ISSN 0100-7203
eISSN 1806-9339

RBGO Gynecology & Obstetrics

Revista Brasileira de Ginecologia e Obstetrícia
Number 12 • Volume 44 • Pages 1081–1168 • December 2022

febrasgo
Federação Brasileira das Associações de Ginecologia e Obstetrícia

OPEN ACCESS

Thieme

ISSN 0100-7203

RBGO Gynecology and Obstetrics
Revista Brasileira de Ginecologia e Obstetrícia

Editorial Office

Bruno Henrique Sena Ferreira

Editorial Production

Thieme Medical Publishers

ISSN 0100-7203

Federação Brasileira das Associações de Ginecologia e Obstetrícia

Brazilian Federation of Gynecology and Obstetrics Associations

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Volume 44, Number 12/2022

RBGO Gynecology and Obstetrics
Revista Brasileira de Ginecologia e Obstetrícia

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

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

ISSN 0100-7203

Editorial

The Use of Three-dimensional Printer Molds for Treatment of Vaginal Agenesis

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Rev Bras Ginecol Obstet 2022;44(12):1081–1082.

Although rare, vaginal agenesis is a relevant condition for gynecologists, who must be familiar with its current treatment.

It results from agenesis of the Mullerian ducts, known as Mayer-Rokitansky-Kuster-Hauser Syndrome (MRKHS), and the incidence is 1:5000 women. In this congenital malformation, genetic alterations affect the development of Mullerian ducts during the embryonic period and there is complete absence or significant hypoplasia of the uterus and vagina, with normal development of the external genitalia and breasts.

More rarely, the absence of the uterus and vagina is identified in patients with 46, XY Disorders of Sex Development (DSD) in which the presence of anti-Mullerian hormone inhibits the formation of the Mullerian ducts. In complete androgen insensitivity (Morris syndrome), the absence of testosterone action on its receptors leads to female differentiation of the external genital organs, and the conversion of testosterone to estrogen in peripheral tissues leads to the development of breasts at puberty. The clinical picture is similar to that of Rokitansky Syndrome, and in most cases, this is the initial diagnosis. The gynecologist will differentiate one from the other; in some cases, the suspicion is based on the lack of pubic and axillary hair and/or the presence of palpable gonads in the inguinal canal, but is confirmed by elevated levels of testosterone and the karyotype. Treatment will be the same as that of Rokitansky's syndrome, except for the recommendation to evaluate the gonads, given the higher risk of developing gonadoblastoma. The current recommendation is to wait for the end of puberty to consider gonadectomy, so that secondary characteristics can develop without the need for hormone replacement therapy.[1]

As soon as the diagnosis is confirmed, the treatment of vaginal agenesis involves the steps established by the American College of Obstetricians and Gynecologists (ACOG). It begins by informing and advising the patient and her family about the condition, options and timing of treatment, and explaining about sexual relationships and reproductive future. It also involves referrals to psychological support and encouraging participation in support groups.[1]

The approach regarding the formation of the neovagina is well established. The time to perform it is decided by the woman, when she manifests the desire to start a sexual relationship and demonstrates maturity and motivation to understand and participate in treatment, which generally occurs at the end of adolescence. Individual aspects inherent to this decision must be considered, such as the family context, religion and sexual orientation.

Since 2006, the ACOG recommends that "Nonsurgical creation of the vagina is the appropriate first-line approach in most patients".[2] This approach is based on a success rate greater than 90%, which is similar to surgery, although with unquestionably smaller morbidity and costs.[1,3]

Dilation is performed by the patient at home, on a daily basis, after detailed guidance from the gynecologist and supervision and follow-up throughout the process. Monitoring with a specialized physiotherapist is always beneficial, and essential when hypertonicity of the pelvic floor muscles is identified.

In Brazil, it is difficult to acquire rigid dilators, which are made of resistant material such as polylactic acid, since they are not commercially available in the country. Adapted devices such as acrylic candles and silicone dilators are commonly used.

The use of Additive Manufacturing (AM) technology and the three-dimensional printing device (3D Printer) have shown great potential for contribution and innovation in the health area. The 3D printer can create an object through its digital design. The model is evaluated and recognized by the three-dimensional printing device (3D Printer) through Computer Aided Manufacturing (CAM), the software that performs the processes of reading, analysis and digital

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DOI https://doi.org/10.1055/s-0042-1760208.
ISSN 0100-7203.

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

slicing. Additive manufacturing technology is based on the deposition of layers to build the physical object.[4]

The high customization capacity and the possibility of creating prototypes quickly, as well as the production of objects with complex geometries, have enabled the use of this technology in the development of products in the medical field. Additive manufacturing is also an economically viable technology in the production of small batches of customized products compared to conventional methods, making it an interesting alternative in the production and research of customized products.[4]

According to a study by Fernandes et al.[5] published in the current issue, the application of this technology in the production of dilators for vaginal agenesis proved to be effective, economically viable, accessible and reproducible. Therefore, dilators can be produced in a gynecological care service equipped with a 3D printer and a qualified professional, allowing women with vaginal agenesis to have access to the recommended treatment for their condition. In addition to women with agenesis, these molds can also be used in other conditions in which dilation may be necessary, such as strictures and shortening of the vagina after radiotherapy or surgery.

There is also the possibility of using it in the manufacture of other devices in Urogynecology, such as customized pessaries for the treatment of genital prolapse and urinary incontinence.

The use of 3D printing technology reveals the importance of combining knowledge in the field of technology and health, as it enables the development of products with direct impact on medical treatment, in addition to opening up promising perspectives in other areas of Gynecology.

Conflicts to Interest
None to declare.

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Randomized Clinical Trial Comparing Quadratus Lumborum Block and Intrathecal Morphine for Postcesarean Analgesia

Ensaio Clínico Randomizado Comparando Bloqueio do Quadrado Lombar e Morfina Intratecal Para Analgesia Pós-cesariana

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Rev Bras Ginecol Obstet 2022;44(12):1083–1089.

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Abstract

Objective To compare the efficacy of quadratus lumborum (QL) block and intrathecal morphine (M) for postcesarean delivery analgesia.

Methods Thirty-one pregnant women with $\geq$ 37 weeks of gestation submitted to elective cesarean section were included in the study. They were randomly allocated to either the QL group (12.5 mg 0.5% bupivacaine for spinal anesthesia and 0.3 ml/kg 0.2% bupivacaine for QL block) or the M group (12.5 mg bupivacaine 0.5% and 100 mcg of morphine in spinal anesthesia). The visual analog scale of pain, consumption of morphine and tramadol for pain relief in 48 hours, and side effects were recorded.

Results Median pain score and/or pain variation were higher in the morphine group than in the QL group ($p = 0.02$). There was no significant difference in the consumption of morphine or tramadol between groups over time. Side effects such as pruritus, nausea, and vomiting were observed only in the morphine group.

Conclusion Quadratus lumborum block and intrathecal morphine are effective for analgesia after cesarean section. Patients undergoing QL block had lower postoperative pain scores without the undesirable side effects of opioids such as nausea, vomiting, and pruritus.

Keywords
- analgesia
- cesarean section
- morphine
- spinal anesthesia
- anestesia
- obstetrical

Resumo

Objetivo Comparar a eficácia do bloqueio do quadrado lombar (QL) e da morfina intratecal (M) na analgesia pós-cesariana.

Métodos Trinta e uma gestantes com $\geq$ 37 semanas de gestação submetidas a cesariana eletiva foram incluídas no estudo. Eles foram alocados aleatoriamente no grupo QL (12,5 mg de bupivacaína a 0,5% para raquianestesia e 0,3 ml/kg de bupivacaína a 0,2% para bloqueio de QL) ou no grupo M (12,5 mg de bupivacaína a 0,5% e 100 mcg de morfina na raquianestesia). A escala visual analógica de dor, consumo de morfina e tramadol para alívio da dor em 48 horas e efeitos colaterais foram registrados.

Palavras-chave
- analgesia
- cesariana
- morfina
- anestesia espinhal
- anestesia obstétrica

received
April 6, 2022
accepted
September 8, 2022

DOI https://doi.org/10.1055/s-0042-1759728.
ISSN 0100-7203.

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

Resultados A mediana do escore de dor e/ou variação da dor foi maior no grupo morfina do que no grupo QL ($p = 0,02$). Não houve diferença significativa no consumo de morfina ou tramadol entre os grupos ao longo do tempo. Efeitos colaterais como prurido, náuseas e vômitos foram observados apenas no grupo morfina.

Conclusão O bloqueio QL e a morfina intratecal são eficazes para analgesia após cesariana. Os pacientes submetidos ao bloqueio do QL apresentaram menores escores de dor pós-operatória sem os efeitos colaterais indesejáveis dos opioides, como náuseas, vômitos e prurido.

Introduction

Cesarean section is the most frequently performed surgical procedure in obstetrics.[1] The number of cesarean deliveries has increased in recent years, accounting for ~ 21% of births worldwide.[2]

During the postoperative period, ~ 1 of 5 women experience acute pain.[3] The effective management of postoperative pain is highly important as it facilitates early recovery, ambulation, and breastfeeding, allowing mothers to provide better care to their newborns.[4,5] Moreover, it helps preventing venous thromboembolism[6] and respiratory complications, decreasing hospital stay.[7] In addition to these benefits, an adequate management of acute postcesarean pain is associated with a 3-fold decrease in the risk of postpartum depression[8] and development of chronic pelvic pain.[9,10]

Morphine (M) has been widely used for postoperative pain relief, due to its favorable pharmacokinetic profile, ease of administration during spinal block and low cost.[11,12] However, the use of opioids is associated with undesirable side effects such as nausea, vomiting, pruritus, and urinary retention, which can reduce patient satisfaction. Furthermore, the fact that M may produce severe maternal respiratory depression underscores the importance of investigating alternative opioid-free analgesia approaches.[13,14]

Another opioid used for postoperative pain relief is Tramadol. This is a synthetic 4-phenyl-piperidine analogue of codeine with a dual mechanism of action. It stimulates μ receptors and, to a lesser extent, δ and κ receptors. Like tricyclic antidepressants, tramadol also activates spinal pain inhibition by decreasing the reuptake of norepinephrine and serotonin.[15]

The blockade of peripheral nerves for analgesia of the abdominal wall after surgery has become more frequent, especially with the development of ultrasound technology.[16,17]

Quadratus lumborum (QL) block is a technique used to inject local anesthetic in the posterior abdominal wall around the quadratus lumborum muscle to anesthetize the thoracolumbar nerves.[18] It can provide somatic as well as visceral analgesia due to its paravertebral spread.[19,20] According to a systematic review by Jin et al.,[21] QL block significantly reduces opioid requirement in cesarean delivery and in renal surgery. Similarly, Graça et al.[22] have reported a reduction in postoperative opioid consumption with the use of QL block in laparoscopic nephrectomy, while Zhu et al.[23] have found that anterior QL block significantly alleviated pain in patients undergoing open liver resection.

The objective of the present study was to compare the efficacy of QL block and intrathecal M for postcesarean delivery analgesia by measuring M/tramadol consumption during the first 48 hours after surgery.

Methods

The present randomized clinical trial was registered at the Brazilian Clinical Trials Registry (RBR-5RHP9J) and was approved by the Research Ethics Committee of the Universidade Federal de São Paulo (UNIFESP, in the Portuguese acronym) (CEP/UNIFESP.CAAE:83549817.3.0000.5505), was conducted at the Hospital São Paulo, UNIFESP.

The inclusion criteria were as follows: pregnant women > 18 years old with gestational age of at least 37 weeks, normal singleton pregnancy, physical status classified according to the American Society of Anesthesiologists as ASAII (mild systemic disease without functional limitations), and ASA III (mild systemic disease with functional limitations), elective cesarean section performed under spinal anesthesia at the Obstetric Center of the Faculdade Paulista de Medicina between June 2019 and December 2019.

Exclusion criteria: inability to understand or provide a verbal self-report of pain on a scale, congenital or acquired coagulation disorders, allergy to local anesthetics, anatomical disorders of the spine leading to neuraxial block failure, BMI > 35 kg/m^2, and local infection.

Initially, we defined that the sample size would be for an established period of time. However, during our study, Salama[24] published a study similar to ours.

Considering total postoperative morphine consumption as significantly lower in the QL block group than in the M group, as reported by Salama,[24] and assuming a statistical power of 80% at a significance level of 0.5%, a sample size of 4 participants in each group was estimated to be enough to compare efficacy between QL block and intrathecal morphine for postcesarean delivery analgesia on the basis of total postoperative M consumption. Thus, we used a secondary outcome obtained in the study by Salama,[24] total postoperative morphine consumption, to calculate our sample size.

However, at that time, we had already collected more patients: 15 to the QL block group and 16 to the M group. So, we decided to present data from all patients studied.

Eligible parturients were invited to participate in the study during the preanesthetic visit. Patients who agreed to participate in the research signed an informed consent form.

Study participants were randomly allocated into two groups: Group M (spinal anesthesia with bupivacaine and M), and Group QL (spinal anesthesia with bupivacaine + QL block). The randomization was performed using software available at http://github.com/Gear61/Random-Number-Generator (v. 2015). This software generated a numerical sequence of 1 or 2. The patient who was randomized with the number 1 would belong to the M group and the one randomized with the number 2 would belong to the QL group. Before the procedure, the patients did not know which group they belonged to.

The study procedures were performed by two anesthesiologists. "Anesthesiologist One" (AO) conducted randomization, filled the syringes with the study medication, and performed the QL block. Anesthesiologist One is a specialist in regional anesthesia, with 5 years of experience in regional blocks. "Anesthesiologist Two" (AT) administered spinal anesthesia but did not know the volume of drugs that each group would receive during spinal anesthesia. Anesthesiologist Two was blind to patient allocation and performed the postoperative assessment.

Both groups received 12.5 mg of 0.5% hyperbaric bupivacaine for spinal anesthesia. To group M, 100 mcg of M, whose onset of action occurs in 60 minutes, was added to the syringe containing bupivacaine.

To group QL, bilateral QL block was performed by injecting 0.3 mL/kg of 0.2% bupivacaine on each side.

Spinal anesthesia was performed in the sitting position at vertebral levels L3-L4 or L4-L5, using a 27-gauge pencil point needle according to the standard hospital protocol. After surgery, AT left the operating room to return 1 hour later to reevaluate the patient.

In the QL group, bilateral US-guided QL block was performed by AO using a Sonosite M-Turbo R System with HFL 38x, 5–8 MHz convex transducer (Sonosite, Bothell, WA, USA). With the patient in the lateral decubitus position, the transducer was placed at the anterosuperior iliac spine level and advanced cranially to visualize the three abdominal muscle layers. The external oblique muscle was followed laterally until its posterior border was visualized with the internal oblique muscle underneath, like a roof over the QL muscle. The transducer was directed downwards to identify the middle layer of the thoracolumbar fascia as a bright hyperechoic line.

After antisepsis of the anterior abdominal wall with alcoholic chlorhexidine, a 22G x 100 mm needle (AEq. 2250, BMD Group, Venice, Italy) was inserted in-plane from the anteromedial to the poster direction, at an angle of 45 degrees to the skin for the injection of bupivacaine. Thus, all patients received type 2 QL block. The performance of QL block took $\sim$ 5 minutes.

Postoperative analgesia for all patients consisted of dipyrone 1 g every 6 hours, and ketoprofen 100 mg every 12 hours, both intravenous. We followed the postoperative rescue analgesia protocol adopted at the hospital: at any time during the postoperative period, patients could request rescue medication for pain relief. If the patient reported a moderate pain score (4–6), tramadol 100 mg was administered intravenously every 6 hours. If there was no improvement in pain after tramadol or if the patient reported severe pain score (7–10), the rescue medication used was M 4 mg, intravenously, every 6 hours.

The AD evaluated the parameters, described below, in all patients at predetermined intervals after surgery (1, 2, 4, 6, 12, 24, and 48 hours); with the main outcome being the consumption of M/tramadol. Morphine/tramadol consumption was measured in milligrams (mg), heart rate in beats per minute (bpm), oxygen saturation in percentage of oxygen carried by the blood (%), noninvasive blood pressure in millimeters of mercury (mmHg). Pain scores were evaluated using the visual analogue pain scale, whose values range from 0 to 10; zero means total absence of pain and 10 the maximum level of pain bearable by the patient, with a score of 1 to 3 considered as mild, moderate from 4 to 6, and severe from 7 to 10. The sedation level was measured as follows: grade 1 = anxious and agitated patient; grade 2 = cooperative, oriented and calm patient; grade 3 = sleepy patient and attentive to commands; grade 4 =patient sleeping, responds quickly to vigorous sound stimulus, grade 5 = patient sleeping, responds slowly to vigorous sound stimulus, and grade 6 = patient sleeping, no response. Pruritus was evaluated as follows: grade 0 = absent, grade 1 = mild, grade 2 = moderate, grade 3 = severe. Nausea was measured as follows: grade 0 = absent, grade 1 = mild, grade 2 = moderate, grade 3 = severe or vomiting. In addition to these parameters, the presence or absence of residual block and other complications was evaluated.

Quantitative variables were compared using the parametric Student *t*-test or the nonparametric Mann-Whitney test. For the comparison of qualitative variables between groups, the chi-squared test, the Fisher exact test or the likelihood ratio test were performed. To compare quantitative variables between groups over time, analysis of variance (ANOVA) with repeated measures or repeated measures ANOVA with rank transform were used. To compare qualitative variables between groups over time, the generalized estimating equation (GEE) model was used. Significance was set at 5% ($p < 0.05$).

Results

As shown in the diagram below, 44 patients were invited to participate in the study; 13 were not included in the study for the following reasons: 1 refused to participate, 12 met the exclusion criteria; 5 had BMI > 36 kg/m2, 4 were < 37 weeks pregnant, and 3 were with multiple pregnancies. Thus, the study population consisted of 31 parturients. Of these, 15 were assigned to the QL group, and 16 to the M group (►**Fig. 1**).

As shown in ►**Table 1**, there was no significant difference between the groups regarding age, BMI, and number of previous cesarean deliveries. Only one patient in the QL group was classified as ASA III, all others in both groups were ASA II, showing the homogeneity of the samples.

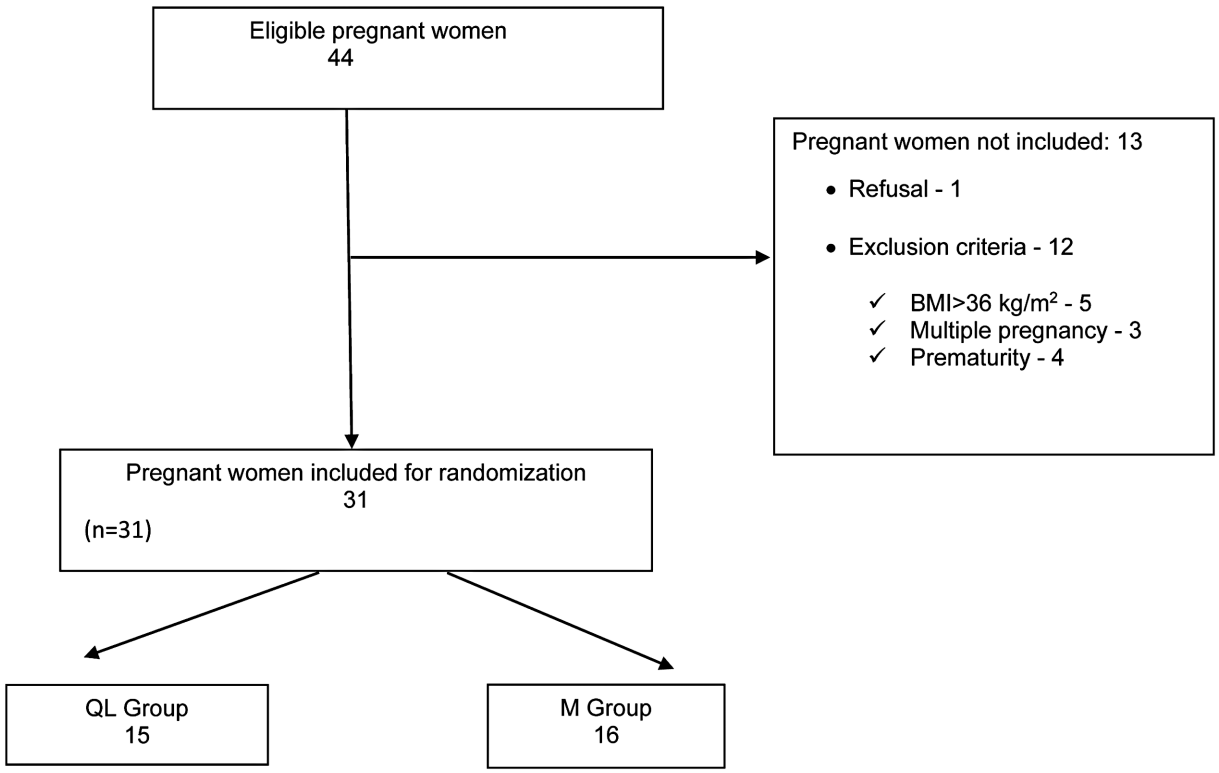

Fig. 1 Study flow diagram.

Table 1 Clinical and demographic characteristics of study patients

Variables by group	QL	M	*p-value*
Age (Years old)			
Mean (SD)	33.5 (6.7)	31.1 (6.4)	0.293(*)
Median (Minimum–Maximum)	37 (19–41)	31 (18–41)	
Total	15	16	
ASA –*n* (%)			
II	14 (93.3)	16 (100)	not calculated
III	1 (6.7)	0 (0)	
Total	15 (100)	16 (100)	
BMI			
Mean (SD)	30.8 (3.9)	30.2 (4.8)	0.669(*)
Median (Minimum–Maximum)	30 (24.5–36)	30.3 (21.6–36)	
Total	15	16	
Previous cesarean delivery –*n* (%)			
No	5 (33.3)	10 (62.5)	
Yes	10 (66.7)	6 (37.5)	0.104(#)
Total	15 (100)	16 (100)	
Previous cesarean delivery			
Mean (SD)	1.2 (1.15)	0.81 (1.17)	0.279(*)
Median (Minimum–Maximum)	1 (0–4)	0 (0–3)	
Total	15	16	

Abbreviation: SD. standard deviation.
(*) Parametric t-Student test; (**) Mann-Whitney nonparametric test; (#) Chi-squared test.

Table 2 Opioid consumption and urinary retention between groups

Time	Consumption of tramadol			Consumption of morphine			Urinary retention	
(Post-operative)	M group *n* (%)	QL group *n* (%)	*p*[a]	M group *n* (%)	QL group *n* (%)	*p*[b]	M group *n* (%)	QL group *n* (%)
1 hour	1(6.25)	0	0.059	1(6.25)	1(6.66)	0.631	0	0
2 hours	2(12.5)	4(26.66)		1(6.25)	1(6.66)		0	0
4 hours	3(18.75)	0		1(6.25)	2(13.33)		1(6.25)	0
6 hours	1(6.25)	4(26.66)		1(6.25)	0		4(25)	0
12 hours	1(6.25)	4(26.66)		2(12.5)	1(6.66)		4(25)	0
24 hours	3(18.75)	2(13.33)		2(12.5)	1(6.66)		4(25)	1(6.66)
48 hours	0	1(6.66)		0	0		1(6.25)	0

Abbreviations: M group, morphine group. QL group: quadratus lumborum group.
[a]Generalized estimating equations model (GEE).
[b]Mann-Whitney nonparametric test.

►**Table 2** shows that most patients in both groups received neither morphine nor tramadol over 48 hours after surgery. Morphine consumption (►**Table1**) was lower in the QL group (33.4%) compared with the M group (43.9%), but no statistical difference was reached. Moreover, there were twice as many patients who used M in group M compared with group QL at 12 hours and 24 hours after cesarean section. In the QL group, tramadol was used by 26.7% of the patients at 2, 6, and 12 hours and by 13.3% at 24 hours. In contrast, the use of tramadol in group M was higher at 24 hours (18.8%) than at 6 and 12 hours (6.3%). Nonetheless, no statistical difference was observed between groups. During the period in which they were evaluated, six patients used both medications: M and tramadol, all of which were in the M group.

As shown in ►**Fig. 2**, the pain scores significantly differed between groups ($p = 0.002$) independently of time ($p = 0.162$). Median pain scores and/or pain variation, despite being higher in group M than in group QL.

Pruritus was not observed in any of the QL patients. On the other hand, in group M, pruritus was present in half of the women after 4 hours, in nearly 70% after 12 hours, and was still present in 12.6% of them 48 hours after surgery. Nausea was not seen in any of the women in the QL group but was present from the first hour to 24 hours postoperatively in 12 to 20% of the participants in group M. Urinary retention occurred in only 1 woman in the QL group, whereas in the M group it occurred in 25% of the patients from 6 hours to 24 hours after cesarean section. No patient had respiratory depression in any of the groups. Residual block was present in only one patient in the QL group. Heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, oxygen saturation, and sedation score did not significantly differ between groups. All patients in the study had a grade 1 sedation score, that is, they remained cooperative, oriented, and calm.

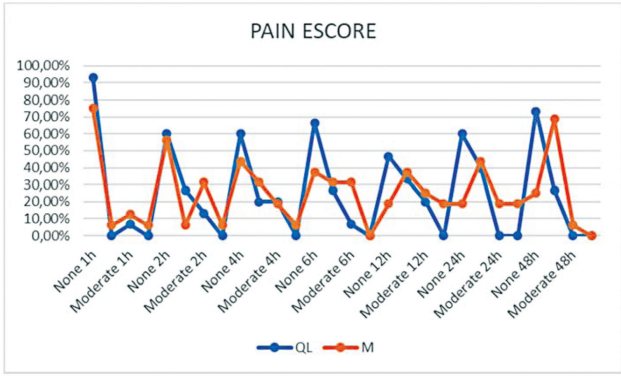

Fig. 2 Distribution of pain score over time among patients in the quadratus lumborum and morphine groups. M: Morphine Group, QL: Quadratus Lumborum Group. p-value = 0.002. Model of Analysis of Variance (ANOVA).

Discussion

The present study demonstrated that QL block and intrathecal M injection are effective in providing postoperative analgesia in patients undergoing cesarean section as there was no significant difference in opioid consumption in 48 hours. In the QL group, pain scores were significantly lower and side effects such as pruritus, nausea, and vomiting were not observed.

Our results show that QL block and intrathecal morphine can effectively relief postoperative pain. Indeed, 86% of the patients in both groups did not require the administration of opioids.

Quadratus lumborum block type 2 was the technique of choice in the present study because it was demonstrated by Blanco et al.[25] to be superior to transversus abdominis plane blocks (TAP blocks) in providing postoperative analgesia. However, a study by Kang et al.[26] comparing the effects of epidural M and major QL block approaches showed that the combination of QL block type 2 and 3 can provide superior postcesarean analgesic effect.

Morphine and tramadol consumption did not differ between the study groups (►**Table 2**). Morphine consumption 6 hours after cesarean section was lower in the QL group,

suggesting that QL block has a longer lasting effect. However, this finding did not reach statistical significance, in opposition to Salama,[24] who observed a significant lower morphine consumption in the QL group. Our results also differ from those of Kang et al.,[26] who reported significantly higher morphine consumption with QL block compared with peridural morphine. These diverging results may be explained by differences in the local anesthetic dose and volume used. While higher concentrations (0.375% ropivacaine) were used by Salama,[24] the participants of the present study received the same concentration used by Kang et al.[26] (0.2% ropivacaine) and Blanco et al.[19] (0.2% bupivacaine). Furthermore, anesthetic volumes also differed; Salama[24] used 24 ml on each side of the block, whereas the volume adopted in the present study, as well as by Blanco et al.[19] was 0.3 ml/kg, and that used by Kang et al.[26] was 30 ml on each side.

Pain scores over 48 hours among our patients were significantly lower in the QL group (►**Fig. 2**), indicating that QL block was effective as an anesthetic technique. The spreading of QL block into the paravertebral space[24] and into thoracic and lumbar sympathetic nerves[27] seems to be the major mechanism of action of this anesthetic approach and might explain the lower pain scores found in our study.

Pain intensity and elective cesarean section have been associated with a negative birth experience,[28] and are related to post-traumatic stress symptoms, and postpartum depressive symptoms.[29] Within this framework, QL block stands as an effective alternative, given that it not only provides analgesia but is also free of undesirable side effects that could render the experience of childbearing more negative.

The incidence of pruritus, nausea, and vomiting in the postoperative period was higher in the M group. As a matter of fact, these symptoms were not seen in the QL group.

Urinary retention was more frequent in the M group than in the QL group, which had only one patient with this symptom. However, this difference was not statistically significant.

No case of respiratory depression was observed in any of the study participants.

Residual block was seen in only one patient of the QL group up to 12 hours after cesarean section. Kang et al.[26] also described this event in two patients undergoing QL block. It is possible that a posterior dispersion of the local anesthetic occurred, and therefore the QL block behaved as type 3, a complication that has been previously described.[30]

Hemodynamic parameters were similar in both study groups, which did not differ regarding heart rate, respiratory rate, systolic and diastolic blood pressure, and oxygen saturation.

It is noteworthy that the groups of patients herein investigated were homogeneous, and that the same investigator performed all blocks. However, the study had some limitations. Obese patients with BMI $\geq 35\,kg/m^2$ were not included. It was not possible to install a patient-controlled analgesia pump, as is done in large centers, due to the infrastructure of the institution, so we chose to use the rescue analgesia protocol adopted in our hospital, which includes the use of tramadol for moderate pain scores. This setback did not affect the progress of the research or the results we arrived at, allowing us to proceed with the research.

Conclusion

The QL block can be seen as a valuable option for those patients with a previous history of nausea, vomiting, and itching. Perhaps performing the quadratus lumborum block with a greater volume and concentration of local anesthetic can provide analgesia for a period longer than 48 hours. In brief, both QL block and intrathecal M were demonstrated to be effective for postcesarean section analgesia. Nonetheless, QL block seemed to be more advantageous, given that it was associated with lower postoperative pain scores and absence of pruritus, nausea, and vomiting.

Contributors

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

Conflict of Interests

The authors have no conflict of interests to declare.

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Relationship between the Prenatal Diagnosis of Placenta Acreta Spectrum and Lower Use of Blood Components

Relação entre o diagnóstico prenatal de espectro da placenta acreta e menor uso de hemoderivados

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Rev Bras Ginecol Obstet 2022;44(12):1090–1093.

Abstract

Objective To describe the clinical results of patients admitted and managed as cases of placenta accreta spectrum (PAS) at a Central American public hospital and the influence of the prenatal diagnosis on the condition.

Materials and Methods A retrospective analysis of PAS patients treated at Hospital Bertha Calderón Roque, in Managua, Nicaragua, between June 2017 and September 2021. The diagnostic criteria used were those of the International Federation of Gynecology and Obstetrics (Fédération Internationale de Gynécologie et d'Obstétrique, FIGO, in French). The population was divided into patients with a prenatal ultrasonographic diagnosis of PAS (group 1) and those whose the diagnosis of PAS was established at the time of the caesarean section (group 2).

Results: During the search, we found 103 cases with a histological and/or clinical diagnosis of PAS; groups 1 and 2 were composed of 51 and 52 patients respectively. Regarding the clinical results of both groups, the patients in group 1 presented a lower frequency of transfusions (56.9% versus 96.1% in group 2), use of a lower number of red blood cell units (RBCUs) among those undergoing transfusions (median: 1; interquartile range: [IQR]: 0–4 versus median: 3; [IQR]: 2–4] in group 2), and lower frequency of 4 or more RBCU transfusions (29.4% versus 46.1% in group 2). Group 1 also exhibited a non-significant trend toward a lower volume of blood loss (1,000 mL [IQR]: 750–

Keywords
- placenta accreta
- prenatal ultrasonographic diagnosis
- surgical procedure
- blood transfusion

received
June 13, 2022
accepted
August 5, 2022

DOI https://doi.org/10.1055/s-0042-1758712.
ISSN 0100-7203.

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

2,000 mL versus 1,500 mL [IQR]: 1,200–1,800 mL in group 2), and lower requirement of pelvic packing (1.9% versus 7.7% in group 2).

Conclusion Establishing a prenatal diagnosis of PAS is related to a lower frequency of transfusions. We observed a high frequency of prenatal diagnostic failures of PAS. It is a priority to improve prenatal detection of this disease.

Introduction

Placenta accreta spectrum (PAS) is a condition associated to massive hemorrhage and polytransfusion,[1] and patients should be cared for by interdisciplinary groups in experienced centers.[2–4] However, the participation of these expert groups relies on a prenatal diagnosis that enables the patient to be guided towards this type of care. The frequency of cases of PAS not diagnosed before laparotomy is variable, but it can be as high as 50%.[5,6] In Nicaragua, among the factors that contribute to the low rate of prenatal diagnoses are the difficulties in training to identify PAS, the absence of centers with a high influx of patients, and the lack of feedback between the centers that carry out the diagnosis and those who deliver treatment. The present work describes the clinical results of the PAS patients managed at a Central American public hospital and the importance of establishing a prenatal diagnosis.

Materials and Methods

A retrospective analysis of medical records was carried out in search for patients with PAS treated at Hospital Bertha Calderón Roque, in Managua, Nicaragua, between June 2017 and December 2021. The diagnostic criteria used was those of the International Federation of Gynecology and Obstetrics (Fédération Internationale de Gynécologie et d'Obstétrique, FIGO, in French).[7] The population was divided into patients with a prenatal PAS diagnosis by ultrasound submitted to surgery for that reason (group 1) and patients in whom PAS was only detected at the time of the caesarean section (group 2). During this period, the management protocol was standard, with no variations. All patients with a diagnosis of PAS underwent cesarean section at 35 weeks, with a plan for total hysterectomy after extraction of the fetus through the uterine fundus. Specific vascular control strategies nor ureteral catheters were used. All patients included had placenta previa and underwent cesarean hysterectomy, same surgical technique was applied. The present retrospective study was approved by the Institutional Review Board/Ethics Committee for Biomedical Research (under no. 1494). A descriptive statistical analysis was carried out; The continuous variables were expressed as median and interquartile range (IQR) values, and they were analyzed using the Mann-Whitney U test. The qualitative variables were expressed as absolute and relative frequencies, and the comparison between them was made using the Chi-squared test or the Fisher exact test according to the case. Statistical significance was defined as $p < 0.05$. The analyses were performed using the STATA (StataCorp LLC, College Station, TX, United States) software, version 14.

Results

During the study period, 114 women with a histological and/or clinical diagnosis of PAS were found: 51 patients had a prenatal PAS diagnosis by ultrasound (group 1), and 63 were only diagnosed when they underwent laparotomy (group 2).

Chart 1 summarizes the clinical results of both groups, showing a lower frequency of transfusions in group 1 (56.9% versus 87.3% in group 2), as well as the use of a lower number of red blood cell units (RBCUs) in said transfused patients (median: 1; IQR: 0–4 versus median: 3; IQR: 2–4 in group 2). The frequency of 4 or more RBCU transfusions was also lower in group 1 (29.4% versus 44.4% in group 2). Group 2 underwent surgery at a higher gestational age (mean: 38 weeks; IQR: 35–39 weeks versus median: 34 weeks; IQR: 32–36 weeks in group 1), with a lower rate of participation of interdisciplinary groups (62.4% versus 90.2% in group 1) and of elective surgeries than group 1 (22.2% in group 2 versus 78.4% in group 1). Group 1 also exhibited a non-significant trend toward a lower volume of blood loss (median: 1,000 mL; IQR: 750–2,000 mL versus median: 1,500 mL; IQR: 1,300–2,200 mL in group 2), lower requirement of pelvic packing with compresses to control bleeding (1.9% versus 7.9% in group 2), surgical reinterventions (11.8% versus 17.5% in group 2), and surgical site infection (1.9% versus 4.8% in group 2) than group 2. In a high percentage of patients (35; 30.9%), the histological diagnosis was not available because the tissue had not been not processed by the pathology department.

Discussion

Less than half of our cases (44.7%) had a prenatal PAS diagnosis (group 1). Patients in group 1 had a lower frequency of transfusions and those among them who received blood components required a lower number of RBCUs. Although some expert groups have reported excellent performance of the PAS ultrasonographic diagnosis,[8,9] even in some high-income countries the frequency of false positives is close to that observed in the Nicaraguan population, with a rate of intraoperative diagnosis close to 50%.[5,6] There are multiple factors that explain a poor performance in establishing a PAS prenatal diagnosis in our population. Although all the patients included in the present study underwent prenatal

Chart 1 Comparison of the clinical results of PAS patients with and without a prenatal diagnosis

		Group 1 (n = 51): WITH prenatal diagnosis	Group 2 (n = 63): WITHOUT prenatal diagnosis	*p*-value
Gestational age at surgery (in weeks)*		34 (32-36)	38 (35-39)	0.003
Surgical time (in minutes)*		103 (82-145)	94 (74-129)	0.235
Interdisciplinary group participation: n (%)		46 (90.2)	33 (62.4)	0.003
Elective surgery: n (%)		40 (78.4)	14 (22.2)	0.002
Bleeding volume (mL)*		1000 (750-2000)	1500 (1300-2200)	0.347
Transfusions: n (%)		29 (56.9)	55 (87.3)	0.005
Number of RBCUs transfused		1 (0-4)	3 (2-4)	0.027
4 or more RBCUs: n (%)		15 (29.4)	28 (44.4)	0.039
Bladder injury: n (%)		7 (13.7)	9 (14.2)	0.923
Ureteral injury: n (%)		2 (3.9)	0	–
Urinary fistula: n (%)		0	1 (1.6)	–
Pelvic packing with compresses: n (%)		1 (1.9)	5 (7.9)	0.380
Reintervention: n (%)		6 (11.8)	11 (17.5)	0.996
Wound infection: n (%)		1 (1.9)	3 (4.8)	0.666
Death: n (%)		1 (1.9)	1 (1.6)	0.104
Histological analysis: n (%)	Placenta acreta	24 (47.1)	34 (53.9)	0.890
	Placenta increta	11 (21.6)	6 (9.5)	
	Placenta percreta	2 (3.9)	2 (3.2)	
	No histological study	14 (27.4)	21 (33.3)	

Abbreviations: PAS, placenta accreta spectrum; RBCU, red blood cells unit.
Note: *Median (interquartile range).

follow-up visits and periodic ultrasonographic scans, Nicaragua has not established protocols to diagnose PAS. Additionally, there are few maternal-fetal medicine specialists or prenatal ultrasonography experts. Finally, there is no chair in the diagnosis and treatment of PAS in the obstetrics training programs in our country. It is important to point out these difficulties as the first step towards improving the prenatal identification of PAS. It is likely that the knowledge of a prenatal PAS diagnosis in group 1 facilitated the scheduling of the surgical procedure, which was elective in 78.4% of these patients, unlike group 2, in which it was elective in 22.2% of the cases, and at a higher gestational age (median: 34 weeks; IQR: 32–36 weeks in group 1 versus median: 38 weeks; IQR: 35–39 weeks in group 2).

One of the advantages of knowing the PAS diagnosis is the possibility of "scheduling" the participation of the interdisciplinary groups during surgery.[10–12] Our hospital does not have an interdisciplinary group dedicated to the treatment of PAS (a "PAS team"); however, patients from group 1 were treated by the more experienced surgeons available, which included the urologist and the teneral surgeon on duty that day. This was possible in 90.2% of the cases in group 1, and only in 62.4% of the cases in group 2. In the event that the diagnosis of PAS was a "surprise" during the laparotomy, calling the surgeon and the urologist on duty was left at the discretion of the obstetricians in charge of the surgery. Other authors[5] have pointed out the importance of prenatal diagnosis and its relationship with lower levels of blood loss and lower use of transfusions, and they also coincide in documenting important differences in the management of patients with and without a prenatal diagnosis.

Our hospital is a reference center for the most critical obstetric conditions in the country, but like many other hospitals with similar characteristics, it does not have a PAS team.[13] Our flaws in the prenatal diagnosis (intraoperative finding of PAS in 55.2% of our cases) and histological analysis (absence of analysis by a pathologist in 35 cases) result in an opportunity to improve the quality of care in our center.

The present study has limitations. Its retrospective design makes it more susceptible to bias. The absence of histological confirmation in 30.7% of the cases enabled the inclusion of non-PAS cases; however, patients whose medical record described macroscopic findings compatible with the FIGO definition were included. The present is the first evaluation of the clinical results of PAS management in Nicaragua, and one of the few that have been carried out in Central America.

The results shed light on the need to design improvement plans at the national level, with the need for multicenter prospective studies to confirm our observations and evaluate the effect of interventions already implemented, such as the creation of a PAS team that is provided with specific training in the management of this disease, the proposal of including PAS screening in routine prenatal care appointments for women with risk factors, and the project of including a section about PAS in the national guidelines for the treatment of postpartum hemorrhage.

Conclusion

The presence of a prenatal diagnosis of PAS is related to a lower frequency of RBCU transfusions. We observed a high frequency of failures within the prenatal PAS diagnostic steps. It is a priority to improve the prenatal detection of this disease.

Contributions

All authors made substantial contributions to the conception and design, data collection or analysis, and interpretation of data, writing of the article or critical review of the intellectual content, and final approval of the version to be published.

Conflict of Interests

The authors have no conflict of interests to declare.

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Perinatal Outcomes in Women with Chronic Kidney Diseases

Resultados perinatais em mulheres com doenças renais crônicas

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Rev Bras Ginecol Obstet 2022;44(12):1094–1101.

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Abstract

Objective To assess maternal and neonatal outcomes in women with chronic kidney disease (CKD) at a referral center for high-risk pregnancy.

Methods A retrospective cohort of pregnant women with CKD was followed at the Women's Hospital of Universidade Estadual de Campinas, Brazil, between 2012 and 2020. Variables related to disease etiology, treatment duration, sociodemographic variables, lifestyle, other associated diseases, obstetric history, and perinatal outcomes were assessed. The causes of CKD were grouped into 10 subgroups. Subsequently, we divided the sample according to gestational age at childbirth, as preterm and term births, comparing maternal and neonatal outcomes, and baseline characteristics as well as outcomes among such groups.

Results A total of 84 pregnancies were included, in 67 women with CKD. Among them, six pregnancies evolved to fetal death, five to miscarriage, and one was a twin pregnancy. We further analyzed 72 single pregnancies with live births; the mean gestational age at birth was 35 weeks and 3 days, with a mean birth weight of 2,444 g. Around half of the sample (51.39%) presented previous hypertension, and 27.7% developed preeclampsia. Among the preterm births, we observed a higher frequency of hypertensive syndromes, longer maternal intensive care unit (ICU) stay in the postpartum period, higher incidence of admission to the neonatal ICU, higher neonatal death, lower 5-minute Apgar score, and lower birth weight.

Conclusion This study demonstrates increased adverse outcomes among pregnancies complicated by CKD and expands the knowledge on obstetric care among such women in an attempt to reduce maternal risks and identify factors related to prematurity in this population.

Keywords
- kidney disease
- high-risk pregnancy
- antenatal care
- perinatal outcomes

received
March 8, 2022
accepted
May 19, 2022

DOI https://doi.org/10.1055/s-0042-1753546.
ISSN 0100-7203.

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

Resumo

Objetivo Avaliar os desfechos maternos e neonatais em mulheres com doença renal crônica (DRC) em um centro de referência para gestação de alto risco.

Métodos Coorte retrospectiva de gestantes com DRC acompanhadas no Hospital da Mulher da Universidade Estadual de Campinas, Brasil, entre 2012 e 2020. Variáveis relacionadas à etiologia da doença, duração do tratamento, variáveis sociodemográficas, estilo de vida, outras doenças associadas, história obstétrica, número de consultas de pré-natal e os resultados perinatais foram avaliados. As causas da DRC foram agrupadas em 10 subgrupos. Posteriormente, dividimos a amostra de acordo com a idade gestacional no parto, pois os nascimentos pré-termo e a termo comparam os desfechos maternos e neonatais bem como as características basais e desfechos entre esses grupos.

Resultados Um total de 84 gestações foram incluídas em 67 mulheres com DRC. Dentre elas, seis gestações evoluíram para óbito fetal, cinco para aborto espontâneo, e uma era gestação gemelar. Foram analisadas ainda 72 gestações únicas, com nascidos vivos; a idade gestacional média ao nascer foi de 35 semanas e 3 dias, e o peso médio ao nascer foi 2.444 g. Cerca de metade da amostra (51,39%) apresentava hipertensão prévia e 27,7% desenvolveram pré-eclâmpsia. Entre os casos de prematuridade (34 casos), observamos maior frequência de síndromes hipertensivas, mais dias de internação materna na UTI no pós-parto, maior incidência de internação na UTI neonatal, óbito neonatal, menor índice de Apgar de 5 minutos e menor peso ao nascimento.

Conclusão Este estudo demonstra o aumento de desfechos adversos em gestações complicadas por DRC e amplia o conhecimento sobre cuidados obstétricos entre essas mulheres na tentativa de reduzir os riscos maternos e identificar fatores relacionados à prematuridade nessa população.

Palavras-chave

- doença renal
- gravidez de alto risco
- cuidado pré-natal
- cuidados perinatais

Introduction

Chronic kidney disease (CKD) is a global health problem that affects ~ 10% of the population. The prevalence has increased in recent decades and is higher among low- and middle-income countries.[1] In Brazil, more than ten million people have CKD. Chronic kidney disease occurs in women and men equally, and reproductive function can be affected in women, in addition to influencing maternal and neonatal outcomes.[2]

Approximately 3 to 4% of women of reproductive age and ~ 1 to 3% of pregnant women have CKD, regardless of the underlying cause.[3,4] In these patients, there is a greater risk of maternal hypertensive complications, fetal growth restriction, and premature birth; therefore, there is a greater chance of hospitalization of the newborn in a neonatal intensive care unit (ICU), stillbirth and neonatal death, in addition to morbidities related to prematurity.[5] Women with CKD are 10 times more likely to develop preeclampsia than women at usual risk, with a reported prevalence of preeclampsia of up to 40% among pregnant women with CKD.[6]

The reported overall prevalence of preterm birth (before 37 weeks) in Brazil is around 10 to 12%. In other countries, rates vary according to other health indicators. One of the factors that can influence this is pregestational creatinine levels. A Canadian study of 56,000 pregnancies showed an increase in therapeutic preterm birth in women with pregestational creatinine above the 95th percentile (0.87 mg/dL), which was not observed in patients with spontaneous preterm births. In this same study, a graph was constructed that illustrates a J-curve supporting the association of serum creatinine and the probability of preterm delivery, with a 1.23-fold increase in the chance of preterm delivery in patients who had some renal dysfunction compared with pregnant women with normal renal function.[7]

Despite the possible unfavorable perinatal outcomes in pregnant women with CKD reported in the literature, there is still a lack of Brazilian studies on the subject. The aim of this study is to evaluate the maternal and perinatal outcomes of women with CKD who underwent prenatal care and delivery at a single Brazilian reference center for high-risk pregnancies, and further compare cases with preterm and term childbirth.

Methods

We performed a retrospective cohort study at the Women's Hospital of Universidade Estadual de Campinas, Brazil, a referral university hospital in southeast Brazil, accounting for a surrounding population of 3,100,000 inhabitants. This study was approved by the research ethics committee of the institution (CAAE report 15429419.5.0000.5404).

We included all pregnancies of women with a previous diagnosis of CKD who underwent prenatal follow-up at the specialized antenatal care (ANC) outpatient clinic and who

gave birth at the Women's Hospital between 2012 and 2020. All patients with high risk of preeclampsia were given prophylaxis with low dose aspirin and calcium supplementation, as recommended by institutional protocol. We collected data from the medical records on an electronic system by completing a data collection form specifically created for the study.

We evaluated variables related to CKD etiology, duration of kidney disease treatment, sociodemographic variables, lifestyle variables, other associated diseases, and obstetric history and perinatal outcomes. In the case of patients with more than one pregnancy during the study period, each index pregnancy was considered, that is, the unit of study was the pregnancy. The data obtained were entered into a database created for this study, in Excel format, which was reviewed to identify inconsistencies. The underlying causes of kidney disease were later grouped into 10 subgroups according to similar characteristics and frequency of diagnoses.

To describe the profile of the sample according to the variables under study, frequency tables of categorical variables were made with absolute (n) and percentage (%) frequency values, and descriptive statistics of numerical variables, with mean values and standard deviation. Subsequently, women who had a viable pregnancy (excluding abortions and fetal deaths) were divided into 2 groups according to the occurrence or not of prematurity (gestational age [GA] < 37 weeks). To compare the categorical variables between pregnancies that ended in preterm birth, the chi-squared test or Fisher exact test (for expected values lower than 5) were used.

The significance level adopted for the statistical tests was 5%. The software used was the SAS System for Windows version 9.2. (SAS Institute Inc, 2002–2008, Cary, NC, USA).[8–11]

All Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) requirements for an observational study were followed and verified in this article.

Results

A total of 84 pregnancies were included, in 67 women with CKD who underwent absolute neutrophil count (ANC) between 2012 and 2020. Of these, 6 pregnancies evolved with fetal deaths and 5 with abortion, totaling 11 gestational losses, which corresponds to 13.1% of this sample. A diamniotic dichorionic twin pregnancy occurred in a 32-year-old primigravid patient with a history of systemic lupus erythematosus (SLE), CKD on dialysis, kidney transplant in 2010 and viral infection with loss of the transplanted kidney. The patient progressed to preterm labor at 32 weeks and underwent a cesarean section; the newborns were born weighing 1,460 g and 1,197 g, with favorable neonatal outcomes. Considering the single pregnancies that progressed to childbirth ($n = 72$), the mean age of the pregnant women was 28.58 years (standard deviation [SD] = 6.34), with a mean time since diagnosis of CKD of 10.61 years (SD = 8.82). Most of the women were white, were in a stable relationship, + and had high school education; none of the participants reported using alcohol or illicit drugs. ►**Table 1** shows the sociodemographic data of the patients included in the study.

We grouped the main causes of CKD into 10 categories, presented from the most frequent to the least frequent: SLE ($n = 21$), glomerulopathy ($n = 12$), nephrotic syndrome ($n = 11$), transplant ($n = 10$), infection ($n = 8$), dialysis ($n = 3$), hypertension ($n = 3$), diabetes ($n = 2$), and other diseases with lower frequency that were included in the "others" group ($n = 2$: one patient with Wegener granulomatosis and the other with rheumatoid arthritis and nephrolithiasis). ►**Fig. 1** shows the cause of CKD of the patients included in the study.

Among the 72 pregnancies that resulted in live births, the mean gestational age at birth was 35 weeks and 3 days (SD = 7.21), with a mean birth weight of 2,443.7 g (SD = 722.48). The majority had a birth at term (52.78%) or late preterm (34.72%). Eight newborns were classified as small for gestational age (11.1%), and 5 of them were children

Table 1 Characteristics of women with chronic kidney disease and singleton pregnancy that progressed to childbirth

	N = 72	%
Age (years)		
< 20	3	4.17
20–29	35	48.61
30–39	31	43.05
≥ 40	3	4.17
Age (mean)		
28.58 years		
Marital status		
Single	26	36.11
Stable relationship	46	63.89
Occupation*		
Paid work	11	15.28
Unpaid work	28	38.89
Schooling**		
Elementary	13	13.06
High school	33	45.83
University	5	6.94
Skin color***		
White	46	63.89
Non-White	24	33.33
Smoking	2	4.17
Number of Pregnancies		
1	31	43.05
2	16	22.22
≥ 3	25	34.73
Previous miscarriage		
0	59	81.94
≥ 1	13	18.06

Frequency missing *33 **21 ***2.

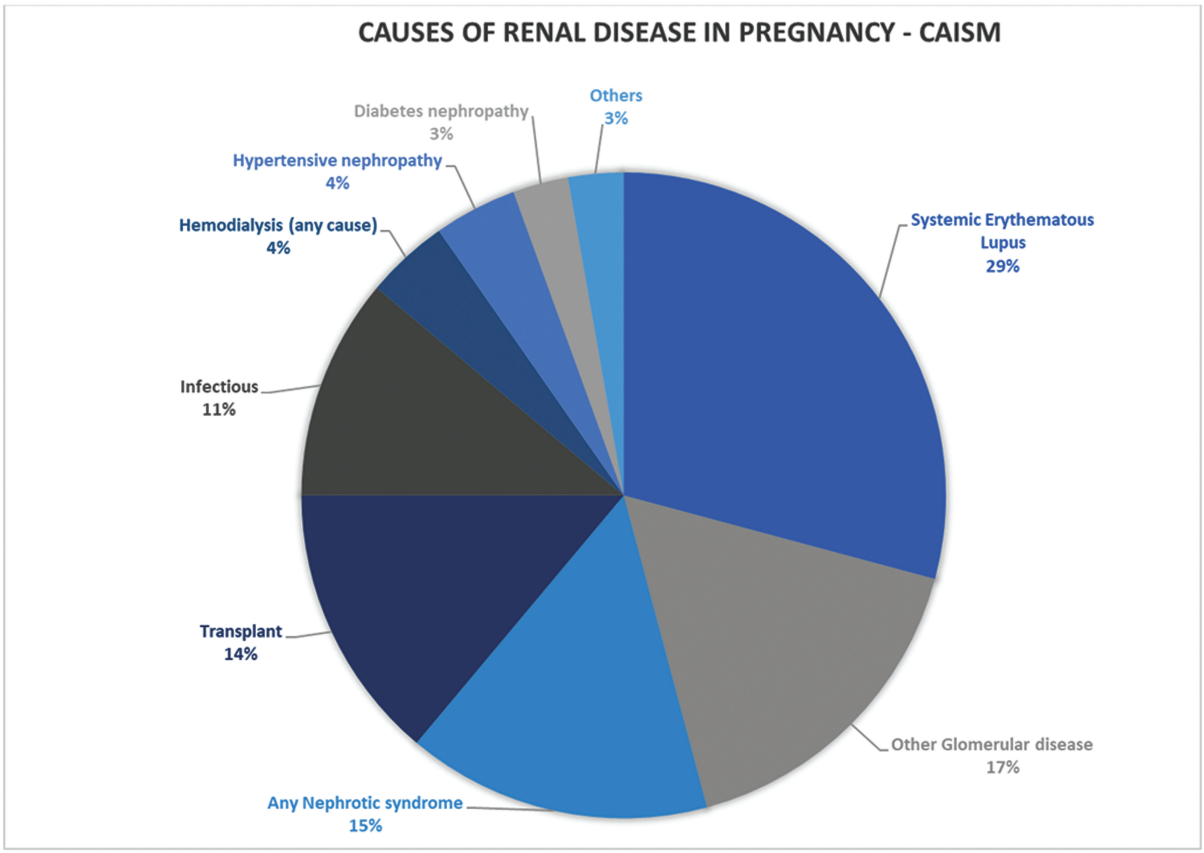

Fig. 1 Main causes of chronic kidney disease among pregnancies followed at high-risk antenatal care ($n = 84$).

of mothers with SLE (⅝ = 62.5%). Five children were classified as low birth weight newborns (0.69%). ►**Table 2** shows obstetric and neonatal data for patients with CKD included in the study. These women attended an average of 9.29 (SD = 3.88) prenatal consults. Approximately a quarter (20/72; 27.78%) of the study population developed preeclampsia during pregnancy.

Considering the high prevalence of preterm birth among the considered cases, and the burden of this condition for mothers and their children in the short and long term, we aimed to investigate conditions associated with this event. We compared the two groups according to the occurrence or not of preterm birth. There was a significant association between the occurrence of premature birth (gestational age < 37 weeks) and the need for a woman to be hospitalized in the ICU after childbirth, a higher occurrence of complications after childbirth, and a greater number of days of hospitalization (►**Table 3**). The majority cause of preterm birth among our population was preeclampsia (12/34 = 35.3%) and premature rupture of membranes (4/34 = 11.7%). This population had more prevalence of ICU admission and more days staying in the hospital.

Discussion

The present study reports increased adverse maternal and neonatal outcomes among cases of CKD followed at a referral maternity hospital. Overall, around 13.1% of pregnancies progressed to abortion or stillbirth, and, among the cases of livebirths, almost half were preterm deliveries, with around one quarter complicated by preeclampsia. The cases of preterm delivery were associated with increased adverse outcomes, with 6 neonatal deaths.

According to international epidemiological data, the average rate of preterm births in the general population is 7 to 12% of births and, of these, ~ 12% occur due to preeclampsia.[12] In our study, as expected, the incidence of premature births was much higher than in the general population (almost 50%), which is most likely due to CKD itself or secondary to the development of hypertensive syndromes and their consequences. The incidence of prematurity among pregnant women with CKD found in our study is similar to the data reported in the literature. A meta-analysis of 23 studies and 506,340 pregnant women concluded that CKD increased the risk of preeclampsia 10-fold, the risk of premature delivery and small-for-gestational-age newborns and led to a 3-fold increased risk of cesarean section.[6] Another study showed an association between CKD stage and its implications, with an increased incidence of prematurity as the CKD stage increased (CKD stage 1: 23.5% preterm; stage 2: 50.6%; stage 3: 78.4%; stage 4–5: 88.9%), using a serum creatinine threshold of 1.9 mg/dL, observed 93% newborn survival, 59% preterm birth, and fetal growth restriction of 37%.[13,14] In our study, we did not distinguish the CKD stage of the patients; however, our data are similar to the data from this study, since the incidence is within this

Table 2 Obstetric history, data on pregnancy, childbirth, and neonatal outcomes of women with chronic kidney disease

	N = 72	%
Hypertensive syndrome		
Chronic hypertension	17	23.61
Chronic hypertension with superimposed preeclampsia	12	16.67
Preeclampsia	8	11.11
Without hypertension	35	48.61
Mode of birth		
Vaginal	23	31.94
C-Section	49	68.06
Maternal morbidities after birth*		
Hemorrhage	6	8.33
Infection	4	5.56
Others****	6	8.33
None	53	76.61
Maternal ICU admission**		
Yes	9	12.50
No	62	86.11
Apgar score at the first minute		
< 7	14	19.44
≥ 7	57	79.17
Apgar score at the fifth minute**		
< 7	3	4.17
≥ 7	68	94.44
Gestational age at birth		
GA < 28	4	5.55
≥ 28 GA < 32	5	6.95
≥ 32 GA < 37	25	34.72
GA ≥ 37	38	52.78
Neonatal ICU admission**		
Yes	26	36.11
No	45	62.50
Neonatal death***		
Yes	6	8.83
No	62	86.11

Abbreviation: GA, gestational age; ICU, intensive care unit.
Missing *3 **1 ***4 (no information due to medical transfer of the newborn to another hospital) ****Others: one hypoglycemia, four with hypertensive spikes, one with hypervolemia and dialysis.

range. Other studies have already shown that there is an association between CKD and prematurity, and one showed a 1.23-fold increase in relative risk of preterm birth in patients with prepregnancy kidney dysfunction, compared with those with normal renal function.[2,7,13,15]

Our data show that prematurity was most likely associated with more severe cases, with a greater number of women hospitalized in adult ICUs among those who had premature births (around one-third of cases), while in patients with term birth, the number of ICU admissions was much lower (less than 10%). Maternal factors associated with CKD can increase the chance of patients being hospitalized in the ICU, due to the complexity of their cases, especially in those undergoing dialysis.

Epidemiologically, the most prevalent risk factors for CKD in the general population are arterial hypertension and diabetes mellitus; however, among pregnant women (mostly young women), other comorbidities are associated with the loss of renal function.[16] In our study, the mean age of the patients was 28.5 years, with multiple other causes for CKD. Additionally, the study hospital is the referral hospital for some diseases, including SLE.

It was also possible to verify that CKD was a risk factor for the development of hypertensive syndromes during pregnancy, more frequently observed in the group of patients whose outcome was preterm birth.

It is known that CKD is a factor for hypertensive syndromes, as observed in several studies. One study of 778 women with CKD reported that 25.3% presented chronic arterial hypertension, and the incidence of preeclampsia was 9.3%.[17] Another study reported an incidence of chronic arterial hypertension of 30.5% and of preeclampsia of 24.6%, with a higher rate of preeclampsia, explained in the study by almost a quarter of patients having CKD at more advanced stages (3–5).[18] In addition, meta-analyses and cohorts show that women with CKD are 10 times more likely to develop preeclampsia, and up to 40% of patients with preeclampsia have had CKD previously.[2,6,19–22]

Acetylsalicylic acid has been recommended as an effective intervention to reduce the incidence of preeclampsia, especially in women with known risk factors, including those with CKD, preferably introduced between 12 and 16 weeks.[19,23,24] A study showed that its use may reduce the chance of developing preeclampsia and intrauterine growth restriction[24], while another showed a reduction in the incidence of severe preeclampsia among patients with CKD stages 3 to 5, with no evidence in this study among patients with CKD stages 1 to 2.[18,24] However, another controlled trial showed a reduction in preterm preeclampsia in patients that used aspirin.[25] Our patients, guided by the institution protocol, used aspirin prophylaxis throughout the pregnancy, as well as calcium supplementation, as this is recommended in some groups of patients such as those with SLE.[26]

The overall incidence of preeclampsia in the general population is $\sim$ 4.6 to 8.1%, depending on the region.[5,19,27] In this study group, we saw a rate of 27.78%, high compared with the general population, but close to the values found in other studies that evaluated populations with CKD. We currently know that CKD, even in its early stages, is associated with the production of proinflammatory cytokines, which triggers endothelial inflammation and consequently increases the chance of developing hypertension. In a normal pregnancy, there is a balance between angiogenic factors (among them PlGF and VEGF) and anti-angiogenic factors (sFlt-1), favoring good placental implantation. However,

Table 3 Comparison of maternal characteristics and outcomes according to the occurrence of preterm birth ($n = 72$)

Variables	Preterm birth ($n = 34$)	Term birth ($n = 38$)	*p*-value
Maternal age (mean / SD)	29.03 (6.44)	28.18 (6.31)	0.560 *
Years since diagnosis (mean / SD)	10.00 (7.68)	11.13 (9.77)	0.894*
Maternal hospitalization in days (mean / SD)	4.85 (2.93)	3.13 (1.44)	0.001*
Group of kidney disease			0.143**
SLE	8 (23.5%)	13 (34.2%)	
Glomerular disease	4 (11.7%)	8 (21.1%)	
Nephrotic syndrome	5 (14.7%)	6 (15.8%)	
Transplant	4 (11.7%)	6 (15.8%)	
Infectious	7 (20.6%)	1 (2.6%)	
Hemodialysis	2 (5.9%)	1 (2.6%)	
Hypertensive nephropathy	2 (5.9%)	1 (2.6%)	
Diabetes nephropathy	2 (5.9%)	0	
Others	0	2 (5.3%)	
Skin color			0.892**
White	23 (67.3%)	23 (63.9%)	
Non-white	11(32.7%)	13 (36.1%)	
Hypertensive syndrome			0.009**
yes	23 (67.7%)	14 (36.8%)	
no	11 (32.3%)	24 (63.2%)	
Preeclampsia			0.178**
yes	12 (35.3%)	8 (21.0%)	
no	22 (64.7%)	30 (78.9%)	
Mode of birth			0.663**
vaginal	10 (29.4%)	13 (34.2%)	
cesarean	24 (70.6%)	25 (65.8%)	
Postpartum maternal ICU			0.006**
yes	11 (34.4%)	3 (11.9%)	
no	21 (65.6%)	35 (92.1%)	0.029**
Adverse maternal outcome #			
yes	11 (35.5%)	5 (13.2%)	
no	20 (64.5%)	33 (86.8%)	

Abbreviations: ICU, intensive care unit; SD, standard deviation; SLE.
* Kruskal-Wallis test, ** Qui-square test, *** Fisher test # adverse maternal outcome: bleeding, infection or other; #2 missing data.

when there is an imbalance between these factors, poor implantation of the placenta or worsening of placental perfusion can occur, leading to a reduction in factors such as PlGF and VEGF and an increase in sFlt-1, causing endothelial inflammation and increasing the chances of developing preeclampsia.[5] Biomarker assessment may be an interesting way to adequately distinguish preeclampsia from other complications that can present with worsening proteinuria and hypertension.[28]

In addition, there is evidence that these proinflammatory factors can cause glomerular damage, leading to proteinuria, which can worsen renal function or favor the development of preeclampsia.[15,29] Some of these studies report that the decline in kidney function is even worse among patients with CKD stages 3 to 5, while other studies did not see any worsening of renal function in stages 1 to 3.[15,18] These data in the literature still lacks consensus and require further investigation.

Our study presented some limitations. Given that our data was from a single center, it was not possible to further investigate the association between the reported adverse outcomes and the diverse CKD reported. In addition, pregnant women were referred to our service after the diagnosis of kidney disease, implying that we had no data related to the kidney biopsy, details about the infections that caused kidney failure or previous treatments. Our patients had a very heterogeneous treatment during pregnancy based on the causes and evaluation of their kidney disease. It was possible only to the group of women who underwent dialysis. The others received basic care to treat the underlying

disease, such as hypertension, lupus, and diabetes. However, our sample is relevant to referral centers in a middle-income setting.

In our study, 68.06% of the patients underwent cesarean section, a number higher than that recommended by the World Health Organization (WHO) and higher than the Brazilian average.[30,31] However, in this case, these are patients with a greater possibility of complications, or acute or chronic fetal distress, which may be factors that increase the chances of opting for cesarean delivery. Even so, it is a high rate of cesarean sections, similar to that seen in other studies, which found cesarean section rates of 37 to 59%.[13,14] This corroborates the results of the study by Zhang et al., which showed a 3-fold increase in the number of cesarean sections in patients with CKD.[6]

Conclusion

These data reinforce that pregnancy complicated by CKD can present increased adverse maternal and perinatal outcomes, in addition to worsening the underlying disease or renal function. It is necessary to counsel these women on adequate family planning, to help plan their pregnancies when their kidney disease is stable and controlled. These are patients who require multiprofessional evaluation at a referral center, with special attention and care during high-risk prenatal care. With a planned pregnancy, it is possible to better evaluate risk factors and prognosis, and evaluate the indication of prophylaxis for preeclampsia, in addition to undertaking maternal-fetal surveillance and monitoring.

Contributors

Marcus Vinicius Pinheiro Zilli: investigation, data curation and writing - original draft. Anderson Borovac-Pinheiro: methodology, data curation and writing - original draft. Maria Laura Costa: investigation, review & editing. Fernanda Garanhani Surita: conceptualization, methodology, data curation, supervision, review & editing. All authors approved the final version to be published.

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgments

The authors would like to thank Helymar Costa Machado, a statistician who made it possible to analyze the data of the study.

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Misoprostol Administration Before Hysteroscopy Procedures – A Retrospective Analysis

O uso do misoprostol prévio aos procedimentos histeroscópicos – Um estudo retrospectivo

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Rev Bras Ginecol Obstet 2022;44(12):1102–1109.

Abstract

Objective To evaluate the use of misoprostol prior to hysteroscopy procedures regarding technical ease, the presence of side effects, and the occurrence of complications.

Methods This is a retrospective, observational, analytical, case-control study, with the review of medical records of 266 patients followed-up at the Gynecological Videoendoscopy Sector of the Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto of the Universidade de São Paulo (HCFMRP – USP, in the Portuguese acronym) from 2014 to 2019, comparing 133 patients who used the drug before the procedure with 133 patients who did not.

Results The occurrence of postmenopausal uterine bleeding was the main indication for hysteroscopy and revealed a statistical difference between groups ($p < 0.001$), being present in 93.23% of the patients in the study group and in 69.7% of the patients in the control group. Only 2 patients (1.5%) in the study group reported adverse effects. Although no statistical differences were observed regarding the occurrence of complications during the procedure ($p = 0.0662$), a higher total number of complications was noted in the group that used misoprostol ($n = 7$; 5.26%) compared with the group that did not use the drug ($n = 1$; 0.75%), a fact that is clinically relevant. When evaluating the ease of the technique (measured by the complete performance of all steps of the hysteroscopy procedure), it was verified that although there was no difference between groups ($p = 0.0586$), the control group had more than twice as many incompletely performed procedures ($n = 17$) when compared with the group that used misoprostol previously ($n = 8$), which is also clinically relevant.

Conclusion The use of misoprostol prior to hysteroscopy in our service indicated that the drug can facilitate the performance of the procedure, but not without side effects and presenting higher complication rates.

Keywords
- hysteroscopy
- misoprostol
- complications
- side effects

received
March 19, 2022
accepted after revision
March 26, 2022

DOI https://doi.org/10.1055/s-0042-1755462.
ISSN 0100-7203.

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

Resumo

Objetivo Avaliação do misoprostol prévio à histeroscopia quanto à facilidade técnica, efeitos colaterais e a ocorrência de complicações durante o procedimento.

Métodos Estudo analítico observacional retrospectivo tipo caso controle com revisão de prontuários de 266 pacientes do Setor de Videoendoscopia Ginecológica do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto - Universidade de São Paulo (HCFMRP – USP), de 2014 a 2019, sendo comparadas 133 pacientes que utilizaram o medicamento prévio ao procedimento com 133 pacientes que não o utilizaram.

Resultados Sangramento uterino após a menopausa foi a principal indicação de histeroscopia, apresentando diferença estatística ($p < 0{,}001$), estando presente em 93,23% das pacientes do grupo de estudo e em 69,17% das pacientes do grupo controle. Apenas 2 pacientes (1,5%) do grupo de estudo relataram efeitos adversos. Não foram observadas diferenças quanto à presença de complicações durante o procedimento ($p = 0{,}0662$), mas observamos um número total de complicações maior no grupo de estudo ($n = 7$; 5,26%) do que no grupo controle ($n = 1$; 0,75%), o que é clinicamente relevante. Não houve diferença entre os grupos quanto à facilidade técnica ($p = 0{,}0586$), mas o grupo controle apresentou mais do que o dobro de procedimentos não completamente realizados ($n = 17$) quando comparado com o grupo de estudo ($n = 8$), o que é clinicamente relevante.

Conclusão O uso de misoprostol prévio à histeroscopia no nosso serviço demonstrou que ele pode facilitar a realização do procedimento, mas não é isento de efeitos colaterais e apresenta maiores taxas de complicações.

Palavras-chave

- histeroscopia
- misoprostol
- complicações
- efeitos colaterais

Introduction

The hysteroscopic procedure emerged ~ 200 years ago, providing the direct visualization of diffuse or focal uterine abnormalities, the anatomical configuration of the cervical canal and the uterine cavity, path permeability, access for biopsies, and direct removal of lesions.[1–3] It is considered a minimally invasive procedure, and its use is quite common both in the diagnosis and in the treatment of several conditions, such as abnormal uterine bleeding, the evaluation of infertile patients, surgeries including myomectomy and polypectomy, the diagnosis of endometrial and endocervix hyperplasia and carcinoma, among others, often being performed in clinics or as outpatient follow-up procedures.[1–5] This method has an important advantage over other diagnostic techniques: the anatomopathological confirmation of lesions visually identified through guided biopsy.[4]

In order to carry out the procedure, it is often necessary to dilate the cervix, especially in surgical hysteroscopies in which the equipment for performing the procedure is larger than the endocervical canal.[6] The most frequent causes of unsatisfactory exams are cervical stenosis, pain or patient intolerance, bleeding that hinders hysteroscopic view, and technical difficulties.[7] In an attempt to reduce these technical problems and the number of unsatisfactory exams, several methods of cervical dilation have been developed over the years, such as the use of hydrophilic laminators, bladder catheter balloons, and Hegar dilators. These techniques, however, cause great discomfort to patients and increase the risk of complications during the dilation process.[3–5,8] The complication rate varies between 0.3 and 5% according to the definition used, the most common being pain, vagal reaction, uterine perforation, false passage formation, and cervical lacerations. Serious complications, such as organ perforation and pelvic infection, are seldom reported.[7,9]

Therefore, there was a need to develop new methods of cervical dilation, which should include cervix preparation for a limited time, acceptable for the patient, with ease of administration, quick action, and providing adequate cervical ripening to facilitate the procedure. Misoprostol is one of the most studied agents in this context.[10] It is a synthetic analog of prostaglandin E1 that has been used for cervical preparation prior to performing hysteroscopy because it promotes effective cervical ripening, as well as being an inexpensive, easy to store and administer, and widely available method.[4,5] The most common adverse effects of misoprostol occur mainly before the procedure and include cramping, abdominal and/or pelvic pain, nausea, changes in intestinal transit, vaginal bleeding of varying intensity, and fever and/or chills. However, these effects are generally described as tolerable and rarely motivate the cancellation or alteration of the procedure.[11,12]

According to the scientific literature, misoprostol is effective in cervical ripening in the preoperative period of hysteroscopy, reducing the time needed for cervical dilation and increasing the mean cervical diameter. Nevertheless, the optimal dose, the route of administration, and the ideal time of administration prior to hysteroscopy, in addition to whether

the drug reduces the rates of pre- and postmenopausal complications, remain unclear, a fact that justifies the importance of carrying out the present study in daily gynecological practice, whose objectives were to assess the ease of the operative hysteroscopic technique with the use of misoprostol, evaluated by the complete performance of the steps of the procedure, to assess the presence of side effects with the use of the drug, and to analyze the occurrence of hysteroscopic complications with its use.[5,8]

Methods

The present analytical, observational, case-control study was conducted by reviewing the medical records of patients followed up at the Gynecological Videoendoscopy Sector of the HCFMRP – USP in the period from 2014 to 2019. Using a list provided by the Medical Support Service (SAME, in the Portuguese acronym), a total of 508 patients with prescriptions for the drug misoprostol for intrahospital use at the HCFMRP– USP were identified in the analyzed period. By cross-referencing the data of patients followed-up at the Gynecological Videoendoscopy Sector of the same hospital and who had used misoprostol prior to hysteroscopy, 207 patients were identified. The medical records of these 207 patients were reviewed, evaluating: age, parity, type of delivery, time since menopause, associated diseases (systemic arterial hypertension [SAH], type 2 diabetes mellitus [DM2], obesity, and other comorbidities), use of continuous medication, symptoms, postmenopausal bleeding, presence of endometrial thickening, side effects of the drug, procedure complications, and complete performance of the procedure. Among the total patients, 74 lacked data in their medical records or had their hysteroscopy procedures suspended for various reasons unrelated to the use of misoprostol or to the procedure itself and were therefore excluded. The 133 patients included in the study were compared with another 133 age-matched patients also followed-up at the Gynecological Videoendoscopy Section of the HCFMRP – USP who underwent hysteroscopy procedures but who did not use misoprostol previously (control group), regarding the ease of the technique, considered easy when all steps of the hysteroscopy procedure were carried out completely, the presence of side effects, and the occurrence of complications. Patients who used misoprostol before the hysteroscopy did so by vaginally introducing 2 tablets of 200 micrograms (µg) each the night before the procedure, totaling a single dose of 400 µg.

After filling out the study database, which evaluated age, parity, type of delivery, time since menopause, associated diseases (SAH, DM2, obesity, and other comorbidities), the use of continuous medication, symptoms, postmenopausal bleeding, presence of endometrial thickening, drug side effects, procedure complications, and its complete performance, a statistical analysis was carried out using SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA). The distribution of the variables was assessed using the Kolmogorov-Smirnov test. Normally-distributed data were analyzed with the *t*-test, while abnormally distributed data were evaluated using the Kruskal-Wallis test. Mean values were presented with statistical significance (SS), which was accepted for $p < 0.05$. Numerical data were presented as mean ± standard deviation (SD) or median and range, depending on their distribution. The chi-squared test was used for variables expressed as percentages, considering a significance level of $p < 0.05$.

Since this was a retrospective study involving medical record analysis, the Research Ethics Committee of the HCRP – USP was asked to waive the application of informed consent through a Letter of Exemption from the collection of the consent form, given most of the patients were no longer being followed-up at the hospital. The present study, as well as the waiver of written informed consent, were approved by the Research Ethics Committee (REC) of the HCRP – USP on February 17, 2020, under CAAE Protocol No. 28983920.0.0000.5440. All ethical precepts were followed as recommended by the Helsinki Convention.

Results

Regarding the clinical characteristics of the studied patients, no significant difference was observed between those who used misoprostol or not prior to the hysteroscopy procedure in relation to age ($p = 0.9005$), the number of pregnancies ($p = 0.4586$), the number of vaginal deliveries ($p = 0.5531$), the time since menopause ($p = 0.9193$), history of previous cesarean delivery ($p = 0.8723$), or regarding the number of prior abortions ($p = 0.8528$) (►**Tables 1** and **2**). When analyzing the comorbidities presented by the patients at the time of hysteroscopy, we observed a significant difference in relation to SAH ($p = 0.0041$), but not regarding DM2 ($p = 0.0622$), obesity ($p = 0.5082$), or other comorbidities ($p = 0.3510$). The fact that the patients used continuous medications for these comorbidities also did not differ significantly between the 2 groups ($p = 0.3023$) (►**Table 2**).

Both groups had the same number of patients before and after menopause, with no difference in hormonal status in relation to the use of misoprostol ($p = 1.000$). The presence of symptoms reported by the patients for the indication of the hysteroscopic procedure showed a difference between the 2 groups ($p < 0.001$); 93.23% of the patients in the group that used misoprostol had at least 1 symptom versus 72.18% of

Table 1 Clinical characteristics of the studied population

	With misoprostol	Without misoprostol	*p*-value
	Mean ± SD	Mean ± SD	
Age (years old)	60.08 ± 8.5	59.95 ± 8.15	0.9005
Pregnancy	3.44 ± 1.96	3.24 ± 2.47	0.4586
Vaginal delivery	2.13 ± 2.17	1.96 ± 2.37	0.5531
Time since menopause	10.98 ± 7.48	11.08 ± 8.22	0.9193

Abbreviation: SD, standard deviation.

Table 2 Clinical characteristics of the studied population

	With misoprostol		Without misoprostol		*p*-value
	n (133)	%	*n* (133)	%	
Cesarean delivery					0.8723
0	61	45.86	69	51.88	
1	33	24.81	27	20.30	
2	23	17.29	23	17.29	
3	15	11.28	13	9.77	
4	1	0.75	1	0.75	
Miscarriage					0.8528
0	99	74.44	99	74.44	
1	24	18.05	23	17.29	
2	8	6.02	6	4.51	
3	1	0.75	2	1.50	
4	1	0.75	2	1.50	
5	0	0.00	1	0.75	
SAH					0.0041
Yes	111	83.46	91	68.42	
No	22	16.54	42	31.58	
DM2					0.0622
Yes	63	47.37	48	36.09	
No	70	52.63	85	63.91	
Obesity					0.5082
Yes	44	33.08	39	29.32	
No	89	66.92	94	70.68	
Other comorbidities					0.3510
Yes	89	66.92	96	72.18	
No	44	33.08	37	27.82	
Continuous use of medications					0.3023
Yes	127	95.49	123	92.48	
No	6	4.51	10	7.52	
Menopause					1.0000
Yes	123	92.48	123	92.48	
No	10	7.52	10	7.52	
Symptoms					<0.001
Yes	124	93.23	96	72.18	
No	9	6.77	37	27.82	
Postmenopausal bleeding					<0.001
Yes	124	93.23	92	69.17	
No	9	6.77	41	30.83	
Endometrial thickening					0.6419
Yes	124	93.23	122	91.73	
No	9	6.77	11	8.27	

Abbreviations: DM2, diabetes mellitus type 2; *n*, number of samples; SAH, systemic arterial hypertension.

the patients in the control group. Among the most reported symptoms was postmenopausal uterine bleeding, which also showed a significant difference between the 2 groups ($p < 0.001$); 93.23% of the patients in the group that used misoprostol had this symptom versus 69.17% of the patients in the control group. Meanwhile, asymptomatic endometrial thickening showed no statistically significant difference between the 2 groups ($p = 0.6419$). Regarding the adverse

Table 3 Complications reported after the hysteroscopy procedure

	With misoprostol		Without misoprostol		*p*-value
	n (133)	%	*n* (133)	%	
Complications					0.0662
Yes	7	5.26	1	0.75	
No	126	94.74	132	99.25	
Uterine Cervical Laceration					0.9999
Yes	1	0.75	0	0	
No	132	99.25	133	100	
Absence of uterine cavity distension					0.2619
Yes	3	2.26	0	0	
No	130	97.74	133	100	
Uterine perforation					0.5079
Yes	2	1.50	0	0	
No	131	98.50	133	100	
Increased fluid absorption					0.9999
Yes	1	0.75	0	0	
No	132	99.25	133	100	
False passage					0.9999
Yes	0	0	1	0.75	
No	133	100	132	99.25	

Abbreviation: *n*, number of samples.

effects observed in the patients who used the drug prior to hysteroscopy, only 2 patients (1.5%) reported symptoms: both presented tremors, and 1 presented with symptoms of anxiety. Although no significant difference was observed in relation to the occurrence of complications during the procedure ($p = 0.0662$), a higher total number of complications was observed in the group that used misoprostol ($n = 7$; 5.26%) compared with the group that did not ($n = 1$; 0.75%), which is clinically relevant. In the control group, the only reported complication was false passage formation. Meanwhile, in the group that used misoprostol, the most frequent complication was the absence of uterine cavity distension, which was observed in three of the patients. The other observed complications included cervical laceration ($n = 1$), uterine perforation ($n = 2$), and increased fluid absorption ($n = 1$), the latter 2 of which compelled the termination of the procedure. In the group of patients who used misoprostol, false passage formation was not reported (►**Table 3**).

Finally, upon evaluating the technical ease (performing all steps of the procedure), we noted that although there was no difference between groups ($p = 0.0586$), the control group had more than twice as many incompletely performed procedures ($n = 17$) when compared with the group that used misoprostol previously ($n = 8$), which is clinically relevant.

Discussion

The present study compared 133 women who used misoprostol prior to hysteroscopy with 133 who did not use the medication. This drug is a prostaglandin E1 analog oxytocin that causes changes in the physicochemical structure of cervical collagen. After its administration, misoprostol undergoes de-esterification in the liver into misoprostolic acid. This active metabolite exerts direct action on prostaglandin receptors, leading to the softening and ripening of the cervix, favoring its dilation, in addition to promoting an increase in intracellular calcium, which is responsible for the contraction of uterine muscles.[13] All of these mechanisms enable progressive cervical effacement and dilation.[4,5]

The systematic review of misoprostol suggests variations in the plasma concentration of this drug depending on the route of administration. Orally, the drug is rapidly and completely absorbed in the gastrointestinal tract; however, it is also quickly and extensively metabolized into its acidic form in the first hepatic pass (de-esterification). A single 400-µg dose of oral misoprostol reaches its peak concentration in 30 minutes and declines in ~ 120 minutes, remaining at a low level. After vaginal administration, on the other hand, there is a gradual increase in the plasma concentration of misoprostol, reaching a maximum level after 70 to 80 minutes, followed by a slow decline, with the drug level still detectable after 6 hours. It has also been reported that the mean concentration peak via the sublingual route is higher than that achieved via the oral and vaginal routes, which is due to the rapid absorption by the sublingual mucosa, avoiding first-pass metabolism in the liver. When administered rectally, the absorption curve of the drug is similar to that seen when using the vaginal route.[14]

Corroborating another study carried out with 77 women between January 2005 and March 2006, we did not observe a significant difference in age and the number or type of previous births between the study group and the control group.[15] Although no significant difference was found in the present study regarding pre- and postmenopausal patients, some studies suggest that the use of misoprostol is more effective in dilating the cervix of premenopausal patients, mainly due to the hormonal difference between these women.[4] Regarding the comorbidities presented by the patients at the time of the procedure, only SAH showed significance.

In our study, postmenopausal uterine bleeding was the most prevalent symptom, observed in 93.23% of the patients in the study group and in 69.17% of those in the control group. A case review coordinated by Gimpelson et al.[16] revealed a high incidence of abnormal bleeding, which was observed in 76% of the cases as the chief complaint of patients to undergo hysteroscopy. In addition, a descriptive, cross-sectional study with 26 women showed that the primary complaint of 65.3% of the patients was uterine bleeding.[17]

The occurrence of adverse effects to the use of misoprostol was reported by only 2 patients (1.5%), who presented tremors and anxiety. A meta-analysis evaluating 14 studies showed that significantly more adverse effects were reported when misoprostol was administered compared with procedures without previous use of the drug (odds ratio [OR] = 3.56; 95% confidence interval [CI]: 1.60–7.93).[18] Two other studies described the incidence of adverse effects among women randomized to 200 or 400 µg of misoprostol, but their data were conflicting: the first did not demonstrate a dose-related increase in adverse effects (nausea and abdominal pain) in women randomized to 200 or 400 µg ($p = 1.0$ and $p = 0.055$, respectively); however, the second study showed a significant increase in the number of adverse events related only to 400 µg ($p = 0.015$), such as fever, abdominal pain, diarrhea, nausea, vomiting, and vaginal bleeding.[18] Regarding the administration time, these studies showed that there was no significant difference in the incidence of abdominal cramps ($p = 0.64$), nausea ($p = 0.79$), diarrhea ($p > 0.99$), genital tract bleeding ($p = 0.62$), and fever ($p > 0.99$) among women who received misoprostol 12 hours or 3 hours before hysteroscopy.[18] One study with 160 women comparing oral, sublingual, and vaginal administration of the drug concluded that the 3 groups were comparable, and all the adverse effects were similar in all groups and were tolerable. This result is in line with a recent meta-analysis that analyzed 7 randomized, controlled studies involving 568 individuals, evaluating the use of misoprostol in surgical hysteroscopy. Compared with the placebo group, there was an increase in side effects (cramps, vaginal bleeding, nausea, and diarrhea) in the misoprostol group (relative risk [95%CI]: 4.28 [1.43Â–12.85]).[19,20]

The incidence of complications in our study was low compared with the mean described in the literature.[9] A total of 7 complications occurred in patients who had previously used misoprostol (5.26%) and in 1 patient who did not use the medication (0.75%). The primary complication reported among patients who used misoprostol was the absence of uterine cavity distension, which occurred in 3 patients. This was also found by Batukan et al.[15] in a randomized, double-blind, placebo-controlled study carried out with the objective of evaluating the efficacy of 400 µg of misoprostol 10 to 12 hours before surgical hysteroscopy in premenopausal women, via the vaginal route. One of the reported disadvantages of vaginal administration was excessive cervical dilation, resulting in difficulty distending the uterine cavity due to fluid leakage through the cervical canal.[8] Another study, prospectively conducted between January 2005 and March 2006 at the Department of Obstetrics and Gynecology of the Faculty of Medicine of Erciyes University, with 77 women, showed that vaginal administration of misoprostol (400 µg) prior to operative hysteroscopy in premenopausal women was superior to the same dose of orally administered misoprostol. The complication rates during cervical dilation, as well as drug side effects, were comparable between the two regimens. Fluid leakage caused by excessive cervical dilation and effacement appeared to be the most important potential disadvantage of vaginal misoprostol. Since the intrauterine pressure did not reach the ideal desired level in these cases, the uterine distension was suboptimal and, therefore, the procedure was more difficult.[15]

In the present study, the other complications observed in patients who used misoprostol were cervical laceration ($n = 1$; 0.75%), uterine perforation ($n = 2$; 1.5%), and increased absorption of distension media ($n = 1$; 0.75%). The patient who did not use misoprostol presented false passage formation as a complication. In a study carried out at Bringham and Women's Hospital, located in Boston, MA, USA, Propst et al.[21] verified a total number of 925 surgical hysteroscopies between 1995 and 1996, with the occurrence of complications in 2.7% of the patients. Among these complications was cervical laceration, which was present in all cases. In another study carried out by Jansen et al.,[22] in which 13,600 hysteroscopies in 82 hospitals in the United States were evaluated in 1997, as well as in the study by Agostini et al.,[23] performed in Marseille, France, in which 2,116 surgical hysteroscopies between 1990 and 1999 were analyzed, the most frequent complication among the surgical procedures was uterine perforation, with 0.76% and 1.61% of cases, respectively.[22,23] The study by Propst et al.[21] also reported complications related to uterine distension media in 1.4% of the surgical hysteroscopy cases. In a randomized, controlled, double-blind study conducted by Oppengard et al.,[24] in which each participant received 1,000 µg of misoprostol or placebo, which was self-inserted vaginally at least 12 hours before operative hysteroscopy, there were a total of 9 (11%) complications reported.

Regarding technical ease, which was evaluated by the complete performance of all steps of the procedure, we observed that although there was no statistically significant difference, the number of patients who did not use misoprostol and did not undergo the complete procedure was more than double in relation to the patients who used the medication (8 patients who used the drug versus 17 patients who did not), which is of substantial clinical relevance. Fernandez et al.[25] reported in a larger series that the administration of 400 µg of oral misoprostol 12 or 24 hours before

surgery or 200 µg of vaginal misoprostol 9 to 10 hours before surgery, respectively, demonstrated greater ease of cervical dilation. However, to date, no placebo-controlled trials have shown a significant decrease in the rate of serious complications such as cervical laceration or perforation.[25]

The prospective study conducted between January 2005 and March 2006 at the Department of Obstetrics and Gynecology of the Faculty of Medicine of Erciyes University showed that vaginally administered misoprostol (400 µg) prior to operative hysteroscopy in premenopausal women was superior to the same dose of orally administered misoprostol in terms of shorter cervical dilation and surgery duration, as well as the need for cervical dilation for No. 9 Hegar.[15] Other previous studies comparing patients who used misoprostol or placebo previously to prepare the cervix, as evidenced by Uckuyu et al.[26] in Ankara, Turkey, also show a relevant rate of failure in dilation with Hegar dilators, especially in patients who had had previous cesarean sections. In the aforementioned study, the reported failure rate of cervical dilation using Hegar dilators was 25%.[26]

Our study had some limitations, such as the absence of a patient-reported pain assessment, given most of the analyzed patients underwent the procedure in the operating room under anesthesia; lack of evaluation of different doses and routes of administration of misoprostol, since all of the patients used the drug at a dose of 400 µg via the vaginal route; the absence of evaluation of the time of misoprostol administration, seeing that, in all patients, the drug was introduced the night before the procedure. Costa et al.[27] conducted a randomized study with 120 postmenopausal women who received 200 µg of vaginal misoprostol or placebo 8 hours before outpatient hysteroscopy. There was a significant reduction in the pain scale during the procedure, a fact that would facilitate the performance of outpatient surgical procedures. In 2018, Fouda et al.[28] evaluated the effect of timing of vaginal misoprostol administration (3 hours versus 12 hours) before diagnostic hysteroscopy in nulliparous women, who are at increased risk for cervical canal stenosis. The group of women given the drug just 3 hours before hysteroscopy reported more pain during the procedure than those given the medication 12 hours earlier. However, the pain intensity 30 minutes after the procedure, its mean duration, and the occurrence of side effects to misoprostol were similar between the 2 groups. The passing of the hysteroscope through the cervical canal was also assessed by the examiners and was found to be easier in the 12-hour group.

Conclusion

The use of misoprostol prior to hysteroscopy in our service showed that the drug can facilitate the performance of the procedure; however, this drug is not free from side-effects and higher complication rates. Also, misoprostol is a well-tolerated drug. We agree with most authors that there is a need for further studies to better identify the ideal dose, route of administration, and time to indicate misoprostol before the procedure.

Contributions

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

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgments

The present study was carried out with the support of de Coordination for the Improvement of Higher Education Personnel - Brazil (CAPES, in the Portuguese acronym).

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Three-dimensional Printer Molds for Vaginal Agenesis: An Individualized Approach as Conservative Treatment

Moldes de impressão tridimensionais para agenesia vaginal: Uma abordagem individualizada como tratamento conservador

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Rev Bras Ginecol Obstet 2022;44(12):1110–1116.

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Abstract

Objective The aim of this study was to evaluate the use of vaginal molds, made with three-dimensional (3D) printing, for conservative treatment through vaginal dilation in patients with vaginal agenesis (VA).

Methods A total of 16 patients with a diagnosis of VA (Mayer-Rokitansky-Küster-Hauser syndrome, total androgen insensitivity syndrome, and cervicovaginal agenesis) from the Federal University of São Paulo were selected. Device production was performed in a 3D printer, and the polymeric filament of the lactic polyacid (PLA) was used as raw material. A personalized treatment was proposed and developed for each patient.

Results There were 14 patients who reached a final vaginal length of 6 cm or more. The initial total vaginal length (TVL) mean (SD) was 1.81(1.05) and the final TVL mean (SD) was 6.37 (0.94); the difference, analyzed as 95% confidence interval (95% CI) was 4.56 (5.27–3.84) and the effect size (95% CI) was 4.58 (2.88–6.28).

Conclusion The 3D printing molds for vaginal dilation were successful in 87.5% of the patients. They did not present any major adverse effects and offered an economical, accessible, and reproducible strategy for the treatment of VA.

Keywords
- 3D printing
- Mayer-Rokitansky-Küster-Hauser syndrome
- vaginal agenesis
- vaginal dilation

Resumo

Objetivo O objetivo deste estudo foi avaliar o uso de moldes dilatadores vaginais, confeccionados com impressão tridimensional (3D), para tratamento conservador através da dilatação vaginal em pacientes com agenesia vaginal (AV).

Métodos Foram selecionadas 16 pacientes com diagnóstico de AV (síndrome de Mayer-Rokitansky-Küster-Hauser, síndrome de insensibilidade androgênica total e agenesia cervicovaginal), da Universidade Federal de São Paulo. A produção dos dispositivos foi realizada em uma impressora 3D e, como matéria-prima, foi utilizado o filamento polimérico do poliácido lático (PLA). Um tratamento personalizado foi proposto e desenvolvido para cada paciente.

Palavras-chave
- impressão 3D
- síndrome de Mayer-Rokitansky-Küster-Hauser
- agenesia vaginal
- dilatação vaginal

received
April 22, 2022
accepted
June 14, 2022

DOI https://doi.org/10.1055/s-0042-1756214.
ISSN 0100-7203.

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

Resultados Quatorze pacientes atingiram um comprimento vaginal final (CVF) de 6 cm ou mais. A média inicial do CVF (DP) foi de 1,81 (1,05) e a média final do CVF (DP) 6,37 (0,94); a diferença (IC 95%) foi de 4,56 (5,27–3,84) e o tamanho do efeito (IC 95%) foi de 4,58 (2,88–6,28).

Conclusão Os moldes de impressão 3D para dilatação vaginal obtiveram sucesso em 87,5% das pacientes. Como impacto secundário, não apresentaram efeitos adversos importantes e ofereceram uma estratégia econômica, acessível e reprodutível para o tratamento da AV.

Introduction

Vaginal agenesis (VA) is a congenital malformation and 90% of cases are associated with Mayer-Rokitansky-Küster-Hauser syndrome (MRKHS). The MRKHS has an incidence ranging from one case for every 4,000 to 5,000 female births, and is characterized by the congenital absence of the uterus and the upper ⅔ of the vagina.[1] Such patients have a female karyotype (46XX), function ovarian and normal sexual characters. Differential diagnosis should be made for patients with a transverse vaginal septum and an imperforate hymen.[1,2]

According to the American College of Obstetricians and Gynecologists (ACOG), the treatment for VA can be conservative or surgical, and has the objective of restoring the vagina's anatomy and function. Vaginal dilation is the method used in the conservative treatment of VA.[3–5] This method was developed by Frank in 1938 and modified by Ingram in 1981, reaching an effectiveness of approximately 90%.[3–5] It is performed using progressively larger sized rigid vaginal molds until the proper vaginal length is achieved.

While there is no consensus on the best therapeutic strategy, the ACOG and most of the scientific community recommend that the least invasive and effective treatment should be adopted, with vaginal dilation being the first line of treatment for VA.[3–5] Additionally, conservative treatment through vaginal dilation is the first choice due to the good results and low rate of complications.[5]

Three-dimensional (3D) printing is gaining wide use in the health care field. Especially in gynecology, it is possible to manufacture various devices, such as pessaries and vaginal molds, using a wide variety of materials.[6] Using this technology, devices that are fit for purpose and cost-effective are created. The objective of this study was to evaluate the use of personalized vaginal molds made with 3D printing for conservative treatment through vaginal dilation in patients with VA.[1]

Methods

The study was performed at the Federal University of São Paulo (UNIFESP), between June 2017 and October 2019, after approval by the Human Research Ethics Committee of the same institution, under the Certificate of Presentation of Ethical Appreciation number (CAAE): 91233917–9 and opinion number 2970405. The interventions were only made after approval, with the aim of offering an individualized and conservative treatment for each patient who voluntarily proposed to participate in the study. The patients who were willing to participate in the study signed an informed consent form.

The present study protocol was purely observational, which obviated the need for registration on clinical trial platforms. Additionally, it was not a randomized study or clinical trial, due to the rarity of the pathology, requiring patients to make a clear choice for conservative treatment before the beginning of the study.

The patients were selected from the Female Genital Malformations Sector at UNIFESP according to the following inclusion criteria: confirmed diagnosis of VA due to SMRKH, androgen insensitivity syndrome (AIS), or cervicovaginal agenesis, and desire to undergo conservative treatment.

The exclusion criterion was not wanting conservative treatment or not having free will or availability to participate in the research. All patients underwent evaluation by a multidisciplinary team: physician, physiotherapist, and psychologist. All patients were properly advised about the anatomy of the external genitalia before treatment.

The study's protocol had three phases: prototype development, patient selection, and mold application. Characteristics, dimensions, and initial parameters were defined through research of devices already available on the market and adjusted for each patient.

The initial geometric parameters were defined (cylindrical mold with the tip tapering progressively). For modeling the prototypes, the AutoCAD (Autodesk Inc., Mill Valley, California, USA) and FreeCAD 3D parametric modeling software were used based on the requirements defined above; computer aided design (CAD) system is the generic name for software used by engineering, geology, geography, health systems, and architecture and design to facilitate technical design and drawing.[6]

The production of the devices was performed using the 3D cube printer, developed by the company 3D Systems (Rock Hill, SC, USA), using the polymeric filament of lactic polyacid (PLA) as raw material. The devices were evaluated by the medical staff for adjustments before application in the study. Three standard molds were created (►**Fig. 1**) with the following sizes (from right to left): Dilator A (1.5×8 cm); Dilator B (2×9 cm); and Dilator C (2.5×12 cm).[6]

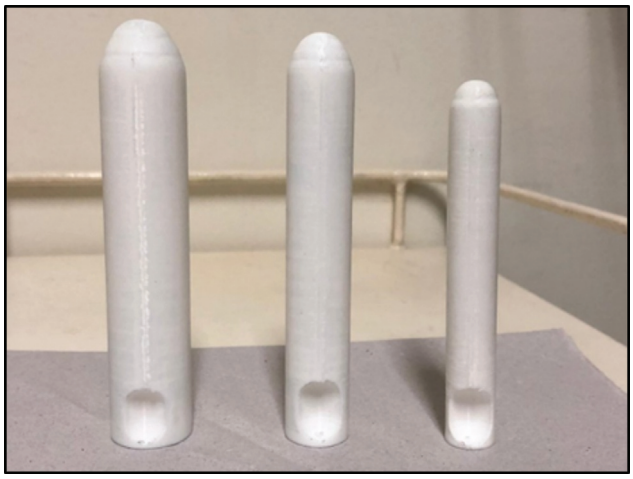

Fig. 1 Vaginal dilators created with 3D printing. Source: Marta Maria Kemp.

The individual molds were reused only by the patient herself. The molds were not sterile, but the patients were instructed to clean them with soap and water and use them with condom protection. During the test period, the authors realized that the sizes described above were the most used. These 3 sizes were used because there was no need to use larger or smaller sizes at any time. Despite the biological plausibility of having no contraindication for use in the supine position, as long as the patient is well oriented, the present study prioritized the systematic methodology of the same position of introduction of the casts in the gynecological position.

The applicability of the molds and the success of the vaginal dilation treatment were evaluated considering variables such as final total vaginal length (TVL), patient satisfaction, complication rate, and cost of mold production.

The patients were instructed to perform light pressure exercises from the vaginal introitus, positioning as shown in ►**Fig. 2**. The first return was within 15 days, and after that there was a monthly follow-up during the first year of the study. Patients who reached 6 cm or more in TVL were considered treated. After 6 cm of TVL, the patients were allowed to attempt sexual intercourse.

The orientation of the direction and strength of the perineal massage vectors was standardized as introduction movements into the vagina and circular movements, toward the sides of the vagina and posterior wall or toward the perineal region, to preserve possible urethral trauma in the anterior region, according to ►**Fig. 3**, for 20 minutes during the study. The strength guidance was individualized, being gradual and progressive according to the sensitivity to pain or discomfort of each patient.

All patients were followed up every month from the beginning of the treatment, during the 1st year, and every 2 months in the 2nd year of the study, with free return as needed. During follow-up, the newly created vaginal canal was analyzed using a speculum and by digital vaginal exam. The aspect, amplitude, and length were observed. All patients were allowed to have sexual intercourse when vaginal length was greater than 6 cm. The clinical aspects of the vagina were subjectively analyzed by the first two independent authors, with no difference regarding the appearance of the neovagina, such as presence or absence of active bleeding, the color of the vaginal mucosa, and granulation tissue in all patients, in the period of 3, 6, 12 and 24 months, and after treatment. The patients remain under follow-up at the same service with possible long-term results in future studies.

To compare the means of the initial and final TVL variable, the Student *t*-test for related samples was used. The D'Agostino normality test was performed for the assumptions of the analysis. To assess the magnitude of the difference, the effect size (d) with a 95% confidence interval (95% CI) was used. According to Cohen,[7] it was agreed that the values of d

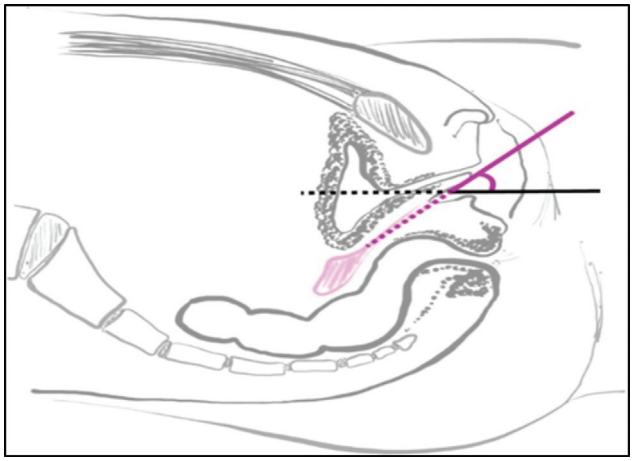

Fig. 2 Positioning the dilator into vaginal introitus (purple). Source: Marta Maria Kemp.

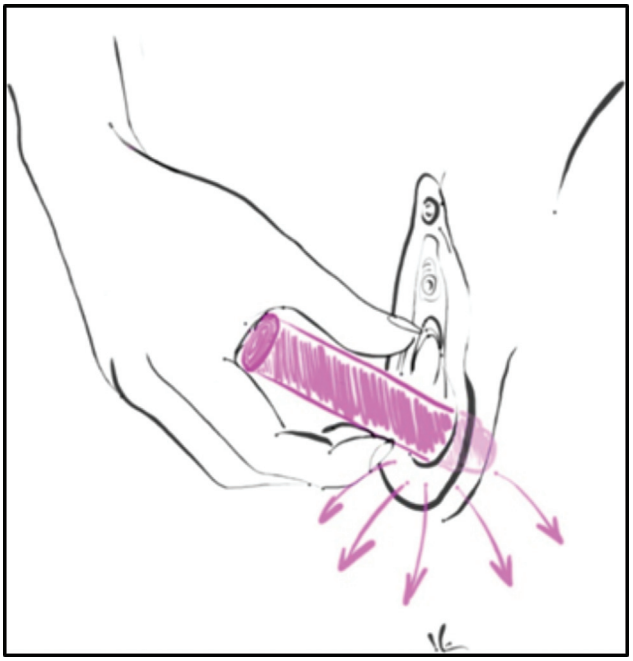

Fig. 3 Orientation of perineal massage with the dilator. Source: Marta Maria Kemp.

Table 1 Initial and final TVL

Patient	Initial TVL (cm)	Final TVL (cm)
1	2	7
2	4	6.5
3	1.5	7
4	1	7
5	2	7
6	4	8
7	1.5	6
8	2	6
9	1	6
10	0.5	6.5
11	1	6
12	1	6
13	1.5	7
14	1	7
15	2	4
16	3	5

Abbreviation: TLV, total vaginal length.

are considered small if ($20 \leq d < 50$); medium if ($50 \leq d < 80$); and large if ($d \geq 80$).

Results

A total of 16 patients were treated with the 3D printing dilators between October 2017 and October 2019. The patients in the present study had no exposure to previous treatments. The mean age was 19 years (standard deviation, SD: 2.84), mean initial vaginal length of 1.8 cm, and 60% of the patients had an associated malformation. Furthermore, 14 patients (87,5%) achieved a TVL greater than 6 cm at the end of the evaluation (►**Table 1**). The median time taken to reach treatment TVL was 5.6 months. The 2 patients who did not achieve TVL (patient number 15 and 16–Table 1) had used the molds for only 2 and 3 months, respectively.

As shown in ►**Table 2**, there was a significant difference ($p < 0.05$) between the initial and final TVL measurements. The effect size was 4.58, reinforcing the great magnitude of this difference.

The patients did not report any adverse effects, such as pain, discomfort, or bleeding, as they were instructed to perform dilation according to their ability, respecting their limitations of pain or discomfort. The authors believe that the absence of complications may be related to the previous educational guidelines and follow-up. Only 2 patients had inadvertent dilation of the urethra at the beginning of the treatment. Both had a smaller vaginal introitus (shorter distance between the urethral meatus and the vaginal furcula). They were reoriented in relation to anatomy and perineal massage exercises. After that, both were able to reach the treatment TVL. The patients were not operated on later because they were satisfied with the conservative treatment's results. They remain under follow-up at the specialized outpatient clinic of the same service for future follow-ups. ►**Fig. 4** shows the evolution analysis of the time of prothesis use by each patient. According to these results, there was no statistically significant difference between the time of use of the 14 patients that patients who adhered and were successful during the evolution of the treatment ($p = 0.189$).

Discussion

In 1938, Frank[4] described the first conservative treatment for vaginal dilation using Pyrex (Corning Inc., Corning, NY, USA) tubes of gradually increasing sizes (0.8, 1.5, and 2.0 cm in diameter). This was used to force the mucous membrane into the vaginal introitus region. No incisions were required for this procedure.[4] The main criticism of this therapeutic modality is that it requires a special dedication from the patients, as the exercises with the dilators make it possible to create a vaginal canal that enables sexual intercourse. Maintaining a vaginal prosthesis is sometimes necessary to keep the vaginal canal patent, as well as performing exercises in the absence of regular sexual practice.

Decades after Frank's first description, several studies reported favorable results using his method.[8–11] In 1981, Ingram[12] suggested that the failures in the technique used by Frank were due to tiredness of the hands and fingers during the procedure, the need to use the embarrassing position, and the inability to perform other productive activities during the procedure.[10] In an attempt to overcome these limitations, Ingram[12] proposed a modification of the original Frank method. In the Ingram method, the patient's weight is used to replace manual and digital effort. The specially designed bicycle seat bench was used to facilitate perineal mold pressure.[12]

Additionally, corroborating the results of the successful experiment by Ingram,[12] Roberts et al.[13] reported a 91% success rate using the Ingram method in their study of 51 patients with MRKHS. When well advised and emotionally prepared, almost all patients (90–96%) will achieve a satisfactory anatomical and functional result with vaginal dilation.[5] A recent study performed at the same reference center

Table 2 Statistical Analysis: Initial and Final TVL

Initial TVL mean (SD)	Final TVL mean (SD)	Difference (95% CI)	Effect size (95% CI)	*p*-value*
1.81 (1.05)	6.37 (0.94)	4.56 (5.27–3.84)	4.58 (2.88–6.28)	0.0001

Abbreviations: CI, confidence interval; SD, standard deviation; TLV, total vaginal length.
Note: * *p*-values < 0.05 were considered statistically significant.

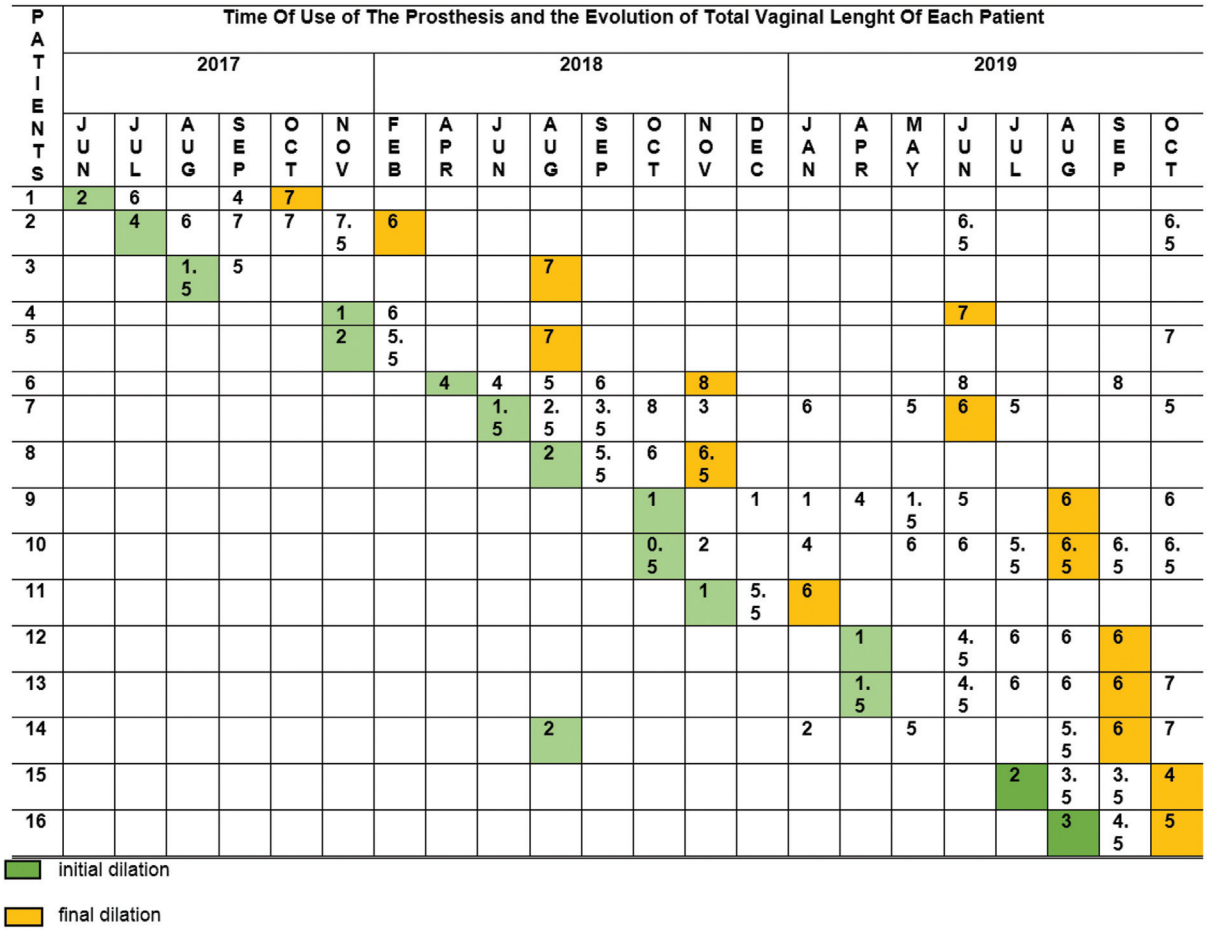

Fig. 4 Time of use of the prosthesis and the evolution of total vaginal length of each patient.

of the present project compared, in terms of anatomical, functional, and sexual aspects, two types of treatment for women with VA: progressive dilation (using the Frank method) or surgical neovaginoplasty (using the modified Abbé-McIndoe technique with oxidized cellulose). According to that study, both treatments had satisfactory efficacy and positive outcomes regarding the analyzed aspects. These data reinforce the reliability of the results from the present study, which indicate that dilation treatment can remain the first-line therapy for VA.[14]

The literature lacks more consistent and robust studies comparing the different surgical techniques with each other and with vaginal dilation. However, so far, no surgical technique has surpassed the success rate of nonsurgical treatment; a fact that, together with the benefit of being a safer technique, places vaginal dilation as the first line in the treatment of VA.[5,15–22] In this context, the present study suggests the development of a personalized conservative treatment for each patient through vaginal dilation with 3D molds.

In 1984, Charles Hull[23] founded the world's first 3D printing company, with the use of production technologies such as Additive Manufacturing (AM) and Rapid Prototyping. The AM is used in the synthesis of a given physical object by adding layers to form a part based on data generated by CAD. These technologies are widely used to quickly prototype products and tools for commercial purposes. Over time, it has also been integrated into other areas, such as the health area, since these tools have enabled the assistance of health professionals in diagnosis, surgical planning, and synthesis of orthotics and prostheses for the rehabilitation of patients.[23]

The use of 3D printing is gaining considerable acceptance in many medical fields, including surgery. The resulting tactile feedbacks significantly help the comprehension of anatomical details, especially the spatial relations between structures. Currently, an increasing number of applications have been successfully tested in many surgical disciplines, extending the range of possible uses to preoperative planning, counselling with patients, education of students and residents, surgical training, intraoperative navigation, and others.[23,24]

In a recent systematic review, Barbosa et al. assess previous publications within 3D printing in human reproduction and gynecology. Based on the included studies, it was possible to design 3D models (uterus, ovaries, uterine cervix, and uterus with fibroids) that provided enriched information to improve presurgical planning, medical training, fertility-sparing surgery, patient comprehension of surgical procedures, and assisted reproduction applications.[25]

Future expectations for 3D printing concern the reduction of manufacturing costs and time to further increase

accessibility, as well as the development of novel techniques and suitable materials for biological structures, making it possible to recreate the architecture and functionality of real human organs and tissues.[23,24]

The choice of devices made using a 3D printer was based on the possibility of offering an individualized treatment for each patient at a low cost and with a low rate of complications, in line with the plausibility of mold development already demonstrated in other areas, such as in Gynecology. The devices can be made with the most diverse formats and materials, which allows them to be adapted to the needs of each patient. Of the 16 patients treated, 14 reached the vaginal length considered for treatment, representing an 86% success rate. The only 2 patients who did not achieve a TVL of 6 cm or greater were still starting treatment (only 2 and 3 months ago).

According to the results of this present study, as well as in the literature,[5,15–22] conservative treatment for VA remains an excellent choice, with good efficacy and few complications, through personalized vaginal molds made with 3D printing. These results highlight the good applicability of the devices, bringing a cost-effective and easily reproducible option for the treatment of VA, making this a promising and accessible tool. Therefore, it would be a fruitful option to facilitate its use over the country, train professionals to apply the treatment, and shorten the distances so that more patients could benefit from it, thus eliminating the bias of distance and regularity in performing the exercises.

The main relevance of this research is the possibility of offering an individualized treatment option that is recommended in the scientific community with ethics, efficacy, and safety for a patient in an international reference center for the treatment of VA. Additionally, this is the first study to analyze reproductible 3D molds with conservative treatment and improve sexual function in women with VA. The homogeneous patient sample, standardized procedures, and prospective model are also strong points.

Another positive impact of this project was the effective response to the guidance of perineal massage exercises with the cast in patients with smaller vaginal introitus. This strategy can be used before the beginning of the dilation itself, aiming to reduce the chance of inadvertent dilation of the urethra.

The present study was not a randomized trial because of ethical issues. The main limitation of this trial was the small sample size. However, VA is a rare disease, with an incidence of 1:4.000 female births. The seriousness and scientific effort of this study are not diminished because of the difficulty to include more patients.

The main difficulties encountered in this study were the lack of motivation, lack of privacy in the patients' home, and distance from the city of origin to the hospital. Another obstacle was the attendance to outpatient follow-ups, since many patients lived in different cities and some even in other districts, as well as the regularity in the performance of the exercises, which depended on the personal motivation of each patient, home privacy, and emotional situation during treatment.

Considering the statements above, the authors believe that the study's strengths overcome its limitations. As VA is a rare disease that affects young women and involves the sensitive issues of sexuality and self-esteem, disclosure of well-structured trials can contribute to gaining knowledge so that an increasing number of women can benefit from the results of the studies.

Conclusion

Based on the present findings, a 3D model device can be offered in a personalized and individualized way as the first-line conservative treatment for VA in nonspecialized health centers in developed and developing countries. Furthermore, the use of 3D printing for making the molds proved to be a promising, effective and reproductible strategy, especially to be applied in health care centers with limited financial resources or a shortage of professionals specialized in the surgical treatment of VA, with low rate of complications. Considering the encouraging outcomes of this project and the rarity of the evaluated clinical condition affecting young women, the authors suggest more well-structured trials should be performed to better treat and benefit this population.

Contributions

MSF contributed to project development, data collection, and writing the manuscript; CCTN contributed to project development and proofreading/editing the manuscript; TTBC and GVM proofread/ edited the manuscript; MJBCG contributed to project development and proofreading/ editing the manuscript; MGFS contributed to project development and proofreading/editing the manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgments

The authors would like to thank all patients who participated in this study; Marta Maria Kemp (gynecologist and urogynecologist) who designed the didactic figures; and the Board of the Urogynecology and Vaginal Surgery Sector of the Department of Gynecology from the Federal University of São Paulo for the inspiration of the values of medicine. This study was funded by the Brazilian National Research Council (CNPq) (code 001). No other funding was provided.

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Association of Obesity and Surgery Outcomes in Patients with Endometrial Cancer: A Single-Center Analysis

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Rev Bras Ginecol Obstet 2022;44(12):1117–1121.

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Abstract

Objective Although obesity can result in high morbidity and mortality in surgical outcomes because of multiple comorbidities, determinants of outcome in obese patients who underwent endometrial cancer surgery remain unclear. The aim of this study is to assess the relationship between body mass index (BMI) and surgical outcomes in obese patients with endometrial cancer.

Methods An institutional retrospective review of the demographic details, clinical characteristics, and follow-up data of 142 patients with endometrial cancer who underwent surgery during a 72-month period was performed. The patients were divided into three groups based on their BMI; patients with BMI < 25 were identified as normal weight, patients with BMI between 25 and 30 were accepted as overweight, and those with BMI $\geq 30\,kg/m^2$ were identified as obese. The groups' demographic and clinical variables were compared.

Results Of the 142 patients, 42 were in the normal weight group, 55 in the overweight group, and 45 in the obese group. Age, surgical procedures, blood loss, preoperative health status, and metastatic lymph nodes did not show a significant difference between groups. However, surgery time and total lymph nodes were higher in the obese group. ($p = 0.02$, $p = 0.00$, and $p = 0.00$, respectively). Common complications were anemia, fever, intestinal injury, deep vein thrombosis, fascial dehiscence and urinary infection. There was no significant difference according to the complications.

Conclusion Our results indicated that higher BMI was significantly associated with a longer duration of endometrial cancer surgery. Minimally invasive surgeries and conventional laparotomy could be performed safely in obese patients.

Keywords
- BMI
- endometrial cancer
- obesity
- surgery

Introduction

Obesity is a well-established risk factor for developing endometrial cancer, more than any other cancer type.[1] Insulin resistance is responsible for releasing growth factors for cellular proliferation, higher levels of interleukins, tumor necrosis factors, and adipokines causing an obesity-related proinflammatory state, and high estrogen levels through

received
May 22, 2022
accepted
September 2, 2022

DOI https://doi.org/10.1055/s-0042-1759632.
ISSN 0100-7203.

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

increased aromatase activity in adipose tissue are proposed as contributors to the increased risk of developing endometrial cancer.[2] Endometrial cancer is known as a hormone-dependent type of cancer. Obesity affects hormone metabolism by increasing the aromatization of androstenedione to estrone in adipose tissues and causes an increase in the circulating levels of estrogen, creating a favorable environment for tumor formation.[3] The incidence of endometrial cancer is projected to rise as women's obesity rates continue to rise. In a study by Ward et al.[4] with 33,232 endometrial cancer patients, it was reported that the 10-year mortality due to endometrial cancer was associated with death due to cardiovascular disease. It was the most common reason related to morbid obesity. Obesity and endometrial cancer have been linked in numerous research studies.[5–8] Although excess body fat is a significant risk factor for endometrial cancer, its impact on survival is unclear.

Surgical procedures for treating endometrial cancer are hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy. Many studies have established that obese patients are at a higher risk of perioperative and postoperative complications, such as longer hospital stay and increased morbidity, even when minimally invasive surgeries or laparotomy are performed.[9–11] Obesity is defined by the World Health Organization (WHO) by using the body mass index (BMI) cutoff point of $> 30\,kg/m^2$, which is calculated as weight in kg divided by height in meters squared. Body mass index has significant public health importance because it correlates well with morbidity and/or mortality and endometrial cancer risk. Although surgery is the standard procedure in the staging and treatment of endometrial cancer, obesity may affect surgical outcomes due to its accompanying comorbid disorders. The impact of morbid obesity on endometrial cancer patients' survival is crucial as postoperative complications among obese women seem to be higher than among their normal-weight counterparts.[12]

The evaluation of the effects of obesity on surgical outcomes may help decrease morbidity and improve prognosis in patients with endometrial cancer. However, there are insufficient data in the current literature that explain the impact of morbid obesity on the surgical outcomes of endometrial cancer and compare it with the endometrial cancer patients with normal weight. This study aims to determine the link between BMI and surgical outcomes in obese endometrial cancer patients.

Methods

Participants

This study was performed in accordance with the ethical standards of the Helsinki declaration. Ethical approval was obtained for this retrospective, cross-sectional study by the ethics committee of the University of Health Sciences, Sisli Hamidiye Etfal Education and Research Hospital. Informed consent was obtained routinely. We reviewed the records of patients older than 18 years with endometrial cancer admitted to our hospital's gynecologic oncology department within a 72-month period from 2014 to 2020.

Inclusion and Exclusion Criteria

The inclusion criteria are listed below:

1. Patients with pathologically proven endometrial cancer.
2. Patients older than 18 years.
3. A detailed medical record including patient's history, clinical findings, laboratory and pathology test results, treatment outcomes, etc.

The exclusion criteria are as follows:

1. Patients without a definite pathologic diagnosis
2. Patients with secondary cancer.
3. Patients with endometrial cancer who were treated conservatively.

Data Collection

The patients' demographic characteristics (age, sex), weight, height and body mass index (BMI), surgical procedure (total hysterectomy-bilateral salpingo-oophorectomy [via laparotomy or laparoscopy] with or without pelvic and para-aortic lymphadenectomy), duration of hospital stay, lymph node involvement, the average number of lymph nodes removed, routine biochemical examination, preoperative evaluation and preparation for anesthesia, perioperative and postoperative complications, and follow-up data were recorded. The patients were divided into three groups based on their BMI. Body mass index [kg/height (m)]2 was calculated and classified according to the World Health Organization (WHO) guidelines. Thus, patients with BMI < 25 were identified as normal weight, patients with BMI from 25 to 30 were accepted as overweight, and those with BMI $\geq 30\,kg/m^2$ were identified as obese. Later, we compared the variables mentioned above and surgical outcomes according to patients' BMI.

Statistical Analysis

Data were analyzed using the IBM SPSS Statistics for Windows, version 23.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics (mean, standard deviation, frequency, and percentage) were used for the demographic and clinical characteristics. The analysis of variance (ANOVA) test followed by Tukey multiple comparison methods among these three BMI groups was performed. The categorical variables were compared using the Chi-squared test. A p-value of < 0.05 was considered to be statistically significant.

Results

During the 6-year period, 142 patients were operated on for endometrial cancer. These surgical procedures were performed via laparotomy or conventional laparoscopy, which were performed at our hospital's gynecologic oncology unit. The mean age of the subjects was 60.52 ± 9.89 years (range, 18–82 years). The in-hospital mortality rate was 0%. The number of patients with BMI < 25 (normal weight) was 42 (29.6%), those with BMI from 25 to 30 (overweight) were 55 (38.7%), and patients with BMI > 30 (obese) were 45 (31.7%).

The demographic and clinical characteristics of patients with a comparison between the three groups are

Table 1 Demographic and clinical characteristics of patient groups

Variables	BMI < 25 (normal weight)	BMI from 25 to 30 (overweight)	BMI > 30 (obese)	*P*-value
Number of patients	42 (29.6%)	55 (38.7%)	45 (31.7%)	–
Age	61.00 ± 11.15	60.00 ± 10.56	60.44 ± 10.42	0.901
Surgical procedure				
Laparotomy	25 (17.6%)	31 (21.8%)	26 (18.3%)	0.952
Laparoscopy	17 (12.0%)	24 (16.9%)	19 (13.4%)	
Menopause				
Premenopause	7 (4.9%)	10 (7.0%)	9 (6.3%)	0.922
Postmenopause	35 (24.6%)	45 (31.7%)	36 (25.4%)	
Estimated blood loss (ml)	253.81 ± 89.25	263.64 ± 108.77	273.33 ± 111.88	0.685
Surgery time (minutes)	142.14 ± 25.50	158.27 ± 36.69	169.89 ± 44.18	0.002
ASA	1.62 ± 0.66	1.49 ± 0.57	1.47 ± 0.59	0.451
Duration of hospital stay (days)	5.64 ± 1.91	5.16 ± 1.75	5.56 ± 2.03	0.404
Pre-CA125	23.98 ± 34.58	48.58 ± 139.33	54.16 ± 132.77	0.436
Number of total dissected pelvic lymph nodes	19.10 ± 10.62	23.47 ± 11.74	34.84 ± 14.31	0.000
Metastatic nodes	1.21 ± 2.08	1.05 ± 2.38	0.93 ± 2.06	0.837
Non-metastatic nodes	18.00 ± 10.76	22.42 ± 12.03	33.91 ± 13.90	0.000

demonstrated in ►**Table 1**. There was no significant difference between the groups regarding age, surgical procedures, presence of menopause, intraoperative bleeding, preoperative health status (ASA), the mean duration of hospital stay, CA125 level, and the number of metastatic nodes. However, duration of surgery, the number of total nodes and non-metastatic nodes differed significantly and were higher in the group of patients with BMI > 30 ($p = 0.02$, $p = 0.00$, and $p = 0.00$, respectively). ►**Table 2** shows the posthoc Tukey test results of these variables.

Patient complaints at the time of admission and complications to our outpatient clinic according to patient groups were summarized in ►**Table 3**. The reasons for patients' admissions were vaginal bleeding, abdominal pain, itching, and routine examination. The symptoms for hospital admission did not differ according to patients' BMI. Anemia (5.6%), fever (1.4%), intestinal injury (0.7%), deep vein thrombosis (0.7%), fascial dehiscence (0.7%), rupture of veins (0.7%), surgical site infections (0.7%), and urinary infection (2.8%) were common perioperative (intraoperative and postoperative) complications among all patients. There was no significant difference between the groups according to the perioperative complications.

Table 2 The posthoc comparisons using Tukey's HSD

Factor	Pairwise Comparison	*P*-value
Surgery time (minutes)	Normal weight vs Overweight	0.083
	Overweight vs Obese	0.256
	Normal weight vs Obese	0.002
Total nodes	Normal weight vs Overweight	0.196
	Overweight vs Obese	0.000
	Normal weight vs Obese	0.000
Non-metastatic	Normal vs Overweighted	0.190
	Overweight vs Obese	0.000
	Normal weight vs Obese	0.000

Discussion

The current study aimed to demonstrate the surgical outcomes pertaining to the management of endometrial cancer patients according to their BMI and to explore which variables were significant in patient morbidity. Our statistical analysis demonstrated that duration of surgery, number of total dissected pelvic lymph nodes, and non-metastatic nodes were higher in endometrial cancer patients with obesity. Demographic, clinical, and laboratory findings, such as patient's age, presence of menopause, blood loss, preoperative health status, hospital stay, and CA125 levels, were not related to patients' BMI. Moreover, our results indicate that surgical procedures which were performed via laparotomy or laparoscopy had no significant relationship with the subjects' weight. The symptoms for hospital admission did not differ according to patients' BMI. In addition, perioperative complications did not significantly differ among patient groups.

Kokts-Porietis et al.[13] reviewed the studies that included estimated body fat with BMI to evaluate the relationship between obesity and mortality among endometrial cancer survivors. They reported that endometrial cancer survivors who were obese at the time of diagnosis had a higher risk of cancer recurrence and all-cause death but not endometrial cancer-specific mortality. In our study sample, the in-hospital

Table 3 Perioperative data and complications according to patient groups

	Clinical features	BMI < 25 (normal weight)	BMI from 25–30 (overweight)	BMI > 30 (obese)	Total (n)
Symptoms for hospital admission	Bleeding	37 (26.1%)	38 (26.8%)	31 (21.8%)	106 (74.6%)
	Abdominal pain	0 (0.0%)	1 (0.7%)	1 (0.7%)	2 (1.4%)
	Itching	0 (0.0%)	1 (0.7%)	1 (0.7%)	2 (1.4%)
	Routine examination	5 (3.5%)	15 (10.6%)	12 (8.5%)	32 (22.5%)
Perioperative complications	Atrial fibrillation	1 (0.7%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
	Anemia	3 (2.1%)	2 (1.4%)	3 (2.1%)	8 (5.6%)
	Fever	0 (0.0%)	1 (0.7%)	1 (0.7%)	2 (1.4%)
	Intestinal injury	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Deep vein thrombosis	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Fascial dehiscence	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.7%)
	Rupture of the iliac vein	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.7%)
	Bleeding of obturator vein	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.7%)
	Urinary infection	1 (0.7%)	2 (1.4%)	1 (0.7%)	4 (2.8%)
	Surgical site infections	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.7%)
	None	37 (26.1%)	47 (33.1%)	37 (26.1%)	121 (85.2%)

mortality rate was also 0%, and we suggest that elevated BMI might not be related to mortality in endometrial cancer.

In a retrospective study by Ward et al.,[4] the authors evaluated the causes of death among women with endometrial cancer. They found that cardiovascular diseases were the leading reason of death from endometrial cancer. Although the causes of death in patients with endometrial cancer were not the main concern of the current study, we found that the patients with BMI > 30 had a lower preoperative health status, which shows the preoperative chronic medical conditions.

In a review by Onstad et al.,[14] the authors suggested that operating on obese patients was more difficult than on normal-weight patients with endometrial cancer due to technical aspects of the surgery that could affect visualization. In the current study, we detected that the duration of surgery in the obese patient group was longer than in the normal-weighted and overweight patients, which supports the researchers' conclusion. However, obesity did not significantly impact the surgical procedures in the three groups of this study. Similar to our results, Gabala et al.[10] reported that obesity did not affect the surgical techniques in endometrial cancer. In a study by Erkanli et al.,[15] they investigated the effect of BMI on clinical and pathologic features and surgical morbidity in 42 patients with endometrial cancer. The number of participants was higher in the current study, and our findings support their results. They also did not find any difference in length of hospital stay and intraoperative or postoperative complications. It can be concluded that the surgical approach might be performed safely in morbidly obese endometrial cancer patients.

There are mixed results in the retrospective studies regarding the impact of obesity on operative complications in the current literature. Similar to previous studies, we detected that postoperative complication rates did not differ significantly between the obese and non-obese patient groups.[10,11,15,16] On the contrary, Bouwman et al.[17] reported that elevated BMI was associated with an increased risk of postoperative surgical complications in morbidly obese patients who underwent laparotomy. Patients' characteristics may explain these different results, and they also depend on surgeons' experience and type of equipment. Only 14.8% of our patient sample had suffered from perioperative complications. Arrhythmia, blood loss, high fever, intestinal injury, deep vein thrombosis, fascial dehiscence, bleeding of veins, urinary infection and surgical site infections were detected. Even though obesity did not affect the course of surgery in this study, we believe that when considering endometrial cancer surgery, it is critical to recognize these complications to avoid them.

Endometrial cancer continues to increase in incidence and mortality. Obesity is now recognized as an independent risk factor for endometrial cancer, accounting for more than half of all cases. Women diagnosed with endometrial cancer with a high BMI have a higher probability of morbidity. For this reason, obesity may adversely affect surgery outcomes. Therefore, we think that more studies determining this relationship between endometrial cancer and obesity are needed in the medical literature.

This study has some limitations. First, only eligible data in the record were assessed because of its retrospective nature. Second, the study was performed at a single center. In

addition, all the patients were operated on by the same experienced surgeons. However, a long-term period and a relatively high number of participants are the strengths of this study.

Conclusion

In conclusion, our findings indicate that increased BMI is related to higher surgery time in patients with endometrial cancer. However, obesity did not impact surgical outcomes such as blood loss, duration of hospital stay, and complication rates. Moreover, mortality rates in endometrial cancer were not affected by BMI. Endometrial cancer surgery can be safely and adequately managed among patients with obesity. Further prospective studies evaluating the impact of obesity on long-term follow-up of endometrial cancer surgery are warranted.

Contributions

S. O. and G. O. D. designed the study. S. O. and G. O. D. collected the data. S. O. analyzed and interpreted the data. G. O. D. drafted the manuscript. All authors were comprehensively involved in all aspects of the study and in the preparation of the manuscript. All authors have read and approved the final version of the it.

Conflict of Interests

The authors have no conflict of interests to declare.

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Expert Recommendations on Monkeypox (MPX) in Pregnancy, Postpartum and Lactating Women

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Rev Bras Ginecol Obstet 2022;44(12):1122–1125.

The Monkeypox Disease

In 2020, Brazil and the whole world faced the COVID-19 pandemic, which caused a high number of deaths. This disease was particularly severe for pregnant and postpartum women and determined a significant increase in the Maternal Death Ratio (MMR). To face the disease and assist health professionals in the qualification of the best care to the maternal-fetal binomial, the Ministry of Health and Febrasgo developed a working group formed by professors and researchers from several universities who worked to establish recommendations for the care of pregnant women and puerperal women by the time of the COVID-19 pandemic.

In 2022, while we are still experiencing the COVID-19 pandemic, we are surprised by another disease caused by a virus that has been alarming the population and worrying public health authorities and gynecology and obstetrics societies in Brazil and worldwide.

It is the infection that is caused by monkeypox virus (MPXV), which is still a not well-known disease, with many of its characteristics not well determined. The knowledge of this disease is fundamental for health professionals working in Obstetrics to plan forms of prevention, as well as the establishment of the diagnosis and treatment of the monkeypox (MPX) disease, preserving the health of the maternal-perinatal binomial. For this reason, the Brazilian Ministry of Health requested the same working group that acted diligently by the time of COVID-19 to establish recommendations for facing MPX, to provide adequate care for pregnant women and puerperal women. These recommendations, based on the knowledge that exists so far, are what guide these orientations and may change depending on new findings that may be presented over time.

The MPXV was named after being identified in laboratory monkeys in 1958. The first case of this virus in humans was recorded in 1970 in a child in Congo and since then has

DOI https://doi.org/10.1055/s-0042-1759635.
ISSN 0100-7203.

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

become an endemic disease in West and Central Africa.[1] In 2003, the first cases were registered outside the African continent, in the United States,[2–4] but that was contained through hygienic measures and stock vaccines. In 2017, there was a major outbreak started in Nigeria and spread to some African countries. In early May 2022, another outbreak of MPXV was identified, this time in several countries outside the African continent, with fast dissemination of cases. As a result, on May 21, 2022, the World Health Organization (WHO) declared the existence of an emerging global outbreak of MPXV infection, and on July 23 has determined that this outbreak constituted a Public Health emergency of international concern.

Pregnant women present clinically with similar characteristics to nonpregnant women, but may evolve with greater severity, being therefore considered a risk group. In addition to maternal clinical repercussions, there are also concerns specific to the pregnancy period, such as fetal vitality, the possibility of vertical transmission and perinatal outcome. It has been verified that MPXV infection can lead to adverse results in pregnancy, such as fetal death and spontaneous abortion.[5,6] A recent publication on the evolution of pregnancy in 4 MPXV-infected women showed spontaneous 1st trimester abortion in 2 pregnant women, without testing of the conception products; an intrauterine death in the 2nd trimester, with clinical, histological and laboratory evidence of intrauterine fetal infection evidencing the very probable vertical transmission of the disease, and a pregnant woman with MPXV infection that evolved with full-term delivery of healthy conceptus.[7]

Close and prolonged skin-to-skin contact, including during sexual activity, seems to be the main means of transmission of MPXV. There are suspicions of transmission of this virus by droplets and aerosols. There is also transmission through biting of rodent animals or even the ingestion of those animals. In addition, contagion by phositis, especially used clothing, can transmit the disease. The quick identification and isolation of affected individuals is fundamental to prevent the spreading of the disease.[8]

Transmission of MPXV occurs in the phase of active skin lesions and only ends when they heal completely, which usually requires isolation of 21 to 28 days.[7,9,10] There are doubts as to whether the contagion could be prior to the phase of skin lesions, since viral DNA has already been identified in the blood and respiratory system of patients prior to the lesions.[5,7] Sexual transmission has been discussed not only by contact, but also because the virus has been identified in seminal material.[5,11]

Patients with MPXV should be isolated in a separate area of their home or in hospital services, especially if they present extensive lesions and/or respiratory symptoms. Skin lesions should be covered (for example, with the use of long sleeves and trousers) to minimize the risk of contact. Everyone should wear a face mask in the presence of an infected person.

Sexual abstinence is also recommended in the phase of unhealed lesions and condom use for any form of sexual act (anal, oral, or vaginal) in the 12 weeks following the healing of the lesions.[7]

Most patients with MPXV will have mild disease and can be cared for at home, where they should remain isolated. Standard cleaning and disinfection procedures should be performed, taking care of clothes and used objects.

The diagnosis of infection can be made by anamnesis and clinical findings, with epidemiological suspicion. The incubation period is, on average, 6 to 13 days, and can be from 5 to 21 days. Next to this, a prodromal period occurs, when fever, sweating, headache, myalgia, fatigue and lymphadenomegaly, which is quite characteristic of the disease, are manifested. About 1 to 3 days later, the rash, which usually affects the face, genitals, and extremities, and has a centrifugal character, appears.

The lesion evolves from macules to papules, vesicles, pustules and, later, crusts.[3] In general, they are well circumscribed and deep, and develop umbilication. They can also be uniform or at different stages of evolution. Lesions are often painful until healing (which happens normally when they are itching).

The severity criteria consider the number of lesions: Mild ($<$ 25 skin lesions), Moderate (25–99), Severe (100–250) and very severe ($>$ 250). Another severity criterium is when one of these signs is present: fever for $>$ 7 days, cervical lymph node, persistent vomiting, dehydration, retrocular pain, respiratory failure, mental confusion, hepatomegaly, and sepsis.

Confirmatory laboratory diagnosis of MPXV can be performed by real-time polymerase chain reaction (qPCR).[12] Sample collection should preferably be performed with swab of ulcerated lesions. If there are only vesicles, the sample can be obtained by means of fine needle puncture, with extreme caution to avoid accidents that allow contagion. If there are only crusts, the material can be obtained by swab or by collection of small fragments. These samples should be stored in dry sterile vials without any preserving liquid. In individuals in whom MPXV is suspected, without any clinical suspicion, oral swab should be tested and vaginal or anal swab may be considered.[13]

Blood samples are oriented for differential diagnosis and/or concomitance of other diseases that could cause lesions, such as syphilis, acquired immunodeficiency syndrome, and herpetic infection.[12,13]

Although the disease is most of the time self-limited and with spontaneous cure, in some cases there may be a need for specific drug treatment. Most of the time, there is only indication of symptomatic treatment for fever and pain with dipyrone, acetaminophen, or even opiate derivatives in the most severe pain conditions. In cases with more important lesions, the use of antibiotics may be indicated to prevent secondary bacterial infection: systemic amoxicillin and ocular chloramphenicol.

There are some patients who have worsening of the condition, and in these circumstances, antivirals are indicated. Antiviral drugs: Tecovirimat (TPOXX), cidofovir (Vistide) and brincidofovir (Tembexa) have been considered. About 5% of patients with MPXV require antivirals.[11,14] There are still no well-established protocols for their use in pregnancy.

Immunoglobulin (VIG), a mixture of purified blood antibodies of individuals immunized with the smallpox vaccine, has already been used for the prevention/treatment of

MPXV. There is no evidence on its effectiveness; however, it has already been considered as prophylaxis in exposed individuals with severe immunodeficiency as a prevention/treatment of MPXV.

There are two vaccines developed to fight human smallpox, which are capable of inducing protective antibodies against MPXV. However, they are not available in Brazil and there are not enough doses for mass vaccination.

The first is ACAM2000, with live vaccinia attenuated but replicating virus, applied in a single dose and with immune response 4 weeks after application. Because it is a live virus vaccine, it is contraindicated for individuals with immunodeficiency and pregnant women.

The second vaccine is Modified Ankara (MVA-BN), produced by Bavarian Nordic, with live, attenuated, nonreplicating virus[15] is sold in Europe as Imvamune or Imvanex and in the United States as Jynneos. It has efficacy of 85%.[16] It can be used in immunosuppressed patients. It is applied in two doses with an interval of 4 weeks, and its protection begins 2 weeks after the second dose.

Monkeypox in Pregnant, Postpartum, and Lactating Women

There are few reports on MPXV during pregnancy.[6] It is known that the virus can cross the placenta and reach the fetus. Thus, as in other viral infections, it may increase the risk of abortion, fetal death, prematurity, and other fetal complications. There is still no way to quantify these risks. Therefore, the care with the pregnant woman and the fetus should be intense in the face of suspicion or confirmation of the infection.

The WHO recognizes maternal-fetal transmission through the transplacental passage, originating the congenital disease, and/or transmission through intimate contact, during and after delivery. In postexposure asymptomatic pregnant women, if MPXV is undetectable, monitoring can be suspended. If MPXV is detectable, home isolation should be maintained for a minimum of 21 days. Self-monitoring of body temperature and skin lesions and teleservice monitoring by the health professionals should be orientated.

In pregnant women with signs or symptoms of MPXV but with negative qPCR, isolation and self-monitoring of temperature and skin lesions should be indicated. Other potential causes should be ruled out, and retesting the patient is indicated if symptoms persist. If the MPXV test is positive, hospitalization is indicated in moderate and severe cases. There are still insufficient data on the use of vaccines in pregnant or lactating women and none of the vaccines are approved in pregnancy. Animal studies did not find adverse fetal effects, and a study with 300 pregnant women did not show an increase in adverse outcomes.[17] It is still unknown whether vaccines are excreted in breast milk. Vaccines with replicant viruses are contraindicated in pregnancy and infants.[18–20] The MVA-BN has been considered safe during breastfeeding.[1] Thus, any woman who is breastfeeding, with substantial exposure to the virus, should be vaccinated after considering the risks of MPXV infection for her and her child.

It will usually only be necessary to use symptomatic for the treatment of MPVX during pregnancy. The use of antivirals is not approved. There are no studies of the antiviral drugs in humans. In animals, Tecovirimat did not induce teratogenicity, and Cidofovir and Brincidofovir were classified as FDA class C because they caused changes in the morphology of the animals undergoing the study. Although little is known about VIG during pregnancy, other immunoglobulins have already been used in pregnancy and have been shown to be safe. Until now, this type of treatment has not been indicated during pregnancy.[18]

In the presence of acute infection, obstetric ultrasound (US) is recommended during the 1st trimester to evaluate the viability of pregnancy. In moderate and severe cases during the 2nd trimester, obstetric US is suggested to evaluate biometrics and fetal morphology as well as to quantify the amniotic fluid index. During the 3rd trimester, when available, fetal biophysical profile and fetal Doppler flowmetry should be done to assess the well-being of the conceptus. After the 26th week, cardiotocography is recommended in cases of infection considered moderate and severe.[19]

After the maternal cure, fetal risks are low, but obstetric US is recommended every 4 weeks for evaluation of fetal growth and well-being.[10] Normally, there is no indication to anticipate delivery.[7] In severe cases or fetal impairment, we should consider delivery, evaluating gestational age and fetal weight. In cases in which preterm delivery is indicated, magnesium sulfate and corticosteroids should be used, according to obstetric indication.

During the delivery, the presence of a healthy companion with the use of personal protective equipment should be ensured, which should be maintained throughout the hospital stay. The delivery should follow obstetrics indications, and there is no reason to indicate cesarean section because of the infection. If the patient presents genital lesions, because of a higher risk of neonatal infection during delivery, c-section will be indicated.[9]

Timely clamping of the umbilical cord is recommended, although skin-to-skin contact between mother and newborn (NB) should be avoided. Immediate macroscopic examination of the NB should be taken and, when available, a swab of throat and any skin lesions.[9] It is recommended that the newborn be sanitized by bathing immediately after delivery. It is up to the doctor to inform the risks of infection and need to keep mother and child in separate rooms during the isolation phase. If this is not possible, strict precautions should be followed during contact: the NB should be fully clothed or wrapped in sheets, just as the mother should wear gloves and surgical mask well-adjusted to the face. Direct breastfeeding should be postponed, but support should be offered for the woman to maintain milk production and allow relactation later. Milked breast milk should be discarded. Precautions should be maintained until isolation criteria are met. If the NB is tested positive, the isolation can be cleared. Action of antiviral drugs and vaccine immunoglobulin are little known in milk production.[20] The discharge should be adjusted considering the isolation time and the ability to follow to the recommendations to avoid the contagion of the NB.

Recommendations for Pregnant, Postpartum, and Lactating Women

- Use of masks, especially in environments with individuals potentially infected with the virus.
- Stay away from people who have suspected symptoms such as fever and mucosal skin lesions.
- Use condoms in all types of sexual intercourse (oral, vaginal, anal) since transmission through intimate contact has been the most frequent.
- Be alert if your sexual partnership presents any lesion in the genital area.
- Seek for medical attention if you have a suspicious symptom, so that a clinical and laboratory diagnosis can be established.

Recommendations for healthcare professionals

- Pregnant women should be at home isolated with constant follow-up by the care team in case of mild illness.
- Cases of greater severity should be followed-up in hospital.
- There is still no specific treatment protocol with antivirals in the pregnancy-puerperal cycle.
- Monitoring fetal vitality should be carefully observed in patients with moderate or severe disease, because of the higher fetal morbidity and mortality in these cases.
- The delivery has obstetrics indications and cesarean section as a routine is not indicated.
- Breastfeeding should be postponed during the isolation period, offering specific support that allows for further relactation.

Conflict of Interests

The authors have no conflict of interests to declare.

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Maternal Mercury Exposure and Hypertensive Disorders of Pregnancy: A Systematic Review

Exposição materna a mercúrio e distúrbios hipertensivos na gestação: Uma revisão sistemática

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Rev Bras Ginecol Obstet 2022;44(12):1126–1133.

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Abstract

Objective The present review aimed to synthesize the evidence regarding mercury (Hg) exposure and hypertensive disorders of pregnancy (HDP).

Data Sources The PubMed, BVS/LILACS, SciELO and UFRJ's Pantheon Digital Library databases were systematically searched through June 2021.

Study Selection Observational analytical articles, written in English, Spanish, or Portuguese, without time restriction.

Data Collection We followed the PICOS strategy, and the methodological quality was assessed using the Downs and Black checklist.

Data Synthesis We retrieved 77 articles, of which 6 met the review criteria. They comprised 4,848 participants, of which 809 (16.7%) had HDP and 4,724 (97.4%) were environmentally exposed to Hg (fish consumption and dental amalgam). Mercury biomarkers evaluated were blood (four studies) and urine (two studies). Two studies found a positive association between Hg and HDP in the group with more exposure, and the other four did not present it. The quality assessment revealed three satisfactory and three good-rated studies (mean: 19.3 ± 1.6 out 28 points). The absence or no proper adjustment for negative confounding factor, such as fish consumption, was observed in five studies.

Conclusion We retrieved only six studies, although Hg is a widespread toxic metal and pregnancy is a period of heightened susceptibility to environmental threats and cardiovascular risk. Overall, our review showed mixed results, with two studies reporting a positive association in the group with more exposure. However, due to the importance of the subject, additional studies are needed to elucidate the effects of Hg on HDP, with particular attention to adjusting negative confounding.

Keywords
- mercury
- pregnancy-induced hypertension
- preeclampsia
- eclampsia and gestational hypertension

received
June 27, 2022
accepted
September 26, 2022

DOI https://doi.org/10.1055/s-0042-1760215.
ISSN 0100-7203.

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

Resumo

Objetivo A presente revisão busca sintetizar as evidências em relação à exposição ao mercúrio (Hg) e os distúrbios hipertensivos da gestação (DHG).

Fontes Dos Dados Os bancos de dados PubMed, BVS/LILACS, SciELO e a Biblioteca Digital da UFRJ Pantheon foram sistematicamente pesquisadas durante junho de 2021.

Seleção de estudos Artigos observacionais analíticos, escritos em inglês, espanhol ou português, sem restrição temporal.

Coleta de Dados A estratégia PICOS foi seguida e a qualidade metodológica foi avaliada usando o checklist Downs and Black.

Síntese de dados Foram encontrados 77 artigos, dos quais 6 atenderam aos critérios da revisão. Foram 4.848 participantes, dos quais 80 (16,7%) tinham DHG e 4.724 (97,4%) estavam expostos ambientalmente ao Hg (consumo de peixe e amálgama dental). Os biomarcadores de mercúrio avaliados foram sangue (quatro estudos) e urina (dois estudos). Dois estudos encontraram associação positiva entre Hg e DHG no grupo com maior exposição e os outros quatro não a apresentaram. A avaliação de qualidade metodológica revelou 3 estudos satisfatórios e 3 bons (média: $19,3 \pm 1,6$ em 28 pontos). A ausência ou não de ajuste adequado para fator de confusão negativo, como consumo de pescado, foi observada em cinco estudos.

Conclusão Recuperamos apenas seis estudos, embora o Hg seja um metal tóxico generalizado e a gravidez seja um período de maior suscetibilidade a ameaças ambientais e risco cardiovascular. No geral, nossa revisão mostrou resultados mistos, com dois estudos relatando associação positiva no grupo com maior exposição. No entanto, devido à importância do assunto, estudos adicionais são necessários para elucidar os efeitos do Hg sobre DHG, com atenção especial ao ajuste de confundimento negativo.

Palavras-chave

- mercúrio
- hipertensão induzida pela gestação
- pré-eclâmpsia
- eclâmpsia e hipertensão gestacional

Introduction

Systemic arterial hypertension (SAH) is a highly prevalent health issue worldwide, leading to significant morbidity and costs for health systems.[1] It is equally an important public health issue during pregnancy and deserves special attention since it is one of the leading causes of maternal and perinatal mortality worldwide.[2] Besides, the traditional risk factors for SAH, including overweight/obesity, age > 60 years old, daily ingestion of sodium > 2 g, and sedentarism, multifetal pregnancy, primigravid women, and multiparas > 35 years old are additional factors for hypertensive disorders of pregnancy (HDP).[1,3,4]

Environmental exposure to heavy metals, such as mercury (Hg), have been associated with adverse cardiovascular effects, including changes in blood pressure levels.[5–10] Although the mechanisms by which Hg may induce hypertension are not yet fully elucidated, some evidence points to an increase in angiotensin-converting enzyme activity, stimulation of the proliferation of vascular smooth muscle cells, induction of renal dysfunction, and an imbalance of the redox system, with an increase in oxidative stress and consequent reduction in nitric oxide bioavailability, endothelial dysfunction, and decreased smooth muscle relaxation.[6,8,11] Also, Hg can accumulate in the placenta tissue and leads to its dysfunction.[9]

Mercury is a ubiquitous environmental toxic substance with adverse results for health.[10] There are three distinct forms of Hg: elemental mercury (Hg^0), inorganic mercury (IHg), and organic mercury (ethylmercury [ethylHg], methylmercury [MeHg]). Its main sources of exposure include gold mining, Chlor-alkali industry, biomass burning, and deforestation, dentist activities (Hg^0), presence of dental amalgams, skin cosmetics use (IHg), vaccines conservative (ethylHg), and fish and shellfish intake (MeHg).[12–15]

The association between Hg exposure and hypertension has produced inconsistent findings.[16] Differences in study populations, and exposure levels, different Hg species, Hg biomarkers used to assess the exposure and absence of proper adjustment for confounding factors may contribute to the discrepancies observed in studies.[8]

Considering the widespread distribution of Hg, the great impact of HDP on public health, and the controversial evidence about their association, the present systematic review aimed to address this topic.

Methods

We followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to conduct and report the present review.[17] In addition, the study protocol was submitted to the International

Prospective Register of Systematic Reviews (PROSPERO), approved under number CRD42022297367.

A search strategy was developed in three electronic databases (BVS/LILACS, PubMed/Medline, and SciELO) and one Digital Library of Theses and Dissertations (Pantheon – Universidade Federal do Rio de Janeiro) in June 2021. We used various combinations of MeSH descriptors associated with the text words: *mercury* AND *hypertension, pregnancy-induced hypertensive disorders of pregnancy* OR *preeclampsia* OR *eclampsia* OR *gestational hypertension*.

Articles were considered for inclusion based on the PICOS strategy, as follows: *P*articipants comprised pregnant or puerperal women; *I*ntervention included assessment of Hg exposure through its measurement in any biological matrix; *C*omparison with normotensive pregnant or puerperal women and documented Hg measurement in any biological matrix; *O*utcome comprised gestational hypertension syndromes with their criteria reported by the authors. *S*tudy: original observational analytical article, written in Spanish, English, or Portuguese, without time restriction. We excluded any article without Hg exposure assessment in a biological matrix, without the criteria used to classify HDP, editorial articles, author's opinions, books, case reports, experimental studies (animal and in vitro); and reviews. The PubMed database was the reference database for cases of duplicate articles.

Two reviewers (Dantas A. O. and Castro T. S. S.) independently assessed the entire study selection process. Any disagreements about study selection were resolved by discussion and, if necessary, a third reviewer (Vianna A. S.) was consulted. The flowchart started by analyzing the titles, followed by the abstract, and later by the full text. Finally, we checked the reference lists of eligible papers to identify additional relevant studies.

One reviewer (Dantas A. O.) extracted the data from the eligible studies using a form that included: 1. Study characteristics: name of the first author, year of publication, country of study; 2. Methods: design, sample size, and exposure site; 3. gestational hypertension (GH) cases: number of cases, age, ethnicity; 4. Hg exposure: source, biological matrix, laboratory technique; 5. Statistical analysis including parametric (Student *t*-test and analysis of variance [ANOVA]) and nonparametric tests (Mann-Whitney and Kruskal-Wallis) for comparison (mean difference), regression tests for measure of association (risk ratio, odds ratio [OR] and/or hazard ratio), and prevalence ratio; 6. Methodological quality score. Another reviewer (Vianna A. S.) checked this step.

Two reviewers (Dantas A. O. and Castro T. S. S.) independently assessed the quality of each eligible study according to the Downs and Black (DB) checklist. It contains 27 items, subdivided into 5 sub-scales, which assess reporting (9 items), external validity (3 items), internal validity (bias and confounding – 13 items), and power (1 item). The 25-item score is: yes = 1, no = 0 and unable to determine = 0. Item 5 (distribution of main confounding variables) presents the score: yes = 2; partially = 1 and not = 2.[18] Item 27 (power) was modified, scoring yes or no for the power calculation. We adopted the categorization of quality proposed by Hooper et al.: excellent (26–28), good (20–25), satisfactory (15–19), or poor ($\leq$14).[19]

Although we had originally planned to perform a quantitative meta-analysis, we considered it inappropriate due to methodological limitations of the selected articles and to the high heterogeneity in exposure assessment with different cutoffs. Therefore, we reported the findings as a systematic qualitative review.

Results

The present systematic review retrieved 77 potentially eligible studies. Of these, 6 met our inclusion criteria, 4 from the electronic databases and 2 from the manual reference consultation, published between 2006 and 2020. The main reason for exclusion was out of scope, comprising 42 articles (30 without Hg and 12 without pregnant women). A flowchart of the search and screening process is displayed in ►**Fig. 1**.

The six studies had the following design: three were cohorts and three were case control. They covered 4,848 participants from 5 countries, 3 conducted in North America (2 in the USA and 1 in Canada), 2 in Asia, and 1 in North Africa. Four studies comprised 4,724 participants (97.4%) involved primarily in environmental exposure to Hg, and 1 study with 124 participants (2.6%) had both environmental and occupational exposure.[20–25]

Out of 4,848 participants, 4,039 were controls (2,514 pregnant women and 1,525 postpartum), and 809 (16.7%) had a HDP diagnosis, comprising 187 (23.1%) GH, and 622 (76.9%) preeclampsia (PE).

The participants had the following characteristics: age ranging between 15 and 49 years old, 406 (8.4%) were smokers, and 2.685 (55.4%) reported their ethnicity, with 1,794 (66.8%) white individuals.

Regarding the source of exposure, half of the studies reported it as follows: amalgam use (64 dentists), presence of dental amalgam (905 participants) and fish intake (1,817 individuals).[23,25] Concerning the latter, one study (1,817 participants) reported the frequency, but not the type of fish consumed.[23] Four studies measured Hg concentrations in blood (whole maternal blood [three], umbilical cord blood [one], and/or red blood cell [one]), and two in urine. The laboratory method more frequently used was inductively coupled plasma mass spectrometry (ICP-MS).[20–24] The detection limit was described in three studies, ranging from 0.12 to 0.33 µg/l (total Hg). No study investigated the association with hypertension according to the type of Hg. In addition, four studies measured other toxicants (metals) during the research.[20–22,24] Two studies investigated the association between the metal mixture and HDP (PE).[21,24]

Statistical analysis of studies included mean difference (two studies no and the other two yes), and measures of association.[20,22,23,25] Concerning the latter, two studies reported positive association (more exposed group [Hg_{urine} = 41.8µg/g]: RR = 3.67; 95%CI = 1.25–10.76 and more exposed group [Hg_{blood} $\geq$1.89µg/L]: aOR multi-metal = 1.60; 95%CI = 1.08–2.38; p = 0.039), and the other four

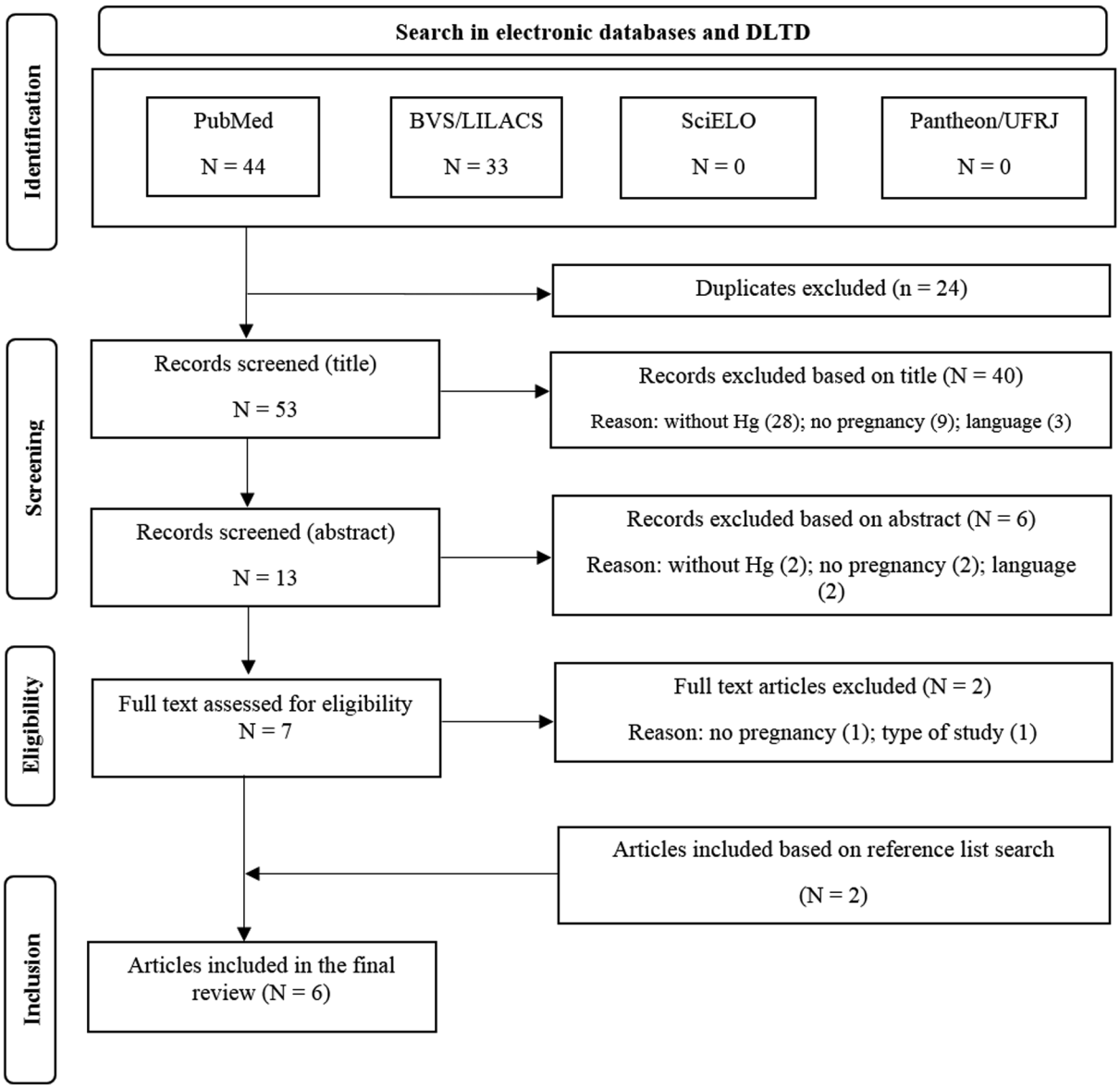

Fig. 1 PRISMA flowchart of the study selection process. Abbreviations: DLTD, Digital Library of Theses and Dissertations; BVS/LILACS, Biblioteca Virtual em Saúde/Literatura Latino-Americana e do Caribe em Ciências da Saúde; SciELO, Scientific Library Online; UFRJ, Universidade Federal do Rio de Janeiro

studies found no association (One unit increase $p > 0.05$; HR single model = 0.90; 95%CI = 0.63–1.28; HR (As, Hg and Sn) = 0.75; 95%CI = 0.39–1.46; Prevalence ratio = 1.03; 95%CI = 0.88–1.20; $p = 0.71$; 1 to 4 dental amalgams group: aOR = 1.31; 95%CI = 0.92–1.85 or $\geq$ 5 dental amalgams group - aOR = 1.32; 95%CI = 0.86, 2.04).[20–25] Regarding the latter, although the authors did not observe any association with HDP, they reported an inverse association with systolic blood pressure (dental amalgam replacement group: $\beta = -1.58$; 95%CI = - 2.95-- 0.02; $p = 0.02$).[23] The characteristics of all six studies are summarized in **Chart 1**.

The assessment of the methodological quality of the articles by the Downs and Black checklist showed that 3 were considered satisfactory and three were rated as good (mean = 19.3 ± 1.6 out of 28 points). The representativeness of the samples and the adjustment for confounding factors were the most often not clearly described items. For example, two studies did not adjust for any confounding factors, four adjusted for them, but only one made an adjustment for fish intake among these three studies.[23] The quality assessments for the selected studies are provided in ►**Table 1**.

Discussion

The present systematic review identified six studies that focused on Hg exposure and HDP, with mixed results. Previously, two systematic reviews had addressed the association of Hg exposure with blood pressure/hypertension in general population.[8,26] Together, they gathered 30 studies, but only 2 comprised pregnant women.

Very few studies have investigated the association between Hg exposure and hypertension during pregnancy and,

Chart 1 Characteristics of the selected studies

Author year country	Study characteristics design; number	Characteristics of the participants		Hg assessment			Outcome	Mean difference/ measure of association
		Age (Mean: years old)	Ethnicity	Site of exposure (source)	Biological matrix (laboratory technique)	Mercury level		
Vigeh et al. (2006),[20] Iran	Case-control; $n = 396$	27	396 NI	Environ	Maternal blood and UBC (ICP-MS)	Maternal blood: PE: 1.35 (0.74); Control: 1.34 (1.19) UBC: PE: 1.69 (1.19) Control: 1.70 (1.33)	PE	Mean difference: no
El-Badry et al. (2018),[25] Egypt	Cohort; $n = 124$	Ex:25.6 NEx: 25.9	124 NI	Environ (fish) Occupat (dentist)	Urine (CVAAS)	Urine 3rd quarter: Ex: 42.8 (13.7); NEx: 7.1 (3.9)	PE	Mean difference: yes; $RR_{Ex} = 3.67$ (1.25–10.76)
Bommarito et al. (2019),[21] USA	Case-control; $n = 383$	32.7	231 white 57 black 95 NI	Environ	Urine (ICP-MS)	Urine 3rd quarter: PE: 0.50 (0.24, 0.76); Control: 0.51 (0.27, 0.97)	PE	HR unimetal = 0.90 (0.63 - 1.28; $p = 0.55$); HR multimetal As, Hg, Sn = 0.75 (0.39–1.46; $p = 0.40$)
Liu et al. (2019),[22] USA	Cohort; $n = 1.274$	27.99	739 black 535 NI	Environ	Maternal red blood cells (ICP-MS)	Maternal blood: PE: 2.1 (1.0–4.7); Control: 2.0 (1.0–3.6)	PE	Mean difference: no; Prevalence ratio = 1,03 (0.88–1.20; $p = 0.71$)
Louopou et al. (2020),[23] Canada	Cohort; $n = 1.817$	31.86	1.563 white 254 NI	Environ (fish, amalgam)	Maternal blood (ICP-MS)	Maternal blood 1st trimester: zero amalgams: 0.58 1 to 4 amalgams: 0.74 $\geq$ 5 amalgams: 0.90	GH	Mean difference: yes; aOR = 1.31 (0.92, 1.85) $<$ 5 dental amalgams group; aOR = 1.32 (0.86, 2.04) $\geq$ 5 dental amalgams group
Wang et al. (2020),[24] China	Case-control; $n = 854$	20–30	854 NI	Environ	Maternal blood (ICP-MS)	Maternal blood: PE: 1.52 (0.97–2.36); Control: 1.49 (0.96–2.08)	PE	aOR = 1,60 (1,08–2,38; $p = 0,039$) in high Hg $\geq$ 1,89

Abbreviations: aOR, adjusted odds ratio; As, arsenic; CVAAS, cold vapor atomic absorption spectroscopy; Environ, environmental; Ex, exposed; GH, gestational hypertension; Hg, mercury; ICP-MS, inductively coupled plasma mass spectrometry; NEx, not exposed; NI, not informed; Occupat, occupational; PE, preeclampsia; Sn, tin; UBC, umbilical cord blood.

Table 1 Methodological assessment of the selected studies

Downs and black checklist – subscales	Vigeh et al.[20]	El-Badry et al.[25]	Bommarito et al.[21]	Liu et al.[22]	Louopou et al.[23]	Wang et al.[24]
Reporting (10 items)	7	7	9	9	9	8
External Validity (3 items)	2	3	3	3	3	3
Internal validity – bias (7 items)	5	5	5	5	5	5
Power (1 item)	1	1	1	1	1	1
Total score	17	18	20	21	21	19

in general, the ones that did it reported inconsistent findings. These discrepancies may partially be explained by the study methodology differences, such as sample size, exposure levels, chemical forms of Hg and its toxicokinetics, Hg biomarkers used to assess the exposure, role of metal mixture, as well as the absence or proper adjustment for confounding factors, including fish intake, a probable cause of negative confounding.[8,16,24,27] Our review also observed mixed results, with four studies reporting no association, despite the level of exposure.[20–23] The other two studies reported a positive association in groups with more exposure, although the authors used different cutoff levels for classification.[24,25] A recent systematic review with meta-analysis reported an association among those exposed to high Hg levels (hair Hg $\geq$ 2 µg/g) and hypertension and blood pressure. The authors suggested these levels might be considered the threshold of the toxic effect of Hg on hypertension.[8] We highlight two studies that addressed the association in both exposure scenarios, single metal, and multiple metals.[21,24] One study evaluated 28 preeclamptic women and reported no association in neither model.[21] The other investigated 854 pregnant women and found an association only in the multi-metal model (aOR multi-metal = 1.60; 95%CI = 1.08–2.38 versus aOR single metal = 1.23. 95%CI = 0.87–1.73).[24] As metals are usually dispersed in the environment, it is essential to examine their possible interactions.[28] In addition, four studies investigated the mean difference and two found greater levels in pregnant women with HDP.[23,25] However, it is pretty challenging to compare mean Hg levels between biomarkers as there is uncertainty about how mercury accumulates and is distributed across tissues.[29]

Although Hg is largely distributed worldwide and hypertension is the most common medical problem encountered during pregnancy, we could retrieve only five studies for the analysis. Only one was from North Africa and none were from Latin America and the Caribbean, despite their high birth rate and low- and middle-income countries. According to 2019 data from the World Bank,[30] the fertility global tax (FGT) was 2.4 children per woman, while in the Sub-Saharan African countries, it reached 4.6. When comparing incomes, high-income countries had a FGT of 1.6, while low- and middle-income countries had 2.5 and low-income countries had 4.6.[30]

All humans are exposed to some level of Hg during their lifetime. In the general population, it mainly occurs through consuming fish and shellfish contaminated with MeHg. Also, they are exposed to relatively low levels of Hg^0/IHg, primarily through dental amalgam, and through inhalation from anthropogenic sources.[8,15] On the other hand, elevated exposure to Hg^0/IHg is found at workplaces, such as gold mines and dentist offices.[8] In our review, most (97.4%) participants were environmentally exposed, probably through diet, although only 1 study did report its frequency, but not the type of fish.[23]

The direct measurement of the level of exposure, one of the major types of biomarkers, lessens the possibility of misclassification.[31] In our review, instead of relying on the history of exposure, we chose to select studies that measured Hg levels in any biological matrix. However, we should point out the different toxicological characteristics of the three types of Hg. MeHg has a higher absorption in the gastrointestinal tract and is usually measured in blood or hair. The first indicates a recent exposure, while it points to long-term average exposure in hair. The target organ for MeHg is the brain. On the other hand, Hg^0 and IHg have high absorption through the respiratory system and usually are detected in urine, suggesting a recent exposure. The target organs for Hg^0 are the brain and kidney, and for IHg, it is the kidney. Of note, only MeHg and Hg^0 readily pass placental barriers, and Hg levels measured in umbilical cord blood suggest an exposure in the 3rd trimester.[32] In our review, four studies assessed Hg exposure through blood samples (maternal blood, maternal red blood cell, and umbilical cord blood),[20,22,23] and two did it in urine samples.[21,25] Thus, we had access to information on recent exposures, not on past ones, due to the biological matrices used.[26]

Overall, the selected studies were considered satisfactory according to the quality assessment tool used. As all studies were observational, confounding is potentially present. The adjustment for confounding factors was one of the items with significant gaps in our review. Two studies ignored it and four adjusted for confounding factors. Among those, only one adjusted for fish intake.[23] Fish is a food source of MeHg and essential nutrients, such as selenium and n-3 polyunsaturated fatty acids, which may have important cardiovascular benefits, such as a small but significant decline in blood pressure.[27,33] When exposure to a toxicant occurs from a food source, such as fish, negative confounding occurs, resulting in underestimating Hg toxicity and fish benefits.[27] Therefore, the four studies that did not adjust for this variable could have hampered the results.

To our knowledge, the present review was the first one to focus on the association between Hg exposure and HDP. As Hg is one of the most toxic substances widely dispersed in nature and pregnancy is a period of heightened susceptibility to environmental threats and cardiovascular risk, addressing their association is of utmost importance for public health.[16] To that end, we followed prespecified methods to review the evidence systematically. However, as a systematic review of observational studies, there are also some inherent limitations. First, the absence or no proper adjustment for confounding factors, especially fish intake, may be a significant reason the evidence is still inconclusive. Second, although we chose to accept studies that assess Hg exposure through measuring it in biological matrices (biomarkers), interindividual variations in the Hg kinetics cannot be disregarded as they are not well known.[32] Besides, using four different biomarkers (maternal blood, maternal red blood cells, umbilical cord blood, and urine) may introduce uncertainty to assess Hg exposure. Third, we observed substantial heterogeneity between the classification of groups according to Hg exposure level (low, middle, or high), even though there is a recommendation regarding human blood levels of Hg for pregnant women of up to 3.5 µg/L.[34] Fourth, we should acknowledge the lack of studies from developing countries, representing a significant gap in the literature, as populations with high fertility rates and living in low- and middle-income countries were also not investigated. Finally, we evaluated the relationship between Hg and HDP (categorical variable) but not with blood pressure levels (numerical variable). Not including the latter may lose studies addressing the Hg effect on blood pressure without necessarily leading to hypertension.

Conclusion

Although Hg is a toxicant widely dispersed worldwide and pregnancy is a life stage of heightened susceptibility, our review retrieved only six studies addressing the association between Hg and HDP. We found mixed results, and two of these studies found a positive association in the groups with more Hg exposure. Besides, absence or no proper adjustment for confounding factors, especially the negative one (fish intake), could hamper the results. Due to the public health impact of this topic, future studies must focus on the potential effect of Hg exposure on HDP, with particular attention to adjusting for negative confounding.

Conflict of Interests

The authors have no conflict of interests to declare.

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Assessment of Pelvic Floor Disorders due to the Gestational Diabetes Mellitus Using Three-Dimensional Ultrasonography: A Narrative Review

Avaliação das desordens do assoalho pélvico decorrentes do diabetes gestacional usando a ultrassonografia tridimensional: Uma revisão narrativa

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Rev Bras Ginecol Obstet 2022;44(12):1134–1140.

Abstract

Gestational diabetes mellitus (GDM)is an entity with evolving conceptual nuances that deserve full consideration. Gestational diabetes leads to complications and adverse effects on the mother's and infants' health during and after pregnancy. Women also have a higher prevalence of urinary incontinence (UI) related to the hyperglycemic status during pregnancy. However, the exact pathophysiological mechanism is still uncertain. We conducted a narrative review discussing the impact of GDM on the women's pelvic floor and performed image assessment using three-dimensional ultrasonography to evaluate and predict future UI.

Keywords
- diabetes
- gestational
- pelvic floor
- pelvic floor disorders
- urinary incontinence
- ultrasonography

Resumo

O diabetes gestacional (DG)é uma entidade com nuances conceituais em evolução que merecem total consideração. O DG leva a complicações e efeitos adversos na saúde da mãe e do bebê durante e após a gravidez. As mulheres também apresentam maior prevalência de incontinência urinária (IU) relacionada ao estado hiperglicêmico durante a gravidez. No entanto, o mecanismo fisiopatológico exato ainda é incerto. Realizamos uma revisão narrativa discutindo o impacto do DG no assoalho pélvico das mulheres e utilizamos o exame de ultrassonografia tridimensional para avaliar e predizer a ocorrência de IU.

Palavras-chave
- diabetes gestacional
- assoalho pélvico
- desordens do assoalho pélvico
- incontinência urinária
- ultrassonografia

received
July 26, 2022
accepted
September 21, 2022

DOI https://doi.org/10.1055/s-0042-1759742.
ISSN 0100-7203.

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

Introduction

We performed a narrative review of the literature with the intention of summarizing a qualitative interpretation of the prior knowledge towards gestational diabetes mellitus (GDM), the implication of the hyperglycemia status to the pelvic floor, and the outcome of postpartum urinary incontinence (UI). Moreover, we also evaluated the importance of the pelvic floor assessment using three-dimensional ultrasonography. In the last few decades, the Diamater Research Group, located at Faculdade de Medicina de Botucatu at Universidade Estadual de São Paulo, has been studying these important physiopathological mechanisms and assessment tools related to pelvic floor disorders. Their primary goal is to synthesize the extent of the body of knowledge regarding these particular research topics. We selected studies that support the critical findings in these areas. Hence, using the method of narrative review, we did not intend to formally assess the quality or the risk of bias in the literature provided.

Gestational Diabetes Mellitus: An Entity with Evolving Conceptual Nuances

Gestational diabetes mellitus is defined as hyperglycemia first detected during pregnancy, with glycemic blood levels that do not meet the diagnostic criteria for diabetes mellitus (DM).[1] It differs from diabetes mellitus (DM) diagnosed during pregnancy, also called overt diabetes, which is when women, without a prior diagnosis, have hyperglycemia detected during pregnancy and present blood glycemic levels that meet the World Health Organization (WHO) criteria for DM in the absence of pregnancy.[1] Brazil has high rates of DM in the adult population, with an estimated total of 14.3 million people aged 20 to 79 years. The population estimated prevalence of hyperglycemia during pregnancy in Brazil is approximately 18%, using the diagnostic criteria currently proposed in the literature.[2]

The International Association of Diabetes and Pregnancy Study Groups (IADPSG) defines that if the pregnant woman presents, in the first prenatal consultation, diagnostic criteria equal to those predetermined for the diagnosis of diabetes outside pregnancy (glycated hemoglobin $\geq$ 6.5%; fasting glycemia $\geq$ 126 mg/dL, or glycemia at any time $\geq$ 200 mg/dL), she will be considered as a carrier of previous DM or overt diabetes, diagnosed in pregnancy.[3] It also defines that the GDM diagnosis should be established when fasting glucose is $\geq$ 92 mg/dL and $<$ 126 mg/dL. Alternatively, at least one of the values of the oral glucose tolerance test with 75 g (75g-OGTT), performed between 24 and 28 weeks of gestational age, is $\geq$ 92 mg/dL at fasting; $\geq$ 180 mg/dL in the 1st hour; and $\geq$ 153 mg/dL in the 2nd hour. The 75g-OGTT is universally recommended for all pregnant women who did not present previous DM or hyperglycemia at the beginning of pregnancy.[4] The HAPO study determined the cutoff points of the 75g-OGTT because they corresponded to an increase in the odds ratio of 1.75 for one of the following neonatal outcomes studied: birth weight above the 90th percentile, percentage of neonatal body fat above the 90th percentile, or C-peptide value in the umbilical cord above the 90th percentile. Thus, pregnant women with one or more points in the 75g-OGTT would have a 75% higher risk of having a newborn with one of these three neonatal outcomes when compared to pregnant women without any of these altered values.[5,6] Given the need to move towards a single criterion for the diagnosis of GDM, the WHO adopted the IADPSG. Two warnings were inserted: 1) that these criteria were valid for any gestational age, and 2) that the blood glucose value of 2 hours of 75g-OGTT should be between 153 and 199 mg/dL for the diagnosis of GDM since values $\geq$ 200 mg/dL correspond to the diagnosis of DM.[7,8]

In prenatal routine, fasting glucose is recommended up to 20 weeks of gestational age to diagnose GDM and overt diabetes. All pregnant women with fasting glucose below 92 mg/dL should perform 75g-OGTT from 24 to 28 weeks. If the onset of prenatal care is delayed after 20 weeks of gestational age, 75g-OGTT should be completed as soon as possible.[1]

Gestational diabetes mellitus leads to complications and adverse effects on the mother's and infant's health during pregnancy. In addition, in the immediate postpartum period, it can delay the onset of breastfeeding and affect the health of the woman and the infant.[9] Women diagnosed with GDM in the first half of pregnancy represent a high-risk subgroup for increased obstetric and clinical complications.[10,11] Women with GDM have a higher chance of recurrence of GDM in future pregnancies and also a higher risk of developing type 2 DM (T2DM) throughout life. Those with obesity or who require insulin for glycemic control during pregnancy have a higher risk of T2DM. Insulin resistance is the pathophysiological basis of both GDM and T2DM and can be addressed with measures that lead to increased insulin sensitivity, such as nutritional adequacy, exercise, and medications. These interventions reduce the risk of T2DM in high-risk women, such as those with a previous history of GDM.[12]

Gestational Diabetes and Postpartum Urinary Incontinence: A Neglected but Common Association

Urinary incontinence (UI) is defined by the International Continence Society as any involuntary loss of urine.[13] It is associated with patients' physical, psychological, and social discomforts. In addition, there are well-established risk factors for UI, including advanced age, obesity, and vaginal delivery.[14]

A systematic review and meta-analysis conducted by Tähtinen et al.,[14] in 2016, reported that vaginal delivery is associated with almost twice as long-term UI, an increase of about 8% when compared to cesarean delivery.

Gyhagen et al.[15] conducted a national cohort study in Sweden to investigate UI's prevalence and risk factors 20 years after a vaginal delivery or cesarean section. The study population consisted of 5,236 women who returned the questionnaire by mail, primiparous with a single pregnancy, had vaginal or cesarean delivery between 1985 and 1988, and had no later births. The prevalence of UI was higher

after vaginal delivery (40.3%) than after cesarean section (28.8%); odds ratio (OR) 1.67; 95% confidence interval (CI) 1.45–1.92. In addition, there was an 8% increase in UI risk for each unit of body mass index (BMI) plus, and maternal age at delivery increased the risk of UI by 3% each year.

The weakening of the pelvic floor muscle (PFM) causes hypermobility of the bladder neck, and urethra, leading to the woman's incompetence of the urethral sphincter. Pregnancy itself is a significant risk factor for UI. The exact causes associated with pregnancy remain not fully understood.[16]

During pregnancy, UI is more frequent as pregnancy progresses, compromising women's quality of life. There are few publications on the prevalence of the pregnancy-specific UI (PS-UI). In addition, little is known about the clinical implications regarding the time of onset of UI during pregnancy, and the factors involved in its pathophysiology remain unexplored.[17] A study conducted in Norway by Wesnes et al.[18] described a cumulative incidence of 46% of pregnant women with UI, and multiparity was the main and most relevant risk factor.

In a large cohort study with 81,845 women to assess the association between type 2 DM and UI, development risk was higher in diabetic women.[19] Women with GDM also have a higher prevalence of UI. However, the exact pathophysiological mechanism is still uncertain. Nevertheless, weight gain, obesity, fetal macrosomia, and any conditions that increase bladder pressure and urethral mobility may be implicated. In addition, hyperglycemia can cause polyuria and detrusor instability. Hence, the risk of UI is higher during pregnancy and persists after childbirth.[20] Kim et al.[20] examined the prevalence of UI among women with GDM. They found that 49% of women reported urine loss during pregnancy, and 50% reported UI in the first 5 years after delivery.[20] Chuang et al.,[21] in a survey of 6,653 women with GDM, described that incontinent women who had GDM had a higher severity of UI 2 years after delivery. Thus, they conclude that GDM is an independent risk factor for postpartum UI, with an essential impact on the severity of symptoms.[21]

A pioneer cross-sectional study in Brazil conducted by Barbosa et al.[22] with 832 selected women evaluated the prevalence of 2-years postpartum UI and found it was 18.9% after cesarean section and 17% after vaginal delivery, with no statistical differences between delivery routes. Women who had increased weight gain during pregnancy were at increased risk for PF dysfunction during pregnancy. Women with GDM had a significantly higher UI prevalence 2-years postpartum (OR: 8.6, 95% CI: 3.0–24.3).[22]

The Pelvic Floor

The PF deep muscles consist of the levator ani muscle (LAM), formed by the puborectalis, pubococcygeus, and iliococcygeus muscles. The superficial muscles of the PF form the urogenital diaphragm and include the cavernous ischium, spongy bulb, and the superficial transverse muscle of the perineum. Fascia interposes these muscles continued with the pelvic endofascia, which involves the pelvic viscera, and contributes to the PF support.[23]

The LAM has a tapered shape, with a central slit through the urethra, vagina, and anus. The puborectalis part is the lowest and is placed in the lower branches of the pubis and later borders the anal canal. The function of the PF muscles is to make voluntary and involuntary contractions, responsible for urinary and fecal continence. The puborectalis portion of LAM is essential in supporting and conserving continence.[24]

Pelvic floor disorders (PFDs), including UI, genital prolapse, and anal incontinence, are highly prevalent in women of all ages. Imaging evaluation methods are essential for diagnosing and treating diseases and studying the integrity of pelvic structures. Many imaging modalities are used to evaluate the PF, such as computed tomography (CT), magnetic resonance imaging (MRI), and contrast-enhanced defecography.[25] As limitations, CT and defecography use contrasts and employ ionizing radiation. Defecography can replicate and evaluate patients' symptoms in real-time during defecation. However, it employs X-ray, it is unpleasant for the patient, and it is challenging to reproduce. Magnetic resonance imaging provides a good evaluation of the soft tissues of the PF without the use of ionizing radiation. However, it requires the use of contrasts, and it is not operator-dependent. In addition, the high cost of the examination, the prolonged time of image acquisition, and the difficulty of availability of the device limit its use in practice and are disadvantages. More importantly, MRI does not allow the proper evaluation of the functional maneuvers of the PF.[26] Ultrasound (US) imaging is widely used for morphological and functional evaluation of the PF. Studies have demonstrated the superiority of the US in conjunction with clinical evaluation compared with manometry, electromyography, and defecography. It is also helpful as a biofeedback tool for functional PF training. Anal ultrasound of the PF is beneficial for evaluating the anal sphincter and diagnosing fecal incontinence. It uses specific high-frequency transducers that ideally reproduce a 360-degree panoramic image to visualize the anal sphincter complex properly. Transvaginal US for PF evaluation employs identical transducers to study internal pelvic structures. However, it has limited use due to the very close proximity to the PF structures, the possible interference of the transducer in the functional evaluation, and especially the limited angle of insonation provided by the transducer for good acquisition of the images.[27]

The transperineal, or translabial, US was one of the first ultrasound modalities used to study the PF. It is a handy and widely available tool, of low cost, little invasive, and easy to reproduce. It also allows the evaluation of the structures of the PF during functional maneuvers. The three-dimensional US (US3D) of the PF is a technique described more than 20 years ago which has gained more notoriety in recent years. It reproduces three-dimensional images of the PF similarly to those obtained by MRI, with the advantages of being more widely available and more affordable, being faster and mainly allowing clinical and functional evaluation of the patient in real-time. In addition, it does not cause more significant discomfort for the patient and does not require contrasts for its execution. It is less user-dependent than the

two-dimensional US, which contributes to greater accuracy of the evaluations and measurements of the PF. The 3DUS provides an adequate and reliable assessment of the anatomy and function of muscles and structures, essential in the clinical and complementary diagnosis, treatment, and follow-up of PF disorders. Therefore, many authors argue that the PF 3DUS should be routinely used to evaluate and manage diseases and dysfunctions. In addition to assessing the structures and functions of LAM, imaging methods are essential to exclude coexisting diseases, propose individualized treatments according to the findings, monitor therapy, better understand therapeutic failures, and support the study of conditions that can cause damage to the LAM.[28]

The comparison between MRI and 3DUS is frequently found in the literature, and the benefits and practicality of using the PF 3DUS are well established and validated.[29]

The etiology of PF disorders is multifactorial. Traumatic damage to support structures during labor and vaginal delivery may be important factors contributing to UI and genital prolapse development.[30]

In 2009, Shek and Dietz,[31] using 3DUS from the PF before and after delivery, concluded that vaginal delivery results in enlargement of the hiatal area (HA), especially after LAM avulsion. However, even without macroscopic alteration of the muscle, there may be greater distensibility of the HA, which may be related to other mechanisms.[31]

The same authors, in 2010, conducted a prospective longitudinal study in 468 nulliparas in the 3rd trimester and after delivery to determine whether the prediction of trauma to the LAM is feasible with the 3DUS, without success. They concluded that prediction is very difficult or even impossible.[32]

In a prospective longitudinal study in Germany, in 2013, Falkert et al.[33] used 3DUS after immediate delivery and 18 to 24 months postpartum. The objective was to evaluate whether the changes observed in the PF after prompt delivery persisted after 18 to 24 months. A total of 59% of women completed the follow-up, and a significant increase in HA was observed in vaginal postpartum compared to cesarean section. However, there were no significant UI changes between the vaginal and cesarean groups. Independently of the mode of delivery, the UI incidence was higher in the larger HA group.[33]

A study conducted in Brazil, in 2013, by Araujo Júnior et al.[34] at Universidade Federal de São Paulo evaluated the changes in the 3DUS of the PF of primiparous women with different delivery modes. They demonstrated higher HA in the postpartum vaginal group and forceps about cesarean delivery.[34]

Chan et al., in 2013,[35] investigated PF biometrics during pregnancy and its correlation with symptoms of PF disorders in each trimester of pregnancy. The HA significantly increased by 15.1 +/- 24.8% at rest and 24.7 +/- 28.5% at Valsalva from the first to the third trimester. Symptoms of UI, bladder neck descent, and prolapse were associated with increased HA.[35]

Siafarikas et al.[36] investigated the association between the PF dimensions at the end of the pregnancy with the second stage of labor duration and the type of delivery. In conclusion, they found a significant association between HA and the shorter duration of the active phase of the second delivery stage and expected vaginal delivery. However, the process of parturition is highly complex, and the pelvic anatomy is only an influencing factor. The clinical findings are inconclusive in determining the risk predictors for dystocic or instrumentalized deliveries.[36] In contrast, Van Veelen et al.[37] showed that smaller HA dimensions during the contraction of the LAM in the first pregnancy were associated with instrumentalized or cesarean delivery. In another study, Van Veelen et al.[38] demonstrated that the HA values and the contractility and distensibility of the LAM increase during the first pregnancy. Thus, regardless of the type of delivery, this more significant distension of the HA persists after birth and may be related to future PF dysfunctions in the woman's life.[38]

Staer-Jensen et al.[39] studied the morphological changes of the PF in a cohort of primiparous women. In conclusion, the LAM can recover after pregnancy and delivery, although not all women recover from the levels demonstrated during pregnancy.[39]

Siafarikas et al. (2013)[40] published a study on the learning process to perform and analyze the images of the PF 3DUS. They concluded that the exam can be learned quickly and that the technique is reliable.[40] The publication addresses the length of the learning process for multiple measures of hiatal functional anatomy, showing that the measurement of all assessed hiatal dimensions could be taught to an acceptable standard within 23 hours of total training, confirming several other studies demonstrating good repeatability of levator hiatal dimensions.

We published a study by Sartorão Filho et al.[41] that evaluated the PF biometry using 3DUS at 2 time points of gestation in pregnant women with GDM. We performed a prospective cohort study at the Perinatal Diabetes Research Center, including 44 pregnant women with GDM and 66 pregnant women without GDM at 24 to 28 weeks of gestation. The minimal hiatal dimensions plane was used to determine the HA biometry at 24 to 28 and 34 to 38 weeks of pregnancy by 3DUS. Of a 110 pregnant women, 100 (90.9%) completed the follow-up. The 3DUS measurements showed a negative biometric change between the 2 time points in pregnancy in women with GDM; in the HA (β coefficient: estimative of effect in biometric progression according to GDM diagnosis, using the non-GDM group as reference = – 6.76; $P = .020$), anteroposterior diameter (β = – 5.07; $P = .019$), and levator ani thickness (β = – 12.34; $P = 0.005$). Pregnant women with GDM had a significantly lower than expected percentage of changes in biometry of levator ani thickness and HA from 24 to 28 to 34 to 38 weeks of gestation when compared with the group of pregnant women with non-GDM. Thus, GDM altered the biometric morphology of PF structures assessed by the 3DUS. This reported complication may be implicated in adverse birth outcomes and may play a role in developing PF dysfunction.[41]

The Pelvic Floor 3DUS Exam Technique

The US3D biometry data of the PF used by the Diamater study group were anteroposterior diameter, transversal diameter, and HA, collected at rest, during maximum contraction, and

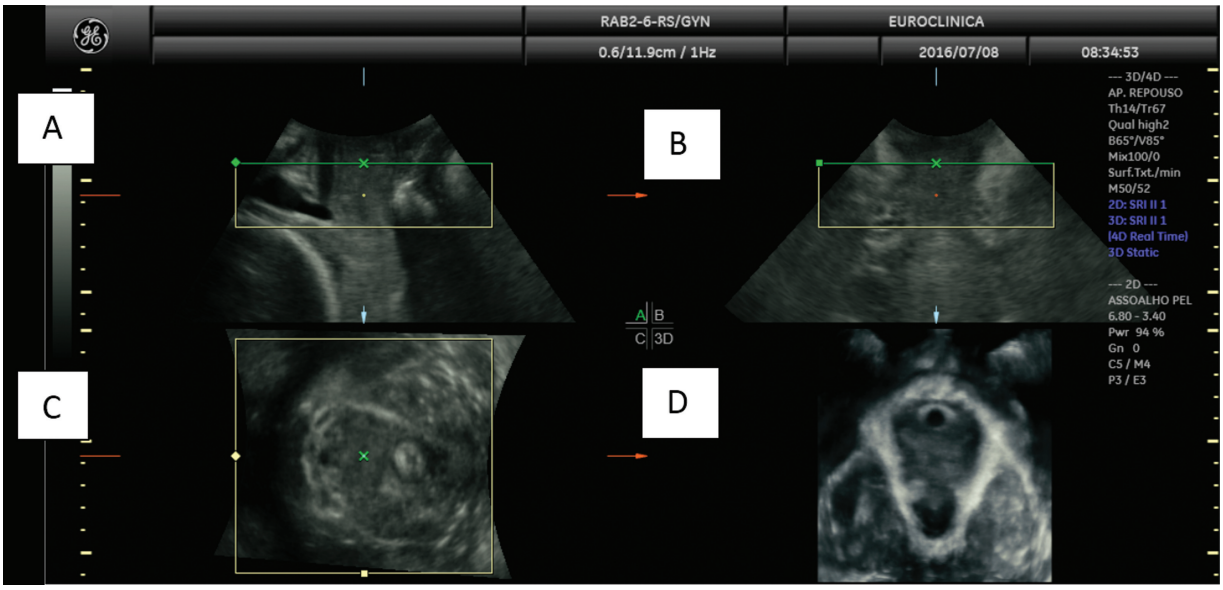

Fig. 1 Image of the three orthogonal planes: A - Mid-sagittal plane, B - Coronal plane, C - Axial plane, D - Axial plane with the rendered image.

maximum Valsalva maneuver. Women were positioned in the lithotomy position after voiding. The equipment used was the GE P8 or the GE Voluson i system with a 2-to-6 MHz curved array three-dimensional transducer (GE Healthcare, Zipf, Austria). We acquired the volume angle setting maximum in the sagittal plane and 85° in the coronal plane. Offline analysis of the rendered volume datasets was blinded using the 4D View (GE Healthcare) software program. Finally, we used the method proposed by Dietz,[27] obtaining the image of the three orthogonal planes as seen in ►**Figure 1**.

►**Figure 2** demonstrates the levator hiatal dimensions, measured in the axial plane of minimal levator hiatal distances, identified in the mid-sagittal image as the minimal distance between the inferior margin of the symphysis pubis and the anorectal junction. The anteroposterior diameter of the levator hiatus was defined as the minimum distance in a mid-sagittal direction and was measured from the symphysis pubis' inferior border to the levator's posterior margin ani. The levator hiatal transverse diameter was measured at its widest part from the internal border of the levator ani muscle, perpendicular to the anteroposterior diameter. The levator hiatus area was measured as the internal area bordered by the LAM, pubic symphysis, and the inferior pubic ramus.[27] The LAM's thickness is another possible measurement, as shown in ►**Figure 1**, although we did not perform or

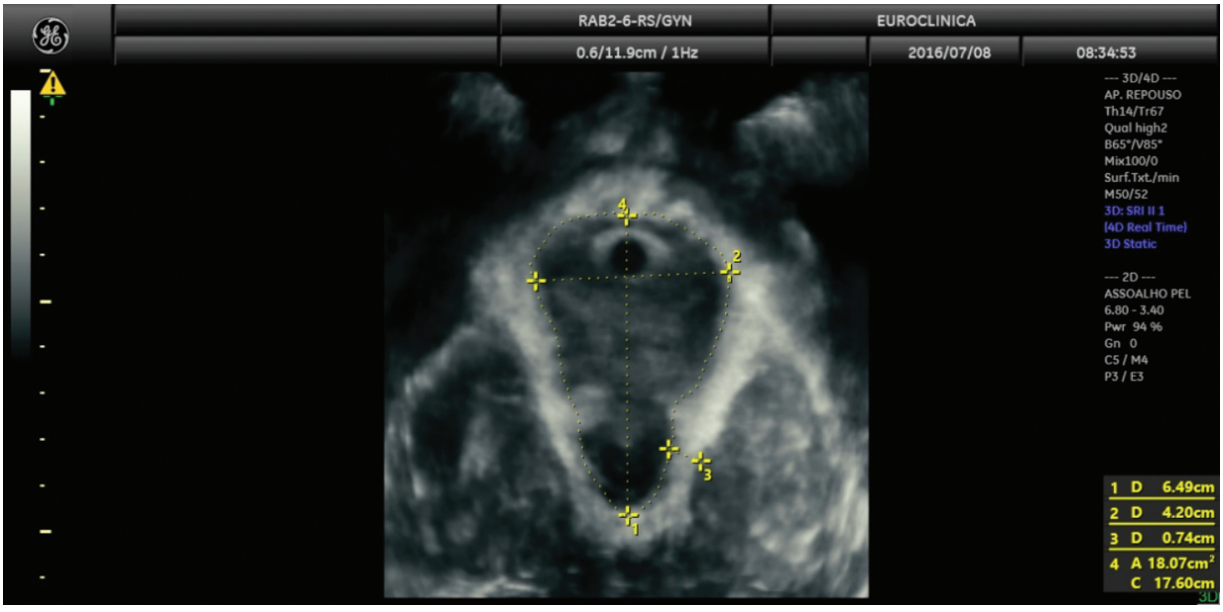

Fig. 2 Axial plane of pelvic floor: 1 - anteroposterior diameter, 2 - transverse diameter, and 3 - Levator ani muscle thickness 4 - hiatal area.

consider it for our research. The transperineal 3DUS learning process is reliable, repeatable, and practical. Thus, it should be incorporated into the modern arsenal of PF evaluation.

Financial Support
The São Paulo Research Foundation (FAPESP) #2016/09710-9 awarded the corresponding author financial support for this research.

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

Acknowledgments
We are very thankful for the support from the Diamater Research Group, led by Professor Emeritus Marilza Vieira Cunha Rudge. Diamater Study Group - Rudge M. V. C., Barbosa, A. M. P., Caldeiron I. M. P., Souza F. P., Berghmans B., de Bie R., Thabane L., Junginger B., Graeff C. F. O., Magalhães C. G., Costa R. A., Lima S. A. M., Kron-Rodrigues M. R., Felisbino S., Barbosa W., Campos, F. J., Bossolan G., Corrente J. E., Nunes H. R. C. Abbade J., Rossignoli P. S., Pedroni C. R., Atallah A. N., Di Bella Z. I. K. J., Uchoa S. M. M., Duarte M. A. H., Mareco E. A., Sakalem M. E., Martinho N., Hallur L. S. R., Reyes D. R. A., Alves F. C. B., Marcondes J. P. C., Prudencio C. B., Pinheiro F. A., Sartorao Filho C. I., Quiroz S. B. C. V., Pascon T., Nunes S. K., Catinelli B. B., Reis F. V. D. S., Oliveira R. G., Barneze S., Enriquez E. M. A., Takano L., Carr A. M., Magyori A. B. M., Iamundo L. F., Carvalho C. N. F., Jacomin M., Avramidis R. E., Silva A. J. B., Orlandi M. I. G., Dangió T. D., Bassin H. C. M., Melo J. V. F., Takemoto M. L. S., Menezes M. D., Calderon T. D., Santos N. J., Lourenço I. O., Marostica de Sá J., Caruso I. P., Rasmussen L. T., Garcia G. A., Nava G. T. A., Pascon C., Bussaneli D. G., Nogueira V. K. C., Rudge C. V. C., Piculo F., Prata G. M.

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Commercial Surrogacy: An Overview

Gestação de substituição comercial: Uma visão global

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Rev Bras Ginecol Obstet 2022;44(12):1141–1158.

Abstract

Objective Surrogacy is the process in which a woman carries and delivers a baby to other person or couple, known as intended parents. When carriers are paid for surrogacy, this is known as commercial surrogacy. The objective of the present work is to review the legal, ethical, social, and cultural aspects of commercial surrogacy, as well as the current panorama worldwide.

Methods This is a review of the literature published in the 21st century on commercial surrogacy.

Results A total of 248 articles were included as the core of the present review. The demand for surrogate treatments by women without uterus or with important uterine disorders, single men and same-sex male couples is constantly increasing worldwide. This reproductive treatment has important ethical dilemmas. In addition, legislation defers widely worldwide and is in constant change. Therefore, patients look more and more for treatments abroad, which can lead to important legal problems between countries with different laws. Commercial surrogacy is practiced in several countries, in most of which there is no specific legislation. Some countries have taken restrictive measures against this technique because of reports of exploitation of carriers.

Conclusion Commercial surrogacy is a common practice, despite important ethical and legal dilemmas. As a consequence of diverse national legislations, patients frequently resort to international commercial surrogacy programs. As of today, there is no standard international legal context, and this practice remains largely unregulated.

Keywords
- bioethics
- fertilization in vitro
- legislation medical
- medical tourism
- surrogacy

Resumo

Objetivo A gestação de substituição é o processo no qual uma mulher engravida e entrega um bebê a outra pessoa ou casal, conhecidos como pais pretendidos. Quando as gestantes são pagas, isto é conhecido como gestação de substituição comercial. O objetivo do presente trabalho é rever os aspectos legais, éticos, sociais e culturais da gestação de substituição comercial, bem como o panorama atual em todo o mundo.

Métodos Trata-se de uma revisão da literatura publicada no século XXI sobre a gestação de substituição comercial.

Resultados Um total de 248 artigos foi incluído nesta revisão. A demanda por tratamentos com gestação de substituição por mulheres sem útero ou com distúrbios

Palavras-chave
- bioética
- fertilização em vitro
- legislação médica
- turismo médico
- gestação de substituição

received
May 16, 2022
accepted
August 25, 2022

DOI https://doi.org/10.1055/s-0042-1759774.
ISSN 0100-7203.

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uterinos importantes, homens solteiros e casais masculinos está aumentando constantemente em todo o mundo. Este tratamento reprodutivo tem dilemas éticos importantes. Além disso, a legislação é amplamente adiada em todo o mundo e está em constante mudança. Portanto, os pacientes procuram cada vez mais por tratamentos no exterior, o que pode levar a importantes problemas legais entre países com leis diferentes. A gestação de substituição comercial é praticada em vários países, na maioria dos quais não há legislação específica. Alguns países tomaram medidas restritivas contra esta técnica por causa de relatos de exploração destas mulheres.

Conclusão A gestação de substituição comercial é uma prática comum, apesar de importantes dilemas éticos e legais. Como consequência de diversas legislações nacionais, os pacientes frequentemente recorrem a programas de gestação de substituição comercial internacionais. Atualmente, não existe um contexto jurídico internacional padrão e esta prática permanece em grande parte não regulamentada.

Introduction

Surrogacy is the process in which a woman carries and delivers a baby to another person or couple, known as the commissioning or intended parents (IPs).[1,2] The first historical report of surrogacy is in the book of Genesis – the case of Sarah and Abraham's child, Ishmael, carried by their servant.[3] However, the first officially recognized surrogacy was performed in 1991.

Traditional or genetic surrogacy occurs when the carrier also provides the oocyte, hence she is the genetic female progenitor of the child. This modality has progressively been abandoned and the American Society of Reproductive Medicine (ASRM) clearly recommends against it.[4] On the other hand, in gestational surrogacy, also called treatment with a gestational carrier (GC), both gametes are provided by other people, so the surrogate woman has no genetic links with the child.[5] Nomenclature regarding this matter may be somewhat misleading – some also call this last modality "partial" (and traditional would be total surrogacy) since the carrier is only providing the womb, while others call it "total" because the embryo is completely genetically unrelated to the carrier (and traditional would be partial surrogacy).[6] Other terms have been used less frequently, such as classical or straight.[7]

Gestational carriers may be a relative, a friend, or a person chosen by the surrogacy agency or in vitro fertilization (IVF) clinic. In the last case, the surrogacy process may be completely anonymous or there may be a direct contact between the IPs and the surrogate.[8] Intended parents may be heterosexual couples, female couples or single women, usually with a uterine condition that limits pregnancy, as well as male couples or single men.

Surrogacy may be altruistic or gestational carriers may be paid for the process, which is called "commercial" or "compensated" surrogacy.

Commercial surrogacy has been practiced for the last decades and is usually associated with important costs. In general lines, there is a written agreement which outlines both the intentions of both parties, defines duties, delineates reimbursements and payments, and allows decision-making when contingencies occur.[9]

There is neither an absolute number of babies born through his technique, nor an exact estimation of its value. In the beginning of the decade of 2010, an estimated 2% of all the IVF cycles in the United States of America (USA) and Canada ended in an embryo transfer to a gestational carrier, 18% of them by foreign patients. In California, in 2015, the percentage of foreign patients was estimated to be 44%.[10–12] In the early 2000s (it was legal by then), the commercial surrogacy business was evaluated by Thai and Indian national departments of health as 125 and 449 million US dollars (USD), respectively.[13] In 2012, the industry of surrogacy in the USA was estimated to be worth around 6 billion USD.[5] There was a 4-fold increase in the number of GC cycles in the USA between 1999 and 2013. Between 2006 and 2010, there was a 1,000% increase in the market of international surrogacy. There are reports of international surrogacy agencies stating a growth of 6,000% in 12 years.[14]

In the USA, a complete process of surrogacy may cost as much as $200,000. Programs usually include $20,000–80,000 for medical expenses, $3,000–15,000 for legal support, $6,000–54,000 for surrogacy recruiting programs and $20,000–55,000 for carrier compensation.[15] In low-income countries, a full surrogacy process usually costs less than half of the USA.[16]

The aim of the present work is to review and summarize information published in scientific journals about commercial surrogacy, with particular attention to the legal, ethical, and sociocultural aspects of this reproductive treatment as well as current practices worldwide.

Methods

This is a review of all articles listed in PubMed concerning commercial surrogacy published in the 21st century. The search was conducted in November 2021 using the query "surrogacy" and limiting to articles published from 2000 (including) on. Articles not related to commercial surrogacy were excluded, as well as editorials, letters to the editor, comments, corrigenda, replies, book chapters and study

protocols. Articles written in English, French, Portuguese, or Spanish were included. References of the selected articles were thoroughly reviewed in order to include other potentially related articles.

Study Appraisal

From the search using the query, a total of 1,278 results were retrieved. All titles and/or abstracts of the articles were analyzed. Duplicates were removed ($n = 3$). Studies not related to the study question ($n = 965$), editorials/letters to the editor ($n = 7$) and answers or comments ($n = 17$) were excluded. From the remaining articles, 5 mentioned only altruistic surrogacy, 28 were not available (mainly because of the year or journal of publication) and 5 were excluded due to language. At end, a total of 248 articles were included as core of this review.

Ethical Issues

Principle of Autonomy

If a surrogate treatment is performed by free will of both intended parents and carrier, one may assume that autonomy is guaranteed.[17] If surrogacy was to be prohibited, both IPs and surrogate would be restrained from having the option to participate in it, which violates their autonomy and free will.[18] Nevertheless, the offspring is not autonomous to take any decision on the matter, and will be restricted the right to completely know his/her biological origins.[19]

Principle of Beneficence

In the same way, if intended parents wish to have a child, their benefit is obvious. The gestational carrier may have her benefit from her personal satisfaction of aiding others and considerable economic compensation. The offspring will be granted the right to live.[20]

Principle of Nonmaleficence

On the other hand, IPs will face important costs, they won't be able to experience pregnancy, they will not have any control on the surrogate or pregnancy, and they will be imposed a potential additional stress caused by the distance to their children-to-be. Couples seldom report fears related to the surrogate process, particularly related to social judgment and legal troubles arising from this procedure.[21] However, studies on IPs show they usually have a good experience throughout the surrogacy process.[22] Carriers will be exposed to the risks of pregnancy, may eventually suffer from social stigma and ostracism (including by their family, which often leads them to move away from their communities to hide pregnancy) and will not have any motherhood rights on that child.[23–27] While studies with surrogates in high-income countries show that GCs perceive surrogacy as a positive experience, studies in low-income countries show high rates of depression and negative feelings in GCs.[28–30] A curious comparison has been made between the carrier and a nanny – if the child is already adopted prenatally by the IPs, the surrogate would play the role of a "prenatal nanny". These authors question the potential maleficence of being a carrier and ask if it would be more outrageous to be a nanny before birth than after.[31] Children may eventually suffer from social stigma and may have difficulties when being told their true origins. They will not be able to know or have any contact with their birth mother.[32,33] Nevertheless, studies about the opinion of children (born after surrogacy) are reassuring, even though evidence to date is limited.[24,34,35] In addition, some doubts have been raised about raising a child in a non-traditional (non "mother and father") family.[36] However, much research has been done on child rearing by same-sex couples and the results are reassuring.[37]

Principle of Justice

If all people were to have the same access to surrogacy, the principle of justice would be granted for everyone, but this implies that surrogacy is not to be limited based on marital status, ethnicity, religion, sexual orientation, or any another kind of discrimination.[38,39] In fact, surrogacy is a way to provide fertility to some infertile couples, singles and same-sex couples.[40] However, in case of commercial surrogacy, the costs are high and not affordable by everyone. As opposed to patients, carriers are not given any legal motherhood rights. In addition, the process of selecting only healthy young women as carriers may lead to discrimination of other candidates willing to participate.[41] As opposed to conventionally-born children, children born through surrogacy are not granted the right to grow with their gestational mother.[17]

Ethical Aspects of Commercial Surrogacy

An important ethical aspect of commercial surrogacy is that women may be regarded as a "way to conception" and children as mere products of conception.[17,42–45] Concerning children, some regard surrogacy as "selling babies" or human trafficking.[46–49] Others consider it does not violate any of the children's rights, it cannot be regarded as a market of babies and that if the conditions of the surrogate arrangement are fulfilled at the end of the process, the best interest of the child is implicitly protected, since this was the manifested desired of both parties, a carrier who was always aware she was not going to be mother, and the IPs who are receiving their most desired child.[50] Some consider these treatments to be exploitative to women.[51–53] In fact, commercial surrogacy opens a door to illegal exploitation if not adequately ruled and monitored, especially in low-income countries.[54,55] In many cases, third party organizations or people receive their compensation and little, if any, is given to the surrogate.[56–59] It is also not uncommon that women are not aware of the risks of this procedure and do not have an opinion on the decision to become a carrier.[60–62] Others regard surrogacy as a different way of prostitution.[63,64] Surrogacy is also seldom compared to donating or selling a kidney *in vivo*.[25,65,66] Interestingly, some argue that paid surrogacy is in no worse position than many other exploitative commercial transactions which take place against a backdrop of global inequality and constrained options, such

as poorly paid and dangerous construction work. Hence, there would be no reason for special condemnation.[67] The criminalization of commercial surrogacy may result in undesirable consequences, removing opportunity for evidence-based law reforms which would regulate the process.[68–71] In the end, some authors argue that the theoretical "do no harm" reasons to refuse surrogacy are far from being proven. Thus, there would be no reasons for banning commercial surrogacy.[72–74]

Motivations

There are several reasons that may lead women to become a GC, such as economic compensation, pure altruism, the wish of going through a different kind of motherhood or cultural beliefs.[63,75] Nevertheless, the majority of carriers undergo this process for the compensation, mostly people with dependent families.[76–78] In fact, some women tend to accept it as a work and regard the surrogacy agency as their "boss".[23,76,79] Other gestational carriers perceive this process as an "exchange of gifts".[79] On the other side, patients who resort to surrogacy are usually women (single or part of a couple) without uterus or with important uterine disorders impairing pregnancy, single men, and same-sex male couples.[80–82] It is not uncommon that clinics, agencies or international intermediates advertise commercial surrogacy treatments specifically to single men and male couples.[83]

Compensation

Depending on national legislation, surrogacy may be commercial or altruistic. Nevertheless, in some countries where only altruistic surrogacy is allowed, carriers may be given a compensation for specific matters related to the process (such as health care expenses, sick leaves, etc.). However, given the considerable costs of healthcare in some countries, a large reward could eventually be acceptable as a mere compensation for these expenses. Thus, it may not be easy to clearly define the border between altruistic and commercial. Depending on the maximum amount allowed (if any), these compensations are seldom used off the record to mask monetary payment for surrogacy.[84] As a consequence, many authors consider the distinction between 'altruistic' and 'commercial' surrogacy increasingly unsustainable both in law and policy.[85] The amounts given to carriers in a commercial surrogacy process vary widely between countries. In the USA a gestational carrier usually receives an average amount of USD 20,000 to 55,000 per pregnancy.[15,86] Multiple pregnancies are usually paid a supplement. A monetary compensation may be regarded as a win-win situation for both parties, as the surrogate gets the money and the IPs get the child, while some believe surrogacy must not be reduced to a business transaction.[87,88] The monetary compensation for surrogacy may lead to a contradiction. On the one hand, paying a low amount may be regarded as compensation for expenses and damage, but also as an exploitation.[89,90] On the other hand, paying higher amounts leads carriers to be better compensated for their efforts, but may also lead to a competitive reproductive market, "machinerizing" of women and treating children and reproductive treatments as commodities.[51] In the Netherlands, some attempts have been made to define lower and upper limits for compensations, mainly based on the oocyte donation models. However, it is not easy to define what would be the true labor associated with surrogacy and if it should be considered as a full or partial-time job, since women will be pregnant 24 hours a day, but they are able to combine surrogacy with their daily activities, including other jobs.[51] Especially in low-income countries, it is not uncommon for surrogates to expect an extra-contractual compensation for the process.[87] In 2005, the European Society of Human Reproduction and Embryology (ESHRE) published its position regarding commercial surrogacy – "Payment for services is unacceptable; only reimbursement of reasonable expenses and compensation for loss of actual income should be considered".[91] The International Federation of Gynecology and Obstetrics (FIGO) also stated that surrogate arrangements should not be commercial.[92,93] On the other hand, the American Society of Reproductive Medicine (ASRM) compares gestational surrogacy to medical research, in which individuals are paid for activities demanding time, stress, physical effort and risk, so they consider financial compensation for surrogacy ethically justifiable.[4] Likewise, the American College of Obstetricians and Gynecologists (ACOG) affirms that compensation is ethical and appropriate for the time, effort and risks taken by a gestational carrier.[94]

Anonimity Regimen

In many states, anonymity of surrogacy is to be guaranteed, which means the choice of the surrogate mother and all the communication between her and the IPs is indirect and mediated by the clinic or agency. This is the perfect regimen for some couples who prefer anonymity and not to know the carrier in any point of the process.[95] On the other hand, there are some states where carriers and IPs are not only obliged to know and approve each other, after checking they match their expectations, but they are also encourage to actively communicate during the process and participate during all its steps.[87,96] Some authors believe this involvement between IPs and carriers and an eventual further relationship of the latter with the child may be beneficial to all parties and may ease some of its ethical issues.[97,98]

Medical Risks

Being a gestational carrier is associated with important adverse medical or psychological outcomes. Obstetric complications are not higher (if not lower) in surrogate singleton gestations, since surrogate mothers are usually young and healthy.[99–103] Nevertheless, no gestation is exempt from risk.[104,105] Also, double embryo transfers are quite common in surrogate processes, because it is usually cheaper than having two separate pregnancies, resulting in more multiple pregnancies.[106–109] In addition, it is believed that cesarean section rates are high among surrogates, not only because IPs may ask for it, but also because low-income surrogates receive medical care in private clinics while in other situation they would be treated in public health systems.[110] Candidates to |GC are often quite misinformed about the procedure

and lack of psychological and legal support.[111] Particularly in developing countries, women are seduced into being GCs. Many of these women live in precarious conditions and use this resource for a better future for themselves and their families. In some cases, women are even forced to be GCs.[112] In some countries, such as India, gestational carriers often live in a hotel hired for the purpose, in order to have more dignified conditions, a healthier lifestyle for their pregnancy and more easily be able to maintain obstetric surveillance, particularly women who live in remote areas.[113] Likewise, children born from surrogacy are not risk free. Nevertheless, current scientific data suggest this option is safe as long as all parties have adequate screening and medical, psychological, and social supports.[99,114] In order to optimize the outcomes of a surrogate gestation, both the United States Food and Drug Administration (FDA) and the ASRM have developed guidelines to help choosing the most adequate gestational carrier.[115] Ideally, candidates to gestational carriers must be between 21 and 45 years old, with an optimal BMI, have at least one previous term uncomplicated pregnancy, but no more than 5 deliveries or 3 cesarean sections and with a 12 to 18 months pregnancy interval. The optimal selection of GC candidates also includes assessment of their mental health, since this may be a very demanding process.[116] Adequate medical counseling to the surrogate candidates must be done in order to promote healthy habits both before and during pregnancy. Women must be encouraged to receive preconception immunizations, if applicable, to avoid potential teratogenic medications, to take folic acid supplements, to restrain from smoking, drinking alcohol, and excessive caffeine intake.[92]

Surrogacy Agencies and Marketing

There are several international agencies exclusively dedicated to intermediate surrogate treatments.[117] The websites of these agencies seldom advertise surrogacy treatments abroad focusing on the needs of IPs, referring to surrogacy as a solution to their problem, privileging genetic parenthood. Many online advertisements of global medical tourism offer "special deals" on commercial surrogacy.[118,119] They seldom include basic and guarantee plans. The difference is that the latter includes all necessary embryo transfer to have a live newborn. The potential for exploitation of the carriers is obviously not exposed and the surrogacy arrangements are advertised as a mutual benefit. In fact, this subject is often a taboo and avoided as much as possible during all the surrogacy process.[120] Surrogacy agencies usually include staff trained in international legislation and marketing. Interestingly, most of the staff of these agencies have also undergone a similar process or is quite familiar with other transnational reproductive treatments by personal experience.[121] They usually provide legal assistance, included in all their plans. Regardless of the countries and their legal context, it is not uncommon for these agencies to advertise that there are no legal risks and there will be no litigation. They take it for granted that the surrogates have no legal rights over the child-to-be, that both the country of treatment and the country of origin will only recognize the motherhood of IPs. These agencies also state that in case of litigation, the law always protects the IPs, when actually in most cases there is no legal framework.[122] However, these agencies are an important means for IPs to easily reach a surrogacy contract, including recruitment of donors, carriers, reproductive treatments, obstetric follow-up, and legal assistance.[123,124]

Legal Issues

Legal conflicts may appear in the country where surrogacy is performed, but also in the country of origin of the IPs ("receiving country"), when returning home with the child.[125–127]

Country Where Surrogacy is Performed

National legislation varies substantially worldwide.[128] Some countries explicitly prohibit any type of surrogacy, others allow surrogacy of any type, while others have some restrictions concerning marital status, sexual orientation, nationality, country of residence, medical reason to undergo a surrogate treatment and the altruistic/commercial nature of the process. In most countries, surrogacy is not regulated at all.[14] All surrogacy arrangements beginning by signing a contract between the IPs and the GC. There are innumerous important points that should be clearly settled in the contract in order to avoid future potential litigation.[129] These include setting out both parties legal parentage and non-parentage rights, agreements on prenatal and delivery issues, compensations and fees, insurances, and assumptions of risks.[130] The central and most important party in any reproductive treatment is the offspring because he/she is the only party that cannot have a word in any preconception contract or agreement. As a consequence, most countries worldwide recognize that the child, regardless of the way in which he/she was conceived, has the same rights guaranteed by the national and international framework of human rights.[131,132] Regarding the mother, defining biological motherhood may be quite challenging in the modern era, especially in assisted reproductive treatment (ART) involving third parties, such as donated gametes or surrogacy. An interesting example is the reception of oocytes from partner (ROPA) method, or lesbian shared IVF, in which both women share biological motherhood, one will be the gestational mother (the one giving birth) and the other will be the genetic mother (the one providing the oocytes).[133] In surrogacy, 3 people may be involved in motherhood: the carrier (which will be the birth mother), the oocyte provider and the intended mother (depending if it is with own or donated oocytes, these last two will be the same or different women, respectively).[134] In the majority of countries, legal motherhood is based upon the fact of birth. The "anonymous" or "secret birth," where a woman may choose to give birth without revealing her identity, is not legal in most countries. Thus, as a rule, the woman giving birth is automatically recognized as mother, until proven otherwise. The requirement for a man to be registered as a father of a child depends upon the circumstances of the case, especially the couple's marital status. In most countries, in a married heterosexual couple, the man is automatically assumed as the father.

However, in most cases, a man may voluntarily acknowledge his legal paternity. Once a child is registered and receives a birth certificate, parents are legally recognized as so for all purposes. However, in most states, it is possible to reverse this process upon genetic proof.[135] One of the main obstacles for couples who resort to surrogacy is the registration of the newborn in their name and the cession of motherhood rights by the carrier.[136] Countries where surrogacy is contemplated by law, as is the case of some states of the USA, a prepregnancy contract is signed between the two parties in which the surrogate waives any rights to motherhood after birth. Therefore, in these cases, the birth certificate is automatically conceived with the name of the intended parents. On the other hand, in countries where surrogacy is not regulated and it is performed not because it is legal, but because it is not illegal, the original birth certificate is usually issued with the surrogate as mother, and the IPs have to ask national authorities to amend the certificate with their names.[137] However, litigation may arise in various points throughout the surrogacy journey, in view of obstetric complications, decisions regarding pregnancy interruption, lack of agreement between the IPs and the surrogate, divorce or separation of the IPs, or changes of mind of one of the parties during the process.[138] Even in the presence of a prior contract, if this practice is not regulated and there is no specific legislation, its legal value is doubtful. The most troublesome scenario is if the surrogate decides not to abdicate her motherhood rights.[139–141] In these cases, a DNA test is seldom required. Thus, parenthood is determined on a genetic basis and the court is asked to declare the motherhood rights of the carrier null. In some cases, parents have to wait months after birth to have the birth certificate amended.[142] This may be even more problematic if pregnancy is a result of double donation (donated oocytes and sperm), in which none of the IPs shares a genetic link with the baby. In any case, in the absence of a deferment by a court, the carrier has full motherhood rights over the child, which prevents the child from leaving the country with the IPs without her consent. There are reports of large amounts of bribes paid to the carrier to finally cooperate by ceding her rights.[143]

Receiving Country

Due to the absence of uniform international legislation, cross-border surrogacy treatments may pose legal issues when returning to the home country of IPs with children who, according to the legislation of the receiving country, have been conceived illegally.[144–147] The main steps where IPs face difficulties most frequently in their home countries are when requiring a passport or any travel documentation at their consular authorities overseas to return home with the child, and when the IPs, back home, wish to register their children as a national citizen.[148] If their native countries do not recognize surrogacy, patients may struggle to register the child as theirs.[149–152] Further problems may arise in cases of singles or same-sex couples from countries where they are not allowed to have children. In these cases, surrogacy itself may not be the sole problem, but the lack of legal framework to recognize both same-sex IPs as legal parents.[143] There are reports of people who were criminally accused of having filed an illegal process abroad. Nevertheless, national courts ended up acquitting them for lack of legal support regarding international affairs, because these procedures were officially recognized in the country they were performed, and because this decision was ultimately considered to be in the best interest of all parties involved, especially the child.[143,153,154] As a consequence of these disparities between legislations and issues of countries regarding international private laws, many judicial authorities of several states have attempted to create solutions to enable children born from an international surrogacy arrangement to return home. The Hague Conference on Private International Law (HCCW) is an intergovernmental organization in the area of private international law that administers international conventions, protocols, and legal instruments. It is an important organization that deals with conflicting international affairs. In 2012, the Permanent Bureau of the HCCW released "A Preliminary Report on The Issues Arising from International Surrogacy Arrangements". Since then, this institution has been trying to create guidelines to standardize the international recognition of surrogacy performed abroad. As of 2021, the HCCW had 90 country as members.[14]

Transnational Surrogacy

The denial of surrogacy in most countries, for all or for some (such as single people or same-sex couples), its cost or the lack of available carriers led to an important transnational search for these (and other) reproductive treatments.[155,156] This phenomena has been called reproductive, procreative or fertility tourism, transnational reproduction or cross border reproductive care.[157–162] In European countries alone and concerning any kind of ART, in 2010, a total of 24,000 to 30,000 cycles of cross border fertility treatment within the continent were estimated each year, involving 11,000 to 14,000 patients.[163] Transnational surrogacy is one of the fastest-growing cross-border reproductive treatments.[164] Choosing where to perform the surrogacy treatment usually entails finding the right equilibrium between legal guarantees and costs.[165] Due to the variety of legislations, costs and availability of donors and carriers between countries, patients may search for other countries to do the entire process of surrogacy, or different phases of the surrogate treatment in more than one country.[158] As an example, a male couple may get their donated oocytes from South Africa, where there are many donors available, do the IVF, recruit the surrogate and embryo transfer in Georgia (*Sakartvelo*), due to attractive prices, and fly the gestational carrier to the USA to deliver the baby, where children may be registered by both parents.[166,167] Countries for gamete donation (when needed) are usually chosen based on the availability of donors, anonymity regimen of donation, costs of the process, compensation to the donors, and ethnic issues. In vitro fertilization, in turn, may pose some legal obstacles in some countries. Legal requirements, as well as costs, the possibility of freezing embryos, performing preimplantation genetic test (PGT) and sex selection are important aspects. Surrogacy itself is the

most complex part of the process. The legal status of surrogacy is by far the most important aspect when it comes to choose the country, not only the presence or not of specific legislation concerning the matter, but also the legal value of surrogate contracts in more delicate situations, such as pregnancy interruption and in case the carrier decides to keep the baby. In addition, same-sex couples may choose the country of delivery in order to be able to share parenthood since birth. The exclusion of motherhood rights from the gestational carrier and the attribution of these rights to IPs may be done immediately after birth, or it may be a court decision after DNA tests to the child, genetic IPs and the carrier.[168] Furthermore, in the case of gay couples, the process of sharing legal parenthood may be much easier if their country of origin accepts joint adoption of a child by same-sex couples. It is very common to cross borders between neighboring countries to undergo surrogacy. Both parents or carrier may be required to cross the border, as well as gametes or embryos, depending on the case. Examples of frequent neighboring border crossings are between the USA and Mexico, and Thailand and Vietnam or Laos.[169] Diverse measures have been taken by many governments to avoid the so called "reproductive tourism". Some countries where treatments used to be performed banned these treatments, at least for foreign patients. Other countries, such as Portugal, decided to approve surrogacy only to national or resident citizens since its very beginning, to avoid reproductive tourism and legal litigation with other countries.[170] On the other hand, receiving countries face important dilemmas when it comes to attribute nationality to the offspring, but they are also in an ungrateful position to limit reproductive treatments abroad.[171] The vast majority of countries have no specific legislation concerning children conceived abroad via surrogacy.[157] Some countries, such as Australia, the Netherlands or the UK, are trying to draw preconception agreements for surrogate treatments abroad.[84] Several scandals have been reported during the last decades, such as the Baby Gammy, a child with Down Syndrome, whose intended parents left him in Thailand while taking home his twin sister, who was not affected by the condition.[172] Another famous case was a Japanese man who tried to conceive seventeen children via surrogacy.[169] In India, a Japanese couple refused to receive the baby because they divorced 1 month before delivery.[173] Following these occurrences, some popular destinations, especially in Asia, have taken legal measures to limit commercial surrogacy or access to foreign patients. Commercial surrogacy was banned in Thailand and Nepal in 2015 and in Cambodia in 2016.[76] In India, same-sex couples were excluded in 2013 and in 2018 this country limited surrogacy to national patients.[166,174] Consequently, the offer of surrogacy destinations has decreased. Over time, the "one-stop" surrogacy destinations have become increasingly rare, especially due to the partial limitation of some of the steps of the process, requiring intended parents to do a "puzzle" with various countries to complete their journey in surrogacy. On the other hand, demand for surrogacy from high-income countries such as European countries and Australia is continuously rising, due to increasing maternal age, single men, and male same-sex couples.

Cultural Aspects

Some social and cultural aspects influence the way society is more or less receptive to gestational surrogacy, especially the country of origin, religion, activism, and the whole social context.[175,176] Religion is one of the most important points, since different religions have various points of view regarding motherhood, marriage, life, and the status of the embryo.[177] Studies show that the vast majority of Muslims are against surrogate treatments, since procreation and childbearing must be carried out only under the framework of marriage.[178,179] However, some acknowledge this may be ethically justified and medically necessary.[180] Polls in Iran, Jordan, and Lebanon revealed a predominant negative attitude among healthcare workers and students toward surrogacy, mainly driven by religious beliefs.[181–183] In Jewish society, cases of donor eggs or surrogacy are also hard to deal with. If one of the women involved is not Jewish, rabbinic authorities disagree about the Jewish status of the child, which may imply that the child undergoes religious conversion.[184] The Catholic church is against any form of ART, especially if there is a third party involved, since reproduction is to be practiced in a marital context. Other branches of Christianism do accept IVF treatments. The opinions concerning surrogacy within Christians are diverse, even though they are, in general, in disfavor of this technique.[185] Hindus regard infertility as a curse, which means they accept ART and surrogacy as a cure for infertility.[185] Regarding Buddhism, since there are few theories written about ART, as long as pain and harm are avoided, all practices are acceptable. However, the very desire for a child through extraordinary means can also be seen as an unhealthy material attachment. As so, the matter of surrogacy is conflicting.[185] Studies report a duality of criteria in high income countries regarding public opinion about surrogacy. Poll-based studies in Australia, France, Germany, Japan, Philippines, Spain and the USA revealed that more than half of general population would be in favor of surrogate treatments for heterosexual and same-sex couples.[186–191] The same goes for reproductive care professionals and students.[192–194] On the other hand, feminists are against any kind of surrogacy.[63,195,196] Curiously, a recent meta-analysis showed that the majority of infertile women were not in favor of surrogacy.[197,198] A study in Romania revealed that women (general population) would rather adopt than resort to surrogacy.[199] On the other hand, studies with Iranian infertile couples reported that the majority has a positive view on surrogacy.[200,201]

Legal Context Worldwide

America

By 2021, 22 USA states have no legal statutes for commercial surrogacy, 16 states explicitly and 7 states implicitly allow it, and in 5 states it is forbidden.[114,202] In Canada, commercial surrogacy is banned, even though altruistic surrogacy is permitted in all states except in Quebec.[5,203,204] In Mexico, legal status of surrogacy is not regulated at a federal level, thus, only a few states, like Tabasco, used to offer commercial

arrangements. Consequently, Tabasco used to be a major destination for transnational surrogacy. In 2016, Tabasco changed the state law to limit surrogacy to heterosexual infertile couples. In June 2021, a Supreme Court decision upheld surrogacy in Mexico – the court endorsed both free and paid surrogacy and even invalidated the provisions of one state that prohibited access to same-sex and foreign couples. Since then, a door opened to any Mexican state to perform commercial surrogacy agreements.[205] In most countries of South America, surrogacy is not regulated, apart from Brazil and Uruguay. In Brazil, surrogacy is allowed only in the altruistic regime. There are 2 circumstances in which a person can resort to surrogacy, a woman who has ovarian reproductive potential but a uterine condition that prevents pregnancy, or a same-sex couple. In either case, the surrogate must be a 1st to 4th degree relative of one of the PIs, such as mother, sister, aunt, or cousin. As a consequence of the lack of legislation banning commercial agreements, some countries, such as Colombia, have become popular surrogacy destinations in the last years (►**Fig. 1**).[206]

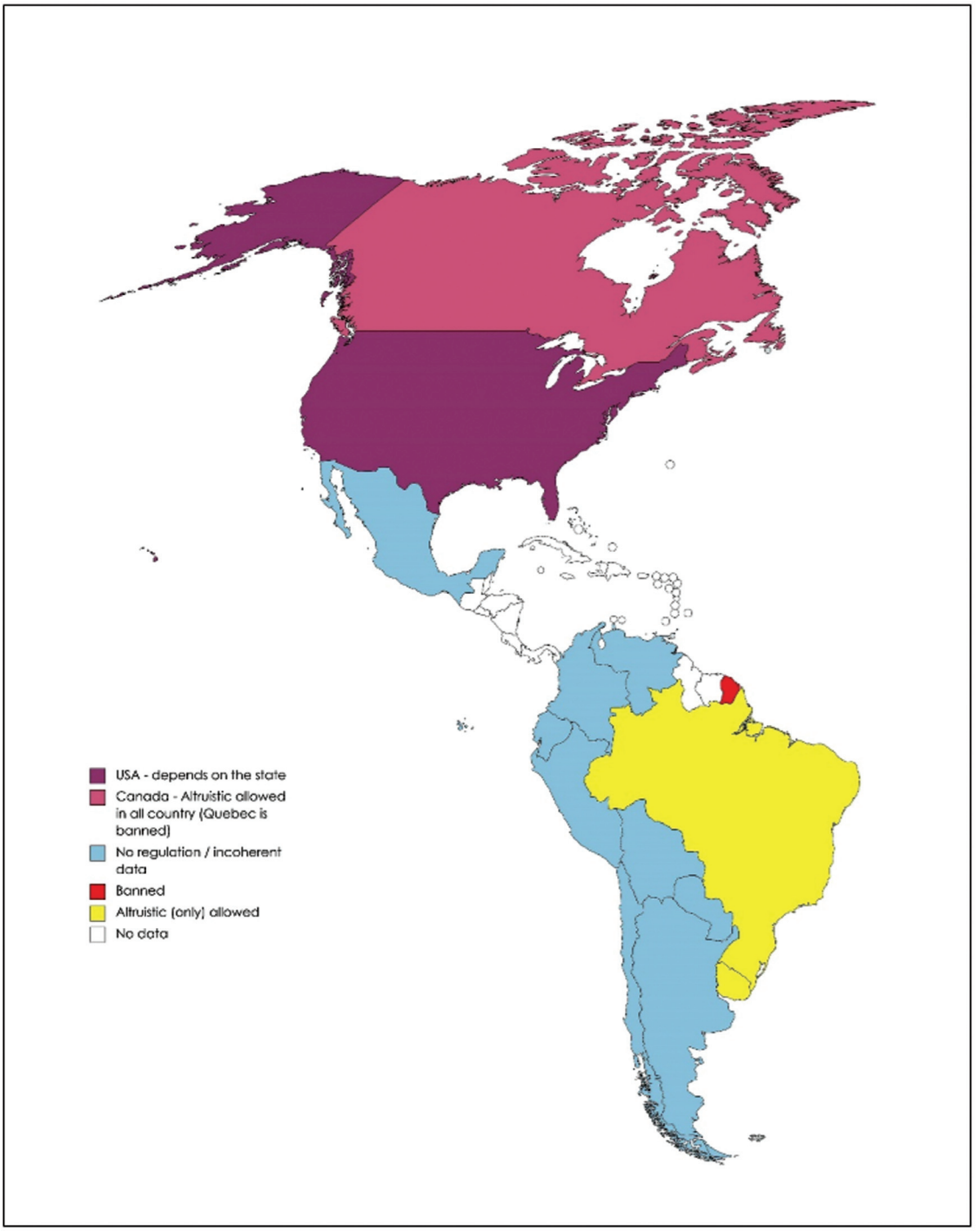

Fig. 1 Map showing the current legal status of surrogacy in America.

Europe

Legislation in Europe varies between different countries.[207] Surrogacy in Europe is allowed or not banned in Albania, Armenia, Belarus, Belgium, Cyprus, Czech Republic, Georgia, Greece, Ireland, Macedonia, Portugal, Romania, Russia, the Netherlands, the UK, and Ukraine.[208] On the other hand, it is completely banned in Austria, Estonia, France, Germany, Italy, Lithuania, Norway, Spain, Sweden, and Switzerland.[157] In most countries where it is regulated, only altruistic surrogacy is permitted, such as Belgium, Greece, Ireland, the Netherlands, Portugal, and the UK (►**Fig. 2**).[170,208,209] In Georgia, Russia, and Ukraine commercial surrogacy is possible, but in general limited to heterosexual couples.[5] Georgia and Ukraine became a major destination for commercial surrogacy, due to its attractive prices and easiness of the process.[5] Since there is no uniform legislation, the European Court of Human Rights (ECtHR) has gained importance regarding transcontinental surrogacy for European citizens, especially for receiving countries with no specific legislation or where it is forbidden.[17,153,210–213] This entity has mediated some complicated processes, in particular in France, ultimately ruling in favor of the legal recognition of the nationality and affiliation of children conceived through international surrogacy, bearing in mind that this would be in their best interest.[85,143,214–216] In addition, in some countries such as the UK, courts have accepted foreign commercial surrogacy, as national legislation supports the concept of surrogacy, provided that the foreign surrogacy is lawful, there are adequate safeguards for the child, the interests of the child being paramount, the arrangements are ethical and not exploitative, and the costs are reasonable.[217–221] In 2009, Spain made an ad hoc regulation of the national registry to facilitate the often unpredictable process of recognition of the filiations resulting from cross-border surrogacy.[222,223] Norway does not allow surrogacy of any kind but recognizes the citizenship of children of Norwegian parents born by surrogacy abroad.[224]

Asia

Asian countries used to be a major destination for commercial surrogacy, until more restricted legislation on the subject has progressively been imposed.[225,226] Since 2018, when commercial and international surrogacy were both banned in India – the Surrogacy (Regulation) Bill – most countries in south or southeast Asia do not recognize commercial surrogacy.[227–231] India, Nepal, Thailand, and Vietnam recognize altruistic surrogacy (if not for all, in some specific situations or for national citizens only) but all these countries have explicitly banned commercial surrogacy.[173,232,233] Japan and South Korea do not have specific regulation regarding surrogacy.[8,234] Mongolia, Pakistan, People's Republic of China and Taiwan explicitly prohibit any kind of surrogacy.[235] Even though prohibited, in People's Republic of China there is an important practice of clandestine commercial surrogacy

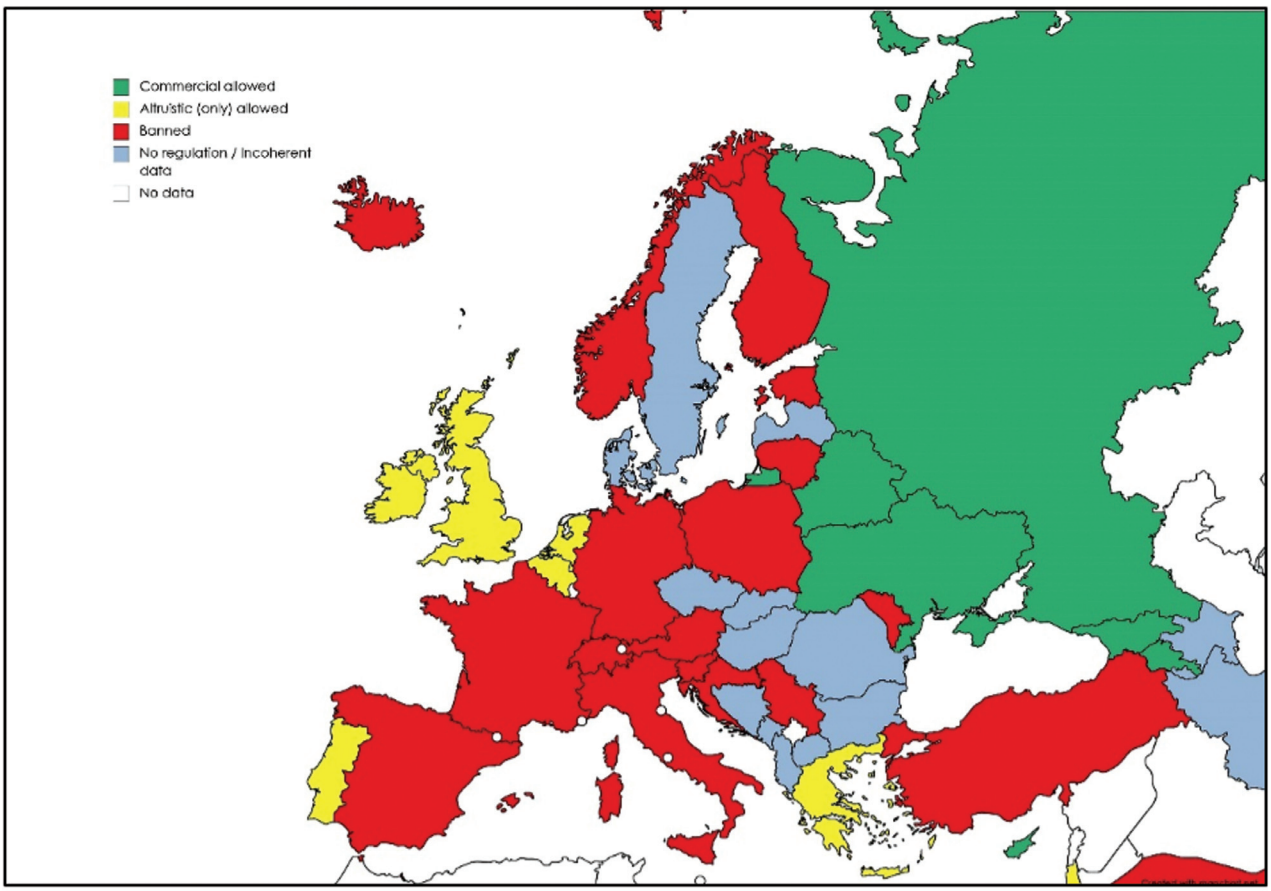

Fig. 2 Map showing the current legal status of surrogacy in Europe.

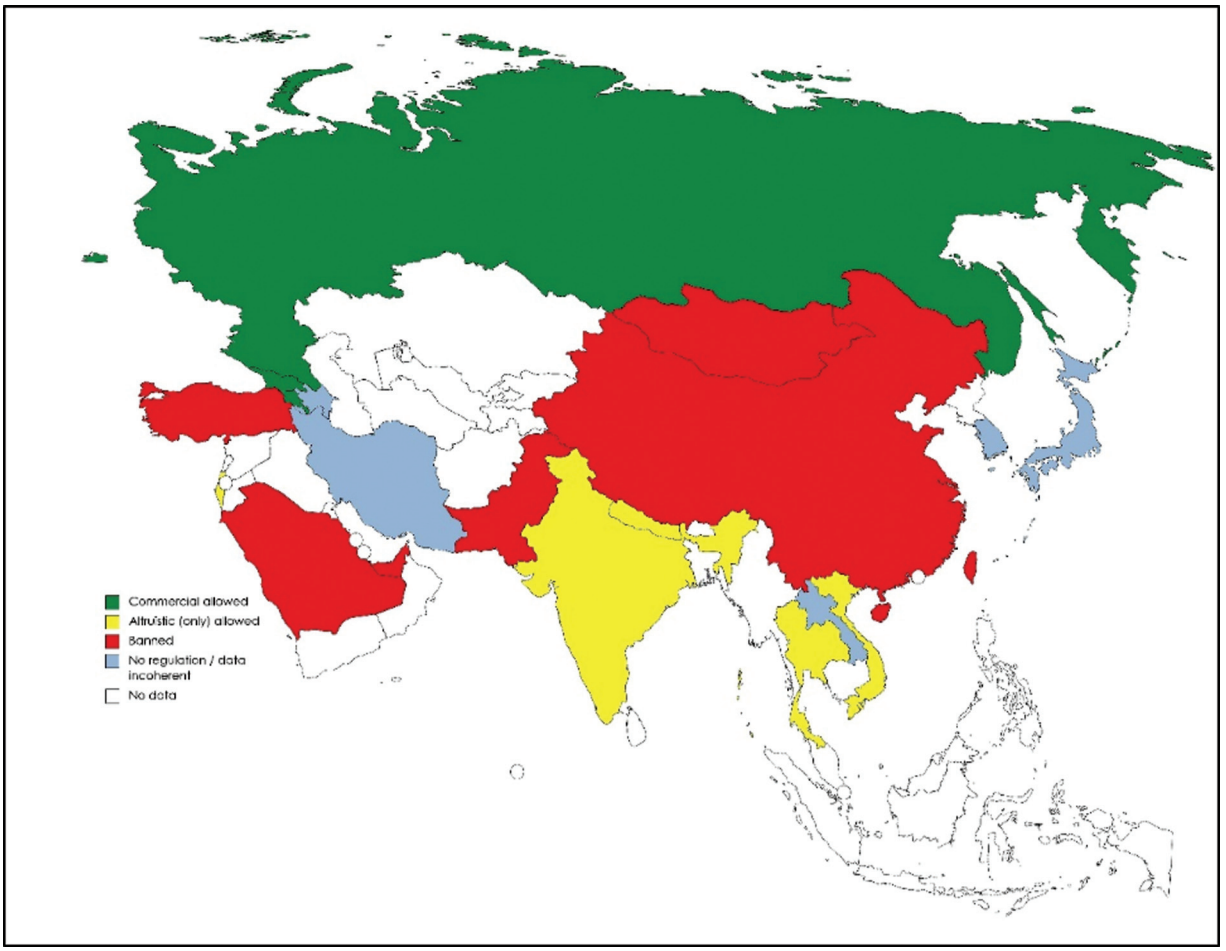

Fig. 3 Map showing the current legal status of surrogacy in Asia.

(►**Fig. 3**).[236] Nevertheless, an important part of these countries have no regulation at all regarding surrogacy, so it is not considered illegal and in some of them it keeps on being performed.[237] As a consequence of the ban to commercial surrogacy imposed by most south or southeast Asian countries, in particular India and Thailand, Laos became a popular choice, sometimes in an hybrid regimen with Thailand.[173] In the Middle East, Israel allows altruistic surrogacy only.[155,238] Iranian legislation is not clear regarding surrogacy and it is not an uncommon practice in the country.[179] In Saudi Arabia and in the United Arab Emirates, surrogacy is completely forbidden.[178,179]

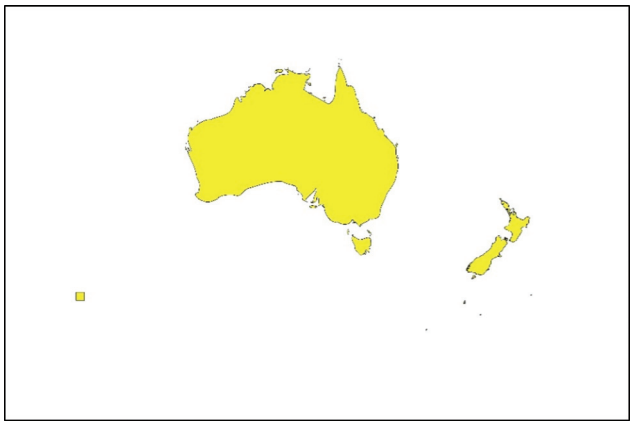

Fig. 4 Map showing the current legal status of surrogacy in Oceania.

Oceania

In Oceania, altruistic surrogacy may be performed in Australia and New Zealand, but commercial surrogacy is illegal (►**Fig. 4**).[232,239–243]

Africa

Most African countries do not have any regulation concerning surrogacy. In Kenya, surrogacy is not regulated, hence it became a popular destination for this practice.[244] In South Africa, altruistic surrogacy is allowed (►**Fig. 5**).[157]

International Affairs

In order to avoid transnational surrogacy, some models of "ideal" commercial surrogacy laws and arrangements have been proposed. Some Australian groups proposed a model targeting a fair and just compensation, enforceability of surrogacy agreements, amended parentage presumptions and the ability to obtain prebirth parenting orders, regulation of surrogacy agencies and brokers, and recognition of approved international surrogacy arrangements.[245,246] Given the legal diversity and the frequent difficulty of fitting foreign activity into national law, there are many calls of action at the

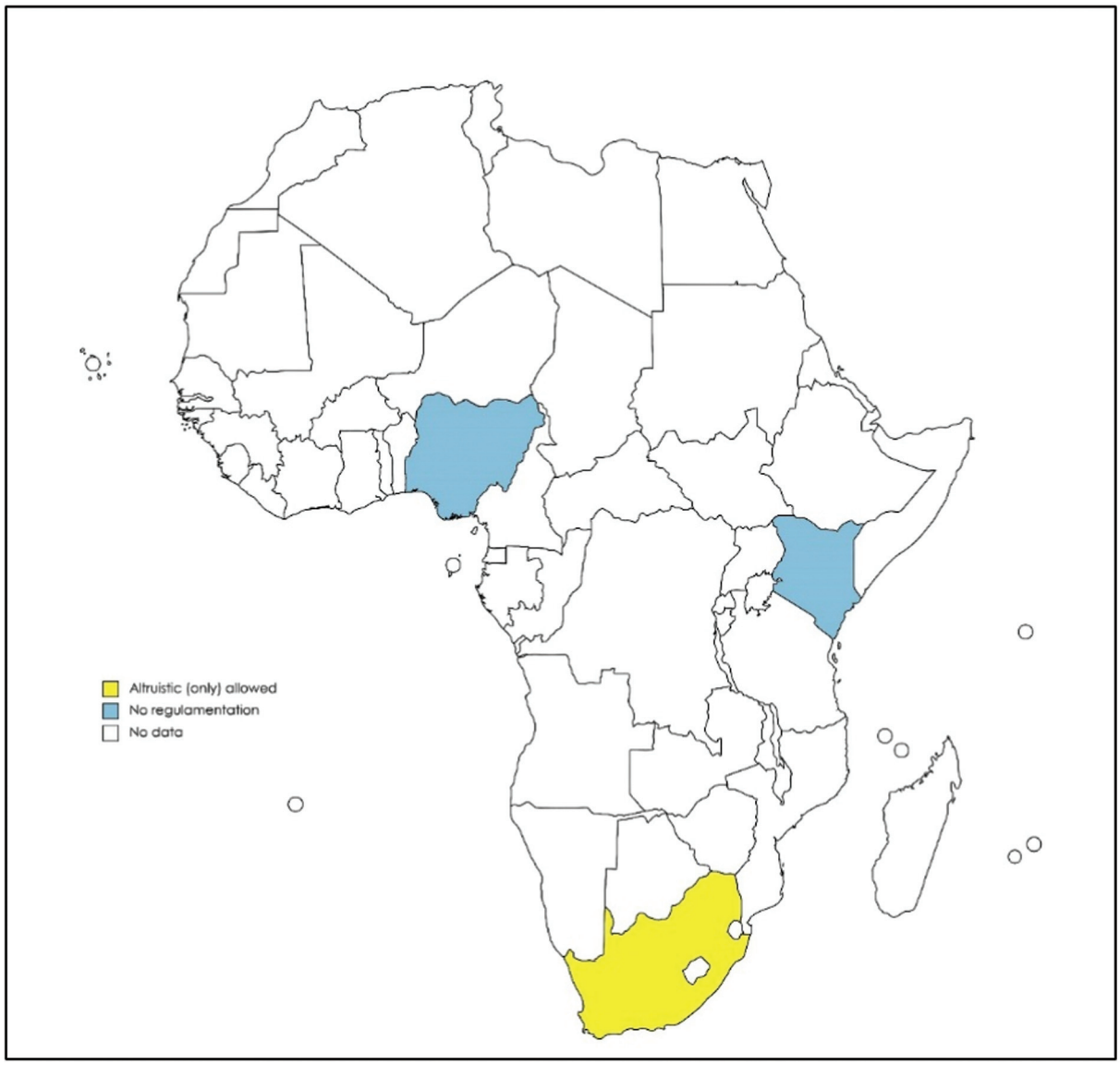

Fig. 5 Map showing the current legal status of surrogacy in Africa.

international, national, and professional levels to establish a human rights based system of international governance based on three regulatory models: public health monitoring, intercountry adoption, and trafficking in human beings, organs and tissues.[247–251] As stated before, many international intermediates make the connection between the IPs, the gametes donors and the carriers, most of the times via specific gamete banks, IVF clinics and surrogacy agencies. Most of these agencies are based in a unique country but they operate with IPs of any nationality, offering surrogacy programs in different countries, adjustable to any case.

Conclusion

Surrogacy is an important means for some people to achieve biological parenthood, in particular women with uterine disorders, single men and male couples. However, this procedure entails important ethical dilemmas and legal issues. As a consequence of the diverse legal contexts worldwide, transnational surrogacy programs are frequently used, despite the possible legal complications. Commercial surrogacy is a common practice, although not regulated in most countries. This technique raises even more ethical and legal dilemmas. Various countries and international organizations made important attempts to regulate this practice in order to standardize its legal context worldwide and avoid litigation. Nevertheless, the situation remains largely unregulated and, as such, there is still a long way to go.

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

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Simulation, A Fundamental Component of Training to Treat Placenta Accreta Spectrum

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Rev Bras Ginecol Obstet 2022;44(12):1159–1160.

Dear Editor,

We thank Professor Chikazawa et al.[1] for their interest in our paper[2] and for highlighting the importance of simulation during training for the management of placenta accreta spectrum (PAS). There are multiple options to manage PAS and although the disease exhibits a wide variety of clinical presentations (spectrum), most groups choose a single therapeutic alternative and apply it to all their patients, making it difficult to respond when deviations from the original plan arise. Few publications propose a clear sequence of inter-

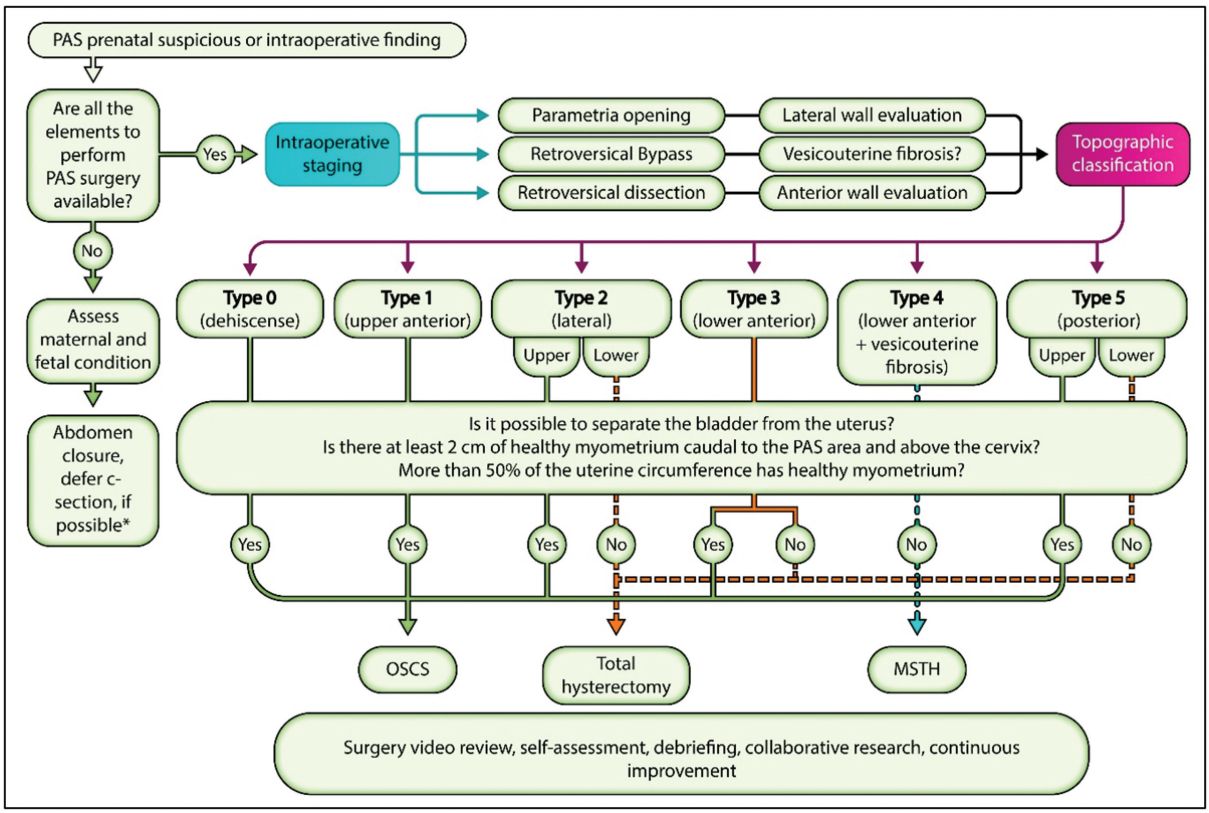

Fig. 1 Protocolized approach to PAS. Abbreviations: MSTH, Modified subtotal hysterectomy; OSCS, One-step conservative surgery; PAS, Placenta accreta spectrum. *If the clinical condition of the patient or her fetus does not allow to defer the procedure, avoid manipulating the placenta.

received
September 15, 2022
accepted
September 26, 2022

DOI https://doi.org/10.1055/s-0042-1760216.
ISSN 0100-7203.

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

ventions applicable to all types of PAS. Our group uses the protocolized approach described by Palacios-Jaraquemada et al.[3] applicable to patients with suspected prenatal PAS, but also to those diagnosed intraoperatively, considering the nature (predominantly hypervascularization or presence of vesicouterine fibrosis) and the topography of the lesion (which uterine wall is affected, and which is the relationship of the lesion with the vesicouterine peritoneal fold).[3,4] This protocol includes four steps (►**Fig. 1**).

First, the evaluation of the available resources and the clinical situation of the patient (to define whether or not to go ahead with the surgery). Doctor Chikazawa et al.[1] rightly point out that the process of training to manage PAS is a long one, and that obstetricians without such training are likely to be faced with the intraoperative finding of PAS. As useful as training in what to do, it is necessary to be very clear about what to avoid in the event of a PAS intraoperative finding, without the appropriate resources (human or technological), the greatest success of the obstetrician would be to avoid a high number of interventions when the clinical situation of the patient allows it.

Second, intraoperative staging through 4 actions: opening of the parametrium (to evaluate the lateral uterine wall), digital evaluation of the retrovesical space (Pelosi maneuver), dissection of the retrovesical space by ligating the vesicouterine pedicles (to evaluate the anterior uterine wall), and exteriorization of the uterus to evaluate the posterior uterine wall.

Third, the recommended treatment will be chosen (one step conservative surgery, total hysterectomy or modified subtotal hysterectomy) based on the topographic classification,[3,4] and after answering the three following questions: Is it possible to separate the bladder from the uterus? Is there >2 cm of healthy myometrium cephalic to the cervix and caudal to the PAS area? Does $>50\%$ of the circumference of the uterus (in an axial section at the level of the PAS area) has healthy myometrium? (►**Fig. 1**).

Fourth and last, it is essential to have photographic and video recording elements of the surgical procedures to later on debrief, self-assess, and provide research activities that facilitate learning and continuous improvement of the performance of the group. A standardized approach facilitates the construction of a mental map that obstetricians can internalize or consult immediately, facilitating decision-making in the face of a planned or unexpected PAS case.

Conflict of Interests

The authors have no conflict of interests to declare.

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Federação Brasileira das Associações de Ginecologia e Obstetrícia

FEBRASGO POSITION STATEMENT

Abnormal uterine bleeding and chronic iron deficiency

Number 11 – December 2022

DOI: https://doi.org/10.1055/s-0042-1760235

The National Commission Specialized in Venous Thromboembolism and Hemorrhage in Women of the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo) endorses this document. The production of content is based on scientific evidence on the proposed theme and the results presented contribute to clinical practice.

Key points

- Abnormal uterine bleeding (AUB) in menacme is the leading cause of iron deficiency anemia (IDA) and iron deficiency (ID).
- All patients with AUB should be investigated and treated.
- Anemia is one of the most common problems in clinical practice that affects millions of people worldwide.
- Non-pregnant women account for 30% of all anemia cases in the world, and approximately 60% of them have ID.
- Oral iron replacement is the most widespread, especially in cases of milder IDA and ID.
- Intravenous (IV) formulations have gained more space in prescriptions as their safety and efficacy have become more evident.

Recommendations

- Abnormal uterine bleeding is a very frequent complaint that negatively affects the quality of life since menacme. Investigation for IDA and ID is mandatory in these patients.
- The approach to patients with AUB prioritizes stabilization in acute cases, using mainly hormones and antifibrinolytics to stop bleeding.
- Etiological investigation will guide the therapy in non-acute cases.
- Treatment selection for ID is driven by several factors, including the presence of inflammation, the time available for iron replacement and the anticipated risk of side effects or intolerance.
- The treatment of choice for ID is preferably via oral (VO). The increase in hepcidin by oral iron supplements limits oral absorption when large amounts of iron need to be administered or in the presence of inflammatory conditions.
- Intravenous iron preparations are indicated for the treatment of ID when oral medications are ineffective or cannot be used. They have applicability in a wide range of clinical settings, including chronic inflammatory conditions, perioperative situations, and disorders associated with chronic blood loss.
- Serious adverse events that occur with IV iron are very rare and well-studied, which provides a basis for educating and preparing staff and patients on how iron infusions can be safely and effectively administered.

Background

One of the most common gynecological complaints worldwide is the occurrence of abnormal uterine bleeding (AUB), a term that refers to abnormalities in the amount, duration or frequency of bleeding from the uterus. With a prevalence of 10-30% among women of reproductive age, it can negatively affect the quality of life and is associated with financial losses, reduced productivity, inadequate health status and greater use of health services.[1,2]

What are the main causes of AUB and how to classify them?

Abnormal uterine bleeding is a symptom, not a diagnosis, and describes bleeding that deviates from the general menstrual pattern of the population. The terms and parameters currently used are described in chart 1. Abnormal uterine bleeding can also be characterized as acute (severe enough episode that requires immediate intervention), chronic (occurring in most cycles in the previous six months) and intermenstrual

bleeding (occurring between defined cycles and predictable menstruation).[1,3]

Chart 1. Definitions of normal and abnormal menstrual bleeding

Parameter	Descriptive term	Definition
Frequency (interval between the start of each cycle)	Amenorrhea	No bleeding for 90 days
	Infrequent	>38 days
	Normal	24 to 38 days
	Frequent	<24 days
Regularity (variation in duration between the longest and shortest cycle in 12 months)	Regular	≤7 to 9 days
	Irregular	≥10 days
Duration (duration of bleeding)	Normal	≤8 days
	Prolonged	>8 days
Volume (total blood loss)	Mild	Patient perceives as mild
	Normal	Patient considers normal
	Heavy	Patient considers heavy
Intermenstrual bleeding (bleeding between regular menstrual cycles)	Absent (normal)	No bleeding
	Random	Present, not predictable
	Cyclic	Present, predictable (at the beginning, middle or end of the cycle)
Unscheduled bleeding in gonadal steroid users (estrogen ± progestin)	Normal	Absent
	Abnormal	Present
	(Not applicable)	No steroid use

Causes

The International Federation of Gynecology and Obstetrics (FIGO) classifies the causes of non-pregnancy-related AUB under the PALM-COEIN acronym, referring to Polyps, Adenomyosis, Leiomyoma, Malignancy and hyperplasia, Coagulopathy, Ovulatory dysfunction, Endometrial disorders, Iatrogenic and Not otherwise classified. In general terms, the first group ("PALM") refers to structural causes (mostly identifiable by imaging exams or histopathology), and the other group ("COEIN") refers to non-structural causes. The term "dysfunctional uterine bleeding" (DUB), in turn, refers to causes related to hemostasis ("C"), ovulatory dysfunction ("O") and endometrial primary disorders ("E"), according to the current FIGO classification system.[3]

Should all patients with AUB be investigated and treated?

Management of patients with AUB includes assessment of hemodynamic instability and anemia, identification of the source of bleeding, and exclusion of pregnancy. Initially, it is important to determine whether it is acute or non-acute bleeding. The etiological diagnosis will guide therapy and treatment success.[4,5] However, in situations of acute and severe bleeding, treatment can be instituted to stop acute bleeding, followed by investigation. Although the uterus is often the source of abnormal bleeding, any part of the female genital tract (vulva, vagina) may have externalized vaginal bleeding, and this differential diagnosis is necessary. Initial physical examination may reveal vulvar or cervical lesions, guiding specific therapy. Anamnesis focused on the bleeding pattern, the use of medications and the association of other characteristics, signs and symptoms can guide the investigation, leading to the most likely etiologies (Chart 2).

How to perform the management and follow-up of AUB?

Acute uterine bleeding

When there is acute and severe blood loss and the patient is anemic and hypovolemic, hypotensive, tachycardic or with orthostatic hypotension, before determining the etiology, measures to stop bleeding are adopted. The first step is reestablishing hemodynamic stability with the use of crystalloids and eventually, the use of vasopressors and blood components.

Pharmacological measures

The use of high doses of intravenous estrogen causes rapid endometrial growth, stimulates contraction of the uterine arteries, and promotes platelet aggregation and clotting. Intravenous conjugated estrogen 25 mg every four to six hours for the first 24 hours is suggested, followed by a combination of estrogen and progestin for the following days.[1,4,6] Combined oral contraceptives (COCs), more widely available in our country, can also be used to treat acute AUB. A COC with 35 mcg of ethinyl estradiol (or other combination of pills to achieve this dose) three times a day for seven days is indicated. However, both estrogen treatments (oral or intravenous) should be avoided in patients at high risk of thromboembolism. An alternative is the use of multiple doses of progestins, especially in cases where estrogens are contraindicated. Medroxyprogesterone acetate 20 mg three times a day, norethisterone 5 mg three times a day, or another high-dose progestogen can be used for seven days, followed by one dose a day for three weeks.[1,4] Another suggested option in the literature is the use of a gonadotropin-releasing hormone (GnRH) agonist

Chart 2. Differential diagnosis of AUB in non-pregnant women of reproductive age

Bleeding pattern	Associated clinical features	Etiologies to consider
Regular, heavy, or prolonged periods	Enlarged uterus on physical examination, with or without palpable masses	Leiomyomas
	Dysmenorrhea Enlarged and softened uterus on physical examination	Adenomyosis
	Family history of blood dyscrasia Symptoms of hemorrhagic diathesis Anticoagulant therapy	Coagulopathies
	Risk factors for uterine cancer	Endometrial carcinoma, uterine sarcoma
Regular periods with intermenstrual bleeding		Endometrial polyp
	Risk factors for uterine cancer	Endometrial carcinoma, uterine sarcoma
	Recent history of cervical or uterine procedure, or delivery/cesarean section, especially if infected	Chronic endometritis
Irregular bleeding, more or less frequent than normal periods, with variable volume and duration		Ovulatory dysfunction
	Hirsutism, acne, obesity	Polycystic ovary syndrome
	Galactorrhea	Hyperprolactinemia
	Recent weight loss or gain Cold or heat intolerance Family history of thyroid disease	Thyroidopathy
	Risk factors for uterine cancer	Endometrial carcinoma, uterine sarcoma

associated with an aromatase inhibitor or GnRh antagonist.[4] All these hormonal options, after a higher loading dose and a lower maintenance dose for a week or period of a menstrual cycle, in general, can be maintained while etiological investigation is performed. In addition to hormonal alternatives, tranexamic acid can be used to manage acute bleeding; 10 mg/kg of body weight are given intravenously every eight hours (most effective) or 20-25 mg/kg orally every eight hours. The use of antifibrinolytics can reduce bleeding by up to 50%. Caution should also be exercised in patients at high risk of thromboembolism.[1]

Nonpharmacological measures

In some emergencies in which hemodynamic instability persists despite the drug treatment instituted, it is necessary to resort to mechanical or surgical procedures. An alternative is to try to tamponade the uterus by inserting a Foley catheter and fill the balloon with 10-30 mL of saline or distilled water. Sometimes it is necessary to perform a uterine curettage to stop bleeding. If severe bleeding persists, uterine artery embolization or even hysterectomy should be considered, depending on reproductive desire and bleeding severity.

Non-acute uterine bleeding

For these patients, the objective is to continue the diagnostic investigation and institute management directed at the cause. Pelvic ultrasound is the complementary test that provides more data for the management of AUB cases and has sensitivity of 96% and specificity of 14% for uterine abnormalities. Saline-infused sonography may better reveal intracavitary pathologies (such as polyps and fibroids). Histopathological evaluation (endometrial biopsy) is always indicated in postmenopausal patients, in those aged 45 years or older and those at high risk for endometrial carcinoma. According to risk factors in patients with suspected coagulopathy, the platelet count, plasma fibrinogen, prothrombin time and activated partial thromboplastin time should be evaluated. Sometimes it is necessary to follow the investigation with a von Willebrand factor and platelet aggregation tests, as well as with a hemophilia test – especially in patients with reports of ecchymosis or easy bleeding and in those with a suggestive family history. Patients using anticoagulants (coumarins, heparins, direct oral anticoagulants) should have their therapeutic regimen optimized. When an infectious cause is suspected, tests for gonococcus, chlamydia, and trichomoniasis are performed. If hormonal causes are suspected, it is critical to evaluate prolactin, thyroid tests, gonadotropins, and androgens, as well as other ways to diagnose chronic anovulation or polycystic ovary syndrome. Generally speaking, management is different for structural and non-structural etiologies.

Structural causes

In causes grouped in the first part (“PALM”) of the PALM-COEIN acronym, the aim of treatment is mostly the structural pathology.

Non-structural causes

The causes grouped in the second part (“COEIN”) of the PALM-COEIN acronym, the so-called “non-structural”, and some structural causes of AUB have the treatment focus on satisfactory control of bleeding, regardless of etiology.

Levonorgestrel intrauterine system (LNG-IUS)

Continuously released levonorgestrel (20 mcg/day) from the LNG-IUS is the most effective measure to prevent heavy menstrual bleeding, leading to a 71-95% reduction in blood loss by promoting endometrial atrophy.

Other isolated systemic progestins

Progestins promote endometrial atrophy and have anti-inflammatory action, although it is not fully understood how they reduce uterine bleeding. They can be indicated for most women, especially those with contraindications to the use of estrogens. Continuous oral progestins are effective in the treatment of AUB, reducing bleeding by up to 87% and promoting amenorrhea in a large percentage of women (10%-15%).[7] Progestogens-only contraceptive pills can be used: norethisterone 0.35 mg, desogestrel 75 mcg, drospirenone 5 mg, or micronized progesterone (200-400 mg/day) in continuous use, or from day 5 to day 26 of the menstrual cycle. Injectable depot medroxyprogesterone acetate (150 mg intramuscularly every three months) can promote amenorrhea in up to 24% of women and is an option for women with increased bleeding. However, there is no conclusive evidence regarding the use of injectable progestin in AUB. Likewise, there are not enough studies to indicate the etonorgestrel implant to manage AUB, even though it promotes amenorrhea in 20% of users.[4]

Estrogen and progesterone combinations

Combined oral contraceptives are able to reduce menstrual bleeding by 35-69%. They are a widely available and effective therapeutic option for most cases of AUB without structural change. Monophasic formulations containing 30 to 35 mcg of ethinylestradiol are the most studied, but the most diverse presentations of COCs are effective.[1,4] A quadriphasic formulation containing dienogest with estradiol valerate (10-30 mcg/day) showed a reduction of menstrual volume thus, is an alternative.[8] Other routes (transdermal patch, vaginal ring) are probably as effective as the oral options, and may be superior when there is an indication to avoid first-pass effect.

Non-hormonal treatments

Tranexamic acid is the most frequently prescribed antifibrinolytic, associated with a 26-54% reduction in the amount of bleeding. When the patient is bleeding, it is used in doses ranging from 1 to 1.5 g, three to four times a day for about three to five days. It can be used by women with the intention of becoming pregnant, but not by women at higher risk of thromboembolism. Non-steroidal anti-inflammatory drugs (NSAIDs) can be used alone or as an adjuvant therapy to some hormonal treatment, reducing the amount of bleeding by 10% to 52%. The most studied medications are mefenamic acid (500 mg orally three times daily) and naproxen (500 mg orally twice daily) while patient is experiencing bleeding. They can be used by women who are trying to get pregnant, but should be avoided by patients with coagulopathies.

Surgical treatments

Endometrial ablation is a less invasive alternative to hysterectomy for patients with AUB without structural damage. The aim is to destroy the basal layer of the endometrium through a series of methods (laser, thermal balloon, vaporization, cryoablation, bipolar radiofrequency, microwave), preventing its regeneration. This is an option only for those who no longer wish to get pregnant. The amenorrhea rate is 40-50% in one year, with good results in uteri with hysterometry less than 10 cm.[4] Hysterectomy is an exception treatment for structural AUB reserved for patients with no reproductive desire and unsuccessful drug management. However, it is the most effective definitive treatment and achieves high levels of satisfaction.

Iron deficiency anemia and iron deficiency: consequence of AUB conditions

In the presence of profuse acute uterine bleeding, acute anemia, hypotension, shock and even death can occur if prompt intervention is not performed. Chronic AUB, in turn, is an important cause of ID, as are parasitic infections, gastrointestinal bleeding, and nutritional deficiencies, which can lead to anemia.[2,9,10] Anemia is defined as a condition in which the concentration of hemoglobin (Hb) in the blood is below normal and can be determined by several factors, with 50% of cases comprising IDA or ID.[11,12] The usual symptoms of IDA include weakness, headache, irritability, restless legs syndrome and varying degrees of fatigue and exercise intolerance or pica (perverted appetite for clay or soil, paper, starch, etc.).[12,13] Patients with low ferritin and without anemia may have the same symptoms. Ice pica may also occur, which is considered quite specific for low ferritin. Some patients with low ferritin, with or without anemia, may complain of tongue pain, decreased salivary flow with dry mouth, and atrophy of the lingual papillae.[13] Other patients may present with alopecia, dry skin, devitalized hair, and koilonychia.[14] However, many patients are asymptomatic, with no typical symptoms, and only recognize symptoms retrospectively after treatment. The differential diagnosis of IDA includes parasitic diseases such as malaria, hookworm and schistosomiasis, nutritional causes such as lack of folic acid, vitamin A and vitamin B12, and genetic causes such as hereditary thalassemia-type hemoglobinopathies.[15]

How to make the laboratory diagnosis of IDA and ID?

When IDA or ID is suspected,[16,17] a complete blood count (with RBC indices and peripheral smear evaluation) and ferritin levels should be requested (Chart 3).[18]

Other measurements, such as serum iron, transferrin, and transferrin saturation, are not mandatory. Patients with IDA have low serum iron, high transferrin, and low transferrin saturation.[12,13] Reticulocyte hemoglobin (Ret-Hb) is a good indicator of the amount of available iron, and its dosage does not interfere with inflammatory processes..[19] According to the diagnostic standards of the World Health Organization, IDA is mild to moderate if Hb is between 7 and 12 g/dL, and severe, if Hb is less than 7 g/dL, with small variations according to age, sex or presence of pregnancy.[20] For the adult female population, Hb values below 12 g/dL are considered as anemia and for men, Hb values below 13 g/dL.[20,21] Although Hb is widely used for the evaluation of IDA, it has low specificity and sensitivity, and a biomarker of iron status, such as serum ferritin, should be requested together.[21] Serum ferritin concentration is the most reliable marker of iron storage in the body. Normal values range from 30 to 200 ng/mL (mcg/L), and there is no clinical situation in which low rates do not mean ID. As long as patients with IDA do not have infection or associated inflammatory disease, the cutoff value of 30 ng/mL gives better diagnostic efficiency, with sensitivity of 92% and specificity of 98%. As ferritin is an acute-phase reactor with increased levels in inflammatory, infectious, malignant, or liver diseases, falsely elevated ferritin may be found in the presence of these diseases and IDA. The effect of inflammation on ferritin is to increase it threefold. Therefore, in these patients, the golden rule is to divide the ferritin value by 3, and values less than or equal to 20 ng/mL suggest concomitant IDA.[22]

What are the main treatments for iron deficiency?

The main treatments for IDA and ID are iron replacement, correction of nutritional aspects and treatment of AUB. The goal of iron replacement is to provide enough iron to normalize Hb concentrations and replenish iron storage, thereby improving quality of life and symptoms.[13] Regardless of the presence of symptoms, all patients with IDA and most of those with ID without anemia should be treated.[23,24] There are two distinct approaches: prevention strategies targeting populations at risk, such as patients with AUB, and active iron supplementation approaches in confirmed IDA.[13]

Nutritional guidance

It is recommended to increase the intake of meat, the main source of heme iron; it is estimated that 100 g of meat corresponds to 1 kg of beans (non-heme iron). Concomitant consumption of fruit juice with vitamin C enhances the absorption of iron from the diet, and the use of an iron pan to prepare meals is also part of the guidelines. It is recommended not to mix milk and tea at the same meal and avoid whole grain cereals and chocolate as a dessert during the period of treatment with ferrous salt. These recommendations are not necessary when ferric salts are used in the treatment, because in these compounds, iron is chelated with sugar or amino acids, and there is no interaction of its absorption with food in general. Foods rich in ascorbic acid (cashew, legumes, guava) and meats in general, favor the absorption of non-heme iron, while phytates, phosphates and carbonates (pineapple, vegetables, milk), tannin (tea, coffee), phosphoprotein (yolk eggs) and drugs that raise gastric pH (antacids, proton pump inhibitors, histamine H2 blockers) make absorption of non-heme iron difficult. Although intestinal iron

Chart 3. Laboratory parameters to define iron deficiency anemia (IDA) and iron deficiency (ID)

	Adult normal values	IDA	Latent ID	IDA refractory to iron treatment	Anemia of chronic disease	IDA + anemia of inflammation
Serum iron (µmol/L)	10-30	↓	N/↓	↓	↓	N/↓
Transferrin saturation (%)	20-45	<20	N/↓	<10	N/↓	<20
Serum ferritin (µg/L)	20-200 (F) 40-300 (M)	<30	<30	Variable	>100	30-300
Reticulocyte hemoglobin (pg)	>29	<29	<29	<29	<29	<29
Hemoglobin (g/dL)	>12 (F) >13 (M)	↓	N	↓	↓	↓
MCV (fL)	80-100	↓	N/↓	↓	N/↓	N/↓

Source: Adapted from Elstrott et al. (2020)[18]

absorption can increase significantly when iron is deficient (from less than 1% to more than 50% of the iron present in the diet), dietary correction alone is not usually sufficient to treat patients with IDA.[13,16]

When and how to prescribe oral iron? What are the main indications and contraindications?

Oral iron replacement is undoubtedly the most widespread, especially for lighter IDA and ID cases. However, doubts about the dosage are common and it is not uncommon to find situations when the drug is apparently ineffective. The recommended therapeutic dose is 2 to 5 mg/kg/day for a period sufficient to normalize Hb values – one to two months – and restore normal body iron stores – two to six months or until serum ferritin is greater than 30-50 ng/mL.[16] Therefore, the duration of treatment varies widely depending on the severity of ID and its cause. In practice, the recommended dose for adult individuals is 150 to 200 mg of elemental iron per day, and the administration of daily doses greater than 200 mg is not recommended, as, in this case, the intestinal mucosa acts as a barrier, preventing the absorption of the metal, and the proportion absorbed decreases significantly.[12,16] Chart 4 shows the products and doses available for oral treatment.

Chart 4. Main compounds with iron salts available for the oral treatment of iron deficiency anemia (IDA) and iron deficiency (ID)

COMPOUND	Total amount of iron	Amount of elemental iron	Registration on the Anvisa website*
Ferrous sulfat (mg)	190	60 40	Henfer/ Anemifer Furp/ Farmanguinhos/ Nesh
Ferric glycinate (mg)	150, 300, 500	30, 60, 100	Neutrofer
Ferripolymaltose (mg)	333, 33/357	100	Endofer, Noripurum

Research has shown that high doses of iron VO induce greater production of hepcidin, a protein produced by the liver that controls serum iron by blocking intestinal absorption and the release of iron from stores.[12] Therefore, the use in sequence or in overdose may paradoxically take away the effect of the drug. In some studies, lower doses of elemental iron per day, 15 to 20 mg, have shown equal effectiveness compared to higher doses, likely because of this mechanism. In addition to ensuring adequate absorption, dosage adjustments allow for better control of side effects (diarrhea, constipation, epigastric pain, nausea, dark-colored stools).[18] Numerous oral iron formulations are available and mostly, they are all equally effective, as long as they are taken.[23] Iron absorption from intestinal mucosal cells occurs through divalent metal transporter 1 (DMT1), a protein located in the duodenum and upper jejunum. Once in the cell, ferroportin transports iron through the cell into the blood, where it is bound by transferrin. The paradigm for iron replacement evolved as evidence began to emerge suggesting that excessive dosage is potentially counterproductive, as it decreases iron absorption and increases side effects without improving iron levels or anemia.[23] More research is needed to define the best strategy for oral iron administration.

When and how to prescribe IV iron? What are the main indications and contraindications?

Intravenous formulations have gained more space in prescriptions as the safety of their use has become more evident. Infusion reactions are rare, usually mild, and if they occur, drug administration can continue at a slower infusion rate. The various injectable formulations have the same efficacy and are especially useful in cases of more vigorous replacement, patients intolerant to oral administration or with malabsorptive processes (for example: patients with inflammatory bowel diseases) and chronic renal patients. Contraindications to use of IV iron are: anemia unrelated to ID, transferrin saturation > 45%, ferritin > 500 ng/mL, active infection/septicemia, severe dysfunction (hepatic or cardiac), pregnant women in the first trimester of pregnancy. Chart 5 shows the IV iron formulations available in Brazil and the main information for the use of these drugs.

Adverse effects of IV iron

Many physicians are reluctant to use IV iron because of concerns about anaphylaxis. True allergic reactions are extremely rare and overrated. In individuals with asthma, inflammatory rheumatic diseases, or multiple drug allergies, premedication with a glucocorticoid alone is generally recommended.

Final considerations

Although AUB is a very common condition, it should be valued and properly investigated, as it can significantly worsen a woman's quality of life. According to the etiology, AUB can be effectively treated by quite effective pharmacological and surgical measures depending on age, reproductive desire and other associated conditions. Abnormal uterine bleeding in menacme is the main cause of IDA and ID. The tests requested for diagnosis must include, at least, the blood count, ferritin and iron profile. Iron replacement should be prescribed for these patients, and treatment monitoring is usually performed between 30 and 60 days, depending on the clinical picture.

Chart 5. Intravenous iron formulations

Compound	Ferric hydroxide saccharate	Ferric derisomaltose	Ferric carboxymaltose
Commercial name	Noripurum; Sucrofer	Monofer	Ferinject
Concentration	20 mg/mL	100 mg/mL	50 mg/mL
Total Dose	Determined individually, according to iron deficiency.*	Determined individually, according to iron deficiency.*	Hb < 10 g/dL: 1.500 mg if weight 35-70 kg; 2.000 mg if weight > 70 kg.
	Simplified mean dosage: 100 to 200 mg one to three times a week	Simplified mean dosage: Hb < 10 g/dL: 1.500 mg if weight 35-70 kg; 2.000 mg if weight > 70 kg Hb > 10 g/dL: 1.000 mg if weight 35-70 kg; 1.500 mg if weight > 70 kg.	Hb > 10 g/dL: 1.000 mg if weight 35-70 kg; 1.500 mg if weight > 70 kg.
Recommended maximum single dose	200 mg per day	500 mg daily, up to three times a week	1.000 mg daily, up to once a week
Infusion time	At least 1 hour	15 minutes	15 minutes
Risk category in pregnancy	B	B	B

* **calculation of iron need:** total iron deficiency (mg) = [weight (kg) x DHb (g/dl) x 2.4] + iron reserves (mg)

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Conflicts of interest: none to declare.

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- **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/

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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.

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