normal menstrual cycle was seen in 222 patients with clinical success within one or two months. Of note, our fertility rate is consistent with those reported in other studies.[8,35] Przybojewski and Sadler[36] reported a novel image guided management of a uterine AVM after failed transcatheter arterial embolization in which they directly injected embolization material into the nidus of the AVM under ultrasound guidance and fluoroscopy after exposing the uterus surgically; the patient had a successful term pregnancy afterward.

With experienced operators, transcatheter arterial embolization is generally safe. Minor complications including hematoma, urinary tract infection, retention of urine, and vessel or nerve injury at the vascular puncture site are common and require only mild supportive care or careful observation.[37] Varying degrees of pelvic pain are also common in the immediate post embolization period. Pain after transcatheter arterial embolization is probably due to ischemia produced by the embolization procedure, usually peaks on the first day after the procedure, responds well to analgesic therapy, and resolves in about a week.[38] Uterine necrosis is another rare life-threatening complication that mandates prompt treatment with antibiotics and hysterectomy. Loss of ovarian function can rarely develop after uterine artery embolization, in particular in women older than 45 years because of their more abundant uterine ovarian arterial anastomoses compared with younger women.[39,40] Other serious potential complications of transcatheter arterial embolization may include perianal skin sloughing, uterovaginal and rectovaginal fistulas, neurologic deficits in the lower extremities, deep venous thrombosis, and pulmonary embolism.[33,41–43] In our study, one minor complication of non-flow-limiting dissection of the internal iliac artery occurred. It was subsequently embolized using microcoils. Otherwise there were no cases with uterine necrosis, non target embolization and other serious complications in our patients. Our study has limitations like 15 patients were eventually lost to follow-up.

Conclusion

Uterine AVM is a rare but potentially serious cause of abnormal vaginal bleeding. Diagnosis should be considered in all patients of reproductive age who have abnormal vaginal bleeding and negative β-hCG test results. Transvaginal ultrasonography is the imaging method of choice. Colour Doppler imaging should be used routinely to enable the correct diagnosis. Transcatheter uterine artery embolization is an excellent treatment option with a low complication rate, high success rate and further preserves future fertility. It is a safe and effective treatment for severe bleeding uterine vascular malformations.

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.

Conflicts to Interest:

The authors have no conflict of interest to declare.

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Mucinous Cystadenoma Arising in a Uterine Isthmocele: A Case Report

Cistadenoma mucinoso surgindo em istmocele uterina: relato de caso

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Abstract

Isthmocele is a discontinuation of the myometrium at the uterine scar site in a patient with a previous cesarian section (CS). The cause of isthmocele appears to be multifactorial. Poor surgical technique, low incision location, uterine retroflection, obesity, smoking, inadequate healing of scars, and maternal age are possible related factors. Most patients with this condition are asymptomatic. However, women can present with postmenstrual bleeding, pelvic pain, subfertility, dysmenorrhea, infertility, and scar abscess. Brazil has one of the world's highest cesarean section rates. One of the consequences of the rising rate of CS is the isthmocele, an emerging female health problem. Here we report a case of mucinous cystadenoma arising in a uterine isthmocele, a complication, as far as we could investigate, not yet described in the literature.

Keywords
- isthmocele
- niche
- diverticulum
- deficient uterine scar
- scar pouch
- mucinous cystadenoma

Resumo

Istmocele é a descontinuidade do miométrio no local da cicatriz uterina em paciente com cesariana anterior. A causa da istmocele parece ser multifatorial. Má técnica cirúrgica, baixa localização da incisão, retroflexão uterina, obesidade, tabagismo, cicatrização inadequada de cicatrizes e idade materna são possíveis fatores relacionados. A maioria dos pacientes com esta condição é assintomática. No entanto, as mulheres podem apresentar sangramento pós-menstrual, dor pélvica, subfertilidade, dismenorreia, infertilidade e abscesso cicatricial. O Brasil tem uma das maiores taxas de cesariana do mundo. Uma das consequências da taxa crescente de cesarianas é a istmocele, um problema emergente de saúde feminina. Aqui relatamos um caso de cistoadenoma mucinoso originado em uma istmocele uterina, uma complicação ainda não descrita, até onde pudemos investigar.

Palavras-chave
- istmocele
- nicho
- divertículo
- cicatriz uterina deficient
- bolsa cicatricial
- cistadenoma mucinoso

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Introduction

Isthmocele is a cesarean scar defect, also named niche, diverticulum, deficient uterine scar, or scar pouch, defined as a discontinuation of the myometrium at the uterine scar site.[1] Radiologists define it as an indentation seen at the cesarean scar site with a depth of at least 2 mm at ultrasound or magnetic resonance imaging.[2] The standard diagnostic procedure for identifying isthmoceles is transvaginal sonography (TVS), and the prevalence ranges from 6.9% to 64.5%.[3] The cause of isthmocele appears to be multifactorial. Poor surgical technique, low incision location, uterine retroflection, obesity, smoking, inadequate healing of scars, and maternal age are possible related factors. Most patients with this condition are asymptomatic, although some of them can present postmenstrual bleeding, pelvic pain, subfertility, dysmenorrhea, infertility, and scar abscess.[2,4] One case of high-grade endometrial stromal sarcoma[4] and one of endometrioid carcinoma[5] originating in the scar has already been described. We have not found any description of mucinous cystadenoma or other tumors to date. Although the occurrence of neoplasm associated with isthmocele is an apparently rare event, considering the increase in the number of cesarean sections, we recommend special attention and investigation of symptoms in patients with previous cesarean.

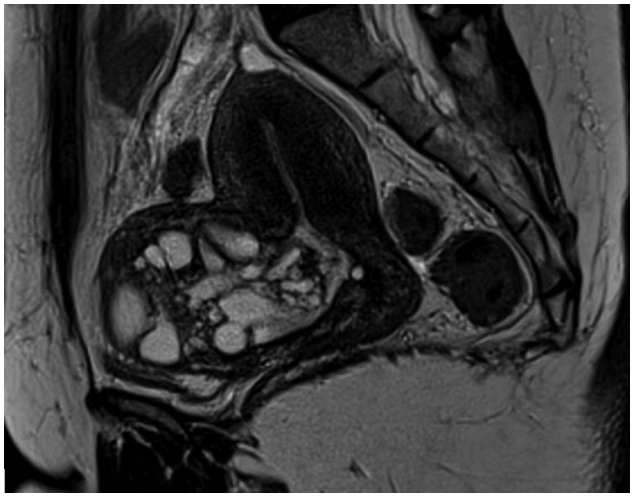

Fig. 1 Magnetic Resonance Imaging (MRI) demonstrating a bulky isthmocele at cesarean section scar with several cysts inside.

Case Description

A 49-year-old woman presented with a history of progressive vaginal fluid discharge of 3 months duration and a palpable pelvic mass. She was submitted to a cesarian section twelve years ago, followed by a history of infertility. The vaginal discharge was irregular, sometimes it happened spontaneously, sometimes during intercourse. She had no history of alcohol consumption or cigarette smoking. Her body mass index (BMI) was 26 kg/m2. A vaginal examination revealed a normal cervix and a heavy mucinous fluid discharge during the examination. Serum tumor marker CA125 levels were normal (CA125; 18 U/mL). Magnetic Resonance Imaging (MRI) demonstrated the uterus in anteversion, measuring $9.2 \times 5.8 \times 4.3$ cm, with a volume of 119.3 cm^3. There was a bulky multiloculated cyst measuring $7.5 \times 7.0 \times 6.6$ cm (volume of 180.1 cm^3) at the level of cesarean scar in the anterior isthmocorporal uterine region (►**Fig. 1**). This complex isthmocele was filled with liquid content with a thick component and communicated with the uterine cavity in an extension of 2.5 cm. Both ovaries were normal.

We performed an extra-fascial laparoscopic hysterectomy plus bilateral salpingectomy (►**Fig. 2**). Pathologic examination revealed a multiloculated cystic lesion in the isthmic uterine scar with two holes communicating the tumor with the endocervix. The cysts were lined by pyloric type mucinous epithelium with goblet cells and some endocrine cells and serous foci. Cysts were surrounded by densely packed round mucinous glands (►**Fig. 3**). The pathological diagnosis was mucinous cystadenoma in the uterine isthmocele. The

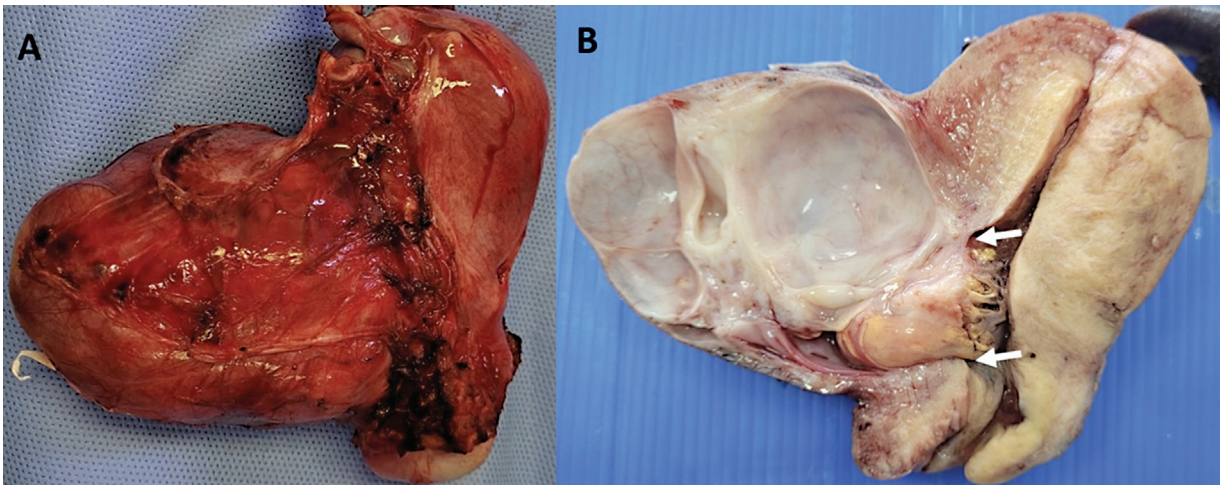

Fig. 2 Surgical specimen showing a multiloculated cystic mass on the anterior uterine wall, in isthmocele associated with cesarean section scar: A) external view, B) uterine sagittal section showing communication of cystadenoma with uterine cavity (arrows).

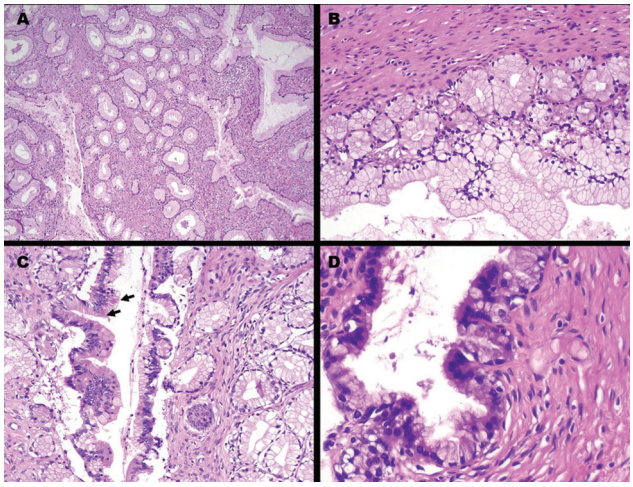

Fig. 3 Mucinous cystadenoma in isthmocele A) densely packet mucinous glands B) detail of gland grouping with mucinous pyloric and goblet cells surrounding cystic space C) area of mild cell proliferation, without atypia, with mucinous and endocrine cells (arrows) D) gland showing numerous ciliated tubal serous-like cells.

patient recovered well in the postoperative period and remains under follow-up, asymptomatic, with normal activities for 2 months, including sexual activity.

Discussion

There is a gradual increase in CS globally. The highest rate is in Latin America, with an estimated CS rate of 42.8 (37.6, 48.0) (95% CI).[6] Brazil has one of the world's highest cesarean section rates.[7] With this increase, a rise in the incidence of isthmocele is expected. Several complications are related to cesarean section scar and isthmocele. The incidence of cesarean scar ectopic pregnancies, for example, is ~1 in 2000 pregnancies.[8] There is a strong association between abnormal uterine bleeding (AUB) and cesarean scar defects (CSDs). These patients experience the so-called prolonged menstruation and early-cycle intermenstrual bleeding.[9] Prelabor uterine rupture is another complication that may result in a severe risk of death.

Clinical and radiologic differential diagnosis may be challenging in some cases. Uterine parietal cysts with sometimes stale/bloody content look like retention cysts, but cannot completely rule out others diseases like tunnel clusters and cervical adenocarcinoma type gastric (former minimal deviation adenocarcinoma or adenoma malignum), that can present the same image aspects. Usually, the histologic findings from uterine specimens of isthmoceles are endocervical mucosa, with cystically dilated glands, and/or an atrophic or disorganized endometrial mucosa of lower uterine segment origin, showing variable regenerative epithelial atypia, fibroblastic stromal reaction, significant inflammation, and hemorrhage.[10]

The association between isthmocele and benign/or malignant uterine tumor is unclear. Yi-Liang Lee et al. reported one case of high-grade endometrial stromal sarcoma in a 45-year-old woman who underwent hysteroscopic isthmoplasty.[4] Gorostidi and Rodriguez presented a case of endometrial carcinoma in a 44-year-old G1P1 woman that involved the isthmocele.[5] No description of mucinous neoplasms were found. This case presented the morphologic pattern seen in ovarian mucinous neoplasms, with gastrointestinal type epithelium, without cytologic atypia and, although showing architectural complexity, with no significant cellular proliferation. The morphological pattern of the mucinous cells was that seen in the lobular endocervical glandular hyperplasia, one of the lesions of the spectrum of gastric type epithelium lesion in uterine cervix. This type of lesion was even present in the endocervical canal. It is possible that the tumor originated in the endocervical mucosa included in the isthmocele or even in the endocervix itself, growing toward the isthmocele. We can hypothesized that the inflammatory microenvironment of the scar favored the neoplastic transformation of the included epithelium. The local inflammatory changes were also one of the discussed factors involved in the origin of the high-grade sarcoma in isthmocele described by Lee et al.[4]

Treatment options are hysteroscopy-guided laparoscopic resection and repair of the cesarean scar,[11] hysteroscopic isthmoplasty,[12] or hysterectomy for those patients without reproductive desire. There is no data about the role between isthmocele and cervical neoplasia. As far as we know, this is the first case of a mucinous cystadenoma originating from isthmocele, However, considering the rising of this condition, it is prudent to investigate all cases of symptomatic isthmocele with pathological examination.

Conclusion

We report what appears to be the first case of a mucinous neoplasm originating from a uterine isthmocele. Isthmocele is a uterine healing defect after a cesarean section. With the global increase in cesarean section rates in the world, and especially in Brazil, isthmocele and its complications may become a growing problem for women's health.

Conflicts to Interest

The authors have no conflict of interest to declare.

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Mirabegron and Anticholinergics in the Treatment of Overactive Bladder Syndrome: A Meta-analysis

Mirabegron e anticolinérgicos no tratamento da síndrome da bexiga hiperativa: metanálise

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Abstract

Objective To compare the use of mirabegron with anticholinergics drugs for the treatment of overactive bladder (OB).

Data Source Systematic searches were conducted in EMBASE, PUBMED, Cochrane, and LILACS databases from inception to September 2021. We included RCTs, women with clinically proven OB symptoms, studies that compared mirabegron to antimuscarinic drugs, and that evaluated the efficacy, safety or adherence.

Data Collection RevMan 5.4 was used to combine results across studies. We derived risk ratios (RRs) and mean differences with 95% CIs using a random-effects meta-analytic model. Cochrane Collaboration Tool and GRADE was applied for risk of bias and quality of the evidence.

Data Synthesis We included 14 studies with a total of 10,774 patients. Fewer total adverse events was reported in mirabegron group than in antimuscarinics group [RR 0.93 (0.89–0.98)]. The risk of gastrointestinal tract disorders and dry mouth were lower with mirabegron [RR 0,58 (0.48–0.68); 9375 patients; RR 0.44 (0.35–0.56), 9375 patients, respectively]. No difference was reported between mirabegron and antimuscarinics drugs for efficacy. The adherence to treatment was 87.7% in both groups [RR 0.99 (0.98–1.00)].

Conclusion Mirabegron and antimuscarinics have comparable efficacy and adherence rates; however, mirabegron showed fewer total and isolated adverse events.

Palavras-chave
- antimuscarínicos
- metanálise
- mirabegrom
- bexiga hiperativa

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Resumo

Objetivo Comparar o uso de mirabegrom com anticolinérgicos para o tratamento da bexiga hiperativa (BH).

Fonte de Dados Buscas sistemáticas foram realizadas nas bases de dados EMBASE, PUBMED, Cochrane e LILACS desde o início até setembro de 2021. Incluímos ECR, mulheres com sintomas de BH clinicamente comprovados, estudos que compararam mirabegrom a medicamentos antimuscarínicos e avaliaram a eficácia, segurança ou adesão.

Coleta de Dados RevMan 5.4 foi usado para combinar os resultados entre os estudos. Derivamos razões de risco (RRs) e diferenças médias com intervalo de confiança (IC) de 95% usando um modelo meta-analítico de efeitos aleatórios. Cochrane Collaboration Tool e GRADE foi aplicado para risco de viés e qualidade da evidência.

Síntese dos Dados Foram incluídos 14 estudos com um total de 10.774 pacientes. Menos eventos adversos totais foram relatados no grupo mirabegrom do que no grupo antimuscarínicos [RR: 0,93 (0,89–0,98)]. O risco de distúrbios do trato gastrointestinal e boca seca foram menores com mirabegrom [RR: 0,58 (0,48–0,68); 9.375 pacientes; RR: 0,44 (0,35–0,56), 9.375 pacientes, respectivamente]. Nenhuma diferença foi relatada entre mirabegrom e drogas antimuscarínicos para eficácia. A adesão ao tratamento foi de 87,7% em ambos os grupos [RR: 0,99 (0,98–1,00)].

Conclusão Mirabegrom e antimuscarínicos têm eficácia e taxas de adesão comparáveis, porém o mirabegrom apresentou menos eventos adversos totais e isolados.

Keywords

- antimuscarinics
- meta-analysis
- mirabegron
- overactive bladder

Introduction

Overactive bladder is a syndrome characterized by urinary urgency, increased daytime urinary frequency, nocturia, with or without urge urinary incontinence, and no evidence of infection or other proven diseases.[1] It is a condition that impairs patients' quality of life by causing depression, anxiety, frustration, low self-esteem, and social isolation.[2]

The economic impact of overactive bladder is exceptionally high, taking into account both the diagnosis and treatment of the disease, as well as the consequences of the disease, and it tends to increase due to longer life expectancy, as overactive bladder has a higher prevalence with increasing age.[3,4]

Overactive bladder treatment can be pharmacological or non-pharmacological. Behavioral and educational treatments are examples of non-pharmacological treatments. Behavioral and educational interventions, such as limiting the intake of bladder irritants like caffeine and alcohol, bladder training, and urgency suppression techniques like pelvic floor muscle exercises, should be included in the therapeutic plan and offered at the outset. These interventions can be used in conjunction with pharmacological treatment, effective in most overactive bladder patients and are the first line of treatment.[5] In case of treatment failure, another possibility would be botulinic toxin or neuromodulation.[5]

Some drugs are both safe and effective in the treatment of overactive bladder. Anticholinergic drugs increase bladder capacity by lowering detrusor muscle tone during the filling phase.[6] Among the anticholinergic drugs mentioned are oxybutynin, tolterodine, darifenacin, and solifenacin. Anticholinergic drugs block and inhibit muscarinic receptors located not only on the bladder. That may lead to adverse events such as dry mouth and constipation and lead to loss of follow up. Anticholinergic drugs can also penetrate the blood-brain barrier and affect cognition, especially in the elderly.

Another class of drugs used to treat overactive bladder is β-3-adrenergic agonists, which directly inhibit afferent nerve activation through the activation of β type adrenergic receptors at the bladder, causing vesical relaxation. This class of drug has less adverse effects on the salivary glands, therefore, less symptoms such as dry mouth or cognition dysfunction. Mirabegron is a β-3-adrenergic drug that is an alternative to anticholinergic medications.[7]

There is disagreement about the efficacy, tolerability, safety, and adherence to anticholinergic drugs and mirabegron treatment. As a result, comparing these classes of medications in the treatment of overactive bladder is critical.

The goal of this study was to conduct a systematic review followed by a meta-analysis of the efficacy, safety, and adherence to treatment with β-3-adrenergic drugs versus anticholinergics for overactive bladder in women, using evidence from randomized controlled clinical trials.

Methods

The systematic review and meta-analysis were performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. PROSPERO was used to register the study protocol (CRD42019135355).

The EMBASE, Medline (PUBMED), Cochrane, and LILACS databases were used to find the studies. The search included all articles published from inception until October 2022. "Overactive Bladder," "Overactive Detrusor Function," "Overactive

Urinary Bladder," "Overactive Detrusor," "Mirabegron," "Oxybutynin," "Solifenacin," "Tolterodine," "Darifenacin" were the keywords used in the search strategy. The full search strategy can be found in supplementary material (SM) 1.

Two different reviewers analyzed the articles found by the search strategy based on the title and abstract, and the publications that met the eligibility criteria were then thoroughly reviewed. The included studies met the following criteria: (1) randomized controlled trial, (2) study with women over the age of 18 with clinically proven overactive bladder symptoms, (3) mirabegron versus antimuscarinics comparative studies (oxybutynin, darifenacin, tolterodine, or solifenacin). This review only included complete published studies in either Spanish, Italian, French, Portuguese or English language.

We did not include articles that only evaluated men or children, pregnant women, or did not assess the selected outcomes. There was no set minimum or maximum follow-up time for this meta-analysis. We excluded duplicate publications, conference proceedings abstracts, case studies, letters to the editor, review articles, editorials, comments, and animal studies. The outcomes of interest were efficacy, safety, and adherence. The drugs' efficacy was determined by the reduction in the number of urinations, episodes of urge incontinence, urgency, and incontinence within 24 hours (unspecified urinary losses). The total number of adverse events reported by patients and the most relevant adverse events assessed separately, such as gastrointestinal tract disorders (constipation, diarrhea, dyspepsia, nausea, dry mouth), nervous system disorders (headache, dizziness, drowsiness, blurred vision), and others (nasopharyngitis, urinary retention, urinary tract infection, cardiac conditions, hypertension), evaluated the safety outcome. Cardiac disorders included atrial fibrillation, tachycardia, palpitation, supraventricular extrasystole, atrial flutter, extrasystole, QT interval prolongation, arrhythmias, tachyarrhythmia, left bundle branch block, sinus arrhythmia, and cardiac arrhythmia. Based on the number of patients who reported them, all adverse events were expressed as a percentage of the total number of patients enrolled in the study.

The adherence outcome was calculated by dividing the total number of patients who completed the study by the total number of patients who participated in the study. The risk of bias of individual studies was assessed using the Cochrane Collaboration Tool (RoB-1) for RCTs and the certainty of the evidence was assessed by the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE).

Reviewers extracted data from the studies using a standardized form using Excel®. The Cochrane Collaboration Review Manager statistical software (Review Manager version 5.4.1) combined results from the various studies and applied the random effects meta-analytic model using the inverse variance method in all calculations. The outcomes of categorical variables were expressed as a risk ratio (RR) and the outcomes of continuous variables as a mean difference (MD), both with 95% confidence intervals (CI). The Q

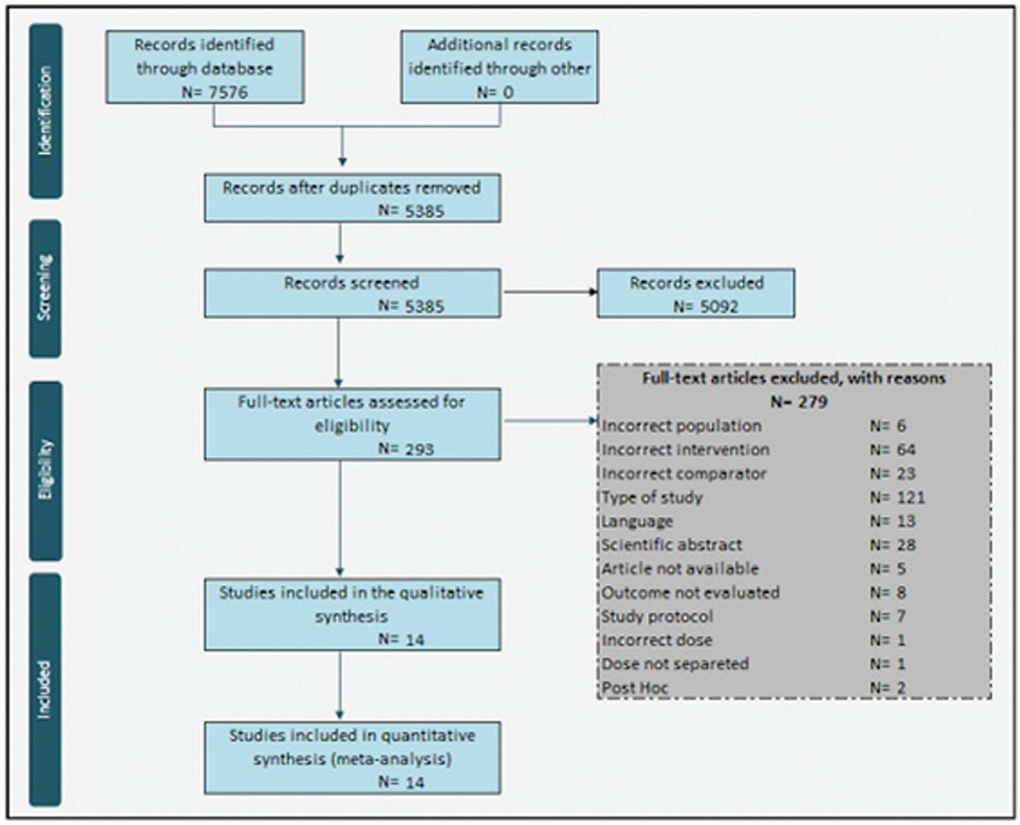

Fig. 1 PRISMA Flowchart.

Chart 1 Essential characteristics of the included studies

Author, year	Country	Intervention group	Comparator group	Number of patients in the intervention group		Number of patients in the comparator group	Percentage of women in the intervention group		Percentage of women in the comparator group	Age of patients in the intervention group (years), mean (SD)		Age of patients in the comparator group (years), mean (SD)
				MIRA 25mg	MIRA 50mg		MIRA 25mg	MIRA 50mg		MIRA 25mg	MIRA 50mg	
Chapple et al. (2013)[8]	Multicentric	MIRA 25 e 50mg	TOL ER 4mg	167	167	85	88%	89.2%	81.2%	57,2 (12,1)	56,9 (12,5)	56,6 (12,8)
Chapple et al. (2013)[9]	Multicentric	MIRA 50mg	TOL ER 4mg	NA	812	812	NA	74.1%	73.9%	NA	59.2 (12.6)	59.6 (12.5)
Khullar et al. (2013)[10]	Multicentric	MIRA 50mg	TOL ER 4mg	NA	493	495	NA	72.4%	72.9%	NA	59.1 (12.3)	59.1 (12.9)
Yamaguchi et al. (2014)[11]	Multicentric	MIRA 50mg	TOL ER 4mg	NA	369	368	NA	84.3%	82.6%	NA	58.3 (13.9)	58.3 (13.7)
Abrams et al. (2015)[12]	Multicentric	MIRA 25 e 50mg	SOL 2.5mg, 5mg e 10mg	77	78	313	67.5%	66.67%	66.1%	55.2 (14.5)	53.4 (14.0)	54,88 (13,9)
Batista et al. (2015)[13]	Multicentric	MIRA 50mg	SOL 5mg	NA	936	934	NA	76.1%	75.9%	NA	56.7 (14.3)	57.4 (13.6)
Kuo et al. (2015)[14]	Multicentric	MIRA 50mg	TOL ER 4mg	NA	338	333	NA	67.5%	64%	NA	54.3 (14.2)	53.9 (14.5)
Kuo et al. (2015)[15]	Multicentric	MIRA 50mg	TOL ER 4mg	NA	76	74	NA	61.8%	59.5%	NA	59.0 (15.1)	56.4 (15.8)
Vecchioli Scaldazza and Morosetti (2016)[16]	Italy	MIRA 50mg	SOL 5mg	NA	31	29	NA	100%	100%	NA	56 (6.25)	58 (7.0)
Herschorn et al. (2017)[17]	Multicentric	MIRA 25 e 50mg	SOL 5mg	423	422	423	77.3%	76.5%	78.3%	56.9 (13.6)	56.7 (13.3)	58.2 (12.8)
Hsiao et al. (2018)[18]	Multicentric	MIRA 50mg	TOL ER 4mg	NA	12	12	NA	100%	100%	NA	53 (3.5)	48,75 (2.6)
Gratzke et al. (2018)[19]	Multicentric	MIRA 50mg	SOL 5mg	NA	302	299	NA	79%	81%	NA	61 (10.7)	60 (11.2)
Staskin et al. (2018)[20]	Multicentric	MIRA 25mg	TOL ER 4mg	316	NA	310	73.4%	NA	75.2%	53.4 (13.9)	NA	53.2 (13.7)
White et al. (2018)[21]	Multicentric	MIRA 25 e 50mg	SOL 5mg	423	422	423	77,3%	76,5%	78,3%	56,9	56,7	58,2

Abbreviations: MIRA, Mirabegron; NA, Not available; SOL, Solifenacin; SD, Standard deviation; TOL, Tolterodine.

test (X^2 test) and the I^2 test were used to assess heterogeneity. Subgroup analysis was performed by mirabegron dosage, 25 mg and 50 mg. Publication bias was assessed using Begg's funnel plot in RevMan version 5.4.1, where each OR point estimate was plotted against its corresponding standard errors (SE) on a logarithmic scale.

Results

Initially, 7,698 studies were found, with 2,207 of them being duplicates, leaving 5,491 articles to be assessed by titles and abstracts. After reviewing, there were 293 studies to be evaluated for a full-text review. This meta-analysis included 14 studies with a total of 10,774 patients (►**Fig. 1**).[8–21] **Chart 1** describes the main characteristics of the included studies. A total of 6 studies with 5,535 patients, compared mirabegron (25–50mg) to solifenacin (2.5mg-5mg-10mg)[12,13,16,17,19,21] and 8 studies with 5,239 patients, compared mirabegron (25–50mg) to tolterodine ER 4mg.[8–11,14,15,18,20] There were no studies that compared mirabegron to oxybutynin or darifenacin.

According to the Cochrane collaboration tool (RoB-1), the overall risk of bias of the included studies was low. Majority of the studies had a high risk of bias for "other sources of bias." The GRADE considered most outcomes evaluated to be low quality of evidence. There was no asymmetry in Begg's funnel-plot for any outcome evaluated, therefore no publication bias was found. There were no differences between the use of mirabegron compared with antimuscarinics concerning efficacy outcomes (►**Table 1**).

Nine studies evaluated the decrease in the number of urinations every 24 hours which included 8,192 patients [MD: -0.00 (-0.16 to 0.16); I^2= 47%] (►**Fig. 2A**).[9–13,15,17,19,20] Seven studies with 4,187 patients evaluated the reduction in urge incontinence episodes [MD: 0.08 (-0.02 to 0.17); I^2= 0%] (►**Fig. 2B**).[9,11–13,15,17,20] Eight studies with a total of 7,582 patients assessed the urgency outcome [MD: 0.04 (-0.10 to 0.19); I^2= 0%] (►**Fig. 2C**).[9–13,15,17,20] Nine studies analyzed 5,285 patients with unspecified urinary losses [MD: 0.04 (-0.10 to 0.19); I^2= 0%] (►**Fig. 2D**).[9–13,15,17,19,20]

Corrigir as citações dos autores no interior da ►**Figura 2** como indicado abaixo:

Eleven studies looked at drug side effects.[8–14,16,17,19,20] In terms of total adverse events, patients treated with mirabegron had fewer adverse events than patients treated with antimuscarinics [RR: 0.93 (0.89–0.98); I^2= 7%; 9,455

Table 1 Results according to the outcomes of interest

		Number of included studies	Number of patients evaluated		Estimated Effect (95% CI)	GRADE	Heterogeneity	
			Mirabegron	Antimuscarinics			I^2	P
Efficacy	Number of urinations/24h	9	4232	3960	MD: -0.00 (-0.16 to 0.16)	Low	47%	0.04
	Urge incontinence episodes/24h	7	2281	1906	MD: 0.08 (-0.02 to 0.17)	Low	0%	0.95
	Emergency episodes/24h	8	3926	3656	MD: 0.04 (-0.10 to 0.19)	Low	0%	0.55
	Episodes of urine leakage/24h	9	2808	2477	MD: 0.06 (-0.09 to 0.20)	Low	34%	0.13
Safety	Total Side Effects	11	1879/4979 (37.7%)	1898/4476 (42.4%)	RR: 0.93 (0.89 to 0.98)	Low	7%	0.38
	Gastrointestinal tract disorders (general)	10	340/4939 (6.9%)	556/4436 (12.5%)	RR: 0.58 (0.48 to 0.68)	Low	31%	0.14
	Dry mouth	10	180/4939 (3.6%)	400/4436 (9.0%)	RR: 0.44 (0.35 to 0.56)	Low	34%	0.11
	Constipation	10	120/4939 (2.4%)	119/4436 (2.7%)	RR: 0.95 (0.73 to 1.22)	Low	0%	0.97
	Diarrhea	2	18/1117 (1.6%)	20/1115 (1.8%)	RR: 0.90 (0.48 to 1.69)	Low	0%	0.78
	Dyspepsia	4	10/2265 (0.4%)	14/1755 (0.8%)	RR: 0.74 (0.32 to 1.72)	Very Low	0%	0.97
	Nausea	2	10/648 (1.5%)	9/410 (2.2%)	RR: 0.76 (0.30 to 1.89)	Low	0%	0.91
	CNS disorders (general)	9	217/4560 (4.8%)	172/4061 (4.2%)	RR: 1,14 (0.93 to 1.39)	Low	0%	0.81
	Headache	7	117/3349 (3.5%)	93/3267 (2.8%)	RR: 1.22 (0.93 to 1.61)	Low	0%	0.91
	Dizziness	5	38/1967 (1.9%)	34/1884 (1.8%)	RR: 1.00 (0.61 to 1.62)	Low	0%	0.55
	Somnolence	3	44/1469 (3.0%)	30/1051 (2.9%)	RR: 1.03 (0.58 to 1.82)	Low	28%	0.25
	Visual blur	4	20/2255 (0.9%)	18/1995 (0.9%)	RR: 1.12 (0.60 to 2.08)	Low	0%	0.69
	Nasopharyngitis	5	81/2131 (3.8%)	76/2292 (3.3%)	RR: 1.18 (0.87 to 1.61)	Low	0%	0.96
	Urinary retention	5	4/3217 (0.1%)	10/2797 (0.4%)	RR: 0.41 (0.14 to 1.26)	Low	0%	0.77
	Urinary tract infection	7	165/3795 (4.3%)	183/3605 (5.1%)	RR: 0.87 (0.70 to 1.07)	Low	0%	0.97
	Cardiac disorders	10	147/4939 (3.0%)	142/4436 (3.2%)	RR: 1.00 (0.74 to 1.35)	Low	18%	0.26
	Hypertension	9	175/4610 (3.8%)	202/4351 (4.6%)	RR: 0.93 (0.76 to 1.13)	Low	0%	0.50
Adherence		11	4175/4762 (87.7%)	3549/4046 (87.7%)	RR: 0.99 (0.98 to 1.00)	Low	2%	0.43

Abbreviations: CI, Confidence interval; CNS, Central nervous system; MD, Mean difference; RR, Risk ratio.

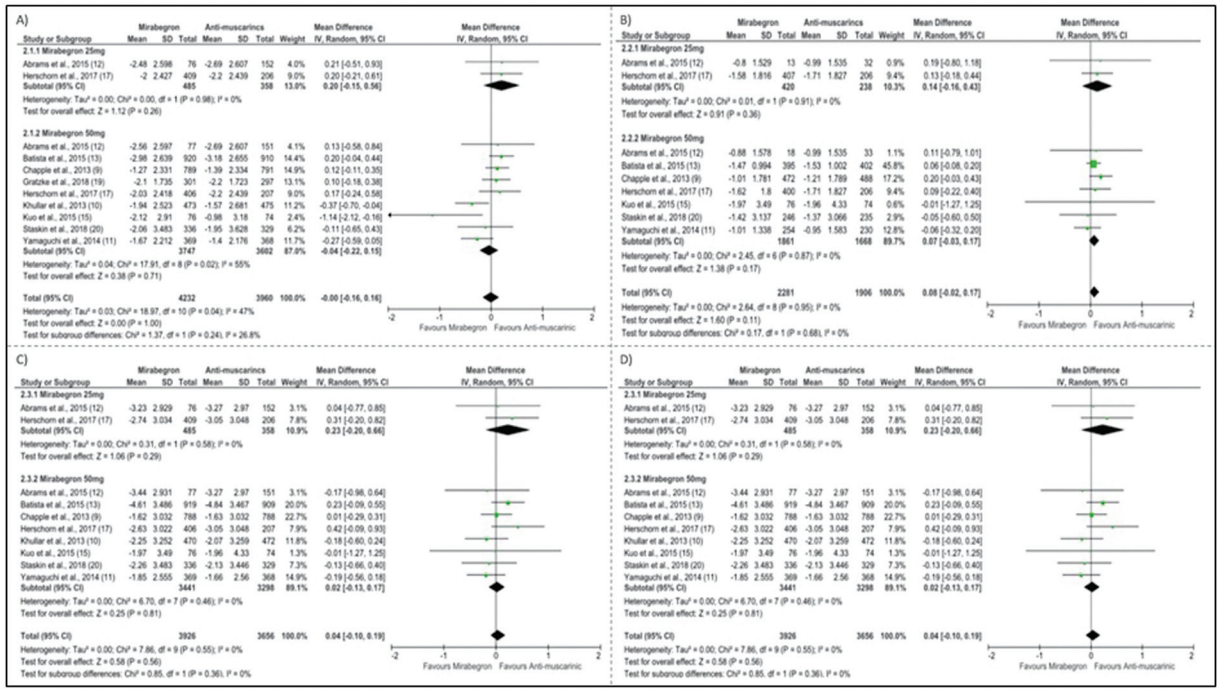

Fig. 2 Forest plots showing efficacy outcome: (**A**) Number of urinations every 24h, (**B**) Urge incontinence episodes, (**C**) Urgency; D: Urinary leakage episodes.

patients] (►**Fig. 3A**). Ten studies with 9,375 patients, examined the number of patients with gastrointestinal tract disorders which was lower with the use of mirabegron [RR: 0.58 (0.48–0.68); I^2= 31%] (►**Fig. 3B**).[8–14,17,19,20] Patients taking mirabegron had a lower incidence of dry mouth [RR: 0.44 (0.35–0.56); I^2= 34%; 9,375 patients] (►**Fig. 3C**). However, when the reviewers examined only the studies with the 25mg dose of mirabegron, these differences were not found (►**Table 1**).

Corrigir as citações dos autores no interior da ►**Figura 3** como indicado abaixo:

When the reviewers compared other adverse events such as constipation, diarrhea, dyspepsia, and nausea separately, there was no difference between the two drugs evaluated (►**Table 1**). There were no differences in adverse events on the central nervous system or elsewhere between patients taking mirabegron or anticholinergics (►**Table 1**). Eleven articles involving 8,808 patients investigated patient's treatment adherence.[8–14,16–20] There was no difference in the treatment of overactive bladder between patients who used mirabegron and those who used antimuscarinics [RR: 0.99 (0.98–1.00); I^2= 2%] (►**Fig. 4**). A total of 87.7% of the patients in both groups completed the proposed treatments.

Corrigir as citações dos autores no interior da ►**Figura 4** como indicado abaixo:

Discussion

Overactive bladder syndrome is a clinical condition that decreases the quality of life.[2] After behavioral or physical therapy measures, drug treatment is considered the second line of treatment. Anticholinergics and, more recently, β-3-adrenergic drugs are the most commonly used classes of drugs in the treatment of overactive bladder.[5] Adherence to drug treatment, on the other hand, can be reduced due to side effects, ineffectiveness, or even the cost of medications.[22,23]

Anticholinergic treatment is estimated to be discontinued in 4% to 31% of patients after 12 weeks, primarily due to adverse events. Its effect on dry mouth and constipation as a cause of treatment discontinuation is well documented.[7,24]

Other anticholinergics, such as solifenacin, darifenacin, and tolterodine, have been developed to reduce side effects while improving adherence and therapeutic outcomes.[5] One of the most commonly used drugs in treating overactive bladder in Brazil is oxybutynin, which has satisfactory efficacy results but has adverse events limiting its use, especially in older people, particularly compromising cognition.[25] In this review, no difference was found between mirabegron and anticholinergic drugs when it comes to adverse effects in the central nervous system, such as cognition dysfunction. These symptoms are more frequent in older patients in chronic use of anticholinergics. In this present review, the average follow-up of the studies was 14 weeks, which might be insufficient to analyze cognitive impairment.

Mirabegron, a β-3 adrenergic receptor agonist, was recently approved to treat overactive bladder, making it an alternative to anticholinergic drugs. This medication acts directly on the detrusor muscle by activating β-3 adrenergic receptors and indirectly on the parasympathetic nerves.[26]

There is some debate over which of these would be the best class of drugs to use in the treatment of overactive bladder. As a result, the goal of this meta-analysis was to

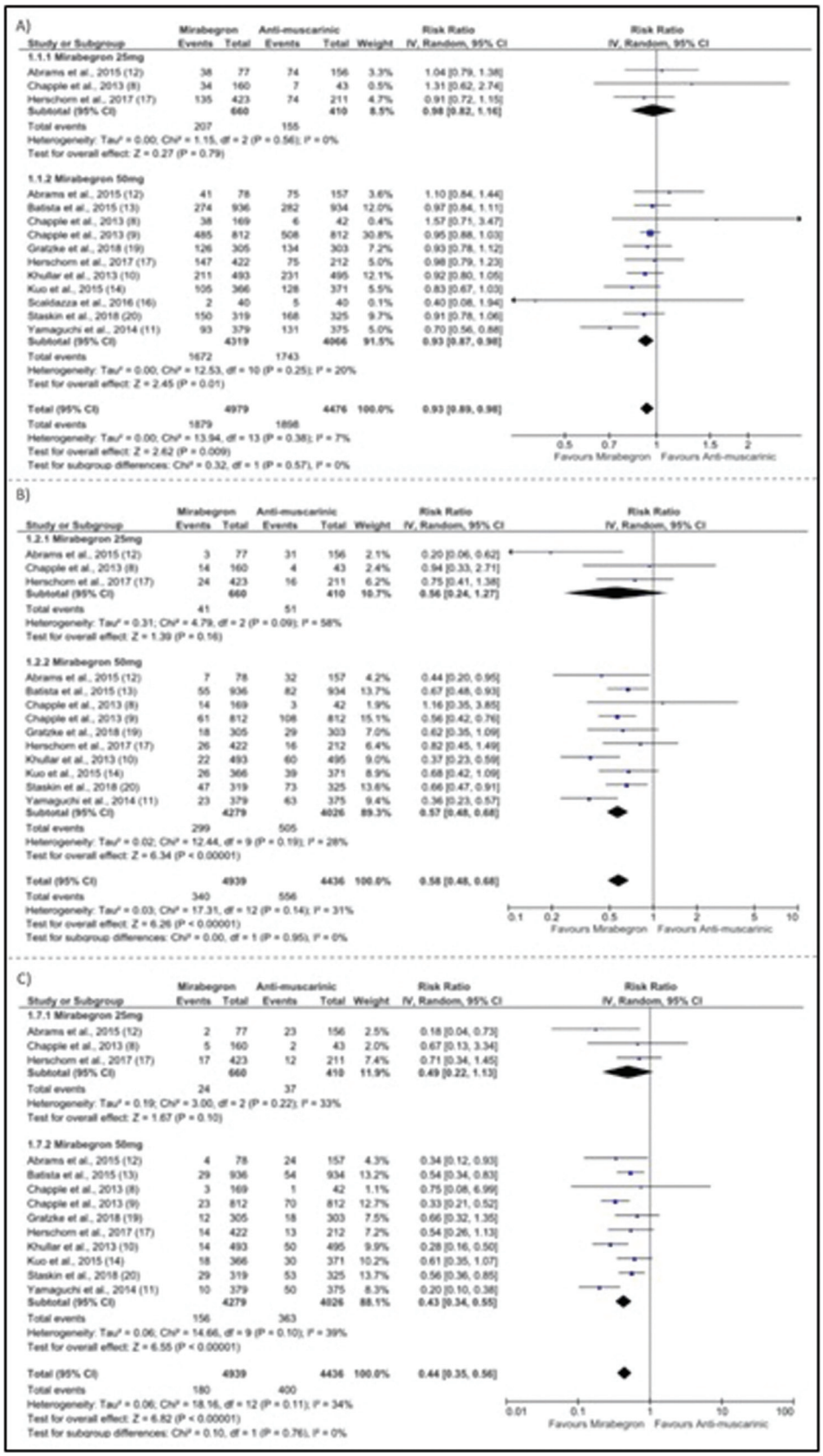

Fig. 3 Forrest plots showing safety outcomes. (**A**) Total number of side effects; (**B**) Gastrointestinal side effects; (**C**) Presence of dry mouth.

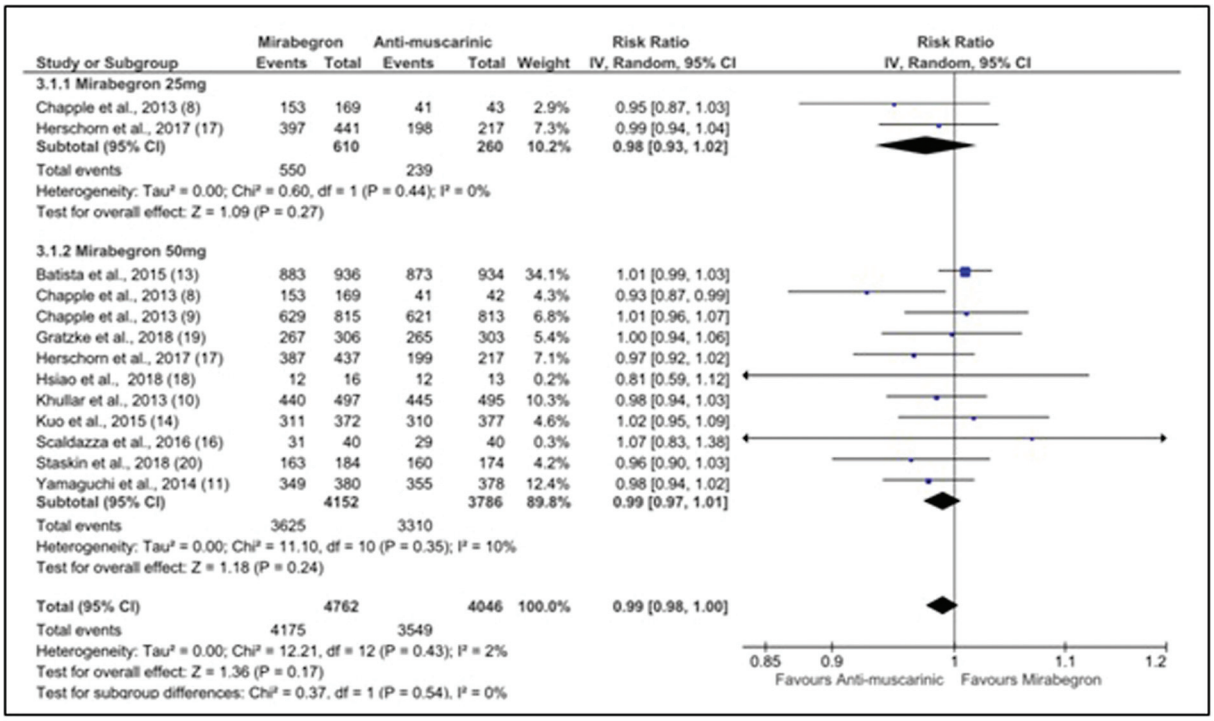

Fig. 4 Forest plot showing adherence outcome.

determine which class of medication is more effective, safe, and has the highest adherence for the treatment of women with overactive bladder.

This meta-analysis demonstrated that mirabegron causes less dry mouth than antimuscarinics, as several authors observed.[25,27,28]

Furthermore, because anticholinergics cross the blood-brain barrier, their use in elderly patients should be cautious. On the other hand, mirabegron is safer in terms of central nervous system side effects.[29] However, this meta-analysis showed no difference between adverse events on the central nervous system, such as dizziness, headache, and somnolence, the only ones described in the studies. This finding could be due to a failure to adequately assess cognitive symptoms, as well as, a failure to differentiate adverse events by age group in the studies examined.

Although the meta-analysis discovered that mirabegron and antimuscarinics have comparable efficacy and adherence rates, mirabegron was safer in terms of total side effects as well as side effects such as general gastrointestinal disorders and dry mouth.

This systematic review's strength was that it only included randomized studies that compared mirabegron to other anticholinergics. The main flaw was that the reviewers found no studies that only looked at women. Studies that did not include adult women were excluded from this meta-analysis to reduce this bias. However, studies that included men did not present outcomes based on patient gender, nor did they report gender inclusion percentages. Furthermore, the articles included in this meta-analysis were deemed low quality because some of the authors had commercial ties to pharmaceutical companies that produced the analyzed drugs. This is a crucial bias to consider, in our opinion. Adherence outcome also has important limitation in the interpretation due to different treatment duration between studies, which ranged from 12 weeks to 18 weeks.

A recent meta-analysis reported that treatment adherence rates vary depending on age, gender, medication type, and the study's year.[30] We believe that studies should be conducted based on the gender of the patients because the causes of overactive bladder and therapeutic responses may differ depending on the patient's hormonal state.

No articles compared mirabegron to oxybutynin, one of the most commonly used drugs in Brazil to treat overactive bladder. However, several studies show that solifenacin and tolterodine outperform oxybutynin, particularly in terms of adverse events.[31–33] As a result, it is reasonable to believe that mirabegron beats oxybutynin in this regard.

Conclusion

As a result, the current meta-analysis observed that while mirabegron and antimuscarinics have comparable efficacy and adherence rates, mirabegron has fewer total and isolated side effects to treat women with overactive bladder. Studies focusing solely on women could shed lighter in the efficacy, safety, and adherence of medications in this population.

Conflicts to Interest

The authors have no conflicts of interest to declare.

Acknowledgments

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COVID-19 and Preeclampsia: A Systematic Review of Pathophysiological Interactions

COVID-19 e pré-eclâmpsia: uma revisão sistemática de interações fisiopatológicas

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Abstract

Objective: To review the literature and synthesize evidence on pathophysiological interactions attributed to the simultaneous occurrence of COVID-19 and preeclampsia.
Methods: A systematic review was conducted from November (2021) to January (2022) to retrieve observational studies published on the PubMed, LILACS, SciELO Brazil and Google Scholar databases. The search was based on the descriptors [(eclampsia OR preeclampsia) AND (COVID-19)]. Quantitative studies that pointed to pathophysiological interactions were included. Literature reviews, studies with HIV participants, or with clinical approach only were excluded. The selection of studies was standardized and the evaluation was performed by pairs of researchers.
Results: In this review, 155 publications were retrieved; 16 met the inclusion criteria. In summary, the physiological expression of angiotensin-converting enzyme-2 (ACE-2) receptors is physiologically increased in pregnant women, especially at the placental site. Studies suggest that the coronavirus binds to ACE-2 to enter the human cell, causing deregulation of the renin-angiotensin-aldosterone system and in the ratio between angiotensin-II and angiotensin-1-7, inducing manifestations suggestive of preeclampsia. Furthermore, the cytokine storm leads to endothelial dysfunction, vasculopathy and thrombus formation, also present in preeclampsia.
Conclusion: The studies retrieved in this review suggest that there is a possible overlap of pathophysiological interactions between COVID-19 and preeclampsia, which mainly involve ACE-2 and endothelial dysfunction. Given that preeclampsia courses with progressive clinical and laboratory alterations, a highly quality prenatal care may be able to detect specific clinical and laboratory parameters to differentiate a

Keywords
- COVID-19
- SARS-CoV-2
- Preeclampsia
- Eclampsia
- Pathogenesis

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true preeclampsia superimposed by covid-19, as well as cases with hypertensive manifestations resulting from viral infection.

Resumo

Objetivo: Revisar a literatura e sintetizar evidências sobre interações fisiopatológicas atribuídas à ocorrência simultânea de COVID-19 e pré-eclâmpsia.

Métodos: Uma revisão sistemática foi conduzida entre novembro (2021) a janeiro (2022) para recuperar estudos observacionais publicados no PubMed, LILACS, SciELO Brasil e Google scholar. A busca foi baseada nos descritores [(eclâmpsia OR pré-eclâmpsia) AND (COVID-19)]. Estudos quantitativos que apontaram interações fisiopatológicas foram incluídos. Estudos de revisão, com participante HIV e apenas com enfoque clínico foram excluídos. A seleção dos estudos foi padronizada com avaliação por duplas de pesquisadores.

Resultados: Nesta revisão, 155 publicações foram recuperadas; 16 preencheram os critérios de inclusão. Em síntese, a expressão fisiológica de receptores da enzima conversora da angiotensina-2 (ECA-2) é fisiologicamente potencializada em gestantes, especialmente no sítio placentário. Os estudos sugerem que o coronavírus se liga à ECA-2 para entrar na célula humana, ocasionando desregulação do sistema renina-angiotensina-aldosterona e da razão entre angiotensina-II e angiotensina-1-7, induzindo manifestações sugestivas de pré-eclâmpsia. Ademais, a tempestade de citocinas conduz à disfunção endotelial, vasculopatia e formação de trombos, também presentes na pré-eclâmpsia.

Conclusão: Os estudos recuperados nesta revisão sugerem que a superposição de alterações fisiopatológicas entre a COVID-19 e a pré-eclâmpsia envolve, principalmente, a ECA-2 e disfunção endotelial. Tendo em vista que a pré-eclâmpsia cursa com alterações clínicas e laboratoriais progressivas, a atenção pré-natal de qualidade pode ser capaz de detectar parâmetros clínicos e laboratoriais importantes para diferenciar a pré-eclâmpsia verdadeira sobreposta por COVID-19, bem como os casos que mimetizam a doença hipertensiva consequente à infecção viral.

Palavras-chave
- COVID-19
- SARS-CoV-2
- Pré-eclâmpsia
- Eclâmpsia
- Patogênese

Introduction

The concurrence of pregnancy-related diseases (gestational hypertension, preeclampsia and eclampsia) with the COVID-19 virus is a clinical novelty, classified as a serious maternal risk.[1,2] A living systematic review with meta-analysis in pregnant and recently pregnant women reported severe COVID-19 infection in 9%; the intensive care unit admission required in 4%; invasive ventilation used in 2%; and extracorporeal membrane oxygenation administered in 0.2%.[3]

Preeclampsia is characterized by new onset hypertensive manifestations occurring with or without proteinuria in the last half of pregnancy or postpartum. In general, its onset occurs after 20 weeks of gestation or earlier in the presence of gestational trophoblastic disease or hydrops fetalis, and normal physiological pressure levels return within 12 weeks after the birth of the conceptus.[4]

The pathophysiology of preeclampsia is still knowledge under construction. Theoretically, there is a failure in the complete remodeling of the maternal spiral arteries that are meant to guarantee adequate blood flow. The impairment conversion from small and higher resistance arterioles into large arteries leads to high resistance of blood flow, hypoperfusion, and hypoxemia, culminating in maternal systemic endothelial cell dysfunction.[4]

Hypertensive disorders of pregnancy affect approximately 10% of pregnant women worldwide, an estimate that includes preeclampsia and eclampsia, gestational hypertension and chronic hypertension.[5] A meta-analysis that included 10 studies and 2988 women estimated the prevalence of preeclampsia in 6.7% with 95% Confidence interval (CI) of 4.9%-8.6%, in Brazil.[6]

A meta-analysis that combined data of preeclampsia in pregnant women infected with the new coronavirus from 10 studies estimated a prevalence of 8.2% (95% CI: 5.7 to 11.7%). In addition, stratification by country showed prevalence of 10.8% (95% CI: 8.1% to 14.3%) and 10.4% (95% CI: 5.0% to 20.1%) for the United States and China, respectively.[7] The concurrence of COVID-19 with preeclampsia has gained popularity in the literature. The possibility that SARS-CoV-2 infection contributes to the development of preeclampsia has been raised, but there is no consensus. For example, the lack of positivity of preeclampsia-specific anti-angiogenic

and angiogenic markers has directed the explanatory reasoning more towards COVID-19 than placental disorders.[8]

Given the severity of the overlap between COVID-19 and preeclampsia, it is imperative to deepen the knowledge of the pathophysiological interactions, which provides information to support clinical approaches and stimulate the development of future investigations. The aim of this review was to present a narrative synthesis on the pathophysiological interactions attributed to the simultaneous presence of COVID-19 and preeclampsia.

Methods

This study is a narrative synthesis systematic review in line with Popay et al. (2006)[9] which was conducted to answer the research question; "What are the pathophysiological interactions determined by the simultaneous presence of COVID-19 and preeclampsia?", which was structured according to the PICO strategy for formulating a research question; P (population/medical condition): (pregnancy and preeclampsia); I (intervention/exposure): COVID-19; C (comparison): not applicable; O (outcome/outcome): not applicable. The review was structured according to the criteria established by *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA).[10]

Search Strategy

The following bibliographic databases were used to retrieve the publications of interest; (i) Medical Literature Analysis and Retrieval System Online (PubMed/Medline), (ii) Scientific Electronic Library Online (SciELO) and (iii) Latin American and Caribbean Health Sciences Literature (LILACS). The Health Sciences Descriptors that were used to build the search strategy were obtained from the Health Sciences Descriptors database; DeCS/MeSH terms for both English and Portuguese. The combinations of terms and boolean operators that guided the search in the Medline/PUBMED database were (Pregnancy AND Preeclampsia OR Eclampsia) AND (COVID-19). In LILACS and SciELO Brasil, the search considered only COVID-19 OR SARS-Cov-2 AND Preeclampsia OR Eclampsia, which were in Portuguese.

Manual Search

An additional broader search strategy was carried out aimed at retrieving information that may have been omitted or not captured by the abovementioned search strategies. This step included consulting the first 200 Google Scholar records, and selecting the relevant literature for full review. In addition, the reference lists of the selected articles were also scanned to obtain articles for full reading.

Inclusion and Exclusion Criteria

The simultaneous manifestation of COVID-19 and preeclampsia in the gestational period (does not include puerperium) was the inclusion criterion in the review. The Exclusion criteria were: (i) review studies (ii), studies with simultaneous Human Immunodeficiency Virus (HIV) infection, (iii) language other than English, Portuguese and Spanish, (iv) studies with an exclusive clinical approach without pathophysiological aspects/ approach. This last criterion actually excluded clinical and/or epidemiological studies that although dealing with clinical aspects and related outcomes, did not discuss the possible pathophysiological mechanisms manifested from the interaction of COVID-19 and preeclampsia in a patient having both conditions simultaneously.

Data Collection

The selection of studies was carried out by pairs of researchers, performed independently and in a standardized way. Discrepancies were resolved with the participation of a third researcher. The data collection included the characteristics of the studies (authors, year, journal, title, country), the population studied (sample size, age of women, gestational age) and possible pathophysiological interactions.

Results

This review retrieved 155 publications from the searches performed in the bibliographic databases of Medical Literature Analysis and Retrieval System Online (PubMed/Medline) (n = 148), Latin American and Caribbean Literature in Health Sciences (LILACS) (n = 5), Scientific Electronic Library Online (SCIELO BRASIL) (n = 2) and other sources (n = 0). After excluding the duplicates (2), inappropriate publications (67) based on the content of the title and abstract were discarded. Of the articles eligible (n = 86) for full text reading, 70 were excluded for the following reasons: HIV infection (n = 1), duplicate (n = 3), study design (n = 33), language (n = 3) and lack of information/approach regarding pathophysiology and interaction (n = 30). Finally,16 studies[11–26] were effectively included in this review (►**Fig. 1**).

The included studies were conducted in the United States (n = 4), Spain (n = 2) and Canada (n = 2). The other studies (n = 8) are from 7 different countries of which one is of multicentric/international origin. Five of the studies are case reports which presented the clinical evolution of pregnant women affected by COVID-19 with symptoms suggestive of preeclampsia. Among the most robust evidence, a case-control study evaluated hypertensive disorders of pregnancy by comparing 173 pregnant women with COVID-19 to 733 with a negative SARS-CoV-2 test and found a higher frequency of gestational hypertension, preeclampsia and preeclampsia with severity features in the positive COVID-19 group in contrast to the negative COVID-19 group.[23] ►**Chart 1** summarizes the characteristics of the studies included.

The selected studies provided key contributions regarding the pathophysiological mechanisms resulting from SARS-CoV-2 infection and the changes in the placental site found in preeclampsia. The role of the Angiotensin-Converting Enzyme 2 (ACE2) was highlighted in most studies. On the other hand, uncertainties were supported by arguments that

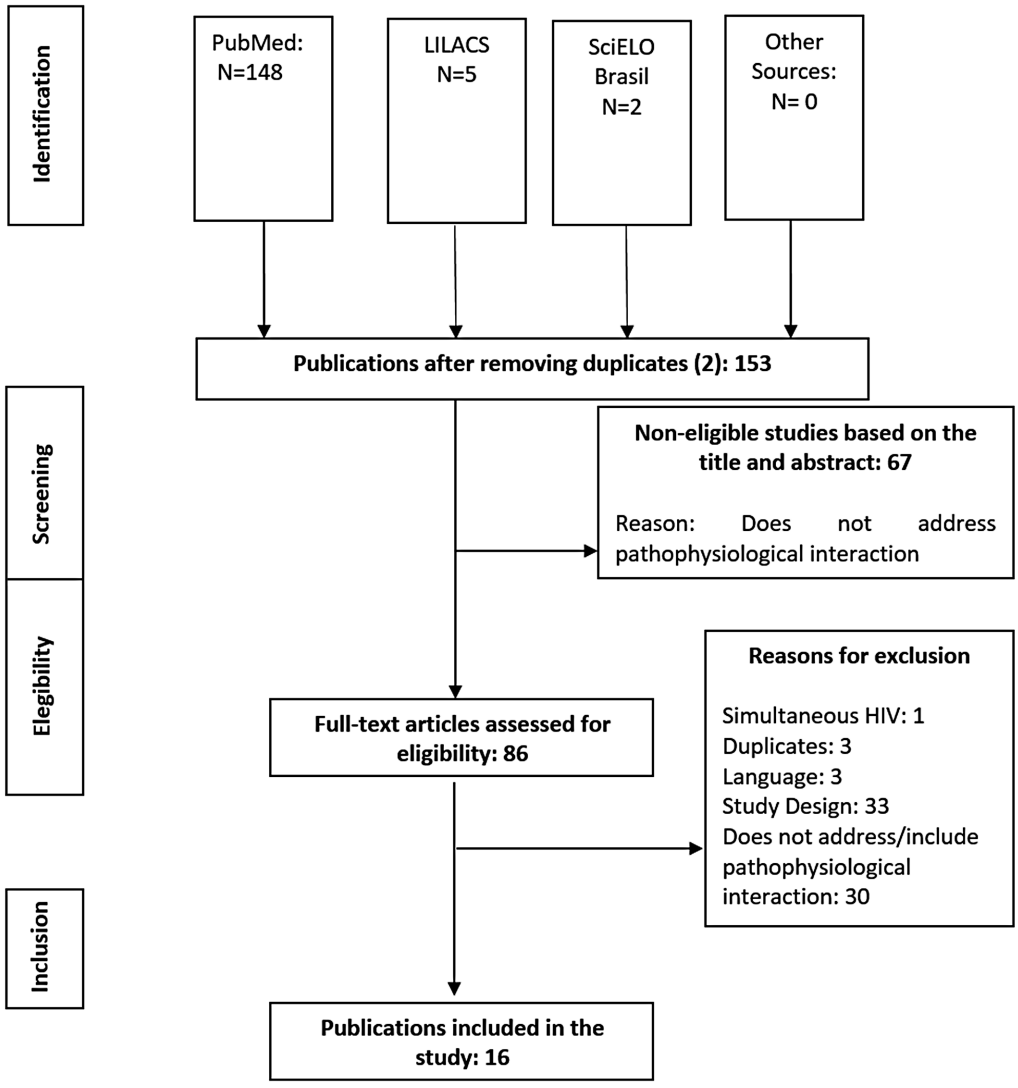

Fig. 1 Flowchart of the steps that were followed during the selection and inclusion of publications.

women diagnosed with preeclampsia or those with higher risk factors were more frequently submitted to SARS-CoV-2 tests, and therefore had confirmed infection.[20] These authors acknowledged that the examination of the placenta could have helped to determine the extent of vasculitis in relation to the severity of infection, and contributed to the understanding of the pathophysiological interaction, a fact that was not contemplated in their study (►**Chart 2**).

In addition to the pathophysiological findings revealed from the evaluation of pregnant women, additional information was extracted from five studies that analyzed the placentas.[15,19,21,23,24] The virus colonization was more abundant in maternal decidua and fetal villous tissue, showing an important inflammatory process with leukocyte infiltration. In addition, there was greater severity in the preterm placenta, with subsequent implication in the expression of ACE2.[15] The expression of genes involved in the entry of SARS-CoV-2 into placental cells appears to be downregulated as pregnancy progresses, thus suggesting greater vulnerability to infection in the first trimester.[23] Syncytial knots in the villi and intervillous bridges indicate the presence of a pre-placental hypoxic state.[19] Marked expression of Vascular Endothelial Growth Factor (VEGF) in the capillary endotheliocytes and syncytiotrophoblast were detected in placental morphology, contributing to the suspicion of pre-eclampsia like syndrome.[19] Compared to placentas from controls which had melanoma, a placenta with maternal vascular malperfusion was a statistically significant finding, accompanied by decidual arteriopathy, fibrinoid necrosis of maternal vessels, and mural hypertrophy of the membrane arterioles.[24]

Discussion

The present review consists of a narrative synthesis on the pathophysiological interactions of COVID-19 and pre-eclampsia reported in primary studies. Despite the gaps that persist, studies highlighted the role of biological mechanisms resulting from the binding of SARS-CoV-2 with angiotensin-converting enzyme-2 (ACE2) receptors and the hypertensive manifestations subsequent to the vasoconstrictor effects. The literature consistently recognizes the overlap

Chart 1 Characteristics of the studies included in the systematic review

Author/Year	Country	Study design	Type of participant	Participant (n)	Other assessments
Naeh et al. (2022)[11]	Canada	Case Report	Pregnant Women	1	X
Aydin et al. (2021)[12]	Turkey	Retrospective Study	Pregnant Women	167	X
Laresgoiti-Servitje et al. (2021)[13]	Mexico	Case-Control	Pregnant Women	298 +/828-	X
Osaikhuwuomwan et al. (2021)[14]	Nigeria	Descriptive	Pregnant Women	19 +/48-	X
Verma et al. (2021)[15]	USA	Descriptive Translational	Pregnant Women	5 +/5-	Placenta
Federici et al. (2020)[16]	France	Case Report	Pregnant Women	1+	X
Ahmed et al. (2020)[17]	UK	Case Report	Pregnant Women	1+	X
Baracy et al. (2021)[18]	USA	Historical Cohort	Pregnant Women	70 +/210-	X
Shchegolev et al. (2021)[19]	Russia	Comparative Morphological Study	x	23 +/7-	Placenta
Papageorghiou et al. (2021)[20]	Multinational	Prospective Observational	Pregnant Women	725 +/1459-	X
Lu-Culligan et al. (2021)[21]	USA	Obervational	Pregnant Women	15+	Placenta
Braga and Sass (2020)[22]	Brazil	Case Report	Pregnant Women	1+	X
Bloise et al. (2021)[23]	Canada	Cross-Sectional Study	Pregnant Women	87+	Placenta
Shanes et al. (2020)[24]	USA	Comparative	Pregnant Women	16+	Placenta
Garcia Rodriguez et al. (2020)[25]	Spain	Case Report	Pregnant Women	1+	X
Mendoza et al. (2020)[26]	Spain	Observational	Pregnant Women	42+	X

X: no additional evaluation was performed. +: number of positive COVID-19 cases. –: number of negative COVID-19 cases.

Chart 2 Pathophysiological interactions highlighted in COVID-19 and preeclampsia studies

Author	Main pathophysiological findings or conclusions
Naeh et al.[11]	"Endothelial dysfunction has been suggested as the mechanism for both manifestations; [...] hypertension and kidney injury ..."
Aydin et al.[12]	"Upon entry into the human body, SARS-CoV-2 spike binds to ACE2 receptor through its receptor-binding domain. ... we found a significant difference in the laboratory parameters among the groups. D-dimer is an indicator of fibrinolysis and plays a key role in the diagnosis of thromboembolism."
Laresgoiti-Servitje et al.[13]	"...we further explored the placentas of a group of pregnant women regarding the presence of placental dysmaturity, vasculopathy, fibrinoid, chorangiosis, chorioamnionitis, hemorrhage, or infarction. The placentas of women infected with SARS-CoV-2 had a higher rate of fibrinoid deposition, a clinical feature of maternal vascular malperfusion, than controls".
Osaikhuwuomwan et al.[14]	"...adverse pregnancy outcomes were high, especially among those with other co-morbidities such as pre-eclampsia or other complications because respiratory syndromes may aggravate pulmonary oedema and decrease oxygen saturation. The endothelial dysfunction associated with pre-eclampsia predisposes patients to respiratory failure from pulmonary oedema."
Verma et al.[15]	"In sum, we demonstrate that SARS-CoV-2 colonizes fetal trophoblasts, stromal cells, and macrophages in the placenta, which express the ACE2 receptor. S binding to ACE2 leads to reduction of the receptor expression and results in alterations of the RAS pathway—changes that are similar to those typically noted in pre-eclampsia."

(*Continued*)

(*Continued*)

Author	Main pathophysiological findings or conclusions
Federici et al.[16]	"HELLP is an acronym which refers to the triad of microangiopathic haemolysis with elevated liver enzymes and a low platelet count. HELLP syndrome is a serious complication of pre-eclampsia [...]. Some biological disorders linked to SARS-CoV-2 infection associated with hypertension may mimic a pre-eclampsia or a HELLP syndrome."
Ahmed et al.[17]	"Both pre-eclampsia and COVID-19 infection are examples of microvascular disease causing endothelial injury. They both cause a high prothrombotic tendency leading to multiorgan failure. The presence of both diseases likely had either a synergistic or an opportunistic effect, which may have led to severe clinical manifestations via the interplay of the renin-angiotensinogen-aldosterone system in their pathogenesis."
Baracy et al.[18]	"When comparing only COVID-19 positive pregnancies, early infection conferred a significantly higher risk for HDP than late infection. This observation is consistent with the inflammatory explanation of increased HDP risk in COVID-19. Through modulation of angiogenic factors and inflammatory cytokines, it is likely that COVID-19 exerts maximal impact on placental physiology at earlier gestations, enabling these physiologic changes to manifest as HDP over time."
Shchegolev et al.[19]	"...study demonstrated increased level of VEGF expression mainly in syncytiotrophoblast of the terminal villi in parturient women with moderate COVID-19 to a greater extent than in women with mild disease severity. These changes, along with increased number of syncytial knots, also indicate the development of placental hypoxia in parturient women with COVID-19. hypoxia promotes increased production of pro-angiogenic factors by placental cells, in particular, VEGF, which not only regulates proliferation and migration of endotheliocytes, but also contributes to BP elevation in pregnant women."
Papageorghiou et al.[20]	"...pre-eclampsia and GH are vascular conditions, preceding infection with SARS-CoV-2, which increase the risk for COVID-19 in the same way essential hypertension does."
Lu-Culligan et al.[21]	"...we found that ACE2 protein was present at significantly higher levels in term placentas collected from COVID-19 cases. These findings suggest that detection of ACE2 mRNA expression is not a reliable surrogate for ACE2 protein expression in the placenta and, importantly, that ACE2-mediated risk for placental infection by SARS-CoV-2 may vary over the course of pregnancy, with our detection of higher ACE2 levels in the first and second trimesters suggesting that the most vulnerability may exist prior to term."
Braga and Sass[22]	"Thrombocytopenia in patients with COVID-19 appears to be multifactorial, including endothelial damage, platelet activation with aggregation and thrombosis, impairment of bone marrow and megakaryocyte activity. [...] synergism of these pathophysiological mechanisms could accelerate the compromise of maternal conditions"
Bloise et al.[23]	"...SARS-CoV-2 present in the maternal circulation has the potential to enter the maternal blood bathed syncytiotrophoblast and infect the placenta via ACE2 binding."
Shanes et al.[24]	"The histologic changes of MVM are thought to represent some chronicity, though exact timing is unknown, and these features can be seen in women who develop pre-eclampsia only during or after childbirth. Whether systemic vascular changes due to maternal COVID-19 are responsible for the histologic changes of MVM cannot be determined. [...] there are increased rates of maternal vascular malperfusion features and intervillous thrombi, suggesting a common theme of abnormal maternal circulation, as well as an increased incidence of chorangiosis"
Garcia Rodriguez et al.[25]	"...we believe SARS-COV-2 infection could promote brain endothelial damage, triggering the cited neurological complications in our patient."
Mendoza et al.[26]	"...this is the first study to describe the incidence of signs and symptoms of PE in a relatively large cohort of pregnancies with COVID-19 and to show that a PE-like syndrome could be induced by severe COVID-19. [...] Several disorders have previously proved to imitate PE since they share some of the clinical and laboratory findings of patients with PE. The pathophysiologic causes of these conditions include vasospasm, platelet activation or destruction, microvascular thrombosis, endothelial cell dysfunction, and reduced tissue perfusion".

of pathophysiological mechanisms common to preeclampsia and COVID-19, highlighting endothelial dysfunction, its inflammatory effects and thrombogenic manifestations.

The increased expression of ACE2 receptors at the placental site in cells promoting blood flow remodeling and trophoblast invasion is a physiological condition, but this seems to make pregnant women more prone to the development of severe COVID-19.[18] To enter the cell, the virus promotes the binding of its spike protein (Spike-like protein) to the ACE2 receptors, reducing the bioavailability of the enzyme. Thus, there is a picture of vasoconstriction without the counterbalance expression of Angiotensin 1-7 responsible for vasodilation and a consequent decrease in blood pressure.[27]

In addition to the vasodilatory effect, Angiotensin 1-7 also has anti-inflammatory and antithrombogenic activity.[27] However, an investigation of the levels of D-dimer,

prothrombin time and International Normalized Ratio (INR) in 167 women with COVID-19 classified into 3 groups defined by gestational age detected lower measurements of prothrombin time and INR in the group $\geq$ 24 weeks, but higher fractions of D-dimer.[12] Although the study included 20 women with preeclampsia and 2 with hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, the authors considered their findings as physiological because the group $\geq$ 24 weeks also included postpartum women.[12]

The fetus determines immunological reactions that require compensatory mechanisms capable of harmoniously leading the pregnancy to term, with decidual natural killer cells playing a key role in placentation and in the maintenance of a healthy pregnancy.[4] The immune function that natural killer cells perform in the peripheral blood differs from the remodeling action they perform in the decidua.[4] In the decidual compartment, they work with the trophoblast to produce uterine vascular remodeling, to the detriment of the naturally expected cytotoxic activity. The SARS-CoV-2 infection disrupts this immunologic harmony and can negatively impact obstetric and perinatal outcomes.[4] Infection by SARS-CoV-2 leads to a decrease in the concentration of this type of cell in peripheral blood since they are mobilized to fight the virus and not directed to the decidua. The reduction in migration culminates into a reduction in the population of natural killer cells in the decidua, which may cause poor placental perfusion, one of the possible etiologies of preeclampsia.[4]

There is a growing body of knowledge regarding the placenta investigating the relationship between SARS-CoV-2 infection and the disruption of the renin-angiotensin system on pregnancy outcomes.[28,29] The infected placentas indicated that the virus was found in multiple compartments of the maternal-fetal interface, including trophoblasts, stromal, immune system, and epithelial cells.[15] In addition, the study reported inflammatory infiltrates in SARS-CoV-2-infected preterm placentas while non-infected preterm placentas had minor or no inflammation. The authors also found a reduction in the expression of ACE2, which leads to an imbalance in the renin-angiotensin system, as well as an increased expression of pro-inflammatory substances accompanied by a simultaneous suppression of the protective arm of the renin-angiotensin system. The disruption of the normal physiological expression of the angiogenic and anti-angiogenic factors determined by the ratio of placental growth factor [PlGF] to soluble fms-like tyrosine kinase-1 [sFIt-1] substantiates the mechanism underlying the endothelial dysfunction present in multiple organ failure.[15]

Although some studies point to an association between COVID-19 and preeclampsia/eclampsia/HELLP syndrome, uncertainties still remain. It is possible that the hypertensive condition constitutes a preeclampsia-like syndrome.[30] Mendoza et al. (2020)[26] investigated the existence of a possible relationship between COVID-19 and preeclampsia by comparing pregnant women with COVID-19 which were categorized as severe (n = 8) and non-severe infection (n = 34). The results indicated that in pregnant women with severe infection, six of them had symptoms suggestive of preeclampsia, but markers of placental disease were only found in one. In view of this situation, the authors recommend caution in the diagnosis of preeclampsia and consider the possibility that pregnant women with COVID-19 may experience a pre-eclampsia-like syndrome. The analysis of markers such as the uterine artery pulsatility index (UtAPI) and the evaluation of antiangiogenic and angiogenic factors (sFlt-1/ PlGF) are crucial in these cases to differentiate the two conditions.[26] Although the distinction between true preeclampsia and preeclampsia-like syndrome resulting from COVID-19 is not straightforward, efforts must be made to characterize each of these conditions in order to avoid interventions and induction of unnecessary childbirth.[12,31]

Another condition that shares similar pathophysiological interactions with preeclampsia and SARS-CoV-2 infection is posterior reversible encephalopathy syndrome (PRES). Although no single mechanism explains the development of PRES, vascular hyperperfusion seems to play an important role when blood hypertensive spikes (sudden high blood pressure) are present and the brain autoregulation process is ineffective, leading to hyperperfusion with extravasation of plasma and macromolecules into brain tissue.[32] Endothelial dysfunction with cytokine release is also prominent in PRES and may be exacerbated by the presence of COVID-19 toxins.[33] The adaptation of the immune system to physiologically accommodate the gestational period is interrupted by viral infection and exacerbated by the concurrence of placental disease and cerebral hyperperfusion. Although establishing the clinical boundaries of the three entities is a challenge, the simultaneous presence of the 3 conditions must be seen as a possible reality during these times of the pandemic.

This study sought to synthesize the pathophysiological mechanisms and interactions that underlie co-occurrence of SARS-CoV-2 infection and preeclampsia, and to improve the understanding of these two entities as well as stimulate the development of studies that investigate this problem. However, this study presented some limitations. At first, the inclusion criteria based on primary quantitative studies may have omitted publications that could possibly help in understanding the problem. To this effect, we employed a combination of designs ranging from case reports to prospective cohorts to minimize or offset this deficiency, providing a wide possibility of representative contributions from specific contexts that used different methodological approaches. Another limitation stems from the language restriction, since the review only included studies written in English, Portuguese and Spanish.

Conclusion

Understanding the risk that the coronavirus poses to pregnant women proved to be vital in these times of the pandemic. In summary, as one of the components of the renin-angiotensin-aldosterone system, the expression of ACE2 receptors is increased in pregnant women, especially at the placental site. The coronavirus binds to ACE2 receptors as part of the mechanism of entry into the human cells and

this leads to the deregulation of the system and in the ratio between angiotensin-II and angiotensin1-7, thus imitating and/or potentiating the picture of preeclampsia. Furthermore, the cytokine storm leads to endothelial dysfunction and thrombus formation, which is also classically present in preeclampsia. Given that preeclampsia courses with progressive clinical and laboratory alterations, a highly quality prenatal care may be able to detect specific clinical and laboratory parameters to differentiate a true preeclampsia superimposed by covid-19, as well as cases with hypertensive manifestations resulting from viral infection. The collective message or consensus arising from the studies in this narrative synthesis is that there is a possible overlap of pathophysiological alterations between COVID-19 and preeclampsia. In view of the importance of ACE2 in maintaining physiological blood pressure levels and the role it plays in the SARS-CoV-2 infectious process, establishing a characteristic pathophysiological distinction between infectious disease and placental disease is a major challenge. Given the complexity of the topic and the merely synthetic narrative purpose that guided this review, it is necessary and recommended that more robust investigations aimed at deepening the knowledge about the pathophysiological interactions of these two important nosological entities should be performed.

Contributions

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

Conflicts to Interest

The authors have no conflicts of interest to declare.

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FEBRASGO POSITION STATEMENT

Misoprostol use in obstetrics

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The National Specialized Commissions on Childbirth, Puerperium and Abortion Care, Antenatal Care, Gestational Trophoblastic Disease, High-Risk Pregnancy, Fetal Medicine, Maternal Mortality, Obstetric Emergencies, Sexual Violence and Pregnancy Interruption Provided for by Law and Professional Defense and Appreciation of the Brazilian Federation of Gynecology and Obstetrics Associations (FEBRASGO) endorses this document. Content production is based on scientific evidence on the proposed theme and the results presented contribute to clinical practice.

Key points

- Misoprostol is a prostaglandin E1 (PGE1) analogue that has been on the World Health Organization (WHO) List of Essential Medicines since 2005.
- Brazil has one of the most restrictive regulations in the world related to the use of misoprostol establishing it is exclusively for hospital use with special control, and sale, purchase and advertising prohibited by law.
- Misoprostol is currently the reference drug for pharmacological treatment in cases of induced abortion, both in the first trimester of pregnancy and at more advanced gestational ages.
- Misoprostol is an effective medication for cervical ripening and labor induction.
- Misoprostol is an essential drug for the management of postpartum hemorrhage.

Recommendations

- The use of misoprostol is recommended for the following situations: legal abortion, uterine evacuation due to embryonic or fetal death, cervical ripening before labor induction (uterine cervix maturation), labor induction and management of postpartum hemorrhage.
- Misoprostol 800 mcg vaginally (four 200 mcg pills) is recommended for uterine evacuation in pregnancy loss up to 13 weeks.
- In cervical preparation for surgical abortion at less than 13 weeks of pregnancy, the use of misoprostol 400 mcg vaginally 3-4 hours before the procedure is recommended.
- The use of misoprostol alone according to the gestational age for uterine evacuation is recommended for termination of pregnancy in legal abortion.
- The use of vaginal misoprostol according to the gestational age is recommended for uterine evacuation in case of fetal death: at 13-26 weeks, 200 mcg every 4-6 hours; at 27-28 weeks, 100 mcg every 4-6 hours; and over 28 weeks, 25 mcg every six hours.
- The use of misoprostol at an initial dose of 25 mcg vaginally every 4-6 hours is recommended for cervical ripening and induction of labor with a live fetus in pregnancies over 26 weeks.
- The use of misoprostol for cervical ripening and induction of labor with a live fetus is not recommended in women with a previous cesarean section due to the greater risk of uterine rupture.
- Misoprostol is a safe and effective option for women with premature rupture of membranes and unfavorable uterine cervix, as long as they do not have contraindications for taking the medication, for example, previous cesarean section.
- Rectal misoprostol 800 mcg is recommended as part of the drug treatment of postpartum hemorrhage.
- In Brazil, misoprostol should be made available to all health services at all levels of care, and it is desirable that outpatient use be allowed, when indicated.

Background

Misoprostol is a synthetic analogue of prostaglandin E1 (PGE1) with gastric secretion inhibitory and mucosal protection properties through the production of bicarbonate and mucus. It was first approved to be used to protect the stomach mucosa in patients using non-steroidal anti-inflammatory drugs.[1] This drug has been widely used in obstetric practice to induce abor-

tion and as an agent to promote cervical ripening in induction of labor at term. The combination of misoprostol and mifepristone is used in medical abortions with a good safety profile in several countries. In Brazil, the commercialization of misoprostol is controlled for use in the hospital environment, in labor induction and legal abortion, or in cases of emptying of the uterus in abortion or retained dead fetus. There is widespread debate about the standardization of dosage in the use of misoprostol. Higher doses of misoprostol are used for induced and retained abortions, and much lower doses are used for cervical ripening and labor induction in term pregnancies.[2] It is also indicated for the treatment of postpartum hemorrhage (PPH).

What are the pharmacokinetic properties of misoprostol?

Misoprostol is a synthetic analogue of PGE1. It is metabolized in the liver, deesterified and becomes the active metabolite, misoprostol acid. It has the ability to bind to uterine smooth muscle cells, increasing the strength and frequency of uterine contractions.[3] In the uterine cervix, it also promotes the breakdown of collagen in the connective tissue and a reduction in cervical tonus.[4] Misoprostol can be used orally, vaginally, sublingually and rectally. In oral administration, the drug reaches its maximum peak 20-30 minutes after ingestion, remaining detectable for up to four hours. Misoprostol administered sublingually is absorbed more quickly and has higher peak concentrations than when administered orally, which tends to cause higher rates of gastrointestinal side effects at any dose.[5] Overall bioavailability of the drug used vaginally is greater, since the absorption is slower than in other routes, and the maximum plasmatic peak is reached in 40-60 minutes, remaining stable up to two hours after application. The vaginal route also allows for greater effects on the cervix and uterus.[6] The pharmacokinetics of rectal misoprostol is similar to that of vaginal misoprostol, although with a lower overall bioavailability and a significantly lower peak plasma level.[7] It has been demonstrated that levels of misoprostol in breast milk are known to peak and decline rapidly with an average half-life of around one hour. Although it normally appears in colostrum and milk, the low levels detected suggest that a minimal amount of misoprostol could potentially be ingested by the newborn.[4]

What are the adverse effects and contraindications for using misoprostol?

Although other prostaglandins can cause myocardial infarction and bronchospasm, misoprostol is not associated with these effects. Toxic doses have not been well established and cumulative doses of up to 2,200 mcg in 12 hours are well tolerated without significant adverse effects.[8] A case of non-lethal misoprostol overdose was reported after ingestion of 6,000 mcg, coursing with hyperthermia, rhabdomyolysis, hypoxemia and metabolic acidosis.[9] One fatal case was reported after ingestion of 12,000 mcg (60 tablets), causing gastrointestinal bleeding with gastric and esophageal necrosis and organ failure.[10] The most common adverse effects of misoprostol are nausea, vomiting, diarrhea, abdominal pain, chills, shivering and fever. All these effects are dose-dependent.[8] Gastrointestinal effects may occur in approximately 35% of women and are more common after oral or sublingual administration. Diarrhea is the most common adverse effect and is usually mild and self-limited to one day.[11] Shivering and fever are also transitory effects and may occur in 28% and 7.5%, respectively, of women who used 600 mcg of misoprostol orally.[12] The occurrence of fever and shivering from misoprostol in the active management of the third stage favors the routine use of oxytocin as the drug of choice for the prevention of hemorrhage.[13] Although dose-dependent, uterine hyperstimulation is one of the most frequent adverse effects in labor induction. The risk of uterine hyperstimulation was high with high doses of misoprostol used in the past. With low doses (≤50 mcg of initial dose), the risk is similar to that of dinoprostone, 4-12%, depending on the route and dosage.[11] In a Cochrane meta-analysis, the risk of hyperstimulation with alteration of fetal heart rate was significantly lower with low-dose oral misoprostol (3.4%) compared to vaginal dinoprostone (7.0%; RR: 0.49; 0.40-0.59). In that same meta-analysis, a lower risk of hyperstimulation with fetal cardiac alteration was also found with oral misoprostol (3.9%), compared to the vaginal route (5.7%; RR: 0.69; 0.53-0.92).[14] Fetal distress, the presence of meconium in the amniotic fluid and uterine rupture may occur as a result of hyperstimulation (hypersystole or tachysystole with or without hypertonia).[15] Uterine rupture is the most feared adverse effect of labor induction, especially in women with previous uterine scar. Although extremely rare, there are case reports of uterine rupture during first-trimester abortion induction. Most cases of uterine rupture have been described in third-trimester inductions and associated with previous uterine scar or other risk factors.[7] The risk of uterine rupture in women with induction of labor for vaginal delivery after cesarean section with misoprostol is 6-12%.[11] Therefore, this is usually a contraindication for using the drug.[16,17] It is important to emphasize that misoprostol can be used in the second trimester in women with a previous cesarean section, since most studies point to a low risk of uterine rupture.[17] A meta-analysis identified that this risk is not significantly different when the woman has had a previous cesarean section (0.47%) compared to no uterine scar (0.08%; RR: 2.36; 0.39-14.32), although it is significantly higher with two or more previous cesarean sections (2.5%; RR: 17 ,55; 3-102.8).[18]

What are the teratogenic effects of misoprostol?

The Food and Drug Administration (FDA) classifies misoprostol as a category X drug (evidence of teratogenesis in animals and humans) in the first and second trimesters of pregnancy. Animal studies have shown a significant reduction in fertility with the use of high doses (6.25 to 625 times the maximum human therapeutic dose). In pregnant rabbits, doses of 300 to 1,500 mcg/kg of misoprostol on days 7-19 of embryogenesis have been associated with teratogenic effects.[19] Misoprostol-related malformations were initially described in case reports in humans.[20-22] These findings were subsequently confirmed in case-control and prospective studies and meta-analyses.[23-26] Most of these data come from Brazil and involve cases of malformations related to failed abortion with the use of misoprostol. In countries where abortion is legally permitted, patients rarely continue with the pregnancy after a failed abortion with misoprostol. In humans, there are several malformations associated with the use of misoprostol in the first trimester of pregnancy, such as: Moebius sequence (compromise of the VI and VII cranial nerves with paralysis of the eyes and facial muscles), arthrogryposis, transverse reduction of extremities and limbs, congenital clubfoot, hydrocephalus, encephalocele, meningocele, hemifacial microsomia, severe trismus.[21,26,27] The risk of any malformation associated with the use of misoprostol is 2.64 (95% confidence interval [CI]: 1.03-6.75) compared to the unexposed group,[25] while the risks for the Moebius sequence and transverse limb reduction were 25.31 (95% CI: 11.11-57.66) and 11.86 (95% CI: 4.86-28.90), respectively.[24] The teratogenic mechanism attributed to fetal malformations and alterations is a result of vascular disruption caused by intense uterine contractions and vaginal bleeding leading to embryonic hypoperfusion with tissue hypoxia, endothelial cell damage and tissue loss.[24,28,29] Fetal malformations and impairments depend on the developmental stage of the embryo, and the greatest risks are related to the use in the first trimester of pregnancy. It is still controversial if the risk of teratogenicity is dose-dependent, since studies indicate, for example, the association of severe malformations such as hydrocephalus with both low (200 mcg) and high doses (800 mcg) of misoprostol.[26,30] Hence, it is not possible to provide certainty regarding the absence or severity of alterations after using any dose of misoprostol in the first trimester of pregnancy.

How to use misoprostol in uterine evacuation after embryonic death?

Misoprostol is used for uterine evacuation in first trimester pregnancy loss. On ultrasound examination, pregnancy loss can be characterized by the following aspects: presence of gestational sac without yolk sac or embryo and with mean diameter ≥ 25 mm; embryo with crown-rump length greater than or equal to 7 mm without cardiac activity; no embryo with a heartbeat two weeks after an examination demonstrating an empty gestational sac or no embryo with a heartbeat at 11 or more days after an examination demonstrating a gestational sac with yolk sac. In these situations, three approaches are possible: expectant management, mechanical uterine evacuation, or pharmacological evacuation.[31] The most effective and safe way to promote pharmacological uterine evacuation is the combination of mifepristone 200 mg followed by misoprostol (1-2 days later), with an efficacy rate of around 90% versus 70% when using misoprostol alone.[32,33] Given the unavailability of mifepristone, since its use is not regulated in Brazil, the isolated use of misoprostol is a reasonable alternative. There are several protocols, and the International Federation of Gynecology and Obstetrics (FIGO)[17] and the World Health Organization (WHO)[34] recommend the administration of 800 mcg vaginally, sublingually or buccally (four 200 mcg tablets). FIGO recommends a second dose three hours later.[17,34] There are no clear definitions regarding the interval and number of complementary doses, if necessary. Longer dosing intervals have the benefit of exposing the patient to a reduced risk of adverse effects. On the other hand, shorter dosing intervals (closer to three hours) may be necessary to generate sufficient uterine activity, particularly if misoprostol is given buccally or sublingually. Although uterine hyperstimulation is rare, particularly in the first trimester, the risk may increase with shorter dosing intervals. In pregnancies of less than 12 weeks, 1-3 doses of misoprostol are usually sufficient to expel the uterine contents.[35] The main advantages of using misoprostol include avoiding uterine perforation and formation of synechiae, reduced risks of sequelae inherent to the mechanical dilation of the cervix, and no need for anesthetic procedure. Disadvantages include a longer resolution time (sometimes days), higher prevalence of some symptoms such as cramps, bleeding, nausea, fever and chills, occasional need for surgical complementation and blood transfusion, and the woman's anxiety because of the waiting.[31,36] When opting for mechanical evacuation of the uterus, misoprostol can be used to prepare the cervix, avoiding or facilitating instrumental dilation before aspiration or curettage. The recommended dose is 400 mcg vaginally 3-4 hours before the procedure. If available, the sublingual route can be used in a shorter time interval (one hour).[17,31] Misoprostol 800 mcg vaginally (four 200 mcg tablets) is recommended for uterine evacuation in pregnancy loss up to 13 weeks.

The use of misoprostol in legal abortion

Brazil has one of the most restrictive regulations related to induced abortion - induced abortion is only legally permitted in cases of pregnancy resulting from rape, risk to the woman's life and fetal anencephaly – and to the use of misoprostol in the world. In a study of countries in Africa, Asia and Latin America, Brazil was close only to Vietnam among those with greater restrictions on access to medical abortion in the world.[37] Brazil is the only South American country where misoprostol is not available directly to women, whether in health services or for sale in pharmacies.[38] Contrary to what one might imagine, these barriers fail to reduce the use of misoprostol by women, since half of illegal abortions in the country are performed with this drug.[39] The regimen of use of misoprostol alone recommended for the induction of abortion in cases provided for by law, is shown in chart 1.[1,17,34] The drug is used until expulsion of products of conception. In the first trimester, three doses of misoprostol are usually sufficient to complete the treatment.[40]

Chart 1. Regimen of use of misoprostol alone according to gestational age for uterine evacuation in induced abortion/legal abortion

Gestational age	Dosage
Up to 14 weeks	misoprostol 800 mcg (vaginally, sublingually, or buccally) every 3 hours
14- 24 weeks	misoprostol 400 mcg (vaginally, sublingually, or buccally) every 3 hours
25-28 weeks	misoprostol 200 mcg (vaginally, sublingually, or buccally) every 4 hours
Over 28 weeks	misoprostol 100 mcg every 6 hours

Source: Krugh M, Maani CV. Misoprostol. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2022 [cited 2022 Dec 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539873/. Morris JL, Winikoff B, Dabash R, Weeks A, Faúndes A, Gemzell-Danielsson K, et al. FIGO's updated recommendations for misoprostol used alone in gynecology and obstetrics. Int J Gynaecol Obstet. 2017;138(3):363-6. doi: 10.1002/ijgo.12181. World Health Organization. Abortion care guideline [Internet]. Geneva: WHO; 2022 [cited 2022 Oct 31]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK578942/pdf/Bookshelf_NBK578942.pdf. [1,17,34]

In cervical preparation prior to surgical abortion in pregnancies over 12-14 weeks, the use of misoprostol 400 mcg (vaginally or orally) 2-3 hours before surgical treatment is routinely recommended.[34] If sublingual route is used, the time until the surgical procedure can be reduced to 1-2 hours.[40] Although cervical preparation should not be used routinely in pregnancies before 12 weeks, it can be beneficial in specific cases such as women at increased risk of complications during cervical dilation, for example, those with cervical anomalies or a history of cervical surgery.[34, 41] Safety and efficacy data of the misoprostol treatment regimen alone for induced abortion were published in a randomized clinical trial of 2,066 women who received three doses of misoprostol 800 mcg.[42] In that study, only 0.04% of women had vaginal bleeding requiring return to the hospital. There were no serious adverse events among study participants. The WHO cites the possibility of the combined use of letrozole and misoprostol as safe and effective in terminating pregnancies of less than 13 weeks in scenarios where mifepristone is not available (letrozole 10 mg orally each day for three days followed by misoprostol 800 mcg sublingually on the fourth day).[34]

Is it safe to use misoprostol on an outpatient basis?

The use of misoprostol on an outpatient basis is considered effective and safe for the treatment of induced abortion, especially in the first 12 weeks of pregnancy. The use of misoprostol during this period has minimal adverse effects, such as diarrhea, vomiting, nausea and fever, which can be easily treated by professionals outside the hospital setting.[42-44] Outpatient use can reduce costs for both the health system and the hospital due to the waiver of hospitalization, as well as for women, since they do not need to remain in hospitals and in most cases, can receive adequate care at health units close to their homes.[34] In cases of induction of labor, the use of misoprostol in a hospital environment is recommended.

How to induce emptying of the uterus with misoprostol in fetal death at 13-24 weeks?

When the diagnosis of fetal death is established, the health professional assisting this pregnant woman and her family must always be able to answer the posed questions with empathy and embracement, even if there are no answers to all. A systematic review including 14 controlled and randomized studies that evaluated the use of misoprostol in fetal death in the second and third trimesters found 100% effectiveness in uterine evacuation within 48 hours.[45] Randomized studies support the use of misoprostol as a first-line agent in the induction of labor in fetal death at 20-24 weeks, including in patients with a history of previous cesarean section.[46,47] Several intervals between doses, dosages and routes of administration are described, but none showed clear evidence of superiority. The regimen of misoprostol recommended for uterine evacuation in the case of fetal death at 14-24 weeks of gestational age is 400 mcg vaginally every 4-6 hours.[34]

How to use misoprostol in the induction of stillbirth after 24 weeks?

In cases of fetal death after more than 24 weeks, labor induction depends on the conditions of cervical maturation. In patients with a favorable cervix (Bishop index ≥

6), labor induction can be started with oxytocin without the use of misoprostol for previous cervical ripening. In patients with an unfavorable cervix and without previous uterine scar, misoprostol is the agent of choice for preparing the cervix and inducing labor.[17,34,48] The following regimens are recommended:

- 25-26 weeks: misoprostol 400 mcg vaginally or sublingually every 4-6 hours;
- 27-28 weeks: misoprostol 100 mcg vaginally or sublingually every 4-6 hours;
- Over 28 weeks: misoprostol 25 mcg vaginally every six hours.

In patients with previous segmental scarring and unfavorable cervix at 24-28 weeks, cervical preparation can be performed with a mechanical method (transcervical balloon) followed by the use of oxytocin. The use of misoprostol seems to be an acceptable alternative at this gestational age, since the risk of uterine rupture is low. In a review study in which misoprostol was used at this gestational age, the risk of uterine rupture was 0.28% (95% CI: 0.08-1.00) in patients with a previous cesarean section versus 0.04% (95% CI: 0.01-0.20) in patients without a previous cesarean section.[18,49,50] However, at 24-26 weeks, low doses of misoprostol (100 mcg to 200 mcg per dose) may be suggested.[50] In pregnancies over 28 weeks, cervical preparation for labor induction should be performed in accordance with recommendations for parturient women with a live fetus.

How to perform maturation of the uterine cervix and induction of labor with misoprostol?

In the labor induction process, when the situation of the uterine cervix is unfavorable, a maturation process is recommended to shorten the duration of induction and increase the chance of vaginal delivery. When the Bishop score is less than 6, the cervix is generally considered unfavorable, and mechanical and/or pharmacological methods can be used in this process.[16,51] Prostaglandins, including misoprostol, are contraindicated for cervical ripening or induction of labor in full-term pregnancies with previous cesarean section or other major uterine surgery due to the association with a higher risk of uterine rupture.[52] Pre-existing regular uterine activity is a relative contraindication to the use of misoprostol, as it can lead to excessive uterine activity. Delaying or avoiding administration should be considered if the patient has two or more painful contractions within 10 minutes, especially in patients who have already received at least one dose of prostaglandin.[53] In Brazil, misoprostol for vaginal use in labor induction is available in tablets containing 25 mcg of the drug. The 50 mcg dose is more effective than the 25 mcg dose, but leads to higher rates of tachysystole, cesarean delivery due to fetal compromise, admission to neonatal intensive care units, and meconium elimination.[16,54] The interval between doses can vary between 3-6 hours. The number of doses required for cervical maturation and/or effective labor varies. If necessary, oxytocin can be started four hours after the final dose of misoprostol. There are no definitions regarding the total limit of doses or the time of maturation and/or labor induction.[50,55,56] In some countries, a pessary with controlled release of misoprostol (200 mcg in 24 hours) is available. Comparative studies with the dinoprostone pessary have shown a significantly shorter mean time to vaginal delivery and a greater chance of tachysystole.[57] A 2021 meta-analysis supported the use of low doses of oral misoprostol for labor induction and suggested that an initial dose of 25 mcg can offer a good balance between efficacy and safety.[14] Other routes for the use of misoprostol in labor induction, including buccal and sublingual administration, have been less studied. Small trials suggest similar or inferior results to those of vaginal or oral administration.[58-60] In pregnancies over 26 weeks, the use of misoprostol at an initial dose of 25 mcg vaginally every 4-6 hours is recommended for cervical maturation prior to labor induction.

How to use misoprostol to induce labor in women with a previous cesarean section?

Women planning a vaginal birth after a previous caesarean section (Trial of labor after cesarean – TOLAC) may need labor induction. There are two concerns: reduced chances of vaginal birth after caesarean section (VBAC) and increased risk of uterine rupture. Having a previous vaginal delivery and a favorable cervix are the main predictors of induction resulting in VBAC.[61] Induction itself does not reduce the chances of VBAC when compared with expectant management.[62] The major risk is uterine rupture related to induction. Regardless of the method used for induction, women with a previous cesarean section and induced labor are at greater risk of uterine rupture than those in labor with spontaneous delivery or expectant management. The frequency of uterine rupture in women at full-term who had labor induced was almost twice as high as the frequency in women in whom labor began spontaneously (1.5% versus 0.8%).[63] The factors associated with an increased risk of rupture during induced TOLAC include:

- No previous vaginal delivery – for example, in a study, the risks of rupture during TOLAC-induced in women without a previous vaginal delivery versus a previous vaginal delivery were 1.5% and 0.6%, respectively;[61,64]
- Use of prostaglandins – induction with prostaglandins appears to be associated with a greater risk of uterine rupture than induction with oxytocin or cervical ripening with mechanical methods followed by administration of oxytocin.[64]

Risk of rupture with prostaglandin use – Data from large randomized trials and from good quality observational studies on the effects of prostaglandins alone or in combination with other agents for cervical ripening in TOLAC are not available. Much data on prostaglandin use in women with a previous caesarean section has been derived from observational studies in which misoprostol (PGE1) was used. Reports on the use of other prostaglandins, such as prostaglandin E2, are limited by their small size, the co-administration of other agents and the lack of stratification by previous vaginal delivery.[65] *Unspecified prostaglandin* – Concern over the use of prostaglandins arose following the publication of a large population-based retrospective cohort study that analyzed data from 20,095 primiparous women who delivered after a single previous cesarean section.[65] In that study, the rate of uterine rupture was similar for women in spontaneous labor and those induced without the use of prostaglandin, but significantly higher among women induced with prostaglandin (type not available). The specific uterine rupture rate by category was:

- Repeat cesarean sections without labor: 1.6 ruptures per 1,000 planned repeat cesareans;
- Spontaneous labor: 5.2 ruptures per 1,000 spontaneous deliveries;
- Induced labor (without prostaglandins): 7.7 ruptures per 1,000 labors induced without the use of prostaglandins;
- Induced labor (with prostaglandins): 24.5 ruptures per 1,000 labors induced using prostaglandins. Compared to repeat cesarean delivery, the relative risk of rupture with the use of prostaglandins was 15.6 (95% CI: 8.1-30.0).

However, despite the very large number of cases, the information in this study is from a database and individual reviews of medical records were not performed to check other medications administered. The risk of uterine rupture reported in this retrospective study was lower in another large prospective study.[66] In that study, the rate of uterine rupture among patients induced with prostaglandin with or without oxytocin was lower – 14 per 1,000 induced deliveries –, although still considerably high. Specifically on misoprostol (PGE1), a randomized trial on the use of misoprostol for cervical ripening in labor induction in women with previous cesarean sections was stopped early because of safety concerns due to uterine rupture.[67,68] This study and several case reports have led some researchers to conclude that misoprostol is associated with a greater risk of uterine rupture than other prostaglandins and therefore should not be used in women planning a TOLAC.[51,68-71] The positions of Gynecology and Obstetrics Societies worldwide are:

- American College of Obstetricians and Gynecologists (ACOG –United States)[64] – advises that misoprostol should not be used for cervical ripening or labor induction in women at term with any previous uterine incision and does not address the use of prostaglandin E2;
- Society of Obstetricians and Gynecologists of Canada (SOGC – Canada)[72] – has the same position regarding the use of misoprostol, but allows the use of prostaglandin E2 (dinoprostone) in some circumstances and after appropriate advice;
- National Institute for Health and Care Excellence (United Kingdom)[51] – concluded that if childbirth is indicated, women who have had a previous cesarean section can receive labor induction with vaginal prostaglandin E2, but do not mention misoprostol.[51,73]

In conclusion, the use of misoprostol in women with previous cesarean is not recommended given the higher risk of uterine rupture. Note that mechanical methods are available, effective and safe.

How to use misoprostol to induce labor in ruptured membranes?

Premature rupture of membranes (PROM) is one of the most common complications of term and preterm pregnancies, but there is a gap in knowledge about how management affects the cesarean rate. As gestational age at delivery is the critical factor influencing perinatal outcome, expectant management is generally adopted when far from term. In PROM at term, the risk of maternal and fetal infectious morbidity increases with longer duration of membrane rupture. Therefore, expectant management should be brief, with instructions for induction of labor.[74] Meta-analyses conclude that misoprostol is an effective and safe agent for inducing labor in women with PROM at term. Compared to oxytocin, the risk of contraction abnormalities and the rate of maternal and neonatal complications were similar between the two groups.[74,75] Misoprostol 25 mcg should be considered as the starting dose for cervical ripening and labor induction in women with PROM. The frequency of administration should not exceed 3-6 hours. Furthermore, oxytocin should not be administered less than 4 hours after the last dose of misoprostol. Misoprostol at higher doses (50 mcg every six hours) may be appropriate in some situations, although higher doses may be associated with an increased risk of complications, including uterine tachysystole with fetal heart rate decelerations.[16] A Cochrane Review suggests the immediate induction of labor in patients with PROM at term. Compared with expectant management, induction of labor is associated with a reduction in maternal and possibly neonatal infection and lower treatment costs, without an increase in cesarean sections.[76] In conclusion, the use of misoprostol is recommended

as a safe and effective option for women with PROM and unfavorable cervix, provided they do not have contraindications for the use of this medication, such as, for example, previous cesarean section.

Misoprostol in the management of postpartum hemorrhage: how to use it?

Postpartum hemorrhage affects around 2% of all patients, and in only 25% of cases the risk factors are pronounced. The obstetrician must perform prophylaxis in 100% of cases and be aware of the occurrence of PPH, even if drug prophylaxis is performed. There is strong evidence that the association of uterotonics prescribed in the immediate postoperative period of childbirth reduces blood loss greater than 500 mL: ergometrine plus oxytocin (RR: 0.70; 95% CI: 0.59-0.84) and misoprostol plus oxytocin (RR: 0.70; 95% CI: 0.58-0.86) and reduces the need for blood products (RR: 0.51; 95% CI: 0.37-0.70).[77] This is not only a result of the combination of the strength of the two drugs, but also because oxytocin is thermolabile and it is difficult to guarantee a cold chain throughout the medication production, transportation and dispensing route. However, the association of two uterotonics increases the occurrence of side events, mainly vomiting (RR: 2.11; 95% CI: 1.39-3.18). Therefore, the use of two uterotonics is recommended for patients at high risk of PPH, always bearing in mind the contraindication of ergometrine for hypertensive/pre-eclampsia patients. The following uterotonics are recommended for the prophylaxis of PPH:

Oxytocin:

- In post-vaginal delivery: single dose of 10 IU intramuscularly right after birth;
- In cesarean section: 5 IU in slow intravenous infusion in three minutes and maintenance solution (20 IU of oxytocin in 500 ml of 0.9% saline solution intravenously at 125 ml/h for 4-12 hours);
- Misoprostol: single dose of 600 mcg rectally;
- Ergometrine: single dose of 0.2 mg intramuscularly.

For the drug treatment of PPH, the use of misoprostol 800 mcg rectally is recommended. It is important to remember that since the onset of action of rectal misoprostol is slower than that of other uterotonics, it should be used as an adjuvant to treatment with oxytocin. Misoprostol should not be used in isolation, maintaining uterine massage until the onset of its effect, which may take 15-20 minutes. Always consider the use of tranexamic acid 1 g intravenously over 10 minutes, with the possibility of repeating the 1 g dose in 30 minutes if bleeding persists.[78]

What regulations are related to the use of misoprostol?

Circular letter number 182/2021 of the Office of the President of the Brazilian Federal Council of Medicine,[79] expressed the impossibility of using misoprostol outside the hospital setting. The letter highlights the Ordinance of the Brazilian National Health Surveillance Agency (Anvisa) number 344/98,[80] of the Secretariat for Health Surveillance of the Ministry of Health, according to which misoprostol is on list C1 that includes substances subject to special control (prescription in two copies), with the addendum that the purchase and use of medication containing the substance misoprostol will only be allowed in hospitals duly registered with the Sanitary Authority. In its guide, the WHO (World Health Organization, 2018)[81] recognizes that the home use of misoprostol is a safe and effective option for women. In addition, the drug was added to the WHO list of essential drugs in 2019, at the same time that the need for in-person medical supervision to administer pharmacological abortion was withdrawn. In Brazil, Anvisa ordinances and resolutions and manifestations of the Federal Council of Medicine currently establish that misoprostol has exclusive hospital use with special control. Compared to other countries in the world and to WHO recommendations, there is excessive difficulty in accessing and releasing the use of misoprostol in Brazil. Given the existence of a robust body of evidence, there are no scientific justifications for imposing other restrictions on misoprostol, in addition to those related to special control drugs, i.e. prescription in two copies with retention of one copy in the pharmacy, and the possibility of identifying who prescribed the induced abortion treatment.

Final considerations

In obstetric practice, misoprostol has been widely used in legal abortion, uterine emptying due to embryonic or fetal death, cervical ripening and labor induction, and management of PPH. Contrary to the accumulated scientific evidence, Brazil has one of the most restrictive regulations in the world related to the use of misoprostol. The great difficulty in acquiring, storing and dispensing the medication imposed by Ordinance No. 344/1998 of Anvisa, still in force, contributes to denying the right to safer outpatient treatments for women who need it. These restrictions also hinder the availability of this medication, essential and mandatory, in obstetric care services.

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Instructions to Authors

About the journal

Basic information

The *Revista Brasileira de Ginecologia e Obstetrícia* (RBGO - Revista Brasileira de Ginecologia e Obstetrícia – ISSN 1806-9339) is a monthly scientific publication of the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo). It is aimed at obstetricians, gynecologists and professionals in related areas with the purpose to publish research results on relevant topics in the field of Gynecology, Obstetrics and related areas. The journal is open to national and international contributions and accepts submissions in English only.

As a **Vision**, the *Revista Brasileira de Ginecologia e Obstetrícia* (RBGO) intends to become an internationally recognized reference as a journal for research in Gynecology and Obstetrics (GO), becoming one of the world's leading journals in the specialty. The RBGO will be an essential vehicle to disseminate Brazilian and international scientific production and it can become a support reference in the training of undergraduate and postgraduate students and residents and in the scientific improvement of preceptors and researchers in GO.

The RBGO's **Mission** is to contribute to the development of Brazilian research in GO and become a facilitating instrument for the dissemination of research results that can contribute to the improvement of women's care and their quality of life.

The **Values** cultivated by the RBGO in its editions will always be innovation and commitment to quality and respect for **Ethics** in research.

Subareas of knowledge of interest GO:

1. Basic and translational science in ObGyn;
2. Bioethics
3. Contraception;
4. Epidemiology and Statistics in ObGyn;
5. Fetal Medicine;
6. General Gynecology;
7. Gynecological Endocrinology;
8. Gestational Trophoblastic Neoplasia
9. Gynecological Endoscopy;
10. Gynecological Oncology;
11. Gynecological Surgery and Urogynecology;
12. High Risk Pregnancy;
13. Human Reproduction and Assisted Fertilization;
14. Image in ObGyn;
15. Lower Genital Tract Diseases;
16. Mastology;
17. Menopause;
18. Multidisciplinarity and ObGyn;
19. Obstetrics;
20. Pediatric and Adolescent Gynecology;
21. Physiology in ObGyn;
22. Primary care in ObGyn;
23. Quality of Life and ObGyn;
24. Sexually Transmitted Infection;
25. Sexuality;
26. Teaching and Training in ObGyn;
27. Technology;
28. Transgender.

Indexing sources:

- PubMed/Medline;
- Isi – Web of Science (*Emerging Sources Citation Index*);
- Scopus;
- SciELO – *Scientific Electronic Library on-line*;
- Lilacs –Latin American and Caribbean Health Sciences Literature

Intellectual property

Sponsors

RBGO does not receive any type of support from funding sources. It is fully maintained by the Brazilian Federation of Gynecology and Obstetrics Associations and receives sponsorships.

Responsibilities of the Editorial Board

Responsibilities of the Editor-in-Chief

- Ensure that the journal is published within the established deadlines.
- Ensure the quality of selected texts and their appropriateness to the interests of readers.
- Establish the policy for manuscript submission, peer review, reviews and resubmission.
- Ensure that articles are reviewed and accepted only on the basis of scientific merit and not on the basis of any influence, whether commercial or personal.
- Maintain transparency throughout the manuscript review and editing process.
- Investigate all complaints and/or doubts related to submissions to the journal, whether accepted or not, and give authors the opportunity to respond whenever necessary.
- Provide support for the selection process of members of the journal's editorial board to define the types of publication and selection criteria for manuscripts accepted by the journal.
- Develop policies and procedures to attract scientific quality manuscripts.
- Examine the digital proofs of the journal, ensuring their quality.
- Adopt procedures protecting ethical issues, conflicts of interest and compliance with the policies adopted by the Brazilian Federation of Gynecology and Obstetrics Associations to which it is affiliated.
- Treat all individuals with respect, impartiality and without discrimination based on gender identity, race, sexual orientation, religion or political beliefs and geographic region.

- Maintain impartiality and clarity in the publication of sponsored supplements and/or with any other type of sponsorship/funding.
- Ensure open access and describe in all articles the Creative Commons license modality adopted by the journal.
- Ensure the organization of all documents related to the journal submission process.

Associate Editor responsibilities

- Read and evaluate the scientific quality of manuscripts received from the Editor-in-Chief.
- Appropriately choose the reviewers of manuscripts under their responsibility.
- Expedite the progress of evaluations made by reviewers and keep the review process within the schedule established by the Editor-in-Chief.
- Analyze the opinions issued by reviewers and assist them in preparing recommendations to authors.

Responsibilities of Reviewers

- Reviewers have the responsibility to review the manuscript objectively and fairly.
- Critically analyze manuscripts by offering suggestions to improve quality and contribute to the decision-making process.
- Maintain the confidentiality of any information provided by the editor.
- Maintain strict confidentiality during the review process. The reviewer must not share information from a manuscript prior to completion of the review and prior to acceptance and publication.
- Inform the editor about any similarity of articles under review to be published or ongoing studies that may be considered plagiarism.
- Disclose any potential conflicts of interest (financial, institutional, collaborative, or other relationships between reviewer and author). If there is a conflict of interest or if the reviewer does not have the necessary expertise, the manuscript must be immediately returned to the editor for the selection of another reviewer.

Responsibilities of the Author(s)

- Attest to the originality of the submitted study and confirm the article is not being considered elsewhere, nor accepted for publication in another journal.
- Ensure approval by the Research Ethics Committee of the institution where the study was developed.
- Participate sufficiently in the work to take public responsibility for its content. Authors' contributions can be made in different ways: conceptual, intellectual, experimental and analytical, and by participating in the writing and review of the manuscript. The final approval of the version to be submitted must be approved and signed by all authors responsible for all aspects of the work (typed or printed name is not acceptable).
- Ensure that studies including humans or animals comply with national and international requirements and guidelines (Declaration of Helsinki [2013], Declaration of Human and Animal Rights [Unesco, 1978]). This information must be stated in the manuscript, and the protocol number or exemption status of approved protocols must be stated in the manuscript at the time of submission for review.
- Inform the registration number referring to the research approval report at the National Council for the Control of Animal Experimentation (Concea). Studies involving animal experiments must comply with Law No. 11.794, of October 8, 2008, which establishes procedural rules for the scientific use of animals in Brazil. International manuscripts must submit local ethical documentation to proceed with the submission process. Any manuscript involving animal or human experiments submitted without proof of approval by institutional or local research committees will not be reviewed and will be returned to authors.
- Inform potential conflicts of interest in a written statement signed by all authors.
- Inform the journal editor when a major error is found in the study and provide all necessary information for publication correction, errata and retraction.
- Provide data records associated with the study when requested by the editor.
- Provide the definitive list of authors and their order at the time of original submission, containing the author registration with the respective Open Researcher and Contributor Identifier (ORCID) at https://orcid.org/signin. Any addition, removal or rearrangement of authors' names in the authorship list should be done only before the manuscript is accepted and only if approved by the journal editor. If that is the case, the corresponding author must obtain agreement of the other authors in writing, justifying the reason for alteration (addition, removal or rearrangement), and send the request by letter or e-mail. The editor will consider adding, deleting or rearranging authors after acceptance of the manuscript only in exceptional circumstances. If the manuscript has already been published in an online edition, any requests approved by the editor will result in rectification.
- Meet the deadlines for corrections and clarifying answers to questions made by reviewers.
- Use language that promotes social inclusion. The manuscript content must respect readers and not contain anything that could imply that an individual is superior to another because of age, sex, race, ethnicity, culture, sexual orientation, disability or health condition. Writing must be free from prejudice, stereotypes, slang, references to the dominant culture and/or cultural assumptions. The recognition of diversity is sensitive to differences, promotes equal opportunities and expresses respect for all people.

Scientific misconduct

Presenting results of animal or clinical research conducted without proper approval and written informed consent, as set out above, is considered unethical scientific behavior. Duplicate publication or when results are falsified, fabricated or plagiarized is also considered unethical. The RBGO allows the partial presentation of data from a manuscript in another means of dissemination, although in these cases, the author must acknowledge the previous presentation and identify the source. The citation of the original publication is essential in the disclosure. Splitting data, analysis and presentation of the same study into smaller units (practice called "salami slicing") should be avoided. Thus, the author must acknowledge in his or her cover letter any similar publications or manuscripts that have been submitted for publication based on the same material.

Investigation of scientific misconduct

Submission of an article implies that the work described has not been previously published, except in the form of an abstract, published lecture or academic thesis. Scientific misconduct may be suspected during the manuscript review process by reviewers. Thus, the RBGO may use additional resources to investigate the author's unethical conduct in order to certify the originality or plagiarism of the article (examples: Crossref Similarity Check, iThenticate and others). All suspected cases will be investigated initially by the Editor-in-Chief and by the Ethics and Professional Defense Committee of the Brazilian Federation of Gynecology and Obstetrics Associations. The author will be notified in writing of the allegations and asked to provide useful information to the investigation, including access to all original data, notes and copies of previous publications. The author's affiliation may also be contacted.

Retraction policy

The retraction policy of the RBGO is based on COPE's Retraction guidelines for advice and guidance for editors (DOI: https://doi.org/10.24318/cope.2019.1.4).

Editors will consider a publication retractable in case:

- It is plagiarism;
- It reports unethical research;
- It contains material or data without authorization for use;

- The copyright has been infringed or there is any other serious legal issue (e.g. defamation, privacy);
- There is clear evidence that results are unreliable, either as a result of a major error (e.g. miscalculation or experimental error) or as a result of fabrication or falsification of data and/or images, for example;
- Findings have been previously published elsewhere without proper attribution to prior sources or disclosure to the Editor, permission for republication or justification (i.e. cases of redundant publication);
- It has been published solely based on a compromised or manipulated peer review process;
- The author(s) have not disclosed a major conflict of interest which, in the Editor's opinion, may have unduly affected the interpretations of the work or the editors' and reviewers' recommendations.

Retraction notices must:

- Be linked to the retracted article in all versions printed or online;
- Clearly identify the retracted article (e.g. including the title and authors in the retraction header or citing the retracted article);
- Be clearly identified as a retraction (i.e. distinct from other types of correction or comment);
- Be published promptly to minimize harmful effects;
- Be freely available to all readers (i.e. open access or available only to subscribers);
- Inform who is removing the article;
- Indicate the reason(s) for the retraction;
- Be objective and factual and avoid aggressive language.

Retractions are generally inappropriate if:

- Authorship is disputed, even though there is no reason to doubt the validity of findings;
- The main conclusions of the work are still reliable and the correction can sufficiently address the errors or concerns;
- An editor has inconclusive evidence to support the retraction or is awaiting additional information, such as from an institutional investigation;
- Authors' conflicts of interest were reported to the journal after publication, but in the editor's opinion, they likely did not exert influence in interpretations, recommendations or conclusions of the article;

The RBGO will follow the flowchart suggested by COPE (DOI:**https://doi.org/10.24318/cope.2019.2.7**) to track an undisclosed conflict of interest in a published article.

Receipt of articles deposited in preprint repositories

Manuscripts submitted and coming from preprint repositories will necessarily be peer-reviewed and receive the definitive DOI issued by the RBGO if approved. Manuscripts submitted for analysis by the RBGO editorial board cannot contain references to articles that have not been published in scientific journals and that have fully complied with the peer review process.

Instructions to authors for manuscript submission

The material sent for analysis must not have been submitted simultaneously for publication in other journals or previously published. The selection of manuscripts for publication involves evaluation of originality, relevance of the topic, quality of the methodology used, its updating and whether it is appropriate and interesting to readers, in addition to adequacy to the editorial standards adopted by the journal.

Evaluation of manuscripts

Manuscripts in English submitted to the journal are received by the editorial office that checks the mandatory documentation and analyzes if the editorial rules contained in instructions to authors have been complied with. If the process is in accordance, the manuscript is sent to the editor-in-chief, who will make an initial merit assessment of the submitted manuscript. If the editor-in-chief concludes the work is in favorable scientific and technical conditions, the manuscript will be forwarded to associate editors, who, in turn, will appoint reviewers (double mind process) to evaluate the work. The reviewers' opinions and the editor's instructions will be sent to authors so they are aware of the editor's decision, criticism and eventual changes to be introduced. Authors must resubmit the text with the suggested changes within the requested deadline. When resubmitting the manuscript, the requested corrections must be highlighted in the text (marked in yellow). In cases of disagreement with the suggestions, the authors must include the justifications and observations in comment balloons. Authors must be assertive and punctual with the inquiry, supporting the hypothesis with references. **IMPORTANT!** Authors must comply with the deadlines. Failure to do so will result in a delay in their publication or even in the shelving of the process. Authors can request the suspension of the process and withdrawal of the work at any point in the process of analyzing and editing the text, except when the manuscript is accepted for publication. The concepts and statements contained in the articles are the responsibility of the authors.

Preparing a manuscript for submission

Mandatory documents for submission

When submitting a manuscript to the RBGO, documents listed below must be attached to the ScholarOne submission platform. Note that failure to submit or incomplete documentation will result in cancellation of the submission process. Mandatory documentation for online submission:

- Authorization for copyright transfer signed by all authors (scanned and attached) – **Template**;
- In accordance with chapter XII.2 of CNS Resolution No. 466/2012, in Brazil, research involving human beings needs to inform the registration number referring to the Certificate of Presentation for Ethical Assessment (CAAE) or the number of the research approval report (CEP/Conep) in the Research Ethics Committee. In the case of manuscripts involving animal experimentation, it must be indicated if it complies with Law No. 11.794 of 8 October, 2008, which establishes procedures for the scientific use of animals in Brazil, informing the registration number referring to approval of the research at the National Council for the Control of Animal Experimentation (Concea). International manuscripts must submit local ethical documentation to proceed with the submission process;
- The cover letter must be written with the purpose of justifying the publication. Authors must be identified with the respective Open Researcher and Contributor Identifier (ORCID), the authors' affiliation institution and the intention of publication. The qualification/title of the corresponding author must be included.

Title page:

- Title of the manuscript in English with a maximum of 18 words;
- Full name of authors without abbreviations (include a maximum of 8 authors per article, except in the case of multicenter studies, consensus, guidelines and position statements of societies or research groups);
- Corresponding author (full name, qualification/title and contact e-mail);
- Institutional affiliation of each author. Example: Department of Gynecology and Obstetrics, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil (Departamento de Ginecologia e Obstetrícia da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, Ribeirão Preto, SP, Brazil);
- Conflicts of interest: authors must inform any potential conflict of interest, whether of resources, political, economic for developing the study or of intellectual property;
- Acknowledgments: acknowledgments are restricted to people and institutions that contributed in a relevant way to the development of the study. Any financial support, whether from funding agencies or private companies, must be mentioned in the **Acknowledgments** section. For Brazilian authors, RBGO requests that funding

from the agencies Conselho Nacional de Pesquisa (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Capes), or any other state research support agency (eg. Fapesp), should be mentioned with the number of the research process or grants awarded;

- Contributions: according to the criteria for scientific authorship of the International Committee of Medical Journal Editors (ICMJE), authorship credit should be based on three conditions that must be fully met: (1) substantial contributions to conception and design, data collection or analysis and interpretation of data; (2) article writing or relevant critical review of intellectual content; and (3) final approval of the version to be published.

Manuscript

The Revista Brasileira de Ginecologia e Obstetrícia(RBGO) publishes the following categories of manuscripts:

- **Original articles:** full prospective, experimental or retrospective works.
- **Case reports:** They are of interest if well documented from a clinical and laboratory point of view and should contain new or unexpected aspects in relation to cases already published. Authors should indicate this information in the referral letter. The text of **Introduction** and **Discussion** sections must be based on an up-to-date literature review.
- **Review articles:** Spontaneous contributions are accepted, including integrative, scoping, or systematic reviews with or without meta-analyses. Narrative reviews will only be accepted exceptionally, given the questionable scientific evidence they represent. The methods and procedures adopted to obtain data inserted in the text must be described and based on recent references, including the current year. As this is still subject to controversy, the review should discuss trends and lines of investigation in progress. In addition to the review text, the synthesis and conclusions must be presented.
- **Letters to the Editor:** Must address editorial matters or not, but present relevant information to readers. The letters may be summarized by the editorial board, always keeping the main points. In the case of criticism or comments on published works, the letter is sent to the authors of the cited article so their response can be published simultaneously. All data presented in the letter must be fully citable and cited in the supporting reference list (unpublished data should not be described in the letter).
- **Editorial:** By invitation of the editor only.

OBS. Manuscripts containing results of original clinical or experimental research have priority for publication

Manuscript structure

Title

When writing a scientific article, the researcher must pay attention to the title of the manuscript. The title is the business card of any publication. It should be prepared with great care and preferably be written only after the article is finished. A good title adequately describes the content of the manuscript. It is usually not a sentence, as it does not contain the subject or arranged verbs and objects. **Abbreviations, chemical formulas, excess of adjectives, names of cities and institutions, among others, should be avoided in titles.** The titles of manuscripts submitted to the RBGO must contain a maximum of 18 words.

Abstract

The abstract must provide the context or basis for the study, establish the objectives, basic procedures of the methodology used, main results and main conclusions. It should emphasize new and important aspects of the study or observations. As abstracts are the only substantive part of the article that is indexed in many electronic databases, authors must ensure they accurately reflect the content of the article and highlight the research contribution/innovation to the topic. Abbreviations, symbols and references should not be used in the abstract. In case of original articles from clinical trials, the authors must inform the registration number at the end of the abstract.

1. Abstract: for original articles

Abstracts of original articles submitted to the RBGO must be structured in four sections and contain a maximum of 250 words:

Objective: Retrospective on the topic and the question posed by researchers.

Methods: How it was done; the method employed, including the material used to achieve the objective.

Results: What was found; the main finding and, if necessary, the secondary findings.

Conclusion: What was the conclusion; the answer to the question asked.

2. Abstract: for systematic review articles

Abstracts of systematic review articles submitted to the RBGO must be structured in six sections and contain a maximum of 250 words:

Objective: State the main objective of the article.

Data sources: Describe the data sources examined, including dates, indexing terms and limitations.

Study selection: Specify the number of studies reviewed and criteria used in their selection.

Data collection: Summarize the conduct used in data extraction and how it was used.

Data synthesis: Present the main results of the review and the methods employed to obtain them.

Conclusions: State the main conclusions and their clinical utility.

3. Abstract: for integrative/scoping reviews

It must contain the essence of the article, covering the purpose, method, results and conclusions or recommendations. Expose enough detail so readers can decide on the convenience of reading the entire text (word limit: 150).

NOTE: An abstract in Portuguese may be optionally added by the authors.

Keywords

The keywords of a scientific work indicate the thematic content of the text they represent. The identification of thematic content, the indexing of the work in databases and the quick location and retrieval of the content are considered the main objectives of the mentioned terms. The keyword systems used by the RBGO are DeCS (Health Sciences Descriptors – Lilacs Indexer) and MeSH (Medical Subject Headings – MEDLINE-PubMed Indexer). Five descriptors that represent the work must be chosen on these platforms.

Manuscript body

Manuscripts submitted to the RBGO should have a maximum of 4,000 words. Tables, charts and figures in the **Results** section, as well as references, are not counted.

Introduction

This part of the article prepares the reader to understand the investigation and the justification for its development. It should include the current state of knowledge on the subject, offering only strictly relevant and up-to-date references. The content to be reported in this section should provide context or background for the study, that is, the nature of the problem and its importance, and state the specific purpose, research objective, or hypothesis tested in the study or observation. The research objective is the final part of the introduction and both the main and secondary objectives must be clear and any analyzes in a pre-specified subgroup must be described. The introduction should not include data or conclusions from the work being reported.

Methods

The **Methods** section of a scientific work aims to present the study in a clear and concise way so that it is understandable and can be replicated. It should state how, when and where the study was developed. The

method comprises the material and procedures adopted in the study in order to be able to answer the main question of investigation. The **Methods** section should be structured starting with the type of study design, to show if it is appropriate to achieve the research objective; the research setting (the place and time in which it was developed); the data collection; the intervention to be performed and evaluated (if any) and also the alternative intervention; the statistical methods used and the ethical aspects of research.

NOTE: the RBGO joined the initiative of the International Committee of Medical Journal Editors (ICMJE) and the EQUATOR Network, aimed at improving the presentation of research results. Check related interactive guides:

Randomized clinical trial:

http://www.equator-network.org/reporting-guidelines/consort/

Systematic reviews and meta-analyses:

http://www.equator-network.org/reporting-guidelines/prisma/

Observational studies in epidemiology:

http://www.equator-network.org/reporting-guidelines/strobe/

Qualitative studies:

http://www.equator-network.org/reporting-guidelines/srqr/

Results

The purpose of the **Results** section is to show the findings of the research. These are original data obtained and synthesized by the author in order to provide an answer to the question that motivated the investigation. Results should be presented in a logical sequence in the text, tables and illustrations, mentioning the most important findings first. Whenever appropriate, the statistical significance of results should be indicated. All information in tables or illustrations should not be repeated in the text, and only important observations should be emphasized or summarized. Additional or supplementary materials and technical details may be placed in an appendix, accessible via a link, that will not interrupt the flow of the text. When data are summarized in the **Results** section, numerical results must be presented not only in derived values (e.g. percentages) but also in absolute values from which the derived values were calculated, and specify the statistical methods used to analyze them. Only the tables and figures necessary to explain the argument of the work and to assess its basis should be used. When scientifically appropriate, analyzes of data with variables such as age and sex should be included. The limit of a maximum of five tables, five charts or five figures must not be exceeded. Tables, charts and/or figures must be included in the body of the manuscript and do not account for the requested limit of 4,000 words. For clarification on the resolution of figures, please check https://www.ncbi.nlm.nih.gov/pmc/pub/filespec-images/.

Discussion

In the **Discussion** section, new and important aspects of the study and the conclusions derived from them should be emphasized. Data or other information presented in the **Introduction** or **Results** sections should not be repeated in detail. In experimental studies, it is useful to start the discussion with a brief summary of the main findings, compare and contrast the results with those of other relevant studies, state the limitations of the study and explore the implications of the findings for future research and clinical practice. Claiming precedence and alluding to incomplete works should be avoided, as well as discussing data not directly related to the results of the research presented. New hypotheses may be proposed when justified, but they must be clearly qualified as such. The last paragraph of the **Discussion** section should include the information of the study that relatively contributes to new knowledge.

Conclusion

The **Conclusion** section is intended to relate the conclusions to the objectives of the study. Authors should avoid unsubstantiated statements and conclusions not appropriately supported by their data. In particular, authors should avoid making claims about economic benefits and costs unless their manuscript includes economic analysis and appropriate data.

References

In manuscripts submitted to the RBGO, authors must number references in order of entry in the work and use these numbers for citations in the text. An excessive number of references should be avoided, selecting the most relevant for each statement and giving preference to more recent works. Do not use citations of difficult to access, such as abstracts of works presented at conferences, theses or publications with restricted circulation (not indexed). Cite primary and conventional references (articles in scientific journals and textbooks). References such as "unpublished observations" and "personal communication" should not be used. Authors' publications (self-citation) should only be used if there is a clear need and they are related to the topic. In this case, include only original works published in regular journals (do not cite chapters or reviews) among the bibliographic references. The number of references should be limited to 35, except for review articles. Citations of references must be placed after the period in superscript, without space after the last word (sequential and numerical citations). Authors are responsible for the accuracy of data contained in the references. To format your references, check **Vancouver:** https://www.ncbi.nlm.nih.gov/books/NBK7256/.

Submission of manuscripts

Articles must be submitted electronically, according to instructions available on the website: http://mc04.manuscriptcentral.com/rbgo-scielo.

Brazilian Journal of Gynecology and Obstetrics

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