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Editorial

What the Transcriptome of the Eutopic Endometrium from Women with Endometriosis tells us about the Disease Pathophysiology: A Brief Reflection

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Endometriosis is characterized by the presence of endometrial-like tissue outside the uterine cavity, usually represented by deep peritoneal, ovarian and/or infiltrative lesions[1,2] and, more rarely, in extrapelvic sites.[3] The estimated prevalence is of 5 to 10% of reproductive-age women,[4–6] despite the suggestion of an actual lower prevalence, of up to 1.8%, in a recently published study based on a population of two million individuals.[7] The incidence, in turn, is more difficult to be estimated, but seems to be between 1.3 to 1.6 cases per 1,000 women in this same age group.[8] Even considering this wide variation, if extrapolating to the Brazilian female population aged between 15 and 50 years estimated in the last census of 2010, there may be between 1 million and more than 5 million women with endometriosis, which is a very expressive number. Women with endometriosis may be asymptomatic or have varied symptoms, with the most frequent being pain (dysmenorrhea, dyskinesia, acyclic pain, dyspareunia) and infertility, followed by abnormal uterine bleeding and ovarian mass.[9,10] Despite these associations, there are no clinical symptoms or signs that are good predictors of the disease,[11,12] which culminates in the difficulty of an accurate clinical diagnosis.[13] Other important aspects are the absence of a correlation between the severity of symptoms and extent of the disease,[14] the presence of endometriosis in a reasonable number of asymptomatic women,[15] and the lack of knowledge about the events determining the natural evolution of the disease, be it spontaneous progression or regression.[16] Nonetheless, the disease is associated with a significant psychological and social impact, negative repercussions on the woman's quality of life[17] and productivity,[18] and relevant socioeconomic burden.[19,20]

Several theories have been proposed to explain the origin of the disease, among which are theories of retrograde menstruation (the most widespread and accepted), celomic metaplasia, lymphovascular metastasis, and, more recently, the theory of neonatal uterine bleeding.[21,22] Although reasonable, by themselves these theories do not explain the origin and evolution of the disease in all its nuances, and other factors need to be considered, such as: genetic, endocrine, immunological, inflammatory, and neuroangiogenic. Regardless of controversies, the eutopic endometrium in women with the disease definitely has peculiarities and a relevant role in the pathophysiological process of the disease.[23–25] If we added genetic susceptibility[26] and immune system dysfunction to this context, including autoimmunity and deficient immune surveillance,[27–29] we would already have a plausible explanation for the question of why only some women develop the disease. Still, there would be another question: what would be or what would lead to this initial alteration of the eutopic endometrium? A potential explanation would be the presence of somatic mutations in the epithelial and/or stromal endometrial components. Despite their relevance to ovarian lesions (endometriomas), they do not appear to be crucial or significant in components of the eutopic endometrium.[30] Another interesting element is the importance of endometrial progenitor cells, or endometrial stem cells in their broadest concept. However, although admittedly associated with the development of the lesion at ectopic sites,[31] primary constitutive changes in these cells, when isolated from the eutopic endometrium, are still controversial. In this scenario of uncertainties about the triggering event of the first changes in the eutopic endometrium of women with endometriosis, it is worth discussing an equally interesting, although less explored, hypothesis of microbiological contamination. Some authors defend intrauterine microbial colonization as the trigger for pathophysiological events that culminate in endometriosis.[32] Furthermore, infections can trigger cumulative genetic and epigenetic changes with the potential to trigger or maintain endometriosis.[33] Although recently published, the concept of an initial eutopic endometrial infection followed by sterile inflammation has been proposed before.[34] These propositions are

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supported by the association between endometriosis and endometritis,[13,35–39] by the microbial contamination observed in the uterine cavity and ectopic lesions,[40–42] and by dysbiosis in the microbiome of the intestine and genital tract of women with endometriosis.[43]

Concomitant to these findings, the modernization of molecular biology techniques in recent decades has allowed great advances in understanding the processes involved in the evolution of several diseases. Currently, these methodologies are more affordable, easy to execute, and have good reproducibility.[44,45] Transcriptome analysis, for example, is a direct reflection of gene expression in tissues. In this sense, the transcriptome analysis of the eutopic endometrium of women with endometriosis has an invaluable potential in contributing to understand local events associated with the condition. In fact, there are already relevant studies evaluating the transcriptome of the eutopic endometrium of women with and without endometriosis.[46–50] However, some limitations are inherent to these studies, such as: reduced casuistry size; heterogeneous sample regarding phenotypic characterization, mainly of the menstrual cycle phase, the extent of the lesions, and associated symptoms; inadequate selection of healthy controls; non-optimized evaluation by the bioinformatics tools available; and redundancy in the interpretation of biological pathways, among others.

To try to remedy these limitations, our group conducted a meta-analysis including raw eutopic endometrial transcriptome data available in international databases from healthy women and from women with endometriosis. We restricted the control group to women with no known disease and stratified women with endometriosis into those with stages I and II disease and those with stages III and IV disease. For both groups, we considered the phase of the menstrual cycle, since it can interfere with the expression of the tissue transcriptome.[51] By using some bioinformatics tools, we were able to predict the tissue microenvironment computationally, that is, we could infer the types of cells present in each sample. The method used can identify 64 cell types, including immune cells, stem cells, and stromal cells, among others. Thus, we observed that the eutopic endometrium of women with endometriosis in stages I and II has more proinflammatory characteristics than the endometrium of women in stages III and IV of the disease. Initial cases have a predominance of activated dendritic cells, effector memory CD4+ T-cells, eosinophils, type M1 macrophages and natural killer T-cells, which are typical of an inflammatory process induced by acute infections. In more advanced cases (stages III and IV), there is a predominance of M2 macrophages and natural killer T-cells. This last cell profile is characteristic of an antiinflammatory process, of tissue healing and repair[52] present in late stages of infectious diseases[53] that may be associated with the promotion of tumor growth.[54] As for biological pathways, in women with endometriosis there is a direct involvement of the processes related to immune surveillance, stem cell self-renewal, and epithelium-mesenchymal transition. These mechanisms are already reported in the literature, but we note that pathways related to greater permissiveness of the immune system to cells in ectopic environments and imbalance between cell growth and survival[55] are more evident in advanced disease. Anyway, the predominance of different cell types added to the interaction between genes and the predominant biological pathways in each condition, regardless of the phase of the menstrual cycle, indicates that the eutopic endometrium of women affected by endometriosis has peculiar characteristics of a tissue that suffered or has been suffering some harm, aggression, or stress caused by an external, potentially microbiological agent.

Based on what was briefly mentioned above, thinking about an initial endometrial aggression, possibly by a microbiological agent, sustained for a variable period of time, and followed by the induction of genetic and epigenetic changes in the tissue and consequent self-sustained inflammation (sterile or not), all occurring in a genetically susceptible woman, whose immune system behaves anomalously and is permissive to the presence of endometrial cells (especially stem cells) in ectopic environments, would be an at least plausible hypothesis and justify further investigations. However, studies must be conducted to resolve limitations that may skew the results obtained, especially a good phenotypic characterization of patients and a good selection of healthy controls.

Conflict of Interests

The authors have no conflict of interests to declare.

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Type of Childbirth and its Association with the Maternal-Filial Interaction

Tipo de nascimento e sua associação com a interação materno-filial

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Abstract

Objective The purpose of the present study was to evaluate the quality of mother-child bonding in three different contexts related to the labor, that is, vaginal delivery, elective cesarean section, and intrapartum cesarean section.

Methods This was an observational, cross-sectional clinical study conducted in two cities within the state of São Paulo, Brazil. The study sample consisted of 81 babies born without any major complications during pregnancy and labor, aged 3 to 4 months, and their respective mothers, aged between 20 and 35 years old, primiparous, living in the cities of Palmital and Ourinhos, state of São Paulo, Brazil. The evaluation of the quality of the maternal-filial interaction was performed through video-image analysis, using the Mother-baby Interaction Observation Protocol from 0 to 6 months (POIMB 0–6, in the Portuguese acronym).

Results Mothers who had vaginal delivery had higher amount of visual contact or attempted visual contact ($p = 0.034$), better response to the social behavior of the child ($p = 0.001$) and greater sensitivity ($p = 0.007$) than the others. Their children also showed more interaction with them, as they looked more frequently at the mother's face ($p \leq 0.008$) and responded more frequently to the mother's communicative stimulus ($p < 0.001$).

Conclusion Considering the occurrence of vaginal delivery, it is concluded that the interaction between the mother-child dyad is quantitatively larger and qualitatively better when compared with intrapartum or elective cesarean section.

Keywords
- cesarean section
- obstetric delivery
- mother-child relationships
- vaginal childbirth

Resumo

Objetivo O objetivo do presente estudo foi avaliar a qualidade do vínculo mãe-filho em três contextos diferentes relacionados ao trabalho de parto, ou seja, parto vaginal, cesariana eletiva e cesariana intraparto.

Métodos Estudo clínico observacional, transversal, realizado em duas cidades do estado de São Paulo, Brasil. A amostra do estudo foi composta por 81 recém-nascidos

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sem maiores complicações durante a gravidez e o parto, com idades entre 3 e 4 meses, e suas respectivas mães, com idades entre 20 e 35 anos, primíparas, residentes nas cidades de Palmital e Ourinhos, estado de São Paulo, Brasil. A avaliação da qualidade da interação materno-filial foi realizada por meio de análise de vídeo-imagem, utilizando o Protocolo de Observação da Interação Mãe-Bebê de 0 a 6 meses (POIMB 0–6).

Resultados Mães que tiveram parto vaginal tiveram maior quantidade de contato visual ou tentativa de contato visual ($p = 0{,}034$), melhor resposta ao comportamento social da criança ($p = 0{,}001$) e maior sensibilidade ($p = 0{,}007$) que as demais. Os filhos também mostraram maior interação com elas, pois olhavam com mais frequência para o rosto da mãe ($p < 0{,}008$) e respondiam com mais frequência ao estímulo comunicativo da mãe ($p < 0{,}001$).

Conclusão Considerando a ocorrência do parto vaginal, conclui-se que a interação entre a díade mãe-filho é quantitativamente maior e qualitativamente melhor quando comparada à cesariana intraparto ou eletiva.

Palavras-chave
- cesariana
- parto obstétrico
- relações mãe-filho
- parto vaginal

Introduction

The attachment between mother and child corresponds to a basic mechanism of the human being, resulting from the establishment of an affective bond. However, it is modeled according to the characteristics of each relationship, that is, attachment patterns differ qualitatively.[1–3]

Renowned authors of psychoanalysis like Freud and Bowlby, among others, contributed with the scientific knowledge related to the early interactions; however, studies that look at and analyze early parent/infant interactions began to be performed more recently, about $\sim$ 50 years ago. These studies consider the interaction between the mother and the baby as fundamental for the bonding formation and for the good development of the child's psyche.[4,5] The behavior of the child is a response to the maternal behavior that generates the interaction between the dyad; however, the specific characteristics of each individual can generate effective and pleasant relationships, or not.[6]

Studies focused on the analysis of early interaction may be of a qualitative and/or quantitative nature. The choice by the observational method of research allows a thorough analysis of the mother-baby interaction through the recording of actions and sequential events between the dyad.[7,8] The Mother-to-Child Interaction Observation Protocol (POIMB 0–6, in the Portuguese acronym) corresponds to an instrument translated by Alfaya et al[4] that allows the qualitative and quantitative analysis of the interaction between mother and child, based on recorded behaviors. According to Schermann,[9] the POIMB 0–6 corresponds to the only protocol that allows analysis of the interaction between mother and baby since birth.

The POIMB 0–6 has been used in the evaluation of interactions recorded in video, made in different types of pre-established environments, be it domicile or laboratorial, and during the most variable moments of interaction, such as during the baby's bath or during the face-to-face moment between mother and child. Shooting time should also range from 5 to 10 minutes, depending on the situation applied, and the camera should be positioned at a side angle that favors recording the best image of the participants. All videos should be analyzed by different trained observers (reliability test) and calculated using the Kappa coefficient.[9]

Taking into account the possibility of evaluating the maternal-filial interaction through the making of the video and the subsequent application of the POIMB 0–6 for quantitative analysis of data, it can be affirmed that the application of the protocol makes it possible to compare groups regarding to quality of the interaction.

In this context, we proposed the study of the maternal-filial interaction and its association with the type of birth delivery, based on the application of the POIMB 0–6, utilizing samples from live births in two cities located in the state of São Paulo (a smaller and a medium city related to demographic density).

Methods

Several instruments and procedures based on different techniques were created with the objective of analyzing the interaction between parents and children. The analysis of interaction through video observation represents an efficient way of studying and recording such interactions. One of the advantages in using videos for the analysis of interactions is the possibility of reviewing the data obtained as many times as necessary. Another advantage is the possibility of analysis by more than one observer. Despite these advantages, the decision to use videos as a form of registration of observations will depend on the objectives and procedures of the research, which should be ethically supported.[1,5,10]

The present study was approved by the Ethics Committee of the Universidade Federal de São Paulo (CAAE: 47395515.6.0000.5505), as of September 30th, 2015. All of the participants signed the Consent Form.

This was an observational and transversal clinical study. The study sample consisted of infants born at term without any major complications during pregnancy and labor, aged 3 to 4 months, and their respective primiparous mothers, aged

between 20 and 35 years old, living in the cities of Palmital and Ourinhos, state of São Paulo, Brazil, consisting of a total of 81 mother-child dyads. This number was calculated, distributing 27 pairs in each group, considering average score of quality, 4, 3 and 2 respectively for groups 1, 2 and 3; 2 was adopted as standard deviation it was adopted 2 as standard deviation, 90% confidence level.

These three distinct groups were composed according the type of delivery: group 1 - vaginal delivery (VD); group 2 - intrapartum cesarean section (ICS), and group 3 - elective cesarean section (ECS). The exclusion criteria were women with twin or multiple gestation history, < 20 or > 35 years old, with psychiatric history and with organic disease, and premature babies, with malformations, syndromes or organic diseases condition.

The evaluation of the quality of the maternal-filial interaction was performed based on video-image analysis, using the POIMB 0–6 translated by Schermann[9] and the application of an objective questionnaire containing gestational data, delivery, puerperium, breastfeeding, as well as sociodemographic data of the family. This protocol is composed by 12 items related to maternal behavior, 8 items related to behavior of the baby and 1 related to the dyad interaction, totalizing 21 items. These items were observed during the moment of the pair interaction, and then, the value of each one was punctuated based on a scale of 5 points. The lowest answer received note 1; and the highest, note 5, for all 21 questions. The videotapes were recorded during the baby's bathing situation, at home environment, and at an average duration of 3 minutes.

To comply with the reliability test and to determine the reliability of the research data, the videotapes were analyzed by 3 observers, 2 of whom were "blinded." One of the observers was the researcher herself (not blind), the other two (blind). One of the blinded observers was a psychologist and a postdoctoral fellow, and the other, a nurse specialist in obstetrics. The camera was hidden to prevent diverting the baby's attention; and it was recommended the mother should behave as naturally/spontaneously as possible.

Results

The sample calculation was performed to compare the elective cesarean section, intrapartum cesarean section and vaginal delivery groups. For this calculation, the average quality score in the elective cesarean section, intrapartum cesarean section and vaginal delivery groups equal to 2, 3 and 4, respectively, were considered. The global standard deviation (SD) adopted was 2. Considering an α significance level of 5%, with a total of 81 individuals, 27 for each group, it will be possible to detect, with a power of 90%, a significant difference between the 3 groups.

The first contact with the sample was established at the maternity hospital in the city of Palmital, through semantic visits and active search in the city of Ourinhos. The women who agreed to collaborate with the present study were contacted again at a later time, when the baby was between 3 and 4 months old. During the survey period, 23 mothers did not agree to collaborate. In addition, even after signing the Consent Form at the maternity hospital, it was not possible to define telephone contact with 11 women to schedule a home visit, 6 gave up the collaboration and, in 1 case, the mother died. At the last moment, therefore, 18 dyads were replaced in new visits to the maternity hospital. However, it was possible to reach a minimum value allowed by the sample calculation and 81 mothers with their children were able to participate in the research (►**Fig. 1**).

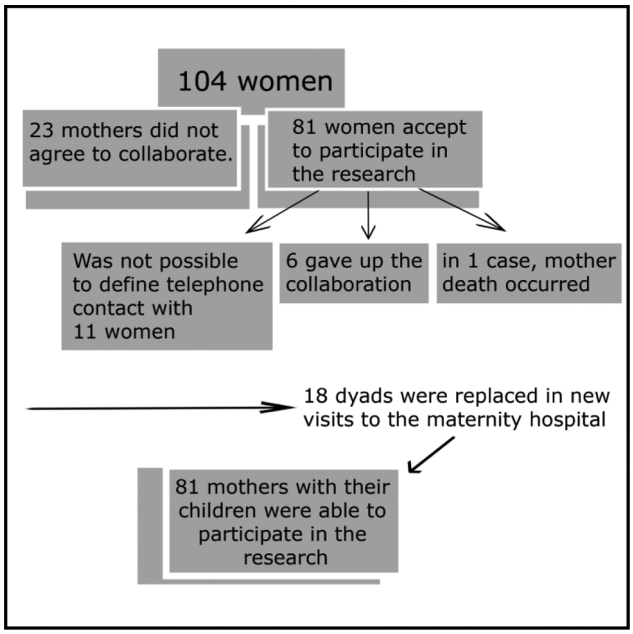

Fig. 1 Flowchart of the patients included in the study.

Analyzing the demographic data, there were no differences between the three groups related to age (26.1 ± 3.7 years old), marital status (64.2% married), schooling level (55.5% higher education complete or incomplete degree), gestational planning (76.5% planned), familiar income (3.0 ± 1.3 minimum wages), type of maternity (public or private institution) (61.7% public), and child age at filming (101.8 ± 3.4 days). On the other hand, there were differences between the three groups on the gestational age at delivery, breastfeeding and weight at birth (►**Table 1**).

Analyzing properly the POIMB 0–6 instrument, 4 questions from 12 items related to the mother behavior showed a statistical difference between the 3 groups (►**Table 2**). Among the 12 maternal assessment items, 7 did not present statistical significance according to observers 1, 2 and 3, respectively: number of verbal communications from mother to child ($p = 0.644$; 0.866 and 0.644), amount of body contact from the child to mother ($p = 0.347$; 0.832 and 0.352), maternal positive expression for the child ($p = 0.348$; 0.219 and 0.274), mother-to-under-child efficiency ($p = 0.776$; 0.744 and 0.859), mother's reaction ($p = 0.137$; 0.137 and 0.174), mother's positive response intensity and child's social behavior ($p = 0.916$; 0.531 and 0.859), mother's negative affect expression ($p = 0.535$; 0.179 and 0.381) and intrusiveness ($p = 0.763$; 0.967 and 0.649).

Table 1 Different demographic characters according the type of delivery

Variables		VD	ICS	ECS	Total	
		($n = 26$)	($n = 27$)	($n = 28$)	($n = 81$)	*p-value*
Marital status	Stable union	19.2%	18.5%	10.7%	16.0%	0.443
	Married	53.8%	59.3%	78.6%	64.2%	
	Single	23.1%	22.2%	10.7%	18.5%	
	Widow	3.8%	–	–	1.2%	
Schooling	Incomplete fundamental	–	7.4%	–	2.5%	0.091
	Complete fundamental	11.5%	14.8%	–	8.6%	
	Incomplete medium	7.7%	11.1%	–	6.2%	
	Medium complete	19.2%	25.9%	35.7%	27.2%	
	Incomplete Higher	23.1%	18.5%	14.3%	18.5%	
	Graduated	38.5%	22.2%	50.0%	37.0%	
Maternal Age	Average	26.6	25.3	26.3	26.1	0.441
	Median	27.0	25.0	26.0	26.0	
	Minimum	20	20	20	20	
	Maximum	32	33	33	33	
	Standard deviation	3.4	4.1	3.6	3.7	
Gestational planning	Yes	19.2%	29.6%	21.4%	23.5%	0.639
	No	80.8%	70.4%	78.6%	76.5%	
Family income (minimum wages)	Average	2.6	3.0	3.4	3.0	0.184
	Median	2.0	3.0	3.0	3,0	
	Mínimum	1	1	1	1	
	Maximum	5	5	7	7	
	Standard deviation	1.2	1.1	1.6	1.3	
Gestational age (weeks)	Average	39.4	39.7	38.7	39.3	< 0.001
	Median	40.0	40.0	39.0	39.0	
	Minimum	38	38	38	38	
	Maximum	42	42	40	42	
	Standard deviation	2.2	1.1	0.7	1.5	
Childbirth institution	Private	30.8%	40.7%	42.9%	38.3%	0.626
	Public	69.2%	59.3%	57.1%	61.7%	
Breastfeeding	Absent	–	14.8%	32.1%	16.0%	0.013
	Exclusive	69.2%	55.6%	35.7%	53.1%	
	Not exclusive	30.8%	29.6%	32.1%	30.9%	

Abbreviations: ECS, elective cesarean section; ICS, intrapartum cesarean section; VD, Vaginal delivery.

In all of these 4 questions, the Kappa coefficient was > 0.86, a value considered strong agreement (> 0.81). All three observers agreed that mothers who had vaginal delivery responded better than others to the social behavior of the child (question 7). Two out of three observers agreed that the sensitivity of mothers who delivered vaginally is higher than that of the others. Only one observer concluded that mothers who had vaginal delivery had higher amount of visual contact or attempted visual contact (question 2); and gave more attention to the child (question 11). All of the other questions (verbal communication, body contact, affective expression, solace for crying baby, reaction to crying/agitation, intensity of positive reaction, negative affective reaction, and intrusiveness were not different between the three groups).

Of the 8 baby assessment items, 4 were not statistically significant according to observers 1, 2, and 3, respectively: amount of child smile ($p = 0.780$; 0.980 and 0.740), child mood during observation ($p = 0.481$, 0.284 and 0.444), amount of vocalization of the child ($p = 0.306$; 0.197 and 0.184) and amount of crying (0.304; 0.553 and 0.503).

For question 21 (quantity and quality of interaction), only observer 1 did not verify statistical significance ($p = 0.137$). For observers 2 and 3, there was significance of $p = 0.012$ and 0.08, respectively. ►**Table 3** shows the behavior of the babies of the three groups.

Table 2 Four items where difference was found between the three groups, observed by three examiners

Question*	Kappa/95%CI	Observer		VD ($n = 26$)	ICS ($n = 27$)	ECS ($n = 28$)	*p-value*
2	0.91	1	Few	–	–		0.034
	0.78–1.04		Moderate	7.7%	29.6%	10.7%	
			Many	88.5%	59.3%	42.9%	
			Always	3.8%	11.1%	32.1%	
		2	Few	–	–	14.3%	0.150
			Moderate	15.%	29.6%	10.7%	
			Many	80.%	59.3%	39.3%	
			Always	3.8%	11.1%	35.7%	
		3	Few	–	–	14.3%	0.095
			Moderate	11.%	29.6%	10.7%	
			Many	84.%	63.0%	39.3%	
			Always	3.8%	7.4%	35.7%	
7	0.91		Few	–	–	14.3%	0.001
	0.81–1.00	1	Moderate	11.5%	18.5%	10.7%	
			Many	34.6%	33.3%	28.6%	
			Always	53.8%	48.1%	50.0%	
		2	Few	–	–	10.7%	0.005
			Moderate	11.%	22.2%	10.7%	
			Many	38.%	33.3%	28.6%	
			Always	50.%	44.4%	46.4%	
		3	Few	–	–	14.3%	0.002
			Moderate	11.%	18.5%	10.7%	
			Many	42.%	37.0%	28,6%	
			Always	46.%	44.4%	50.0%	
10	0.86	1	Moderate	–	7.4%	10.7%	0.007
	0.73–0.99		Many	15.4%	40.7%	14.3%	
			Always	84.6%	51.9%	39.3%	
		2	Moderate	–	7.4%	46.4%	0.072
			Many	26.%	40.7%	14.3%	
			Always	73.%	51.9%	39.3%	
		3	Moderate	–	7.4%	46.4%	0.018
			Many	19.%	40.7%	10.7%	
			Always	80.%	51.9%	42.9%	
11	0.91	1	Moderate	19.2%	37.0%	46.4%	0.104
	0.82–1.00		Many	34.6%	44.4%	28.6%	
			Always	46.2%	18.5%	32.1%	
		2	Moderate	11.%	37.0%	39.3%	0.026
			Many	42.%	48.1%	28.6%	
			Always	46.%	14.8%	32.1%	
		3	Moderate	19.%	37.0%	39.3%	0.082
			Many	30.%	44.4%	32.1%	
			Always	50.%	18.5%	28.6%	
						39.3%	

Abbreviations: CI, confidence interval. ECS, elective cesarean section; ICS, intrapartum cesarean section; VD, vaginal delivery.
*2) Amount of visual contact or attempted eye contact from mother to child; 7) Mother's response to the child's social behavior; 10) Maternal sensitivity to the child; 11) Attention of the mother to the child.

Table 3 Five items where difference was found between the three groups, observed by three examiners related to the baby behavior and dyad interaction

Question*	Kappa/95%CI	Observer		VD ($n = 26$)		ICS ($n = 27$)		ECS ($n = 28$)		*p-value*
13	0.85	1	None	–	–	1	3.7%	1	3.6%	0.001
	0.77–0.93		Few	3	11.5%	1	3.7%	8	28.6%	
			Moderate	5	19.2%	8	29.6%	12	42.9%	
			Many	11	42.3%	13	48.1%	7	25.0%	
			Always	7	26.9%	4	14.8%	–	–	
		2	None	–	–	1	3.7%	1	3.6%	0.001
			Few	3	11.5%	2	7.4%	8	28.6%	
			Moderate	5	19.2%	9	33.3%	12	42.9%	
			Many	12	46.2%	12	44.4%	7	25.0%	
			Always	6	23.1%	3	11.1%	–	–	
		3	None	–	–	1	3.7%	1	3.6%	0.008
			Few	3	11.5%	1	3.7%	7	25.0%	
			Moderate	7	26.9%	8	29.6%	13	46.4%	
			Many	11	42.3%	14	51.9%	5	17.9%	
			Always	5	19.2%	3	11.1%	2	7.1%	
14	0.82	1	None	–	–	–	–	2	7.1%	< 0.001
	0.72–0.91		Few	–	–	1	3.7%	7	25.0%	
			Moderate	7	26.9%	16	59.3%	13	46.4%	
			Many	13	50.0%	9	33.3%	5	17.9%	
			Always	6	23.1%	1	3.7%	1	3.6%	
		2	None	–	–	–	–	2	7.1%	< 0.001
			Few	–	–	2	7.4%	7	25.0%	
			Moderate	7	26.9%	15	55.6%	12	42.9%	
			Many	12	46.2%	9	33.3%	6	21.4%	
			Always	7	26.9%	1	3.7%	1	3.6%	
		3	None	–	–	–	–	2	7.1%	<0.001
			Few	–	–	1	3.7%	7	25.0%	
			Moderate	7	26.9%	15	55.6%	11	39.3%	
			Many	13	50.0%	10	37.0%	7	25.0%	
			Always	6	23.1%	1	3.7%	1	3.6%	
15	0.84	1	Few	–	–	1	3.7%	1	3.6%	0.065
	0.72–0.96		Moderate	3	11.5%	7	25.9%	11	39.3%	
			Many	19	73.1%	17	63.0%	13	46.4%	
			Always	4	15.4%	2	7.4%	3	10.7%	
		2	Few	–	–	1	3.7%	2	7.1%	0.038
			Moderate	4	15.4%	11	40.7%	10	35.7%	
			Many	18	69.2%	13	48.1%	14	50.0%	
			Always	4	15.4%	2	7.4%	2	7.1%	
		3	Few	–	–	1	3.7%	2	7.1%	0.030
			Moderate	4	15.4%	7	25.9%	11	39.3%	
			Many	17	65.4%	17	63.0%	13	46.4%	
			Always	5	19.2%	2	7.4%	2	7.1%	
16	0.79	1	Moderate	–	–	1	3.7%	3	10.7%	0.079
	0.66–0.91		Many	8	30.8%	9	33.3%	13	46.4%	

Table 3 (*Continued*)

Question*	Kappa/95%CI	Observer		VD ($n = 26$)		ICS ($n = 27$)		ECS ($n = 28$)		*p-value*
			Always	18	69.2%	17	63.0%	12	42.9%	
		2	Moderate	–	–	1	3.7%	5	17.9%	0.008
			Many	8	30.8%	11	40.7%	14	50.0%	
			Always	18	69.2%	15	55.6%	9	32.1%	
		3	Moderate	1	3.8%	–	–	4	14.3%	0.054
			Many	8	30.8%	10	37.0%	13	46.4%	
			Always	17	65.4%	17	63.0%	11	39.3%	
21	0.80	1	Moderate	3	11.5%	8	29.6%	12	42.9%	0.137
	0.69–0.91		Many	15	57.7%	14	51.9%	9	32.1%	
			Always	8	30.8%	5	18.5%	7	25.0%	
		2	Moderate	3	11.5%	8	29.6%	12	42.9%	0.012
			Many	15	57.7%	14	51.9%	14	50.0%	
			Always	8	30.8%	5	18.5%	2	7.1%	
		3	Moderate	2	7.7%	7	25.9%	12	42.9%	0.008
			Many	17	65.4%	15	55.6%	14	50.0%	
			Always	7	26.9%	5	18.5%	2	7.1%	

Abbreviations: CI, confidence interval. ECS, elective cesarean section; ICS, intrapartum cesarean section; VD, vaginal delivery.
*13) Number of times the child looks at the mother's face; 14) The child's responses to the mother's communicative stimulus; 15) Intensity with which the child responds positively to the attempt to establish communication; 16) to establish verbal and/or physical contact with the mother; 21) Quantity and quality of the interaction (communication, contact).

All the 3 observers agreed that children who were born vaginally looked more frequently at the mother's face (question 13, $p \leq 0.008$) and responded more frequently to the mother's communicative stimulus (question 14, $p < 0.001$).

Two observers agreed that the children who delivered vaginally responded more positively and intensively to their mothers' communication attempts (question 15). In these 3 questions, Kappa coefficients showed strong concordance (Kappa > 0.81). A higher amount of eye/body contact to the mother from the baby born vaginally (question 16) than in the elective cesarean group was observed by only one examiner. This test was considered to have good concordance according to the Kappa coefficient (0.79, between 0.61 and 0.80). Finally, considering the dyad interaction (question 21), its Kappa coefficient showed good concordance (0.80). In this question, the children born vaginally also had better interaction.

All of the other questions (amount of smile, child humor, child vocalization and amount of crying) were similar between the three groups. It can be said that the present study allowed the observation of the existence of a better interaction between the dyads representing normal delivery.

Discussion

According to the English psychoanalyst Bowlby,[11] it is important that the development of attachment and the relationship between mother and baby occur in the first months of the child's life. According to the author, attachment can be measured, as it is the result of behaviors and interactions.

Childbirth represents a holistic phenomenon, as it involves biological, psychological, social, economic and cultural factors, which influence in choosing the mode of delivery. Women who opt for vaginal delivery justify their choice due to rapid recovery after childbirth.[12,13] On the other hand, fear of childbirth is one of the main justifications for a preference for cesarean section.[12]

In Brazil, there is a "cesarean culture", where childbirth means different medical care, childbirth without pain, preserved sexuality, among others.[14] Both types of delivery can generate both benefits and harms for the mother and baby, especially with regard to psychological aspects. The memories of the experience of childbirth, especially of the first child, influence maternal perceptions for a long period, they remain intact on the cognitive and psychological level. In this context, despite cesarean section being a safe procedure, it should be performed only when its benefits are shown to outweigh the risks.[14,15]

One study verified the existence of greater neonatal morbidity in newborns delivered vaginally when compared with neonates born by cesarean section. On the other hand, it pointed to higher maternal morbidity in puerperal women submitted to cesarean sections.[16] Mothers of babies born by vaginal delivery, according to a study, show a higher frequency of loving behavior directed to their babies, registering the presence of a better interaction in the occurrence of vaginal births.[17]

►**Table 4** shows an analysis of studies that compared the mother-child interaction with the mode of delivery. It is worth mentioning that none of the studies mentioned used the POIMB 0–6 as an instrument for analyzing the interaction.

The analysis of the results of the present study showed that the mother's response to the child's social behavior, the child's response to the mother's communicative stimulus

Table 4 Results of studies related to the quality of mother-child interaction according to the mode of delivery

Authors / Year of publication	Title	Main findings
Bradley et al (1983)[18]	A prospective study of mother's attitudes and feelings following cesarean sections and vaginal deliveries.	According to the results of the study, women who had vaginal delivery had the best attitudes toward the baby.
Cranley et al (1983)[19]	Women's perceptions of vaginal delivery and cesarean section	Among the three groups studied – vaginal delivery, emergency cesarean section and elective cesarean section – the emergency cesarean group had more negative perception regarding the experience of delivery. In addition, women in cesarean groups are less likely to breastfeed, a fact that disqualifies mother-child interaction.
Hwang (1987)[20]	Cesarean childbirth in Sweden: Effects on the mother and father infant relationship.	The results of the study show that mothers of babies born by caesarean section reacted less positively when they first saw their children and had more difficulty breastfeeding than mothers of vaginal deliveries.
Gathwala et al (1991)[17]	Influence of cesarean section on mother-baby interaction	Mothers in the representative group of vaginal delivery show an affective more significant behavior compared with mother's representative of the cesarean section.
Rocha et al (2003)[21]	[Mother-child attachment: a comparative study between mothers with vaginal delivery and cesarean section]	Mothers of cesarean section need more attention to initiate breastfeeding. Both perform well in the care of the newborn in the postpartum period.
Olza Fernández et al (2013)[22]	Mode of delivery may influence neonatal responsiveness to maternal separation	No differences were observed related to the mode of delivery; however, it was observed that children born by caesarean section cry less when they are separated from their mothers.
Carlander et al (2010)[23]	Contact between mother, child and partner and attitudes toward breastfeeding in relation to mode of delivery	The mode of delivery does not seem to affect the way mothers experience their contact with the newborn. However, mothers who had a vaginal delivery started breastfeeding in a less stressful manner than mothers who had cesarean delivery.
Zanardo et al (2010)[24]	Elective cesarean delivery: does it have a negative effect on breastfeeding?	Emergency and elective cesarean sections achieve lower success rates in exclusive breastfeeding compared with vaginal delivery.
Lai et al (2015)[25]	Postpartum fatigue, babycare activities, and maternal-infant attachment of vaginal and cesarean births following rooming-in.	Women undergoing cesarean section had greater postpartum fatigue and, consequently, greater difficulty in baby care activities than women who had vaginal delivery.
Pilch (2015)[26]	The influence of birth modus on the emotional state of the mother, bonding, and the newborn's neurobehavioral state	Babies born vaginally had higher levels of cortisol and more frequent direct contact with mothers after delivery, which creates favorable conditions for the formation of bonds.

and maternal sensitivity were the highest in the vaginal delivery group. In addition, higher rates of exclusive breastfeeding were found in this group. The process of interaction between mother and child triggered by vaginal delivery may follow a sequence of behavior modulating events, allowing to positively interfere with the interaction in relation to representative groups of elective cesarean section and intrapartum cesarean section.

When establishing in the methodology of research that the analysis of the evaluation between the dyad would be realized from the making of video footage, the following question arose: could the mother act unnaturally because she knew that she was being filmed? In this context, in addition to the previous requests given to the mother regarding the importance of acting naturally, it also supported the question of intrusiveness – exaggerated behavior of the mother toward the child – that is, an abnormal or forced reaction related to being filmed could be detected in the analysis and would decrease the score related to item 12 corresponding to the intrusiveness analysis. Maybe related to the mothers, they can behave unnaturally, but not the children. Then, we can trust that the choice of the POIMB 0–6 in the present study was satisfactory, since it allowed the detailed analysis of interaction patterns from action sequences and events between the subjects. When there was difference between groups, the concordance between two or three observers was larger related to the children (four questions) than mother behavior (two questions).[2] Children

born vaginally seem to interact better with their mothers than those born by caesarean section.

In animal models, the oxytocin release during parturition is essential for awaking maternal behavior.[27] Maybe the human being is not so distant from these mammals, related to the importance of this "oxytocin inundation" to the onset of maternal-infant bond, including breastfeeding event.

A justification for a better interaction can be understood according to an endogenous oxytocin action, which can trigger a sequence of actions and produce effects that allow continuous activation of the hormone after delivery. In other words, sharing is accompanied by the intense activation and onset of a neuroendocrine cascade that triggers lactation and stimulates interaction.

The possibility of measuring the serum levels of endogenous oxytocin is considered, and its concentration being able to relate to the quality of the maternal-filial interaction. Such possibility of research causes instigation and, therefore, may reinforce the results presented by the present study. From this psychosomatic point of view, it is interesting the research in neuroscience to determinate in which proportion oxytocin is an important factor for affective behavior. It would be a reflection made by obstetricians related to the high incidence of elective cesarean section without medical indication.

Despite the results found and the established conclusion, it is wrong, or perhaps daring, to affirm or suggest that the interaction between the dyads representing the occurrence of cesarean section is negative, since, in addition to the close scores, there are several other factors that may, perhaps, interfere in the results, even if in a camouflaged way. However, it is a fact that the occurrence of vaginal delivery corresponds to an important trigger for the initiation of the oxytocin release process, acting as a facilitator in the process.

Given that this possible higher difficulty exists in the interaction of cesarean sections, it is important that health professionals pay attention to these cases with regard, for example, to stimulation of breastfeeding and skin-to-skin contact with the newborn, even if late.

Conclusion

In summary, when assessing the quality of maternal-filial interaction through the POIMB 0–6 in relation to the type of delivery, considering the occurrence of vaginal delivery, intrapartum cesarean section and elective cesarean section, it is concluded that the interaction between the mother-child dyad is quantitatively larger and qualitatively better in vaginal delivery when compared with intrapartum or elective cesarean section.

Contributors

Santos Neto C. H., Oliveira F. S., Gomes G. F., Araujo Júnior E., Nakamura M. U. and Souza E. declared to have contributed with the conception of the study, collection and tabulation, intellectual critical review, drafting of the manuscript 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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The Influence of Preeclampsia, Advanced Maternal Age and Maternal Obesity in Neonatal Outcomes Among Women with Gestational Diabetes

A influência da pré-eclâmpsia, idade materna avançada e obesidade materna em desfechos neonatais entre mulheres com diabetes gestacional

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Abstract

Objective The present study aims to analyze adverse fetal or neonatal outcomes in women with gestational diabetes, including fetal death, preterm deliveries, birthweight, neonatal morbidity and mortality, as well as the synergic effect of concomitant pregnancy risk factors and poor obstetric outcomes, as advanced maternal age, maternal obesity and pre-eclampsia in their worsening.

Methods The present cohort retrospective study included all pregnant women with gestational diabetes, with surveillance and childbirth at the Hospital da Senhora da Oliveira during the years of 2017 and 2018. The data were collected from the medical electronic records registered in health informatic programs Sclinico and Obscare, and statistical simple and multivariate analysis was done using IBM SPSS Statistics.

Results The study participants included 301 pregnant women that contributed to 7.36% of the total institution childbirths of the same years, in a total of 300 live births. It was analyzed the influence of pre-eclampsia coexistence in neonatal morbidity ($p = 0.004$), in the occurrence of newborns of low and very low birthweight ($p < 0.01$) and in preterm deliveries ($p < 0.01$). The influence of maternal obesity ($p = 0.270$; $p = 0.992$; $p = 0.684$) and of advanced maternal age in these 3 outcomes was also analyzed ($p = 0{,}806$; $p = 0.879$; $p = 0.985$).Using a multivariate analysis, the only models with statistic significance to predict the three neonatal outcomes included only pre-eclampsia ($p = 0.04$; $p < 0.01$; $p < 0.01$).

Conclusion Only coexistence of pre-eclampsia showed an association with adverse neonatal outcomes (neonatal morbidity, newborns of low and very low birthweight and preterm deliveries) and can be used as a predictor of them in women with gestational diabetes.

Keywords

- gestational diabetes
- advanced maternal age
- maternal obesity
- preeclampsia
- neonatal outcomes

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Resumo

Objetivo O presente estudo tem como objetivo analisar desfechos fetais ou neonatais adversos em mulheres com diabetes gestacional, incluindo morte fetal, partos prematuros, peso ao nascimento, morbilidade neonatal e mortalidade, bem como o efeito sinérgico de fatores de risco e maus desfechos concomitantes da gravidez, como idade materna avançada, obesidade materna e pré-eclâmpsia no seu agravamento.

Métodos O presente estudo retrospetivo de coorte incluiu todas as gestantes com diabetes gestacional, com vigilância e parto no Hospital da Senhora da Oliveira durante 2017 e 2018. Os dados foram obtidos dos registos clínicos eletrónicos dos programas informáticos de saúde Sclinico e Obscare, e a análise estatística simples e multivariada foi feita utilizando o IBM SPSS Statistics.

Resultados Os participantes do estudo incluíram 301 gestantes que contribuíram para 7,36% do total de partos da instituição, num total de 300 nados vivos. Foi analisada a influência da coexistência de pré-eclâmpsia na morbilidade neonatal ($p = 0{,}004$), na ocorrência de recém-nascidos de baixo e muito baixo peso ao nascimento ($p < 0{,}01$) e em partos prematuros ($p < 0{,}01$). Também foi analisada a influência da obesidade materna ($p = 0{,}270$; $p = 0{,}992$; $p = 0{,}684$) e da idade materna avançada nesses 3 desfechos ($p = 0{,}806$; $p = 0{,}879$; $p = 0.985$).Usando uma análise multivariada, os únicos modelos com significância estatística para predizer os três desfechos neonatais incluíram apenas a pré-eclâmpsia ($p = 0{,}04$; $p < 0{,}01$; $p < 0{,}01$).

Conclusão Apenas a coexistência de pré-eclâmpsia mostrou associação com desfechos neonatais adversos (morbilidade neonatal, recém-nascidos de baixo e muito baixo peso e partos prematuros) e pode ser utilizada como preditor destes em mulheres com diabetes gestacional.

Palavras-chave

- diabetes gestacional
- idade materna avançada
- obesidade materna
- pré-eclâmpsia
- desfechos neonatais

Introduction

Gestational diabetes is a type of diabetes defined as any degree of glucose intolerance with onset or first recognition during pregnancy, after excluding women with previous diabetes. It usually constitutes ~ 90% of all diabetes complicated pregnancies and it is one of the most frequent complications during pregnancy. A gradual increase in its prevalence has been observed worldwide. According to some authors, this increment was due to increasing rates of maternal obesity, which is not consensual among others. The global prevalence of gestational diabetes stands nowadays between 1 and 22% and varies from country to country, depending on the genetic background, diagnostic methods employed and environmental factors. ►**Box 1** shows some of the common risk factors that may contribute to this increase. There is a higher risk of multiple maternal, fetal and neonatal adverse outcomes due to gestational diabetes. Considering some studies, body mass index (BMI) and maternal age showed to have the heaviest impact on pregnancy outcomes in women with gestational diabetes.[1–37]

Box 1 Common risk factors that may contribute to the increase of gestational diabetes

Common risk factors that may contribute to the increase of gestational diabetes
Previous diagnosis of gestational diabetes
Previous poor obstetric outcomes
Previous macrosomia
Advanced maternal age
Increasing prevalence of obesity
Polycystic ovarian syndrome
Family history of diabetes
Modern lifestyle with reduced physical activity and changed dietary habits
Smoking

Pregnancy at advanced maternal age has become more common in both developed and developing countries over the last decades. Advanced maternal age is considered to be ≥ 35 years, being very advanced maternal age considered to be ≥ 40 or 45 years. Advanced maternal age is an independent risk factor for gestational diabetes and early onset pre-eclampsia and is a known risk factor for other maternal and fetal adverse outcomes, such as miscarriage and ectopic pregnancy. Nevertheless, the correlation between advanced maternal age and adverse neonatal outcomes is still a matter of controversy in several studies.[1–37]

The number of obese pregnant women, individuals with BMI $\geq$ 30.0 kg/m2, is increasing over time.[5,12,18] Pregestational BMI is a risk factor for the development of maternal and perinatal complications.[24,27] In the clinical practice, obesity and gestational diabetes commonly coexist and it is controversial which one the two conditions (gestational diabetes or maternal obesity) is more strongly associated with risk for adverse maternal and neonatal outcomes.[10,13,19] Considering some authors, it seems that obese women with gestational diabetes have an increased risk of adverse outcomes compared with diabetic nonobese women, but more scientific evidence is necessary.[23,35,36]

Pre-eclampsia is one of the major pathologies in pregnancy and is a major health issue for women and their descendants worldwide.[17,34] This disease is characterized by hypertension developing in pregnancy associated with new-onset proteinuria or other end-organ dysfunctions.[34] According to some studies, pre-eclampsia complicates between 2 and 5% of all pregnancies.[34] This disease seems to raise the risk of some important adverse pregnancy outcomes, raising morbidity and mortality not only in pregnant women but probably also in their offspring.[17,34]

It remains unclear whether the combination of gestational diabetes and other pregnancy risk factors and poor obstetric outcomes, such as advanced maternal age, maternal obesity and pre-eclampsia, represents a synergic risk in pregnancy, and whether the diagnosis and treatment of gestational diabetes among these women modifies this risk. So, it seems crucial to examine the results of current clinical care and assess if this care is sufficient or if it needs to be changed. The purpose of the present study was to analyze adverse fetal or neonatal outcomes of women with gestational diabetes, measured by fetal death, presence of preterm deliveries, birthweight, neonatal morbidity and neonatal death, as well as the synergic effect of concomitant pregnancy risk factors and poor obstetric outcomes, as advanced maternal age, maternal obesity and pre-eclampsia in the worsening of these outcomes.

Methods

Identification of the Patients and Setting of Study

This is a retrospective cohort study focusing on adverse fetal and neonatal outcomes of women with gestational diabetes whose pregnancy surveillance and childbirth took place at the Hospital da Senhora da Oliveira (HSO, in the Portuguese acronym), a tertiary center, during the years of 2017 and 2018. The data were collected from the medical records registered in HSO's health informatic programs Sclinico and Obscare. These programs contain data on all births in the mentioned hospital, including information on diagnosis, procedures, interventions, deliveries and newborns, as well as hospital outpatient care. Using these medical records, the following data were retrieved and analyzed: the incidence of gestational diabetes among all the deliveries occurred in 2018 in the HSO; as well as, among the women with gestational diabetes: maternal age, coexistence of pre-eclampsia, maternal BMI, gestational age and preterm deliveries, onset of labor (spontaneous or induced), mode of birth (normal birth, instrumental birth or cesarean), gender of the newborn, birthweight, fetal death, admission in a neonatal intensive care unit, neonatal morbidity and mortality.

Variables Description

Advanced maternal age was defined as maternal age ≥ 35 years old and maternal obesity as a BMI $\geq 30\,kg/m^2$, using the pregestational weight of each pregnant woman for the ratio between weight and height squared. Preeclampsia was defined by hypertension (arterial pressure $\geq$ 140/90 mmHg) developing in pregnancy associated with new-onset proteinuria (protein to creatinine ratio in occasional urine $\geq$ 0,30 or proteinuria in 24h urine ≥ 300 mg) or other end-organ dysfunctions. Fetal death was defined as death in the gestational period. Neonatal mortality was defined as death in the neonatal period (from childbirth up to 28 days postpartum), and neonatal morbidity included pathological diagnosis in the same period, being them respiratory distress, metabolic acidosis, hypoxic-ischemic encephalopathy, hypoglycemia, hyperbilirubinemia, low Apgar scores at the 1st and 5th minutes of life, and congenital anomalies in the neonatal period. Birthweight was divided into 3 different categories: normal if ≥ 2500 g, low if < 2500 g but ≥ 1500 g, and very low if <1500 g. Preterm deliveries were defined by the gestational age on the moment of birth < 37 weeks of gestation.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). A descriptive statistic was used to describe some of the most important variables, as maternal age, gestational age and birthweight. To verify the distribution of each variable, the Shapiro-Wilk normality test was used, more appropriated for the size of the studied sample. A simple analysis with linear regression was first done to compare each one of the variables with the studied outcomes. The independent sample *t*-test and the Mann-Whitney U-test were used to compare the means of continuous and categoric variables. To analyze the influence of a categoric variable in another categoric variable, the chi-squared test was used. Afterwards, a multivariate analysis was performed to assess the concomitance of maternal risk factors in neonatal outcomes, using a multiple regression. A $p\text{-}value < 0.05$ was considered statistically significant, and a 95% confidence interval (CI) was used. Analysis of differences between groups, tables, circle charts and histograms were also executed, all created in IBM SPSS for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). The results are expressed in percentages, and the means, ranges and standard deviations (SDs) are reported when appropriate. The present investigation was approved by the hospital's ethics committee and authorized by the Board of Directors of the Hospital da Senhora da Oliveira.

Results

The present study included a total number of 301 unifetal pregnancies (146 from 2017 and 155 from 2018). It was decided to exclude the 8 cases of twin pregnancies (3 from 2018 and 5 from 2017) from these data, since twin pregnancies are from the beginning associated with worse outcomes, which could interfere with our results.

The women had a mean maternal age of $33{,}37 \pm 5{,}12$ years old, with a minimum of 18 years old and a maximum of 47 years old, and their pregnancies had a median of gestational age of $38{,}00 \pm 2{,}00$ weeks, with a minimum of 30 weeks and a maximum of 41 weeks of gestation. They contributed to 301 childbirths within a total number of 4089 childbirths that occurred in 2017 and 2018 (2036 in 2017 and 2053 in 2018) in the HSO, corresponding to 7,36% of childbirths, and led to 31 cases (10,30%) of preterm births ($<$ 37 weeks). The onset of labor was mainly spontaneous

(56.10%) and it was normal in about half of the cases (54.15%). These 301 childibirths resulted in 300 live births (99.70%) and 1 case of fetal death and stillbirth (0.30%). There were no cases of neonatal mortality and 6.30% of cases of neonatal morbidity. The birthweight of the newborns had a mean of 3,146.97 ± 500,66 g, with a minimum of 990 g and a maximum of 4,645 g, and there were almost 8% of newborns with low and very low birthweight. The description of the study participants and pregnancy and neonatal outcomes can be analyzed in ►**Table 1**.

Regarding maternal age, there were 45.20% of cases of advanced maternal age and 54.80% of maternal age < 35 years. The incidence of neonatal morbidity, newborns with low and very low birthweight and of preterm deliveries was similar among both categories (6.0%, 7.40% and 10.40% in pregnant women with advanced maternal age versus 6.70%, 7.90% and 10.30% in pregnant women without advanced maternal age, respectively). The influence of the advanced maternal age in these three outcomes was analyzed ($p = 0.806$; $p = 0.879$; $p = 0.985$, respectively). It's possible to analyze the aforementioned results in ►**Table 2**.

Considering the coexistence of pre-eclampsia with gestational diabetes, there were 6% of cases in both conditions versus 94% with only gestational diabetes. The incidence of neonatal morbidity, newborns with low and very low birthweight and of preterm deliveries was higher in the first group (22.20%, 33.30% and 61.10% in pregnant women with pre-eclampsia and gestational diabetes versus 5.30%, 6.00% and 7.10% in pregnant women with only gestational diabetes, respectively). The influence of pre-eclampsia in these 3 outcomes was analyzed ($p = 0.004$; $p < 0.01$; $p < 0.01$, respectively). It is possible to analyze the aforementioned results in ►**Table 3**.

In respect to the coexistence of maternal obesity (BMI ≥ 30kg/m2) with gestational diabetes, there were ∼ 26% of cases in these conditions versus 74% of cases with just gestational diabetes. The incidence of neonatal morbidity and of preterm deliveries was higher in the first group (9.00% and 11.50% versus 5.40% and 9.90%, respectively). The

Table 2 Influence of coexistence of advanced maternal age with gestational diabetes in neonatal morbidity, low and very low birthweight and incidence of preterm deliveries

Influence of coexistence of advanced maternal age with gestational diabetes			
Pregnancy and Neonatal outcomes	**Maternal Age < 35 years old**	**Maternal Age ≥35 years old**	***p-value***
Neonatal Morbidity Absence (%) Presence (%)	154 (93.30) 11 (6.70)	126 (94.00) 8 (6.00)	0.806
Birthweight ≥2500 g (%) < 2500 g (%)	152 (92.10) 13 (7.90)	125 (92.60) 10 (7.40)	0.879
Deliveries Term (%) Preterm (%)	148 (89.70) 17 (10.30)	121 (89.60) 14 (10.40)	0.985

Table 1 Description of study participants and pregnancy and neonatal outcomes

Characteristics	Number of cases - %
Maternal characteristics	
Number of pregnant women (unifetal pregnancies) with gestational diabetes	30–100
Advanced maternal age: Presence versus Absence	136 versus 165–45.20 versus 54.80
Preeclampsia: Presence versus Absence	18 versus 283–6 versus 94
Maternal Obesity: Presence versus Absence (missings)	77 versus 223 (1)–25.60 versus 74.10 (0.30)
Pregnancy outcomes	
Onset of labor: Spontaneous versus Induced versus Absence (missings)	169 versus 95 versus 35 (2)–56.10 versus 31.60 versus 11.60 (0–70)
Type of labor: Normal versus Instrumental versus Cesarean section (missings)	163 versus 45 versus 89 (4)–54.15 versus 14.95 versus 29.57 (1.33)
Number of unifetal deliveries among all the 2017 and 2018 deliveries in the mentioned hospital	301/4,089–7.36
Preterm deliveries versus Term deliveries (missings)	31 versus 269 (1)–10.30 versus 89.40 (0.30)
Perinatal and neonatal outcomes	
Live births versus Fetal deaths and stillbirths	300 versus 1–99.70 versus 0.30
Male newborns versus Female newborns	165 versus 135–55 versus 45
Birthweight: Normal versus Low versus Very low	277 versus 20 versus 3–92.30 versus 6.70 versus 1
Neonatal mortality: Presence versus Absence	0 versus 300–0 versus 100
Neonatal morbidity: Presence versus Absence (missings)	19 versus 280 (1)–6.30 versus 93.30 (0.30)
Admission in a neonatal intensive care unit: Presence versus Absence	17 versus 283–5.70 versus 94.30

Table 3 Influence of pre-eclampsia coexistence with gestational diabetes in neonatal morbidity, low and very low birthweight and incidence of preterm deliveries

Influence of coexistence of preeclampsia with gestational diabetes			
Pregnancy and Neonatal outcomes	**Without preeclampsia**	**With preeclampsia**	***p-value***
Neonatal Morbidity Absence (%) Presence (%)	266 (94.70) 15 (5.30)	14 (77.80) 4 (22.20)	0.004
Birthweight ≥2500 g (%) < 2500 g (%)	265 (94.00) 17 (6.00)	12 (66.70) 6 (33.30)	< 0.01
Deliveries Term (%) Preterm (%)	262 (92.90) 20 (7.10)	7 (38.90) 11 (61.10)	< 0.01

incidence of newborns with low and very low birthweight was similar between both categories (7.70% versus 7.70%, respectively). The influence of maternal obesity in these three outcomes was analyzed ($p = 0.270$; $p = 0.992$; $p = 0.684$, respectively). It is possible to analyze the aforementioned results in ►**Table 4**.

A multivariate analysis was performed to assess the concomitance of maternal risk factors in neonatal outcomes, using a multiple regression. In what concerns to the prevision of the outcome neonatal morbidity, the only model with statistic significance was the model including only preeclampsia: [F (1.297) = 8.274; $p < 0.004$; $r^2 = 0.28$]. A *p-value* = 0.934 and $p = 0.530$ were obtained for models including 2 variables (pre-eclampsia and advanced maternal age) and including 3 variables (pre-eclampsia, advanced maternal age and maternal obesity), respectively. In what concerns to the prevision of newborns of low and very low birthweight, the only model with statistic significance was the model including only preeclampsia: [F(1.298) = 26.761; $p < 0.01$; $r^2 = 0.084$]. A p-value = 0.474 and $p = 0.686$ were obtained for models including two variables (pre-eclampsia and advanced maternal age) and including 3 variables (pre-eclampsia, advanced maternal age and maternal obesity), respectively. In what concerns to the prevision of the outcome of preterm deliveries, the only model with statistic significance was the model including only preeclampsia: [F (1.298) = 64.364; $p < 0{,}01$; $r^2 = 0.183$]. A *p-value* = 0.340 and $p = 0.312$ were obtained for models including two variables (pre-eclampsia and advanced maternal age) and including 3 variables (pre-eclampsia, advanced maternal age and maternal obesity), respectively.

Table 4 Influence of maternal obesity coexistence with gestational diabetes in neonatal morbidity, low and very low birthweight and incidence of preterm deliveries

Influence of coexistence of maternal obesity with gestational diabetes			
Pregnancy and Neonatal outcomes	**Without maternal obesity**	**With maternal obesity**	***p-value***
Neonatal Morbidity Absence (%) Presence (%)	209 (94.60) 12 (5.40)	71 (91.00) 7 (9.00)	0.270
Birthweight ≥2500 g (%) < 2500 g (%)	205 (92.30) 17 (7.70)	72 (92.30) 6 (7.70)	0.992
Deliveries Term (%) Preterm (%)	200 (90.10) 22 (9.90)	69 (88.50) 9 (11.50)	0.684

Discussion

As our results showed, the current literature also demonstrated that women with gestational diabetes are at risk of both maternal, fetal and neonatal adverse outcomes, including pre-eclampsia and eclampsia (8-fold raise), increased risk of preterm birth, higher need for labor induction, caesarean section, stillbirths, macrosomia, full term low weight infants, newborns large for gestational age, neonatal morbidity (namely hyperbilirubinemia and jaundice, respiratory distress and asphyxia, hypoglycemia and congenital malformations), increased need to admission in neonatal intensive care unit and neonatal death (5-fold raise).[2,11,16] However, there are also some studies that do not share the same scientific opinion. Some authors stated that the prevalence of newborns large for gestational age, cesarean section and preterm deliveries in gestational diabetes was not elevated.[1]

The statistically significant influence of pre-eclampsia coexistence in women with gestational diabetes in the ocurrence of neonatal morbidity, newborns of low and very low birthweight and preterm deliveries was at some point expected, since pre-eclampsia is per se a severe obstetric pathology with severe well-known pregnancy outcomes in the literature revision, as mentioned by many investigators: newborns small for gestational age, preterm birth and 5 minute Apgar score < 7.[17,34] Nevertheless, the verified absence of influence of maternal obesity and advanced maternal age in the same group of women in these 3 outcomes, was instead against most of the authors, who do not only point them as risk factors for gestational diabetes, but also in most studies as aggravating factors of its outcomes. Considering the findings of some authors, an increased maternal insulin resistance in pregnancies with obesity and gestational diabetes promote the placental growth and inhibit its efficiency, being this pathophysiological mechanism responsible for the adverse outcomes in pregnant obese women with gestational diabetes.[26,35] According to other investigators, prepregnancy obesity increased the likelihood of neonatal hypoglycemia among infants of mothers with gestational diabetes.[13] In certain studies, the mentioned association will increase the risk for obstetric and neonatal complications, in particular preterm birth and infant birth weight above the 90th percentile.[23,36] Nevertheless, according to some other studies, obesity (without gestational diabetes) is more frequently associated with adverse perinatal outcomes (including births at < 33 weeks of gestation, birthweight > 4000 g and low 5-minute Apgar scores) than the association of obesity and gestational diabetes or than gestational diabetes in nonobese

mothers, and, so, it's at least so crucial to treat prepregancy obesity as to prevent gestational diabetes in future mothers.[35] This same finding is concordant with the results of the present study, which showed that maternal obesity doesn't seem to be an aggravating factor of gestational diabetes, which could be explained by the greater number of prenatal visits and strict vigilance of women with gestational diabetes that should be enough to achieve a more rigorous diet and weight control, as already mentioned in the recent literature.[2,4,11] In the same way, other authors considered advanced maternal age as a potential risk factor of gestational diabetes, as well as an aggravating factor of it, capable to raise the incidence of adverse outcomes for mothers, newborns and infants, as spontaneous late preterm deliveries, fetal growth restriction, small for gestational age infants and birthweight < 2500 g.[3,14,21] However, according to some authors, maternal age does not significantly influence birthweight.[25] Despite the findings in the literature, the present study did not find advanced maternal age as an aggravating factor of gestational diabetes, which could be explained also by a more rigorous vigilance of these pregnant women.

It is proven by the findings of many studies that early screening, high utilization of prenatal visits and subsequent treatment of gestational diabetes to promote maternal–fetal health allows the adhesion to a more balanced diet and to a regular exercise program, which leads to a more strict weight reduction and better glycemic control in the 3 months prior to birth, with a consequent improvement of some known adverse outcomes, such as preterm deliveries, neonatal morbidity, infants requiring neonatal intensive care unit (NICU) admission or maternal risk for diabetes later in life.[2,4,30] Therefore, the verification of maternal obesity and advanced maternal age as nonaggravating factors of gestational diabetes in the present study may be a proof of an adequate obstetric vigilance and strict metabolic control of the pregnant women with gestational diabetes in the present tertiary center.

Using the multivariate analysis, it was shown that only pre-eclampsia in women with gestational diabetes can be used to predict the three studied outcomes (neonatal morbidity, newborns of low and very low birthweight and preterm deliveries). Neither maternal obesity nor advanced maternal age are predictors of these neonatal outcomes in women with gestational diabetes. As mentioned above, the severity of this obstetric pathology can be a reasonable explanation.

As strengths of the study itself, it could be mentioned the good amount of information of the participants, as well as the outcomes evaluated. Moreover, the majority of the variables in the present study (maternal age, BMI, fetal death, birthweight, neonatal mortality) were objective parameters, not influenced by inter or intraobserver variability in their measurement. As limitations of the present study, it could be enumerated the retrospective character of the study instead of a prospective one and the selection of the study population from one single hospital, and not from many, which could be resolved by a multicenter study, possibly more representative, not only in respect to the number of pregnant women involved but also considering different settings and backgrounds of the population analyzed.

Conclusion

Although the coexistence of pre-eclampsia and gestational diabetes showed a statistically significant association with adverse neonatal outcomes, neither the association of advanced maternal age nor maternal obesity with gestational diabetes had a negative influence on these outcomes. Moreover, in a multivariate analysis, it was shown that only pre-eclampsia can be used to predict the neonatal outcomes (neonatal morbidity, newborns of low and very low birthweight and preterm deliveries) in women with gestational diabetes.

Contributors

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

Conflict of Interests

The authors have no conflict of interests to declare.

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Worldwide Original Research Production on Maternal Near-Miss: A 10-year Bibliometric Study

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Abstract

Objective To evaluate the global productivity regarding original articles on maternal near-miss (MNM).

Methods We conducted a bibliometric analysis of original articles published from 2008 to November 2019 in the journals indexed in the Scopus database. The averages of the number of articles by author, of the number of authors by article, of the number of citations by article, and the total number of documents with one or more authors were obtained. An analysis of the co-citation of authors and a co-occurrence analysis of the terms included in the titles and abstracts were performed and were presented as network visualization maps.

Results A total of 326 original articles were analyzed. There was an increase in the number of articles ($p < 0.001$; average annual growth rate = 12.54%). A total of 1,399 authors, an average number of articles per author of 4.29, with an index of authors per document of 0.23, and an index of co-authors per document of 8.16 were identified. A total of 85 countries contributed with original articles on MNM. Among the top ten countries regarding the contribution of articles, five were low and middle-income countries (LMICs). Brazil had the highest volume of production (31.1%), followed by the US (11.5%). Terms related to countries and the measurement of the rates and cases of MNM and the associated factors were found in recent years in the analysis of the co-occurrence of terms.

Conclusion There was an increase in the production of original articles on MNM, with a significant participation of authors and institutions from LMICs, which reveals a growing interest in the use of MNM indicators to improve the quality of maternal health care.

Keywords
- near-miss
- healthcare
- maternal health
- maternal health services

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Introduction

Maternal mortality is the indicator traditionally used to assess the quality of maternal health services and health systems.[1,2] However, maternal deaths represent only the "tip of the iceberg" of maternal health problems, and for every woman who dies from causes related to pregnancy, another 20 or 30 experience acute or chronic morbidity.[3,4]

Currently, the measurement of the rate of maternal near-miss (MNM) as an indicator of the evaluation of maternal health is being promoted.[5] MNM is a term that describes the case of a woman who presented a medical condition related to a potentially-fatal pregnancy but survived. There are several definitions and criteria to determine a case of MNM.[5] Therefore, the World Health Organization (WHO) in 2008, established a definition for MNM: a complication that occurred during pregnancy, childbirth or within 42 days of the termination of pregnancy; it also established criteria for the determination of cases of MNM and championed surveillance of the cases of MNM for the improvement of the quality of health systems.[5,6]

The concept of MNM has been attracting growing interest in the scientific community as a benchmark indicator to evaluate the results in maternal health of the population, with advantages over the evaluation from mortality. The study of women who survived a life-threatening complication enables the identification of the shortcomings and successes regarding assistance, and it also enables physicians to deepen the understanding of the disease process from the perspective of the patients, situations that are not possible in cases of maternal death.[7–9] Since the last decade, several studies have been using bibliometric methods to evaluate scientific productivity in several biomedical fields.[8,9] Although the measurement of the rate of MNM is promoted as an indicator of the quality of maternal health care,[6,10] in the scientific literature there is a lack of studies that estimate the global production of research on MNM.

The present bibliometric analysis sought to assess the global productivity of original articles on MNM, including the quantity, quality, and an analysis of the citations by authors and of the co-occurrence of terms in documents, to determine if there has been an increase in the scientific production and what are the characteristics of the original articles published on MNM after the promotion of its use for the evaluation and improvement of maternal health.

Methods

Study Design

We conducted a bibliometric analysis of original articles published from 2008 (the year in which the definition and criteria of MNM proposed by the WHO were made available) to November 2019 in journals indexed in the Scopus (https://www.scopus.com/) database. While this database of bibliographic citations includes various types of documents, only original articles were included in the present analysis.

Data Source

Scopus is the largest database of citations and abstracts of peer-reviewed scientific literature to date, including more than 24 thousand titles from more than 11 thousand publishers.[11] Scopus was used as a source of information since it includes all MEDLINE documents (the most widely-used free-access citation database), and includes additional features about the authors and the citations per document, which are useful for the quality and quantity measurements proposed for the present study.[11]

Search Strategy

The search strategy was developed by a librarian (DC), dated between January 1, 2008, and November 30, 2019, including free terms to be searched in the title, summary, and keywords of the documents indexed in Scopus. The search strategy used was as follows: ((KEY (mothers)) OR (TITLE-ABS-KEY (maternal)) OR (TITLE-ABS-KEY (mother*)) OR (TITLE-ABS-KEY (pregnan*)) OR (TITLE-ABS-KEY (obstetric*))) AND ((TITLE-ABS-KEY ("Near-Miss")) OR (TITLE-ABS-KEY ("Near-Misses")) OR (TITLE-ABS-KEY ("Life-Threatening"))). The validity of the search strategy was tested through a manual review of the retrieved articles by an author (GBQ) independently.

Table 1 Number of publications on maternal near-miss by year and top ten authors

Characteristics	Number of articles	% of articles
Year		
2008	9	2.76%
2009	16	4.91%
2010	17	5.21%
2011	15	4.60%
2012	16	4.91%
2013	21	6.44%
2014	37	11.35%
2015	36	11.04%
2016	42	12.88%
2017	45	13.80%
2018	39	11.96%
2019	33	10.12%
Author		
Cecatti JG	53	16.26%
Souza JP	37	11.35%
Parpinelli MA	33	10.12%
Sousa MH	32	9.82%
Costa ML	31	9.51%
Haddad SM	24	7.36%
Pacagnella RC	23	7.06%
Surita FG	22	6.75%
Say L	18	5.52%
Pattinson RC	16	4.91%

Data Collection

The complete records of each publication retrieved in the search were downloaded as a .csv file from Scopus and imported into the Rayyan (https://rayyan.qcri.org) web application, in which an author (GBQ) selected, by title and summary, the articles that met the inclusion criteria (having been published since 2008, and presenting results on MNM or MNM rates).

Only original articles published since 2008 were included because this was the year the definition and criteria proposed by the WHO for the definition of cases of MNM were published.[5,6]

Bibliometric Analysis

The Bibliometrix R-tool (http://www.bibliometrix.org/) was used for the bibliometric analysis. Since documents with erroneous attributions in the author's name and affiliation domains were detected, a standardization was performed manually by one of the authors (AHV). The characteristics of the documents analyzed were described, including the average of articles by author, the average of authors per article, the average of citations per article, and the number of documents with one or more authors. Additionally, some useful rates for the bibliometric evaluation were described, such as the rate of authors per article (ratio between the total number of articles and the total number of authors), the rate of co-authors per article (average number of co-authors per article) and the ratio of collaboration (ratio between the total number of authors of articles with several authors and the total of articles with several authors). More information about the calculation and how these bibliometric rates are obtained can be reviewed on the Bibliometrix website.[12]

The VOSviewer (Leiden University, Leiden, The Netherlands) software was used to build and visualize bibliometric networks based on analyses of bibliographic couplings, co-authorships, and co-citations, using information about the authors, journals, institutions and countries associated with the publications. A threshold was established for the co-occurrence of terms in titles and summaries of five mentions (the terms *human*, *health*, *women's health*, *mnm*, and *article* were excluded).

Results

The results of 326 original articles published between January 2008 and November 2019 (►**Table 1**) were analyzed. During the study period, there was an increase in the number of original articles on MNM ($p < 0.001$; $R^2 = 0.77$), with an average annual growth rate of 12.54%.

A total of 1,399 authors were identified with 2,660 occurrences. Only four original articles had a single author. An average of the number of articles per author of 4.29 was found,

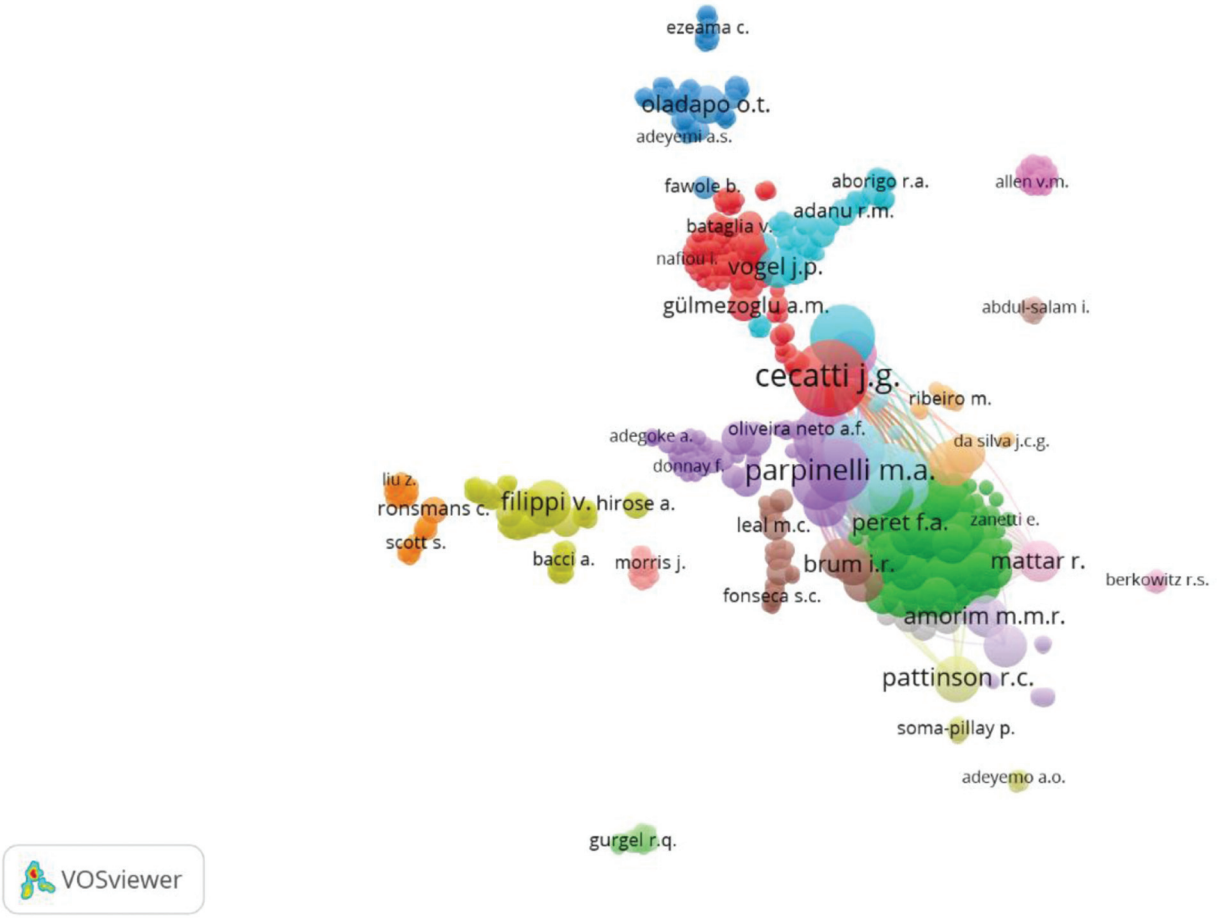

Fig. 1 Analysis of co-authorship with the VOSviewer software regarding publications on maternal near-miss.

Table 2 Top ten countries with more publications on maternal near-miss, and some citation indices

Rank	Country	Number of articles	% of articles	Single-country publications	Multiple-country publications	Multiple-country publication ratio
1	Brazil	65	31.1	54	11	0.17
2	USA	24	11.48	13	11	0.46
3	India	18	8.61	17	1	0.06
4	United Kingdom	18	8.61	9	9	0.5
5	Uganda	6	2.87	6	0	0
6	China	5	2.39	4	1	0.2
7	Canada	4	1.91	1	3	0.75
8	Nigeria	4	1.91	4	0	0
9	Pakistan	4	1.91	4	0	0
10	Sweden	4	1.91	1	3	0.75

with an index of authors per document of 0.23, and an index of co-authors per document of 8.16. The rate of collaborations was of 4.33. Ceccatti JG (53 documents) and Souza JP (37 documents) were the authors with the highest number of publications (►**Table 1**). Among the top ten authors with the highest volume of production of original articles, eight were affiliated with an institution in Brazil. In ►**Fig. 1**, a co-authorship analysis is presented, including authors with more than five original articles, with each circle representing an author. The size of the circle indicates the volume of the productivity (the larger the circle, the greater the number of author's documents) and the proximity of the circles indicates a close collaboration. As a result, the formation of collaborative networks around the aforementioned authors with a greater volume of scientific production is evident.

A total of 85 countries contributed with original articles on MNM. According to the country of origin of the institutional affiliation of the authors of the original articles on MNM, Brazil had the highest proportion of publications (31.1%), followed by the US (11.5%). Among the top ten countries regarding the contribution of original articles on MNM, five were low and middle-income countries (LMICs) according to the 2019 World Bank classification. Similarly, the countries of origin of the institutions of the most frequent correspondent authors were Brazil and the US (65 and 24 documents respectively) and they presented the largest number of collaborative documents with institutional affiliations from different countries (11 for each country). Brazil presented the largest number of documents as the only country of the institutional affiliations of the authors: 54) (►**Table 2**).

Regarding the citations, the original articles had an average of 13.47 citations. The articles by Say L et al[5] (2009) and Souza JP et al[13] (2014) presented the highest number of citations (391 and 300, with a citation average of 35.55 and 42.86 per year respectively). On the scientific journals, *BMC Pregnancy and Childbirth* published the largest number of MNM publications (44; 13.50%), followed by the *International Journal of Gynecology and Obstetrics* (23; 7.06%) (►**Table 3**).

In the co-occurrence analysis of terms (►**Fig. 2**), the terms: *prospective surveillance*, *score*, *main outcome measure*, *mortality ratio*, *case fatality rate*, *delayed mortality*, *association*,

Table 3 Top ten journals publishing original articles on maternal near-miss

Journal	Number of articles	% of articles	2018 *h*-index*
BMC Pregnancy and Childbirth	44	13.50%	66
International Journal of Gynecology and Obstetrics	23	7.06%	88
BJOG: An International Journal of Obstetrics and Gynecology	20	6.13%	148
PLOS ONE	16	4.91%	268
Reproductive Health	13	3.99%	41
Journal of Obstetrics and Gynecology of India	11	3.37%	12
Acta Obstetricia et Gynecologica Scandinavica	7	2.15%	93
Biomed Research International	6	1.84%	94
Revista Brasileira de Ginecologia e Obstetrícia	5	1.53%	19
Tropical Medicine And International Health	5	1.53%	101

Note: *The *h*-index is an index that attempts to measure both the productivity and impact of the published work of a scientist or scholar.

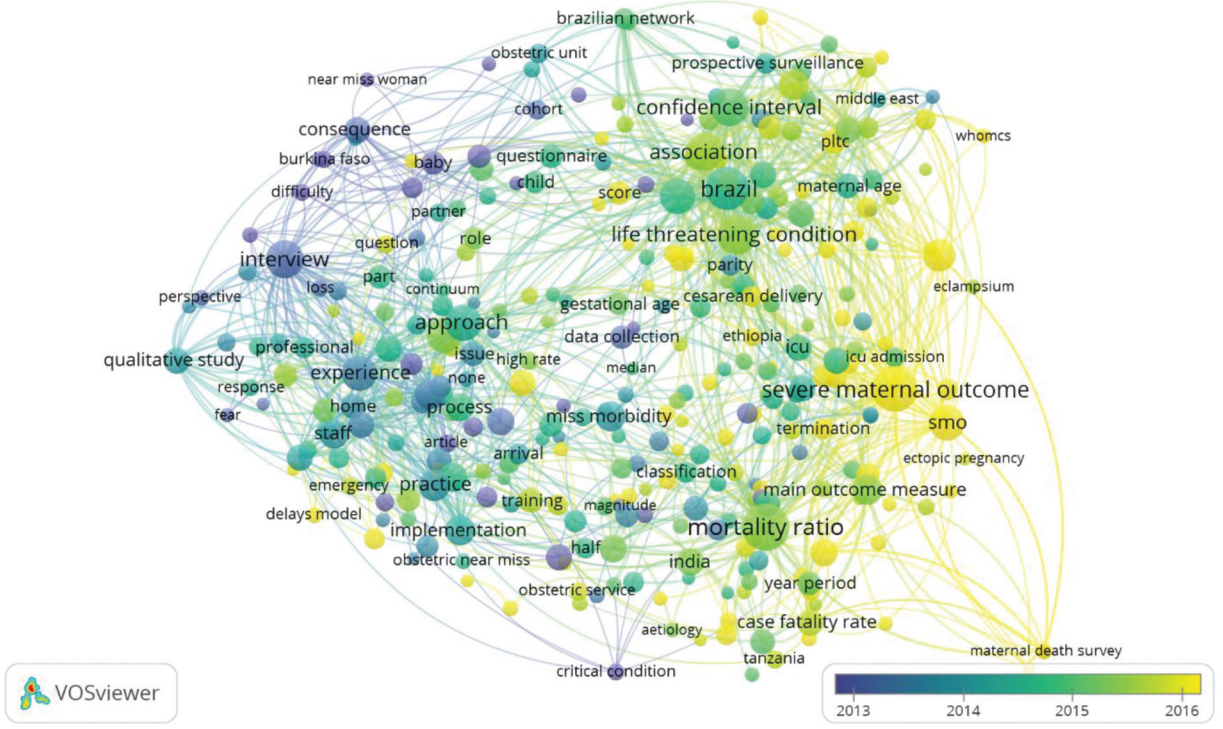

Fig. 2 Analysis of the co-occurrence of terms in titles and abstracts (overlay visualization) and their temporal evolution with the VOSviewer software regarding publications on maternal near-miss.

training, *maternal death survey*, *severe maternal outcomes (smo)*, *cesarean*, *preeclampsia*, *potentially life-threatening condition (pltc)*, as well as terms about countries such as Brazil, Ethiopia, India, and Tanzania, were found for recent years.

Discussion

The present study aimed to determine the production and characteristics of the original articles on MNM published since the WHO defined the concept and criteria to measure the cases and rates of MNM. As a result, an increase in the production of original articles on MNM was found during the last decade. Almost a third of the scientific production on MNM is from Brazil, the country of origin of the institutional affiliations of the most productive authors. Additionally, half of the countries in the top ten with the highest volume of production on MNM are LMICs, with the other half composed of high-income countries, such as the US and the United Kingdom. The analysis of the co-occurrence of terms indicated that in recent years the cases and rates of MNM and its associated factors have been measured in various countries, in addition to the study of health systems around MNM. These results indicated that the scientific production on MNM has been increasing, it comes mostly from LMICs, and has been presenting a tendency to study associations or to report experiences of measuring the rates and cases of MNM in various health systems.

During the study period, an increase in the number of original articles on MNM is evidenced. International initiatives have been promoting an improvement in maternal health indicators, such as the United Nations Sustainable Development Goals (SDG), which propose a reduction by 2030 in the global maternal mortality rate to < 70 per 100,000 live births and the provision of universal access to sexual and reproductive health care services and the integration of reproductive health in national strategies and programs.[2] Thus, an international context of improvement of maternal and child care could be a promoter of a greater scientific production on MNM, having been described through other bibliometric studies, the increase of the scientific production in obstetrics in the.[14,15] Given the priority that exists in the evaluation of health systems for the improvement of maternal health and the consequent reduction in mortality,[13] the increase in the production of original articles on MNM reveals a scenario in which the measurements are increasing on maternal health care, which can provide useful information for the improvement of health systems.

Among the top ten countries regarding the production of original articles on MNM, five (Brazil, India, Uganda, Nigeria, and Pakistan) are classified as LMICs by the World Bank,[16] with Brazil being the country that leads this ranking. Countries such as the US and the United Kingdom, which occupied the second and fourth places regarding the volume of scientific production on MNM, usually lead the rankings of scientific production, including in the area of health, and the field of obstetrics is not an exception.[14] Given that maternal mortality in LMICs is higher compared with that of high-income countries,[17,18] one would expect that high-income countries would be in the top ten regarding the scientific production on MNM (because in countries with low rates of maternal death, the measurement of the cases and rates of

MNM is useful to identify a greater number of cases for the audit of the care provided in establishments with maternal functions compared with the traditional systems of surveillance of maternal mortality). The fact that Brazil is the country with the highest volume of scientific production, even greater than that of high-income countries, corresponds to what was found for the MNM collaboration networks:these networks are led by researchers affiliated to Brazilian institutions, and almost all top ten authors with more articles on MNM are affiliated to Brazilian institutions. These results suggest that countries with different levels of income have been measuring MNM for the improvement of the maternal health of their populations, which determines an opportunity for the health systems to be able to have more data for the analysis and improvement of their attention processes at the local level.

In the analysis of the co-occurrence of terms, we found that, in recent years, terms such as *maternal death survey*, *delayed model*, *obstetric service* and *score* reflect that MNM has been evaluated from the perspective of maternal health services. The use of standards for maternal health care, including electronic or non-registration, surveillance, and response systems on maternal care data has been described to improve decision-making.[19,20] Since the measurement of the rates and cases of MNM contributes to the audit of the quality of maternal health care, these results would reflect the interest in the evaluation or development of maternal health surveillance systems worldwide, which corresponds to some articles found on MNM published over the previous years. Other terms reported in more recent studies, such as *cesarean section*, *preeclampsia*, *severe maternal outcome (smo)*, *termination*, *case fatality rate*, *association* and *potentially life-threatening condition (pltc)*, as wellas terms that describe countries such as Brazil, Ethiopia, India, and Tanzania reflect that, in recent years, the authors have been conducting studies that measure the cases and rates of MNM according to specific maternal health conditions and their associated factors,[21–25] or studies for the validation of the MNM criteria in these countries.[26–29]

Terms related to severe acute maternal morbidity were not included, since this is a term interchangeable with MNM, and the WHO does not recommend refering to severe, life-threatening obstetric complications. Similarly, since we did not include articles that did not have MNM as the main subject mentioned in the title, abstract or keywords, it is possible that some studies that evaluated MNM but did not include this information in these fields may have been excluded. Hence, considering that studying MNM is in line with the proposed goals for the improvement of maternal health indicators as part of the SDGs, despite the limitations of the present study, we consider adequate the use of the year 2008 as a point of review about the status of MNM publications to evaluate the worldwide research production of studies on MNM. Furthermore, the search strategy used in the present study was developed by a librarian with extensive experience in developing search strategies in the field of health to ensure the quality of this procedure.

Conclusion

In conclusion, there was a sustained increase in the scientific production of articles on MNM since 2008, with an important participation of authors and institutions from LMICs. Brazil is the leading country in terms of scientific production and collaborative networks. The current publications on MNM aim to measure the associations or results of surveillance systems or to validate the criteria to measure the rates and cases of MNM at the local level for the improvement of maternal health. Given the benefits of the measurement of maternal health indicators from the perspective of MNM compared with the traditional measurements or health surveillance of maternal mortality, the increase in the scientific production of articles in recent years on the evaluation of systems of surveillance of MNM reveals an interest in improving the quality of maternal health care from a different perspective, and that should favor clinical decision-making and planning at the level of the health system.

Ethical Considerations

The present study did not require the approval of an ethics committee since the data obtained from Scopus represents secondary data that does not include sensitive information.

Contributors

All of the authors made substantial contributions to the manuscript, and met the ICMJE authorship criteria.

Conflict of Interests

The authors have no conflict of interest to declare.

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Cervical Pessary Plus Progesterone for Twin Pregnancy with Short Cervix Compared to Unselected and Non-Treated Twin Pregnancy: A Historical Equivalence Cohort Study (EPM Twin Pessary Study)

Pessário cervical associado a progesterona em gestações gemelares com colo curto comparado a gestações gemelares não selecionadas e não tratadas: estudo de coorte histórica de equivalência (Estudo de Pessário em Gêmeos EPM)

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Abstract

Objective The present study aims to determine if the use of cervical pessary plus progesterone in short-cervix ($\leq$ 25 mm) dichorionic-diamniotic (DC-DA) twin pregnancies is equivalent to the rate of preterm births (PBs) with no intervention in unselected DC-DA twin pregnancies.

Methods A historical cohort study was performed between 2010 and 2018, including a total of 57 pregnant women with DC-DA twin pregnancies. The women admitted from 2010 to 2012 ($n = 32$) received no treatment, and were not selected by cervical length (Non-Treated group, NTG), whereas those admitted from 2013 to 2018 ($n = 25$), were routinely submitted to cervical pessary plus progesterone after the diagnosis of short cervix from the 18th to the 27th weeks of gestation (Pessary-Progesterone group, PPG). The primary outcome analyzed was the rate of PBs before 34 weeks.

Results There were no statistical differences between the NTG and the PPG regarding PB $<$ 34 weeks (18.8% versus 40.0% respectively; $p = 0.07$) and the mean birthweight of the smallest twin (2,037 $\pm$ 425 g versus 2,195 $\pm$ 665 g; $p = 0.327$). The Kaplan-Meyer Survival analysis was performed, and there were no differences between the groups before 31.5 weeks. Logistic regression showed that a previous PB ($<$ 37 weeks) presented an odds ratio (OR) of 15.951 (95% confidence interval [95%CI]: 1.294–-196.557; $p = 0.031^{*}$) for PB $<$ 34 weeks in the PPG.

Keywords

- preterm birth
- cervical pessary
- dichorionic-diamniotic twin pregnancy
- short cervix
- vaginal progesterone

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Conclusion In DC-DA twin pregnancies with a short cervix, (which means a higher risk of PB), the treatment with cervical pessary plus progesterone could be considered equivalent in several aspects related to PB in the NTG, despite the big difference between these groups.

Resumo

Objetivo Este estudo tem como objetivo determinar se o uso de pessário cervical associado a progesterona em gestações de gêmeos dicoriônicos-diamnióticos (DC-DAs) com colo do útero curto ($\leq$ 25 mm) apresenta taxa de parto prematuro (PP) equivalente à de gestações gemelares DC-DA sem nenhuma intervenção/não selecionadas.

Métodos Um estudo de coorte histórica foi realizado entre 2010 e 2018, incluindo um total de 57 mulheres grávidas com gestações gemelares DC-DA. As mulheres admitidas de 2010 a 2012 ($n = 32$) não receberam tratamento, e não foram selecionadas pelo comprimento cervical (grupo Não Tratado, GNT), enquanto as admitidas de 2013 a 2018 ($n = 25$) receberam pessário cervical rotineiramente associado a progesterona após o diagnóstico de colo curto entre a 18ª e a 27ª semanas de gestação (grupo Pessário-Progesterona, GPP). O desfecho primário analisado foi a taxa de PP antes de 34 semanas.

Resultados Não houve diferenças estatísticas entre o GNT e o GPP em relação ao PP $<$ 34 semanas (respectivamente, 18,8% versus 40,0%; $p = 0{,}07$) e ao peso médio ao nascer do gêmeo menor (2.037 $\pm$ 425 g versus 2.195 $\pm$ 665 g; $p = 0{,}327$). A análise de Kaplan-Meyer foi realizada, e não houve diferenças entre os grupos antes de 31,5 semanas. A regressão logística demonstrou que o nascimento prematuro anterior ($<$ 37 semanas) apresentou razão de probabilidades (*odds ratio*, OR) de 15,951 (intervalo de confiança de 95% [IC95%]: 1,294–196,557; $p = 0{,}031^{*}$) para o nascimento prematuro $<$ 34 semanas no GPP.

Conclusão Em gêmeos DC-DA com colo uterino curto (o que significa maior risco de nascimento prematuro), o tratamento com pessário cervical associado a progesterona pode ser considerado equivalente em diversos aspectos relacionados à prematuridade no GNT, apesar da grande diferença entre os grupos.

Palavras-chave
- parto pré-termo
- pessário cervical
- gestação gemelar dicoriônica-diamniótica
- colo curto
- progesterona vaginal

Introduction

Despite the low prevalence of twin pregnancies (only 2%), they are responsible for 15% of all spontaneous early preterm births (PBs) $<$ 32 weeks. The higher number of PBs probably occurs due to uterine overdistension. The rate of PBs in twin pregnancies $<$ 37 weeks is around 50%, and the mean gestational age at delivery is around 36.5 weeks.[1–3]

A cervical length $<$ 25 mm measured between 20 to 24 weeks in twin gestations is accepted as a good predictor for PB. A short cervix increases the risk of preterm birth before 28 weeks of gestation from 3.5% to 25.8%, and from 41.2% to 75.5% before 37 weeks of gestation.[4,5]

Although the prediction is relatively well determined with short cervical length, the intervention is still a challenge in twin pregnancies. Different strategies for prevention of preterm delivery in twin pregnancies have been considered, such as vaginal progesterone, cervical pessary, and cervical cerclage.[6–8]

A recent metanalysis[9] of individual data concluded that vaginal progesterone in twin gestations with short cervix ($<$ 25 mm) reduced the risk of PB before 33 weeks from 43.1% to 31.4% (relative risk [RR]: 0.69; 95% confidence interval [95%CI]: 0.51–0.93), and reduced the risk of composite neonatal morbidity and mortality from 40% to 27.4%[10] (RR: 0.61; 95%CI: 0.34–0.98), when compared with no treatment, but these results are not a consensus in literature.[11,12] Another multicentric randomized controlled trials (RCT) in twins demonstrated that the prophylactic use of the cervical pessary could reduce the rate of early PB in the subgroup with a short cervix. Despite this evidence, the largest study[13] using the cervical pessary in twin pregnancies did not demonstrate the benefits of its use.

In 2016, in New Jersey, a retrospective study[8] compared the use of cervical cerclage to no treatment in twin pregnancies with short cervix ($<$ 25 mm), and significant results were obtained in favor of cerclage (odds ratio [OR]: 0.22; 95% CI: 0.058–0835), despite the fact that previous studies[14] did not corroborate this data.

Neither cerclage, the cervical pessary or progesterone could be considered a better choice for intervention in twin pregnancies with a short cervix, nor have they been

discarded as an option for this particular type of pregnancy.[15] But some studies observe favorable results in the pessary group after the comparison with progesterone (regarding PB and morbidity) in twin pregnancies with short cervix.[16,17] Moreover, an economic analysis[18] was published recently with positive results for the pessary group in twin pregnancies with a short cervix.

At the present moment, there is no publication comparing the use of the cervical pessary in twin gestations with a short cervix to low-risk dichorionic-diamniotic (DC-DA) twin pregnancies. The objective of the present study was to determine the equivalence of the use of the cervical pessary associated with progesterone in DC-DA twin gestations with a short cervix compared with no intervention in unselected twin pregnancies.

Methods

The present historical equivalence cohort study in asymptomatic DC-DA twin pregnancies was performed from January 2010 to July 2018 in Escola Paulista de Medicina, Universidade Federal de São Paulo, a public quaternary service in Brazil; it was approved by the Ethics Committee (under CAAE number 30873613.8.0000.5505; http://plataformabrasil.saude.gov.br/login.jsf), and was called the EPM Twin Pessary Study. From January 2013 to July 2018, after obtaining informed consent, we included in the study 25 women with cervical length ≤ 25 mm measured by transvaginal scan (Samsung Ultrasound System WS80A, Seongnam-si, Gyeonggi-do, South Korea), during gestational age between 18 to 27 weeks and 6 days (Pessary-Progesterone group, PPG). The PPG received 200-mg daily doses of vaginal micronized progesterone, and the Ingámed (Maringá, PR, Brazil) AM cervical pessary was placed (Figure B – Addendum), which is registered in the Brazilian Medical Regulatory Agency (Agência Nacional de Vigilância Sanitária, ANVISA, in Portuguese), under number 80086720036.[19] Baseline characteristics and outcomes were compared with 32 DC-DA twin pregnancies from the same university from January 2010 to December 2012, neither selected by cervical length nor treated (Non-Treated group, NTG). The exclusion criteria for both groups were fetal malformation, selective fetal growth restriction, or refusal to sign the informed consent form. The exclusion criteria for the PPG were also exposed membranes, rupture of membranes, or labor.

For a description of the technique of the transvaginal cervical ultrasonography and the cervical pessary insertion, see the Addendum.

The primary outcome was defined as PB < 34 weeks. The secondary outcomes were defined as the mean gestational age at delivery ($\pm$standard deviation), the mean weights of the biggest and smallest newborns, the comparison of the rate of PB < 37, 35, 32 and 28 weeks, the performance of consecutive deliveries during the study, the Kaplan-Meyer survival analysis, and the backward stepwise logistic regression for PB < 34 weeks for PPG.

Univariate logistic regression nor adjusted was performed for PPG considering in vitro fertilization (IVF), ethnicity (white/non-white), smoking, body mass index (BMI; > 30), maternal age (≥ 35 years), gestational week at the inclusion in the study (> 23 weeks), previous PB (< 37 weeks), multiparity, and the PPG versus the NTG considering preterm birth < 34 weeks.

The risk of PB < 37 weeks in both study groups was assessed using the Kaplan-Meyer Survival analysis. The consecutive gestational age deliveries compared both groups and evaluated the performance and the learning curve of groups during the study.

The continuous variables were expressed as medians and standard deviations, and the categorical variables were presented in numbers and percentages (%). The comparison between the outcome groups was made using the Chi-squared (χ^2) test or the Mann-Whitney *U* test for the categorical variables, and the Student *t*-test for the continuous variables. Significance was set at a *p*-value < 0.05, two-tailed, and marked with an asterisk (*).

Using the primary outcome measure of PB < 34 weeks of gestation, with an effect size of 40% and an error level of $\alpha = 0.5$, a sample size of 60 women (30 in each group) achieved a power of 72%. For the analyses of the data, we used the Statistical Package for the Social Sciences (SPSS, IBM Corp., Armonk, NY, US) software, version 23.0, and Statplus (Mac v5 for Excel, AnalystSoft, Inc., Walnut, CA, US).

Results

Demographic Characteristics

In total, 57 women with DC-DA twin pregnancies participated in the study. Considering both groups, 40 (70.2%) women were primigravidas, and 17 (29.8%) were multiparous; 32 (56.1%) were white, and 25 (43.9%) were non-white. The differences between the groups are expressed in ►**Table 1**. For the PPG, the gestational age at the diagnosis varied between 18 and 27 weeks and 4 days (mean age of 24 weeks and 1 day $\pm$ 2.4 weeks). The mean cervical length of these gestations at the time of the pessary placement was of 14.3 ± 7.1 mm.

Outcomes

Parametric Comparison

In our consecutive ($n = 32$) DC-DA twin pregnancy NTG, the mean gestational age at delivery was of 35.83 ± 8.7 weeks, and in the PPG ($n = 25$), it was of 34.59 ± 2.72 weeks ($p = 0.11$), a difference of only 1.24 weeks, despite the big difference between the groups regarding the risk of PB due to the short cervix. The mean interval of permanence of the cervical pessary was of 10.18 ± 3.6 weeks.

Non-parametric Comparison

The Rate of Preterm Birth

The comparison of the rate of PB between the PPG and NTG demonstrated the following perinatal results respectively: < 32 weeks: 16% (4/25) versus 9.4% (3/32) ($p = 0.45$); < 34 weeks: 40.0% (10/25) versus 18.8% (6/32) ($p = 0.07$); < 35 weeks: 44.0%

Table 1 Demographic characteristics of the study sample

Demographic characteristics	Not-Treated group ($n = 32$)	Pessary-Progesterone group ($n = 25$)	*p*-value
Maternal age (years; ± standard deviation)	27.5 ± 4.79	35.2 ± 4.07	< 0.0001*
Body mass index (>30)	9 (28.1%)	2 (8.0%)	0.27
In vitro fertilization	10 (42.9%)	14 (61.1%)	0.41
Smoking	2 (6.2%)	1 (4.0%)	0.76
Ethnicitys (white)	15 (46.8%)	17 (68.0%)	0.06
Previous preterm birth	3 (9.4%)	4 (16.0%)	0.42
Multiparity	10 (31.2%)	8 (32.0%)	0.19
Week of inclusion	17.94 ± 5.83	24.22 ± 2.40	< 0.0001*

Note: *Baseline characteristics of the study subjects (Student *t*-test for maternal age and week of inclusion; Chi-squared test for all other categorical variable). The asterisk (*) marks *p*-value statisticaly significant.

(11/25) versus 28.1% (9/32) ($p = 0.21$); < 37 weeks: 80.0% (20/25) versus 50.0% (16/32) ($p = 0.02$*); < 28 weeks: no preterm delivery was registered in both groups.

Comparison of Birthweight

Regarding birthweigth for the smallest twin, the findings for the PPG and NTG were respectively: 2,038 ± 426 g versus 2,195 ± 665 g, and they were not statistically significant ($p = 0.327$). For the heaviest twins, the difference was statistically significant (2,148 ± 434 g versus 2,493 ± 643 g; $p = 0.028$*). Furthermore, the use of the cervical pessary did not influence the birthweight difference between the bigger and smaller fetuses in each group. For the NTG, the mean difference was of 12 ± 6%; for the GPP, it was of 11 ± 2% ($p = 0.375$).

Logistic Regression

Univariate logistic regression nor adjusted was performed for PPG, and it considered maternal age (≥ 35 years), ethnicity (white and non-white), BMI (> 30), smoking, week of inclusion in the study (< 23 weeks), IVF, previous PB (< 37 weeks), and multiparity, considering the number of deliveries < 34 weeks as a dependent variable. A statistical difference was observed only for previous PB (OR: 15.951; 95%CI: 1.294–196.557; $p = 0.031$*), as shown in ►**Table 2**, and none of the other variables analyzed could be classified as relevant to determine PB < 34 weeks (Hosmer-Lemeshow Test; $p = 0.08$) (►**Table 2**).

Cumulative Outcome and Learning Curve

To analyze the performance of the PPG, the age at delivery of each case was plotted consecutively in the chart in ►**Fig. 1**. The performance of the GPP in the middle of the consecutive analysis was decreasing, and, in the end, it presented a recovery (red curve). In comparison, the cervical length decreased continuously without a similar recovery (green curve). In contrast, the performance of the NTG was homogeneous, and was overlapping the 36th week during the whole period of the analysis (blue curve).

Kaplan-Meyer Survival Analysis

The cumulative percentage of participants who did not give birth spontaneously before 37 weeks was statistically significant between the two groups after the Kaplan-Meyer analysis. The median gestational age at delivery for the PPG was of 35.14 (95%CI: 33.88–36.40) weeks, that is, slightly lower than that of the NTG (36.86 weeks; 95%CI: 35.90–37.80), and it was

Table 2 Univariate logistic regression nor adjusted

All cases ($n = 57$)	Odds Ratio	Inferior 95% confidence interval	Superior 95% confidence interval	*p*-value
Pessary-Progesterone group versus Non-Treated group	0.243	0.043	1.368	0.109
Maternal age (≥ 35 years)	0.913	0.175	4.758	0.914
Ethnicity (white/non-white)	1.316	0.309	5.607	0.71
Smoking	1.116	0.138	9.016	0.918
Body mass index (> 30)	1.212	0.186	7.912	0.841
Week of inclusion (< 23 weeks)	3.038	0.622	14.844	0.17
In vitro fertilization	1.153	0.281	4.732	0.843
Previous preterm birth (< 37 weeks)	15.951	1.294	196.557	0.031*
Multiparity	0.638	0.098	4.145	0.638

Note: Univariate logistic regression nor adjusted considering the main maternal characteristics compared with the number of deliveries < 34 weeks. The asterisk (*) marks *p*-value statistcaly significant.

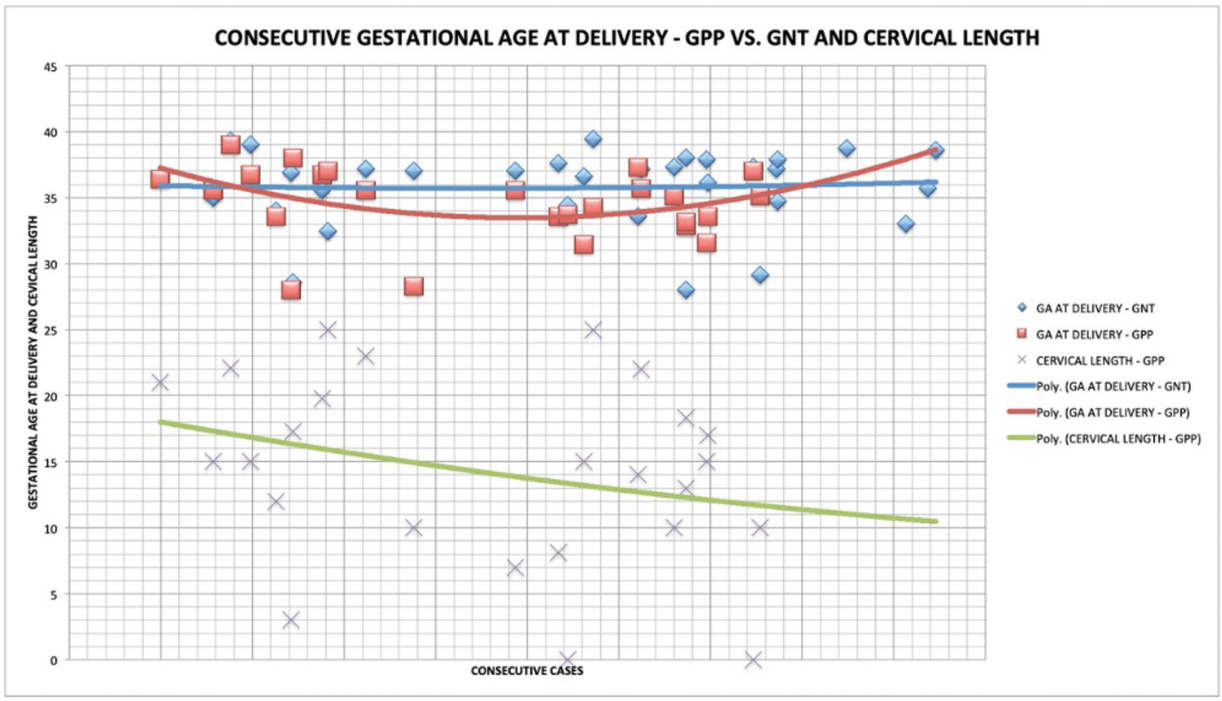

Fig. 1 Chart of consecutive twin pregnancies during the study. The blue dots represent the Non-Treated group (NTG) (blue line). The red dots represent the Pessary-Progesterone group (PPG) in the shape of a hyperbole (red line). The dots marked with an X (cervical length) represent the line without the shape of a hyperbole (green line).

statistically significant (Breslow [Generalized Wilcoxon]; $p = 0.025^{*}$). Before 31.5 weeks, there was no difference between the groups, and the difference between them at 35 weeks, a landmark in twin pregnancies, was of 20% (black lines) after the Kaplan-Meyer survival analysis (►**Fig. 2**).

Discussion

The short cervix is a rare complication in human pregnancy, and only 1% to 2% of women have a cervix shorter than 25 mm. Considering the prevalence of twin pregnancies as

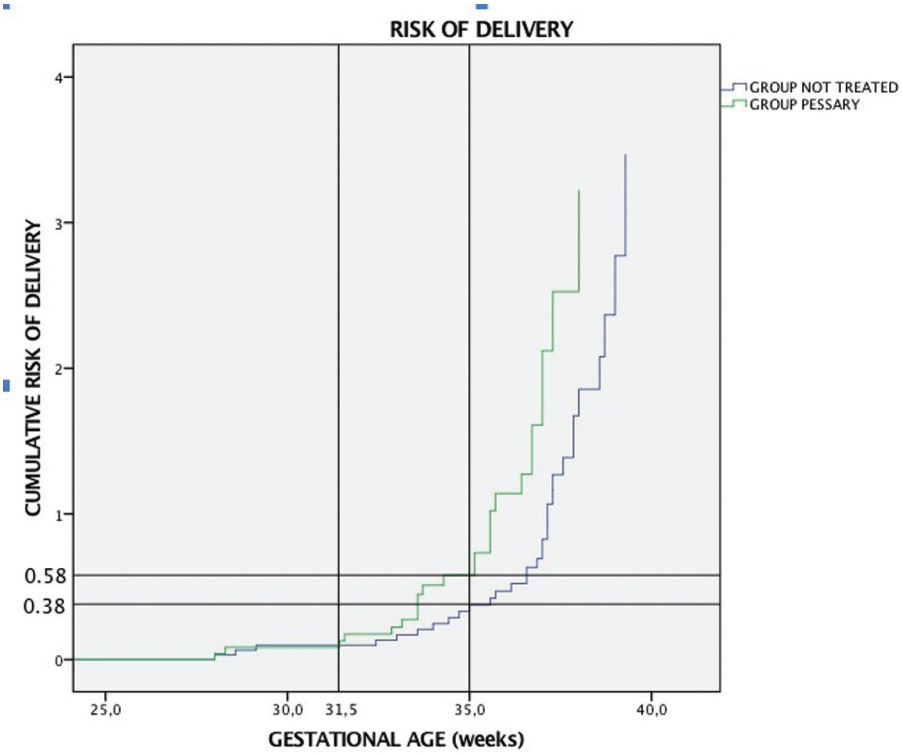

Fig. 2 Plot of the probability of continued pregnancy without delivery in the PPG (green) and NTG (blue) in the Kaplan-Meyer survival analysis (cumulative risk of delivery).

1% to 2%, we can speculate that the prevalence of short cervices in twin pregnancies is extremely rare, ~ 1 to 2/10,000 gestations. For that reason, it is very probable that in the NTG there was a small number of women with short cervices, justifying the difference regarding this maternal characteristic between the groups.[20,21]

An important main finding of our study was the absence of difference in birthweight regarding the smaller twins of patients with short cervices when compared with the low risk for PB twin pregnancies. For the heavier twins, the difference was statistically significant, but they are less susceptible to an unfavorable outcome. The study sample had enough power to demonstrate the statistical difference between the biggest newborn presenting ($p = 0.028^*$), but that difference was not sustained on the smallest newborn ($p = 0.327$), although the sample had theoretical power to do so. This observation enables us to assume that regardless of the important difference between the groups regarding the risk of PB, considering perinatal results for the smallest dichorionic twin, both groups are equivalent.

In the same way, there was only one variable with a statistically significant difference between the groups. In the univariate logistic regression, we could classify the variables relevant to PB, and previous PB was the only important variable to determine PB < 34 weeks on PPG. The OR demonstrates odds almost 16 times higher of delivery < 34 weeks if previous PB (< 37 weeks) was on the clinical history ($p = 0.031^*$). So, if previous PB is associated with a short cervix and a twin pregnancy, the risk of preterm delivery is so high that neither the cervical pessary nor vaginal progesterone will be enough to prevent it.

The Kaplan-Meyer analyses of the present study suggest that the differences between the groups were significant ($p = 0.025^*$); furthermore, analyzing the risk until 31.5 weeks, there was no difference in the cumulative risk in the survival analysis, and the biggest difference between the groups was only 0.2 at 35 weeks, an important landmark on gestational age for twins (►**Fig. 2**). These numbers could be hopeful if we consider that the results of the association of twin pregnancies and short cervices without treatment, and of the cervical pessary with progesterone, could be an alternative in rare cases with this association to reach better outcomes in twin pregnancies, corroborating the data of the ProTwin Study.[22,23]

In a recent randomized clinical trial[24] from Egypt, El-Refaie et al analyzed the outcome of twin pregnancies with short cervices after the administration of placebo or vaginal progesterone. We could compare the results of the aforementioned study (progesterone and controls) with those of the present study. The rate of PB < 34 weeks was of 40% (PPG) versus 35% (El-Refaie et al progesterone group) versus 52.8% (El-Refaie et al controls); and the rate of PB < 32 weeks was of 16% (PPG) versus 12% (El-Refaie et al progesterone group) versus 29.6% (El-Refaie et al controls).

The percentages of PB are similar for the PPG and the El-Refaie et al progesterone group, but when compared with the El-Refaie et al controls, the performance of the PPG was superior in both gestational ages. We must consider that these results from the El-Refaie et al progesterone group were not reproducible in the most relevant studies in twin pregnancies treated with isolated progesterone, and some articles even demonstrated that intramuscular progesterone could increase PB in twin pregnancies more intensely < 32 weeks.[10,25–31]

We can consider that the cervical pessary plus progesterone may have a better performance in the protection against PB in twin pregnancies compared with isolated progesterone, especially < 32 weeks, as our data indicated a similar performance on the Kaplan-Meyer survival analysis(< 31.5 weeks).

A weakness of the methodology employed in the present study is the demographic characteristics demonstrating that the groups were comparable except for maternal age and gestational age at inclusion; it is a potential risk of bias. Older maternal age is more frequently pointed out as a variable associated with PB, but in our cohort, regarding this characteristic, it is statistically different. There were more older pregnant women in the PPG, which is a clear factor to increase the risk on that population, despite this statistical difference in demographic characteristics. All of these factors clearly increased the risk of PB in the PPG. However, surprisingly, the PPG demonstrated similar results in the prevention of prematurity, and the intervention was probably the reason for that.

Another potential risk of bias is that the gestational age at inclusion was statistically significant, and the difference was of 6.28 weeks. As an inclusion criterion, all patients in the sample were between the 18th to 27th weeks of gestation. This important difference is not so relevant as a risk of bias, because the NTG received no intervention; therefore had the inclusion occurred at any gestational age, there would have been no difference in the final results of the NTG.

Another weakness of this methodology is the difference regarding the cervical length, because the cervical length of the PPG must be much shorter than that of the NTG, and this characteristic was probably responsible for the worse performance of the PPG regarding PB.[4]

One strength of the present study could be the change in the rates of PB using a mechanical device, which has been demonstrated as secure, and with a low rate of fetal and maternal complications; due to the presence of the device, the patients described that they felt safer regarding the attachment to the cervix itself, and these data had not yet been described on the literature.[32]

Another strength of the methods herein employed was the application of transvaginal ultrasound after the insertion of the pessary. It was only because of the ultrasound that we were able to recognize patients with the pessary in a bad position; after the diagnosis, the device was repositioned in all of those cases.[33,34]

Our data also suggest that it was the relocation of the pessary in a bad position that was responsible for the better performance in individual rates of PB (red line) during the study, as demonstrated by the learning curve, even despite the reduction in cervical length (green line) (►**Fig. 1**). This is important information, because medical experts could be more efficient in using this device. The learning curve can be

enhanced through better prediction of the risk of PB during pregnancy, and sometimes by increasing rest, or treating with antibiotics if the cases are associated with amniotic fluid sludge or repositioning of cervical pessary when it is not correctly placed around the cervix.[35,36]

Due to the expertise of the team involved, there was a lower rate of unnecessary interventions, such as the unreasonable removal of the cervical pessary, probably because of fear of the unknown, which was very common in the first years of the study of the device in hospitals that were not familiarized with it.

The present is one of the first studies published with this new pessary developed in Brazil; it is very similar in shape to the Arabin (Dr. Arabin GmbH & Co., Witten, Germany) pessary, and our staff in the present study started the research, in a single center, in 2012 after the study by Goya et al.[33] The team involved in the present study is headed by two senior medical researchers who acquired, over the course of 7 years, a lot of experience in cervical pessaries by using them and analyzing our perinatal results (this was how our team acquired experience: with practice and aligned to the literature).[33]

The Brazilian pessary has three differences in comparison with the Arabin pessary: 1) the surface of the internal ring is not soft, producing a "grasping" effect on the cervix, and during the entire study (which involved around 200 cervical pessaries in women at different gestational ages and in singleton pregnancies), we did not have any problems to remove this pessary, and probably because of this structure we did not have any escape of the pessary after 1 week of insertion; all re-insertions or maneuvers for pessary reposition (when necessary) occurred at the first week after insertion; 2) it is made with a harder silicone if compared with the Arabin, but it is completely malleable and adaptable to the vagina. This non-soft silicone with tighter adherence to the cervix placed over the perineal muscles can improve resistance against the pressure exhorted on the cervix by the uterus; and 3) it is a single-size cervical pessary, and sometimes the adjustment is not easy, especially in multiparous women in whom the cervix is commonly larger than that of primigravidas.

More studies are necessary to evaluate the real efficacy of the cervical pessary plus progesterone on PB in DC/DA twin pregnancies, and new trials must be designed with this purpose. It is relevant for the success of the new studies to consider the appropriate training of the researchers regarding insertion and evaluation by ultrasound of the correct position of the pessary, which should completely involve the cervix, as well as the development of a protocol regarding the performance of the transvaginal ultrasound during routine prenatal appointments to ensure a better performance on the prevention of PB.

In conclusion, the comparable birthweight of the smallest twin, the similar risk of preterm birth < 31.5 weeks (by the Kaplan-Meyer survival analysis), the absence of statistical difference regarding important variables in the logistic regression, and the absence of statistical difference in the rate of PB < 28, 32, 34 and 35 weeks can suggest an equivalence between the NTG and the PPG concerning some important aspects, despite the big difference between these groups.

Contributors

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

Conflict of Interests

The authors have no conflict of interests to declare.

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Addendum

Patients and Methods

The technique of transvaginal ultrasound for cervical measure

The transvaginal ultrasound cervical measure for inclusion was performed during the appointment of routine anomaly 2nd trimester scan and was used, by itself, to determine whether to place the pessary or not, with the cervical length between 0 to 25 mm. Each transvaginal scan was performed over a period of about 10 minutes and the shortest of three measurements was considered. The exclusion criteria for GPP were the exposed membranes, rupture of membranes or labor.

All sonographers involved in this study obtained the appropriate Certificate of Competence for Cervical Assessment of The Fetal Medicine Foundation (https://courses.fetalmedicine.com).

After pessary insertion we performed transvaginal ultrasound during a regular monthly prenatal appointment to check the position of the pessary and evaluate funneling inside the pessary or suspicion of membranes protrusion.

The technique of pessary insertion

With a patient in gynecological position, sterile cervical pessary was folded in the middle and inserted in the vagina, it was unfolded after the insertion with the minor orifice involving the entire cervix, and the major orifice supported by the posterior vaginal wall. This insertion did not require any other equipment, besides sterile gloves and lidocaine gel to lubricate the distal part of the vagina and minimize the discomfort of the insertion. A digital vaginal examination was performed after the insertion to check the correct position of the device, and immediately after the clinical exam, a transvaginal ultrasound was performed with a similar intention. If the pessary was considered in a questionable position (►**Figure C** - Addendum), some maneuvers to relocate the device were performed. These maneuvers consisted in pushing the pessary against the cervix, or

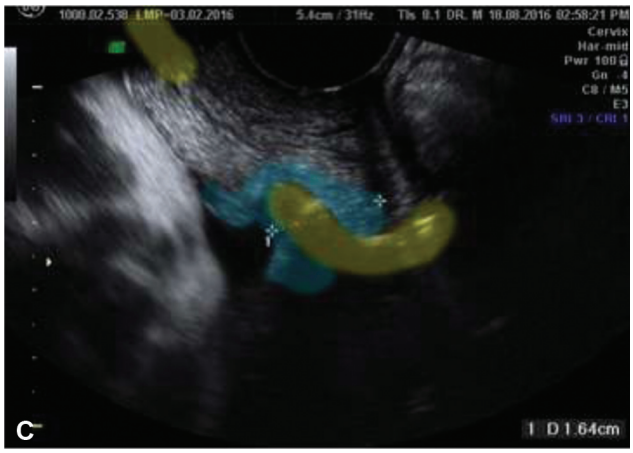

Fig. C Ultrasound image of short cervix not completely involved by cervical pessary (yellow area). It is important notice that posterior lip is not inside the pessary orifice (transversal section of pessary). Cervical gland area (CGA-blue area) is not inside pessary; it was considered for our team in a questionably position and reposition was required.

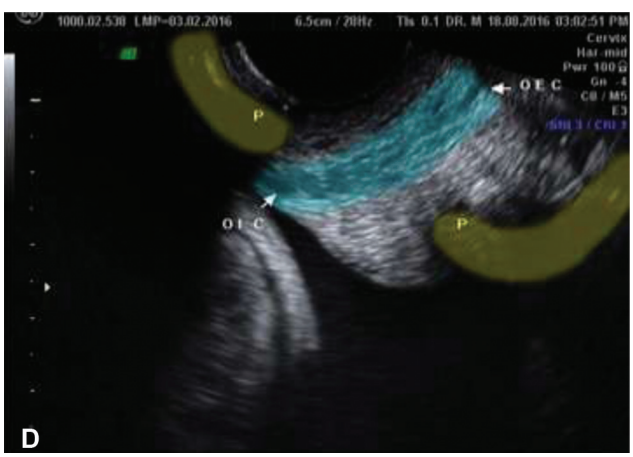

Fig. D Ultrasound image of short cervix completely involved by pessary (yellow area). It is relevant observe that CGA is centralized (blue area); it was considered for our team well positioned and no further procedures was required after this image. Both images are from the same patient, with difference a couple minutes (5 minutes difference between each image).

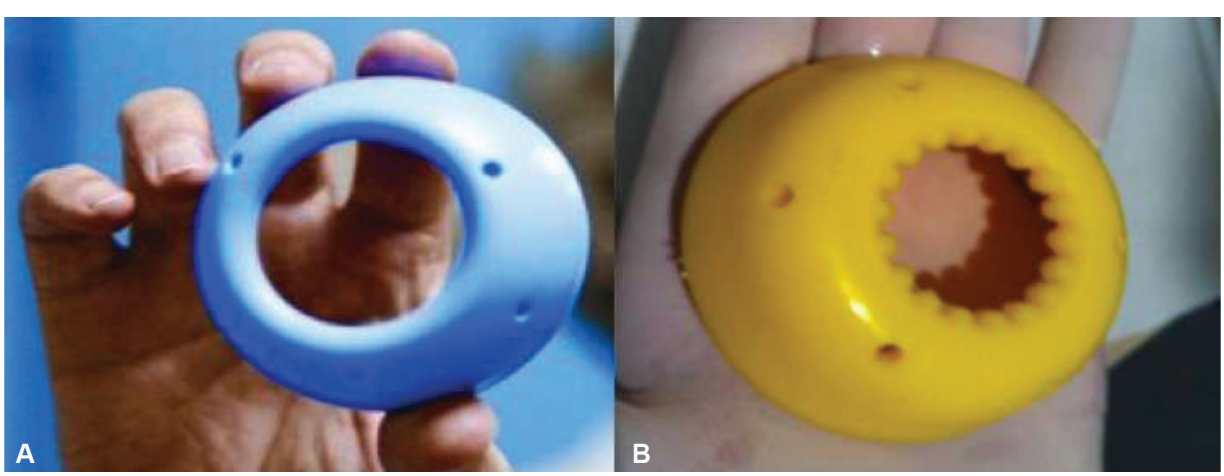

Fig. A/B Comparison between the Arabin cervical pessary (**A**) and the AM - Ingamed cervical pessary (**B**): they are similar regarding design, size and texture. The dimensions (largest lower diameter × smallest upper diameter × height) of the most frequently used Arabin pessary are 70 × 32 × 25 mm, and of the Ingamed cervical pessary the dimensions are 70 × 30 × 25 mm.

rotating the pessary to involve the entire cervix, or pushing the vaginal anterior wall to put the posterior lip of the cervix inside the pessary, or even a mix of these maneuvers (►**Figure C**/**D** - Addendum).

One week after pessary placement, we have performed transvaginal ultrasonography to identify the position of cervix concerning internal aperture of pessary. This is done to give us feedback on pessary placement. This feedback training us on placing the device as high as feasible and reduces inter-operator variability. This information is used to determine whether to reposition pessary if it is not completely involving the cervix (►**Figure D** - Addendum).

The Relationship between Serum Ischemia-Modified Albumin Levels and Uterine Artery Doppler Parameters in Patients with Primary Dysmenorrhea

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Abstract

Objective Primary dysmenorrhea occurs due to abnormal levels of prostanoids, uterine contractions, and uterine blood flow. However, the reasons for pain in primary dysmenorrhea have not yet been clarified. We examined the blood flow alterations in patients with primary dysmenorrhea and determined the relationship between ischemia-modified albumin (IMA) levels, as an ischemia indicator, and primary dysmenorrhea.

Methods In the present study, 37 patients who had primary dysmenorrhea and were in their luteal and menstrual phase of their menstrual cycles were included. Thirty individuals who had similar demographic characteristics, who were between 18 and 30 years old and did not have gynecologic disease were included as control individuals. Their uterine artery Doppler indices and serum IMA levels were measured.

Results Menstrual phase plasma IMA levels were significantly higher than luteal phase IMA levels, both in the patient and in the control groups ($p < 0.001$). Although the menstrual phase IMA levels of patients were significantly higher than those of controls, luteal phase IMA levels were not significantly different between the two groups. Menstrual uterine artery pulsatility index (PI) and resistance index (RI) of primary dysmenorrhea patients were significantly different when compared with luteal uterine artery PI and RI levels. There was a positive correlation between menstrual phase IMA and uterine artery PI and RI in the primary dysmenorrhea.

Conclusion Ischemia plays an important role in the etiology of the pain, which is frequently observed in patients with primary dysmenorrhea. Ischemia-modified albumin levels are considered as an efficient marker to determine the severity of pain and to indicate ischemia in primary dysmenorrhea.

Keywords

- ischemia-modified albumin
- primary dysmenorrhea
- uterine artery Doppler

Introduction

Dysmenorrhea is one of the most frequently encountered gynecological complaints, and it is characterized by cramps in the pelvic or lower abdominal region that initiate either just before or together with menstruation. Dysmenorrhea is classified as primary or secondary dysmenorrhea, and there is presence of pain in primary dysmenorrhea, even though there is no pelvic pathology.[1] Although primary dysmenorrhea is associated with abnormal myometrial contractions

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due to abnormal elevation in the levels of prostaglandins, reduction in uterine blood flow, and generalized ischemia due to vasoconstriction, the underlying cause of pain in primary dysmenorrhea has not yet been clarified.[2]

During the menstrual cycle, there is a decrease in the uterine artery pulsatility index (PI) values parallel to blood flow in the uterine artery during the luteal phase to ensure compliance with implantation. However, it is observed that the uterine artery PI values are high during the menstrual cycle.[3] In clinical studies, the PI and resistance index (RI) of patients with primary dysmenorrhea in the arcuate and uterine arteries in the first day of menstrual cycle were significantly higher than those of asymptomatic patients.[4] Decreased uterine blood flow most probably leads to strong and abnormal uterine contractions, and, thus, myometrial ischemia pelvic pains, such as cramps. occur. Observing higher uterine artery resistance compared with asymptomatic controls in uterine artery Doppler studies also supports the relationship between primary dysmenorrhea and ischemia.[5]

Even though the mechanism has not yet been clarified, it has been thought that ischemia-modified albumin (IMA) is formed as a result of the alteration in metal-binding sites of albumin due to the effect of reactive oxygen species. Amino terminal (N-terminal) of the albumin molecule is the binding site for metals such as cobalt, nickel, and copper. This binding site alters in case there are ischemia, acidosis, and free-radical damage and the binding capacity is decreased for metals. This different form of the albumin is named as IMA.[6] Ischemia-modified albumin is a promising marker in the evaluation of ischemic events, and serum IMA levels increase in various diseases related to ischemia. It has been shown that IMA is not only associated with cardiac ischemia, it is also increased in patients with liver cirrhosis, pulmonary embolism, end-stage renal disease, cerebrovascular disease, cancer, systemic sclerosis, preeclampsia, habitual miscarriage, and polycystic ovary syndrome.[7]

Up to the present, IMA levels have not yet been examined in patients with primary dysmenorrhea. In the present study, we aimed to determine whether or not there is a relationship between Doppler parameters and IMA levels in uterine arteries in the menstrual and luteal phases.

Methods

In the present prospective cross-sectional study, we included 37 patients who were admitted to our hospital with primary dysmenorrhea and 30 healthy individuals with similar demographic characteristics and who did not have menstrual pain during the menstrual period as a control group. The study was approved by the local ethics committee of Ankara Numune Training and Research Hospital, where the present study was performed. Medical and gynecological histories of all patients were recorded. Here are the eligibility criteria of the patients: being between 18 and 35 years old, nulliparity, having a regular menstrual cycle (24–38 days), having at least 4 painful periods from previous 6 menses, and having normal ultrasound findings on the uterus and adnexa. The exclusion criteria were as follows: having recurrent pelvic and lower abdominal pain outside the menstrual period, such as secondary dysmenorrhea, and other diseases of the reproductive organs, such as endometriosis or uterine fibroids; having a history of abnormal vaginal discharge; having a history of significant gastrointestinal, genitourinary, endocrine, rheumatic, or surgical procedure; being pregnant and in the lactation period; using prostaglandin synthesis inhibitors or any other concomitant drugs. The control group was composed of nulliparous individuals, in the same age group, without dysmenorrhea and abdominal pain during the menstrual period. We recorded the demographic features, weight (in kilograms [kg]), height (in meters [m]), and body mass index (BMI) (kg/m2) of patients.

Evaluation of Ultrasound Results

The 6.5-MHz abdominal transducer with a color Doppler capability Medison SONOACE X8 4D Convex Ultrasound Probe 3DC2-6 (Samsung Group, Seoul, South Korea) was used to perform the ultrasonographic assessments. In all patients, we performed the sonographic assessments in the menstrual (1–4th days) and luteal (21–23th days) phases of the spontaneous menstrual cycles. The conventional B-mode ultrasound technique was used to observe the uterus and ovaries. Color Doppler imaging lateral to the internal cervical os, in a longitudinal plane, was used to observe the uterine arteries. Then, a pulsed Doppler range gate was applied across the vessel to ensure that the angle between the Doppler beam and the vessel was close to 00. We calculated the RI and the PI by using the following formula: PI = (S- D)/mean, RI = (S - D)/S, where S is the peak shifted Doppler frequency, D is the minimum Doppler shifted frequency, and 'mean' is the mean maximum Doppler shifted frequency over the cardiac cycle. It was observed that the lowest values of uterine artery PI and RI were not significantly different between the right and the left uterine arteries. Only one researcher performed sonographic and Doppler techniques to avoid the false positive interobservation variations.

Ischemia-Modified Albumin Measurement

We collected blood samples in the day of the Doppler flow analysis. Blood samples were left to clot for 30 minutes, and then they were centrifuged 10 minutes at 4,000 rpm. Supernatants were collected and stored at -80°C. Reduced cobalt to albumin binding capacity (IMA level) was tested by using the rapid and colorimetric method, and findings were shown as absorbance units (ABSUs).

Statistical Analysis

The Statistical Package for the Social Sciences for Windows version 20.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data. All data were shown as mean ± standard deviation (SD). Student *t*-test and Pearson tests were used to perform statistical analyses for normally distributed continuous data. Pearson or Spearman coefficients were calculated. Statistical significance was set as $p < 0.05$.

Results

In ►**Table 1**, demographic, biochemical, and pelvic Doppler sonographic parameters of primary dysmenorrhea patients

Table 1 Clinical, biochemical, and pelvic Doppler sonographic parameters of women with primary dysmenorrhea and of the control group[a]

Dysmenorrhea	Primary	Control	*p*-value
	(*n* = 37)	(*n* = 30)	
Age (years)	19.57 ± 2.89	20.90 ± 4.43	NS
BMI (kg/m^2)	21.57 ± 4.07	22.80 ± 4.05	NS
Menstrual UAPI	3.41 ± 0.15	2.76 ± 0.29	0.001*
Luteal UAPI	2.75 ± 0.21	2.72 ± 0.30	NS
Menstrual UARI	0.91 ± 0.14	0.82 ± 0.13	0.001*
Luteal UARI	0.82 ± 0.12	0.81 ± 0.17	NS
Menstrual IMA (ABSU)	0.55 ± 0.07	0.47 ± 0.08	0.001*
Luteal IMA (ABSU)	0.40 ± 0.04	0.39 ± 0.03	NS

Abbreviations: ABSU, absorbance unit; BMI, body mass index; IMA, ischemia-modified albumin; NS, not significant; UAPI, uterine artery pulsatility index; UARI, uterine artery resistance index.
[a]Values are given as mean ± SD.
*$p < 0.05$.

Table 2 Correlation of uterine artery pulsatility and resistance indices with the ischemia-modified albumin levels of women with primary dysmenorrhea and of the control group

	Menstrual IMA			Luteal IMA	
	PD	Control		PD	Control
r	r	r		r	r
Menstrual UAPI	0.357*	0.417*	Luteal UAPI	0.036	0.101
Menstrual UARI	0.451*	0.378*	Luteal UARI	0.090	0.712

Abbreviations: IMA, ischemia-modified albumin; PD, primary dysmenorrhea; UAPI, uterine artery pulsatility index; r, Pearson correlation coefficient; UARI, uterine artery resistance index.
*$p < 0.05$.

and of the control group can be seen. The age and body mass index (BMI) values were not significantly different between the patient and control groups. Mean uterine artery PI and RI values in the menstrual phase were significantly higher in the primary dysmenorrhea group when compared with the control group ($p < 0.05$). There was no difference between the two groups in terms of the mean PI and RI values in the luteal phase. Mean uterine artery PI and RI values in the menstrual phase were significantly higher when compared with the values of the luteal phase. Even though the mean PI and RI values in the menstrual phase were higher when compared with the values of the luteal phase in the control group, this difference was not statistically significant. The menstrual phase IMA levels of the primary dysmenorrhea group were significantly higher than those of the control group. However, there was no difference between the two groups in terms of their IMA levels in the luteal phase. The menstrual IMA levels of both primary dysmenorrhea and control groups were significantly higher compared with their luteal IMA levels.

The uterine artery PI and RI as well as the IMA of the primary dysmenorrhea and control groups can be seen in ►**Table 2**.

There was a positive correlation between the menstrual period uterine artery Doppler PI and RI values of primary dysmenorrhea patients. However, there was no relationship between IMA values and Doppler indices in the luteal phase. In the control group individuals, there was a positive correlation between menstrual phase uterine artery Doppler PI and RI values, whereas no significant relationship was observed in the luteal period IMA values and Doppler indices.

Primary dysmenorrhea is commonly observed among young women, and it is an important social problem that can negatively affect women's occupational and academic lives. Even though the reason for pain in primary dysmenorrhea has not yet been explained, it is believed that it occurs due to increased prostaglandin levels that lead to abnormal myometrial constructions; thus, generalized ischemia occurs due to the decreased uterine blood circulation.[2] There is an increased prostaglandin production in the endometrium due to the decreased progesterone levels as a result of the luteal phasing in patients with primary dysmenorrhea. Prostaglandin F2 α (PGF2 α) is a strong myometrial stimulant and vasoconstrictor, and it can lead to pelvic pain due to the myometrial contractions and ischemia. Furthermore, it has been detected that there is a positive correlation between endometrial prostaglandin levels and the severity of pain.[8]

In studies performed with patients with primary dysmenorrhea, even though there are uterine artery blood flow changes in the menstrual period depending on the myometrial contractility and increased intrauterine pressure, the reasons for these changes have not yet been explained. Dmitrović[9] detected that uterine artery PI and RI values of primary dysmenorrhea patients were higher in the first day of the menstrual cycle. In another study, it was observed that uterine artery PI and RI values were higher in patients with severe dysmenorrhea compared with patients with the mild version of the condition.[10] In a study performed by Altunyurt et al,[4] similarly to our study, the uterine artery mean PI and RI values of patients with primary dysmenorrhea were significantly higher when compared with the values of the midluteal phase. In this study, the higher uterine artery resistances of patients compared with asymptomatic controls support the relationship between the primary dysmenorrhea and ischemia. Even though we did not find a statistically significant difference in the control group, it was detected that uterine artery Doppler indices in the menstrual period were higher. These findings show that there is an intrauterine pressure increase in women without primary dysmenorrhea during the menstrual period. However, this increase is lower compared with the values of patients with primary dysmenorrhea.

Ischemia-modified albumin is a modified form of serum albumin, and it is formed as a result of binding of metal atoms such as cobalt, nickel, or copper to the N-terminal of albumin because of the superoxide and oxygen free radicals produced due to the oxidative stress.[11] Even though IMA is detected in

the circulation as a secondary response of ischemia in the hypoxic myocardial tissue, it has been recently used as the indicator for the hypoxic intrauterine area.[7,12]

Conclusion

In our study and in other studies in which uterine artery Doppler is used to diagnose dysmenorrhea, the role of ischemia in the development of dysmenorrhea is supported. Recently, our study is the first one in which the increased IMA levels in ischemic processes are examined by using the Doppler technique. In our study, the mean menstrual phase IMA values of the primary dysmenorrhea group were significantly higher when compared with the mean menstrual period IMA values of the control group. Furthermore, it was observed that there was a positive correlation between IMA values and uterine artery Doppler PI and RI values in patients with primary dysmenorrhea during the menstrual period. These findings support the relationship between the pain and ischemia in patients with primary dysmenorrhea. Conclusively, our findings show that ischemia has important roles in the etiology of pain in patients with primary dysmenorrhea, and IMA level measurement can be used as a promising marker to indicate the ischemia process during primary dysmenorrhea. In further studies in which the relationship between the severity of pain and ischemia is assessed, in case there is an association between pain and IMA levels, this relationship can be used to determine the medications for the effective treatment or to indicate the severity of the pain of these patients.

Contributors
All of the authors contributed to the conception and design of the present study, to the data collection, or to the analysis and interpretation of data, as well as to the writing of the article or to the critical review of the intellectual content and final approval of the version to be published.

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

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Laboratorial Aspects of Cytolytic Vaginosis and Vulvovaginal Candidiasis as a Key for Accurate Diagnosis: A Pilot Study

Aspectos laboratoriais da vaginose citolítica e candidíase vulvovaginal como uma chave para o diagnóstico preciso: Um estudo piloto

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Abstract

Objective To identify clinical, microscopic, and biochemical characteristics that differentiate cytolytic vaginosis (CV) from vulvovaginal candidiasis (VVC).

Methods The present cross-sectional study analyzed the vaginal contents of 24 non-pregnant women aged 18 to 42 years who were attended at the Genital Infections Clinic at Centro de Atenção Integral à Saúde da Mulher da Universidade Estadual de Campinas (CAISM-UNICAMP). They were diagnosed either with (CV = 8, VVC = 8) or without vulvovaginitis or vaginal dysbiosis (controls). The socio-demographic, clinical, and gynecological data were obtained from a detailed patient interview. Samples of the vaginal contents were collected for analysis of vaginal pH, gram stain, and specific fungal culture. The Kruskal-Wallis and Fisher exact tests were used to compare the differences between the groups. Odds ratios were used to compare the categorical variables. The significance level was considered at $p < 0.05$.

Results Both women with CV and VVC had a lumpy vaginal discharge ($p = 0{,}002$) and vaginal hyperemia ($p = 0.001$), compared with controls. The inflammatory process was more intense in the VVC group ($p = 0.001$). In the CV group, there was statistical significance for the lactobacillus amount ($p = 0.006$), vaginal epithelium lysis ($p = 0.001$), and vaginal pH ($p = 0.0002$).

Conclusion Cytolytic vaginosis and VVC diagnoses rarely differ on clinical characteristics but have different laboratorial findings. The present study highlights the importance of conducting an accurate investigation through laboratory tests rather than clinical criteria to avoid misdiagnosis.

Keywords

- cytolytic vaginosis
- dysbiosis
- gram stain
- vaginal bacterioscopy
- vulvovaginal candidiasis

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Resumo

Objetivo Identificar características clínicas, microscópicas e bioquímicas que diferenciam a vaginose citolítica (VC) da candidíase vulvovaginal (CVV).

Métodos O presente estudo de corte transversal analisou o conteúdo vaginal de 24 mulheres não grávidas, com idades entre 18 e 42 anos, atendidas no ambulatório de Infecções Genitais do Centro de Atenção Integral à Saúde da Mulher da Universidade Estadual de Campinas (CAISM-UNICAMP). Elas foram diagnosticadas com (CV = 8, CVV = 8) ou sem vulvovaginite ou disbiose vaginal (controles = 8). Os dados sociodemográficos, clínicos e ginecológicos foram obtidos em uma entrevista detalhada do paciente. Amostras do conteúdo vaginal foram coletadas para análise do pH vaginal, coloração de Gram e cultura específica de fungos. Os testes exatos de Kruskal-Wallis e Fisher foram utilizados para comparar as diferenças entre os grupos. A razão de chances foi utilizada para comparar as variáveis categóricas. O nível de significância considerado foi de $p < 0,05$.

Resultados As mulheres com VC e CVV apresentaram corrimento vaginal irregular ($p = 0,002$) e hiperemia vaginal ($p = 0,001$), em comparação aos controles. O processo inflamatório foi mais intenso no grupo CVV ($p = 0,001$). No grupo VC, houve significância estatística para a quantidade de lactobacilos ($p = 0,006$), lise do epitélio vaginal ($p = 0,001$) e pH vaginal ($p = 0,0002$).

Conclusão Os diagnósticos de VC e CVV raramente diferem nas características clínicas, mas apresentam achados laboratoriais diferentes. O presente estudo destaca a importância de conduzir uma investigação precisa por meio de testes laboratoriais, em vez de critérios apenas clínicos, a fim de evitar erros de diagnóstico.

Palavras-chave

- vaginose citolítica
- disbiose
- coloração de Gram
- bacterioscopia vaginal
- candidíase vulvovaginal

Introduction

Vulvovaginal candidiasis (VVC) infection caused by the *Candida* species affects millions of women every year and is considered the second most common vaginitis among women after bacterial vaginosis.[1] It is estimated that ~ 10 to 15% of asymptomatic women are colonized by *Candida* sp and 70 to 75% of women of reproductive age experience at least one acute episode during their life. About 50% of these will have a second episode, and 5 to 10% will develop the recurrent form.[2] Vulvovaginal candidiasis gives rise to much discomfort in many patients, poses a threatening problem to clinicians, and generates considerable direct and indirect economic costs associated with medication and healthcare visits,[3] representing a cost estimate of $2.84 billion in the United States alone.[4] Most women will experience only one or two episodes of VVC, but there is a large, albeit poorly defined, subset that experiences multiple recurrences.[4–7] Among all cases of VVC, *C. albicans* is the most common species identified among women, representing 80 to 90% of the cases, followed by non-*C. albicans* species, usually *Candida glabrata*.[8] The VVC manifests itself as an inflammatory process, which, depending on the degree of local inflammation, has variable symptom intensity and is commonly misidentified as cytolytic vaginosis (CV), leading to inadequate treatment.[9,10] Cytolytic vaginosis is characterized by symptoms that are very similar to those of VVC, but the laboratorial findings may be quite different. The CV criteria proposed in 1991 by Cibley and Cibley[11] are: absence of *Trichomonas*, *Gardnerella*, or *Candida* on wet smear, an increased number of lactobacilli, paucity of leukocytes, high vaginal epithelium cytolysis, presence of a lumpy discharge, and vaginal pH between 3.5 and 4.5. Clinical characteristics of women with VVC include white flocculent vaginal discharge along with vulvovaginal pruritus, which may present with vulvovaginal pain and fissures. An intense inflammatory process can be observed in the vulva and/or the vagina due to the aggression on the epithelium caused by fungi.[1] Both present with symptomatology that is accentuated in the premenstrual period. Vulvovaginal burning is usually more frequent in CV, while vulvovaginal pruritus is a common symptom from women with VVC.[12] However, women can have either symptom or present difficulty when reporting their symptoms to clinicians, misleading the diagnosis and, as a consequence, the treatment.[10,13,14] The identification of clinical and microscopic characteristics that can differentiate CV from VVC in the outpatient setting is essential in improving the accuracy of the diagnosis, treatment, and management for women with vaginal discharge complaints. Thus, the aim of the present study was to compare the clinical and laboratorial findings of women with CV and VVC to define more accurate criteria to differentiate these two conditions.

Methods

Selection of Subjects and Sample Collection

In total, 42 sexually active women from 18 to 45 years old who attended the Genital Infections Outpatient Clinic of Universidade Estadual de Campinas from November 2016 to March 2017 were invited to participate in the study. Following the clinical routine of the hospital, all patients were submitted to a detailed anamnesis and gynecological

examination. Using a sterile Dacron swab, material from the vaginal wall was collected to identify cervicovaginal diseases and to verify vaginal ecosystem conditions. Women diagnosed with endocervicitis, bacterial vaginosis, trichomoniasis, and mixed infections were ruled out. After checking for eligibility, eight women diagnosed with VVC, eight with CV and eight women with normal vulvovaginal flora and clinical characteristics (control group) were included in the study. All of the women selected were interviewed about their clinical complaints and signed the informed consent form. The local ethics committee board approved the study (process number is CAAE: 60648016.8.0000.5404).

Measurement of Vaginal pH

This test was performed with a MERCK colorimetric tape (Merck & Co., Inc., Kenilworth, NJ, USA) (ranging from 4.0–7.0 with variation intervals of 0.3) by placing the tape in the middle third of the vaginal wall for one minute and avoiding contact with the cervical mucus. After removal, the vaginal pH at that moment was checked according to the scale.

Bacterioscopy by Gram Staining and Wet Mount Microscopy

A sample of the vaginal contents was spread on a microscope slide and left to dry for Gram staining. It was characterized by the type of vaginal microbiota (Lactobacillus species predominance and/or other types of bacteria), the cellularity in the smear, bacterial morphology, the leukocytes, the presence or absence of inflammation (absent, 1–4, or > 4), and identifying pathogens as fungi. Also, the presence of hyphae was confirmed by visualization of the fungi on wet mount light microscopy of a vaginal sample. The diagnosis of bacterial vaginosis was based on the Nugent criteria.[9,10]

Fungal Culture

A sample of the vaginal contents was collected from the middle third of the vaginal wall with a sterile swab and sown in Sabouraud's growth medium, which was sent to the Clinical Pathology Laboratory of the Clinical Hospital (HC) (microbiology laboratory), where they were processed, analyzed, and released into the hospital system.

Statistical Analysis

The Fisher exact test and odds ratio were used to compare the categorical variables, and Kruskal-Wallis compared continuous variables with abnormal distribution among the three groups studied. The significance level adopted for the statistical tests was 5% ($p < 0.05$), with a study power calculated to 80%. The SAS System for Windows version 9.2 (SAS Institute Inc, Cary, NC, USA) was used for the statistical analysis.

Results

Regarding the sociodemographic and gynecological characteristics, no statistically significant differences were observed among the three groups (►**Table 1**).

Table 1 Sociodemographic and medical characteristics of the study subjects

Characteristics		VVC	CV	nl	*p*-value*
Age in years**		36	34.75	31.13	0.379
White		62.5% (5)	37.5% (3)	62.5% (5)	
					0.378
Non-white		37.5% (3)	62.5 (5)	37.5% (3)	
Years of schooling		16.13	11.63	13.88	0.058
	0	62.5% (5)	12.5% (1)	50% (4)	
Pregnancies	1	25% (2)	50% (4)	12.5% (1)	0.283
	> 1	12.5% (1)	37.5% (3)	37.5% (3)	
	0	87.5% (7)	62.5% (5)	100% (8)	
Abortions	1	12.5% (1)	25% (2)	0%	0.273
	> 1	0%	12.5% (1)	0%	
Recent sex partners (last 6 months)	0	12.5% (1)	0%	0%	
	1	87.5% (7)	62.5% (5)	87.5% (7)	0.273
	> 2	0%	37.5% (3)	12.5% (1)	
Use of condoms	Never	75% (6)	37.5% (3)	75% (6)	
	Sometimes	12.5% (1)	37.5% (3)	0%	0.385
	Always	12.5% (1)	25% (2)	25% (2)	
Smoking	No	87.5% (7)	100% (8)	87.5% (7)	1.000
	Yes	12.5% (1)	0%	12.5% (1)	

Abbreviations: CV: cytolytic vaginosis; nl, control group; VVC: vulvovaginal candidiasis.
*p-value according to the Kruskal-Wallis test for comparison of values among the 3 groups, followed by Dunn test for multiple comparisons ($p < 0.05$).
**Age average per group.

The frequency of vaginal hyperemia in VVC and CV was higher than in the control group, as well as the pasty discharge aspect for both conditions ($p = 0.0002$). The statistical analysis showed the same significant variables when comparing the categorical variables by groups (►**Table 2**), confirming even more precisely the results presented.

We can observe that the most prevalent complaints by the patients with VVC and CV are the existence and quantity of vaginal discharge, accompanied by dyspareunia (supplementary material 1). Vaginal itching and burning are reported by both groups, but itching and vulvar hyperemia are more related to VVC. Through the laboratorial characterizations, it was possible to confirm the diagnosis. Through the measurement of vaginal pH, it was demonstrated that the pH was lower in CV (3.8–4.0) and higher in VVC (4.5–4.7) (►**Table 3**).

In women with VVC, CV, and controls, the vaginal microbiota was primarily composed of Gram-positive lactobacilli. The lysis of the vaginal epithelium and the number of lactobacilli were significantly represented in the CV group, and the presence of inflammatory process was observed in the VVC group (►**Table 3**). The vaginal bacterioscopy of the groups studied is represented by ►**Fig. 1**. The presence of inflammatory process and *Candida* spp blastospores as well as of hyphae characterizing VVC are shown in ►**Fig. 1A** and **1B**. Intense lysis and increased number of lactobacilli, absence of inflammatory process, and visualization of nude nuclei, complementary to patients' complaints, accurately indicate CV (►**Fig. 1C**).

The integrity of the decayed epithelial cells, the absence of inflammatory process, and the normal number of lactobacilli reflect the quality of the vaginal environment and the maintenance of the basic conditions for the stability of the vagina microenvironment and is represented by ►**Fig. 1D**. All women in the VVC group presented positive fungal culture.

Table 2 Odds ratio analysis for categorical variables comparison of the groups of study

		nl x CV	*p*-value	nl x VVC	*p*-value	CV x VVC	*p*-value
White		1.0.	0.619	1.0.	1.000	1.0.	0.619
Non-white		2.78; IC95%: (0.37; 21.03)		1.00; IC95%: (0.13; 7.57)		0.36; IC95%: (0.05; 2.73)	
Number of pregnancies	0	1.0.	0.223	1.0.	0.648	1.0.	0.231
	1	16.00; IC95%: (0.72; 354.78)		1.60; IC95%: (0.10; 24.70)		0.10; IC95%: (0.01; 1.54)	
	> 1	4.00; IC95%: (0.27; 60.32)		0.27; IC95%: (0.02; 3.65)		0.07; IC95%: (0.01; 1.51)	
Number of abortions	0	1.0.	0.200.	1.0.	1.000	1.0.	0.569
	1	7.73; IC95%: (0.31; 193.44)		3.40; IC95%: (0.12; 96.70)		0.36; IC95%: (0.03; 5.11)	
	> 1	4.64; IC95%: (0.16;135.57)		0		0.24; IC95%: (0.01; 7.21)	
Recent sex partners (last 6 months)	0	0	0.569	1.0.	1.000	1.0.	0.200.
	1	1.0.		0.33; IC95%: (0.01; 9.57)		0.45; IC95%: (0.02; 13.41)	
	>2	4.20; IC95%: (0.33; 53.12)		0.11; IC95%: (0.01;10.27)		0.05; IC95%: (0.01; 3.73)	
Use of condoms	Never	0.50; IC95%: (0.05; 5.51)	0.256	2.00; IC95%: (0.14; 28.42)	1.000	4.00; IC95%: (0.25; 63.95)	0.413
	Sometimes	7.00; IC95%: (0.22; 218.95)		5.00; IC95%: (0.11; 220.62)		0.67; IC95%: (0.03; 18.06)	
	Always	1.0.		1.0.		1.0.	
Smoker	No	1.0.	1.000.	1.0.	1.000	1.0.	1.000.
	Yes	0.29; IC95%: (0.01; 8.37)		1.00; IC95%: (0.05; 19.36)		3.40; IC95%: (0.12; 96.70)	
	Discharge aspect	Liquid		1.0.		0.010.	
1.0.		0.010	1.0.	1.000.			
Lumpy	49.00; IC95%: (2.53; 948.62)		49.00; IC95%: (2.53; 948.62)		1.00; IC95%: (0.05; 19.36)		
	Yes	1.0.	0.119	1.0.	0.569	1.0.	0.619

Table 2 (*Continued*)

		nl x CV	*p*-value	nl x VVC	*p*-value	CV x VVC	*p*-value
Vulvar hyperemia	No	11.67; IC95%: (0.92; 147.53)		4.20; IC95%: (0.33; 53.12)		0.36; IC95%: (0.05; 2.73)	
Vaginal hyperemia	Yes	1.0.	0.007	1.0.	0.001	1.0.	1.000.
	No	44.20; IC95%: (1.80; 1,088.14)		4.20; IC95%: (0.33; 53.12)		2.33; IC95%: (0.17; 32.58)	
Lactobacilli amount	Normal	1.0.	0.007	1.0.	1.000	26.71; IC95%: (1.14; 624.23)	0.026
	High	44.20; IC95%: (1.80; 1,088.14)		1.80; IC95%: (0.21; 15.41)		1.0.	
Vaginal epithelium lysis	Low	1.0.	0.001	1.0.	1.000	187.0; IC95%: (3.21;10884.8)	0.001
	Moderate	1.00; IC95%: (0.01; 999.99)		1.80; IC95%: (0.21; 15.41)		119.0; IC95%: (1.95; 7,273.18)	
	High	221.00; IC95%: (3.85;12,694.7)		0		1.0.	
Inflammatory process	None	1.0.	1.000.	1.0.	0.001	1.0.	0.001
	1–4	0.29; IC95%: (0.01; 8.37)		35.0; IC95%: (1.12;1,094.7)		119.0; IC95%: (1.95; 7,273.2)	
	>4	0		165.0; IC95%: (2.81; 9,675.7)		187.0; IC95%: (3.21; 10,884.8)	
pH	3.8	63.00; IC95%: (0.98; 4,042.07)	0.003	1.00; IC95%: (0.01; 999.99)	0.239	1.0.	0.013
	4	81.00; IC95%: (1.30; 5,046.33)		0.07; IC95%: (0.01; 2.33)		2.33; IC95%: (0.07; 76.67)	
	4.4	3.00; IC95%:(0.09; 95.17)		0.20; IC95%: (0.01; 5.45)		7.00; IC95%: (0.17; 291.34)	
	4.5	1.0.		1.0.		63.00; IC95%: (0.98; 4,042.1)	
	4.7	0				35.00; IC95%: (0.50; 2,435.7)	
Nugent score	0–3	Homogeneous sample	No test	1.0.	0.077	1.0.	0.077
	3–6			13.22; IC95%: (0.55; 316.64)		13.22; IC95%: (0.55; 316.64)	
	7–10			5.67; IC95%: (0.19; 169.53)		5.67; IC95%: (0.19;169.53)	

Abbreviations: CV: cytolytic vaginosis; nl, control group; VVC: vulvovaginal candidiasis.
*p-value according to Fisher exact test.
[a]Categorical variables comparison between the control group (nl) and cytolytic vaginosis.
[b]Categorical variables comparison between the control group (nl) and vulvovaginal candidiasis.
[c]Categorical variables comparison between cytolytic vaginosis and vulvovaginal candidiasis.

Table 3 Clinical, microbiological, and biochemical aspects of vaginal content

Characteristics		VVC	VC	nl	*p*-value
Discharge aspect	Liquid	12.5% (1)	12.5% (1)	87.5% (7)	0.002
	Lumpy	87.5% (7)	87.5% (1)	12.5% (1)	
Vulvar hyperemia	Yes	37.5 (3)	62.5 (5)	12.5 (1)	0.171
	No	62.5 (5)	37.5 (3)	82.5 (7)	
Vaginal hyperemia	Yes	87.5 (7)	75 (6)	0	0.001
	No	12.5 (1)	25 (2)	100 (8)	
Lactobacillus amount	Normal	62.5% (5)	0%	75% (6)	0.006

(*Continued*)

Table 3 (*Continued*)

Characteristics		VVC	VC	nl	*p*-value
	High	37.5% (3)	100% (8)	25% (2)	
Vaginal epithelium lysis	Low	62.5% (5)	0%	75% (6)	
	Moderate	37.5% (3)	0%	25% (2)	0.001
	High	0%	100% (8)	0%	
Inflammatory process	None	0%	100% (8)	87.5 (7)	
	1–4	37.5% (3)	0%	12.5% (1)	0.001
	> 4	62.5% (5)	0%	0%	
pH	3.8	0%	37.5% (3)	0%	0.0002
	4	12.5% (1)	50% (4)	0%	
	4.4	12.5% (1)	12.5% (1)	50% (4)	
	4.5	50% (4)	0%	50% (4)	
	4.7	25% (2)	0%		
Nugent score	0–3	50% (4)	100% (8)	100% (8)	
	03–06	37.5% (3)	0%	0%	0.015
	07–10	12.5% (1)	0%	0%	

Abbreviations: CV: cytolytic vaginosis; nl, control group; VVC: vulvovaginal candidiasis.
*p-value for Kruskal-Wallis test for comparison of values among the 3 groups, followed by Dunn test for multiple comparisons ($p < 0.05$).

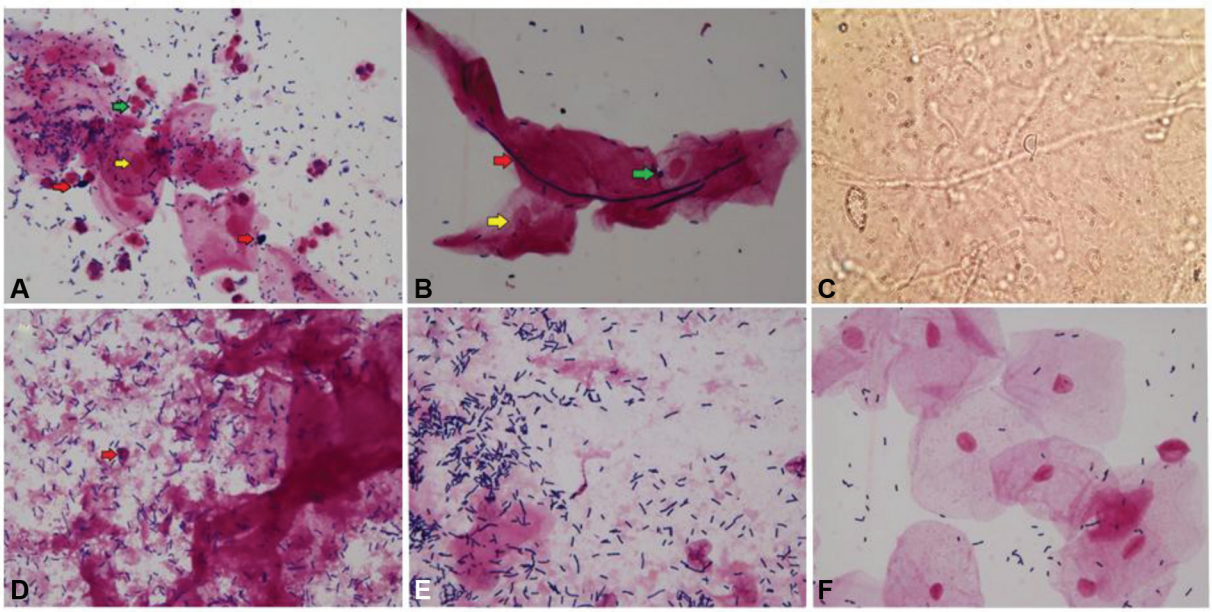

Fig. 1 Vaginal bacterioscopy of the groups. (**A**) Vaginal microbiota with predominance of *Lactobacillus* sp. with neutrophils (green arrow), presence of blastospores (red arrows), predominance of intermediate vaginal epithelial cells (yellow arrow). Diagnosis: vulvovaginal candidiasis. (**B**) Presence of hyphae (red arrow) and blastospores (green arrow) and predominance of intermediate vaginal epithelial cells (yellow arrow). Diagnosis: vulvovaginal candidiasis. (**C**) Presence of hyphae in wet mount microscopy. D and E: Vaginal microbiota with predominance and abundance of *Lactobacillus* sp., intense lysis in the vaginal epithelium, naked nuclei (red arrow in D) and no inflammatory process. Diagnosis: Cytolytic vaginosis. F: Normal number of lactobacilli, no inflammatory process, and predominance of intermediate vaginal epithelial cells. Diagnosis: normal. Pictures captured at the Genital Infections Outpatient Clinic of Hospital da Mulher da Universidade Estadual de Campinas, Campinas, SP, Brazil.

Discussion

The vaginal discharge complaint is one of the main factors that lead women to gynecological consultation, but it is often not so easy for the physician to make a correct diagnosis. In regard to signs and symptoms, CV is very similar to VVC. Most of the women who have CV are incorrectly diagnosed with complicated VVC refractory to treatment and, in some cases, are referenced for psychiatric treatment.[11,14] Due to the fact that clinical presentation in CV and VVC is similar, a

high level of suspicion is necessary for a correct diagnosis, especially if there is illness with a history of recurrence to specialists from several areas, symptomatology systematically refractory to various antifungal/antibiotic agents, or a diagnosis of complicated candidiasis.[11,14–16] In addition to VVC, there is another pathology whose signs and symptoms are similar to CV: Döderlein lactobacillus. In this situation, there is an increase in the size of lactobacilli, which is also accompanied by a more modest increase in bacterial load. However, there is no cellular cytolysis.[17,18] Microscopic examination of vaginal discharge is the pillar of the differential diagnosis among these pathologies, which is particularly important since the treatment differs according to the entity in question.[11,13,17,18] In view of this, a set of clinical and laboratorial criteria must be available that, when evaluated together during the gynecological examination, can provide the physician with support for an accurate diagnosis. First, when analyzing the sociodemographic variables, we did not find significant differences among the three groups studied. We only observed a higher frequency between the number of pregnancies and women with CV, but without statistical significance, similar to what had been previously reported.[13] Regarding the clinical and pH characteristics, we found that factors such as vaginal discharge and vaginal hyperemia were more frequent in women with CV and VVC, when compared with the control group. The vaginal pH is significantly different between women with CV and VVC.[10] Some species of lactobacilli, by action of different mechanisms, are able to maintain an acidic vaginal pH, with lactate being its main product. Acidic vaginal pH is essential for the protection of the vaginal epithelium against pathogenic microorganisms that develop best at basic pH.[19,20] A study conducted by our research group found a higher concentration of L-lactate in women with cytolytic vaginosis.[21] The exacerbated growth of lactobacilli leads to higher vaginal acidity due to the action of this lactate, and the increase of this acidity can be routinely detected in the outpatient clinic through vaginal pH tapes. The pH strip with more detailed variation of color, the use of markers for the presence of leukocytes (leukocyte esterase), or cell lysis presence of histamine or other lysis marker would be relevant. When evaluating Gram-stained vaginal smears, we observed a marked cellular lysis in all women with CV, associated with a large number of lactobacilli and an absence of polymorphonuclear cells. Similarly to these bacterioscopic results, it was found that lactobacilli overgrowth, increased cytolysis, and absence of polymorphonuclears in the cervical smears are factors associated with cytolytic vaginosis.[13] However, these authors focused only on the morphological diagnosis by bacterioscopy, whereas in our study we also considered clinical signs and vaginal pH, which are criteria that, added to bacterioscopy, could increase the accuracy of the diagnosis of CV.

Conclusion

Cytolytic vaginosis has sufficient laboratorial characteristics to differentiate it from VVC. We can delineate bacterioscopic criteria capable of distinguishing CV and VVC: low pH, increased number of lactobacilli, and marked cytolysis, as well as absence of fungi and polymorphonuclear scarcity in the Gram smear. Such criteria are easy and applicable in clinical practice, providing a more detailed consultation, which may allow the patient to leave the consultation with an appropriate treatment. This study highlights the importance of conducting an accurate investigation through laboratory tests rather than clinical criteria to avoid misdiagnosis.

Contributions

J. M. S.: Design, collection, analysis and interpretation of the data and writing of the article; P. C. G. design and data analysis and final revision. M. B. data analysis; R. A. collection and interpretation of the data; M. G. D. writing and revision of the article; L. R. data analysis and final revision.

Conflict of Interests

The authors have no conflict of interests to declare.

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Assessment of Preoperative Endometrial Histopathological Sampling as a Predictor of Final Surgical Pathology in Endometrial Cancer

Avaliação do diagnóstico histopatológico endometrial pré-operatório como preditor do diagnostico patológico final em câncer de endométrio

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Abstract

Objective To evaluate the agreement between the histopathological diagnoses of preoperative endometrial samples and surgical specimens and correlate the agreement between the diagnoses with the impact on surgical management and the survival of patients with endometrial adenocarcinomas.

Methods Sixty-two patients treated for endometrial cancer at a university hospital from 2002 to 2011 were retrospectively evaluated. The histopathological findings of preoperative endometrial samples and of surgical specimens were analyzed. The patients were subjected to hysterectomy as well as adjuvant treatment, if necessary, and clinical follow-up, according to the institutional protocol. Lesions were classified as endometrioid tumor (type 1) grades 1, 2, or 3 or non-endometrioid carcinoma (type 2).

Results The agreement between the histopathological diagnoses based on preoperative endometrial samples and surgical specimens was fair (Kappa: 0.40; $p < 0.001$). However, the agreement was very significant for tumor type and grade, in which a higher concordance occurred at a higher grade. The percentage of patients with lymph nodes affected was 19.2%. Although most patients presenting with disease remission or cure were in the early stages (90.5%), there were no significant differences between those patients who had a misdiagnosis (11/16; 68.8%) and those who had a correct diagnosis (25/33; 75.8%) based on preoperative endometrial sampling ($p = 0.605$).

Conclusion Our findings corroborate the literature and confirm the under staging of preoperative endometrial samples based on histopathological assessment, especially for lower grade endometrial tumors. We suggest that the preoperative diagnosis should be complemented with other methods to better plan the surgical management strategy.

Keywords

- cancer of the endometrium
- histopathological diagnosis
- diagnostic method
- endometrial cancer surgery

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Resumo

Objetivo Avaliar a concordância entre os diagnósticos histopatológicos de amostras endometriais pré-operatórias e cirúrgicas de pacientes com adenocarcinomas endometriais e avaliar o impacto da concordância entre os diagnósticos no planejamento cirúrgico e sobrevida das pacientes.

Métodos Dados de 62 pacientes com câncer de endométrio operadas entre 2002 a 2011 em um hospital universitário foram avaliadas retrospectivamente. As pacientes foram submetidas à histerectomia e tratamento adjuvante, se necessário, e acompanhadas clinicamente de acordo com o protocolo institucional. Foram avaliados os resultados das análises histopatológicas das amostras endometriais pré-operatórias e cirúrgicas. As lesões foram classificadas como tumor endometrioide (tipo 1) graus 1, 2 ou 3 ou carcinoma não endometrioide (tipo 2).

Resultados De modo geral, houve uma concordância baixa entre os diagnósticos histopatológicos das amostras endometriais pré-operatórias e cirúrgicas (Kappa: 0,40; $p < 0,001$). Entretanto, uma alta concordância entre os diagnósticos foi observada nos tumores de graus mais elevados. Comprometimento de linfonodos ocorreu em 19,2% das pacientes e a maioria das que apresentaram remissão ou cura foram diagnosticadas nos estágios iniciais da doença (90,5%). Não houve diferença significativa na taxa de remissão ou cura entre as pacientes que tiveram concordância (25/33; 75,8%) ou divergência (11/16; 68,8%) entre os resultados histopatológicos pré-operatórios e cirúrgicos ($p = 0,605$).

Conclusão Nossos achados corroboram a literatura e confirmam o sub-estadiamento de amostras endometriais pré-operatórias com base na avaliação histopatológica, especialmente para tumores endometriais de baixo grau. Outros métodos complementares são necessários para um diagnóstico pré-operatório mais preciso a fim de melhorar o planejamento cirúrgico.

Descritores

- câncer do endométrio
- diagnóstico histopatológico
- método diagnóstico
- cirurgia de câncer endometrial

Introduction

Endometrial cancer is the second most common gynecological malignancy and the fourth most common malignancy in women. It represents 7% of cancers in women and the 6th most common cause of death by cancer in women. The estimates show $\sim$ 60 thousand new cases and 12,000 deaths during the year 2016 in the United States.[1] In Brazil, almost 7,000 new cases were estimated for 2018.[2] The survival rate after 5 years of follow-up is 90% when the tumor is diagnosed in the early stage, but the survival is only 30% if detected later.[3] Abnormal vaginal bleeding is the initial symptom, and diagnosis is usually made in the early stages of the disease (e.g., in 75% of patients).[4]

Tumor grading, defined by the International Federation of Gynecology and Obstetrics (FIGO) in 1988 and revised in 2009, is based on histopathological analysis of surgical specimens. The samples obtained during hysterectomy and bilateral adnexectomy with pelvic and para-aortic lymph node dissections are necessary, and the involvement of tumor grading from intraoperative specimens is a key point.[5] However, the initial diagnosis is established by the histopathological analysis of endometrial biopsies.[6] The histological subtype and the grade of endometrial cancer are key factors related to the probability of disease spread and recurrence.[7–10]

Total hysterectomy remains the standard treatment for the management of endometrial cancer.[11] However, the benefit of systematic lymphadenectomy for women with early stage endometrial cancer is a matter of debate, and is basically defined according to the preoperative histopathological grade.[12–14] Thus, the accuracy of preoperative histopathological analysis of endometrial biopsies is imperative because it directly affects the surgical management.[15,16]

Studies published since the 1980s have demonstrated discordance between the histopathological analysis of preoperative endometrial samples and surgical specimens. Moreover, the discordance rates vary according to grades and other factors, such as the method of sample collection.[16–24] Thus, the study of preoperative endometrial sampling as a predictor of surgical specimen grading and its value on surgical decisions and patient prognosis is still debated.

The present study aimed to evaluate the agreement between the histopathological diagnoses of preoperative endometrial samples and surgical specimens and to correlate it with the impact on surgical management and survival of patients with endometrial adenocarcinomas from our university hospital.

Methods

The present study was performed at the Gynecologic Oncology discipline of the Gynecology Department of the Universidade Federal de São Paulo (UNIFESP), São Paulo,

Brazil. The study was approved by the Ethics Committee of the UNIFESP (CAAE: 02003912.5.0000.5505). The study presents a mixed design of cross-sectional and retrospective cohort, as it was developed into two steps. A cross-sectional study was performed to evaluate the association of pre and postoperative specimens' diagnosis of endometrial cancer. Then, a retrospective cohort strategy was also applied to explore the impact of agreement or not of the histopathological classifications, determined from the preoperative endometrial samples and surgical specimens, on patients survival.

Patients

Consecutive patients treated for endometrial cancer from 2002 to 2011 at the Gynecology Department of the Universidade Federal de São Paulo (UNIFESP) had their data reviewed from a prospectively maintained patient database. A total of 122 patients referred to our service with a previous endometrial cancer diagnosis were elected for this study. The inclusion criteria were women presenting endometrial cancer with a preoperative histopathological evaluation. For the patients referred from other institutions, our protocol was to review the biopsy specimens, and then, 57 patients whose preoperative biopsies specimens were not available for review were excluded from the study. Three women who did not had the postoperative data available in the datasheet were excluded as well. The final data analysis included 62 women with complete data about pre and postoperative histological evaluation. The preoperative endometrial sampling was performed by hysteroscopy with biopsy or curettage and histopathological analysis. The preoperative histopathological analysis or reviews were performed by an experienced pathology team from our institution that also performed the histopathological analysis of surgical specimens as per the department protocol. Patients were subjected to hysterectomy with bilateral salpingo-oophorectomy, associated or not with lymphadenectomy, and adjuvant treatment if necessary. The clinical follow-up of patients was performed according to the institutional protocol.

According to the World Health Organization and the Royal College of Pathologists' definitions for tumor cell type, the lesions were classified as endometrioid adenocarcinoma (type 1) or non-endometrioid adenocarcinoma (type 2, mostly serous and clear cells). Endometrioid adenocarcinomas were sub classified as grades 1, 2, or 3 according to the FIGO) with a higher grade corresponding to less-differentiated lesions. Preoperative cancer samples could also be classified as atypical hyperplasia.

Data Analysis

Cases were grouped by preoperative and surgical histopathological diagnoses, and the correlation between them was assessed. Lymph node involvement and number of lymph nodes involved were registered for each group as features related to a higher risk of disease recurrence. Survival and clinical prognosis were also registered for each patient. Continuous variables were described as the mean and standard deviation and categorical variables as frequency and percentage. The McNemar and Chi-square tests were used to compare proportions of histopathological diagnoses between the preoperative samples and surgical specimens. The Kappa correlation evaluated the agreement between the preoperative and surgical specimens. Overall survival was estimated using Kaplan-Meier curves and log-rank test. For that, the time of statistical analysis was performed using SPSS for Windows version 21.0 (IBM Corp., Armonk, NY, USA), and p-values < 0.05 were considered statistically significant.

Results

We identified 62 cases that met our inclusion criteria. Most patients had preoperative endometrial sampling by hysteroscopy (60.0%), 18 were obtained by curettage and biopsy (32.7%) and 4 (7.3%) had missing endometrial sampling methods. ►**Table 1** summarizes the findings of the

Table 1 Histopathological review of the cases grouped by preoperative endometrial samples and surgical specimens

	Surgical specimens					
Preoperative endometrial samples	**Atypical hyperplasia N (%)**	**Endometrioid adenocarcinoma grade 1 N (%)**	**Endometrioid adenocarcinoma grade 2 N (%)**	**Endometrioid adenocarcinoma grade 3 N (%)**	**Non-endometrioid adenocarcinoma N (%)**	**Total n(%)**
Atypical hyperplasia	0 (0)	10 (55.6)	5 (27.8)	1 (5.6)	2(11.1)	18 (100)
Endometrioid adenocarcinoma grade 1	0 (0)	16 (64.0)	7 (28.0)	0 (0.0)	2 (8.0)	25 (100)
Endometrioid adenocarcinoma grade 2	0 (0)	2 (25.0)	4 (50.0)	1 (12.5)	1 (12.5)	8 (100)
Endometrioid adenocarcinoma grade 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (100)
Non-endometrioid adenocarcinoma	0 (0)	1 (9.1)	0 (0)	1 (9.1)	9 (81.8)	11 (100)

Chi-square - $p < 0.001$.

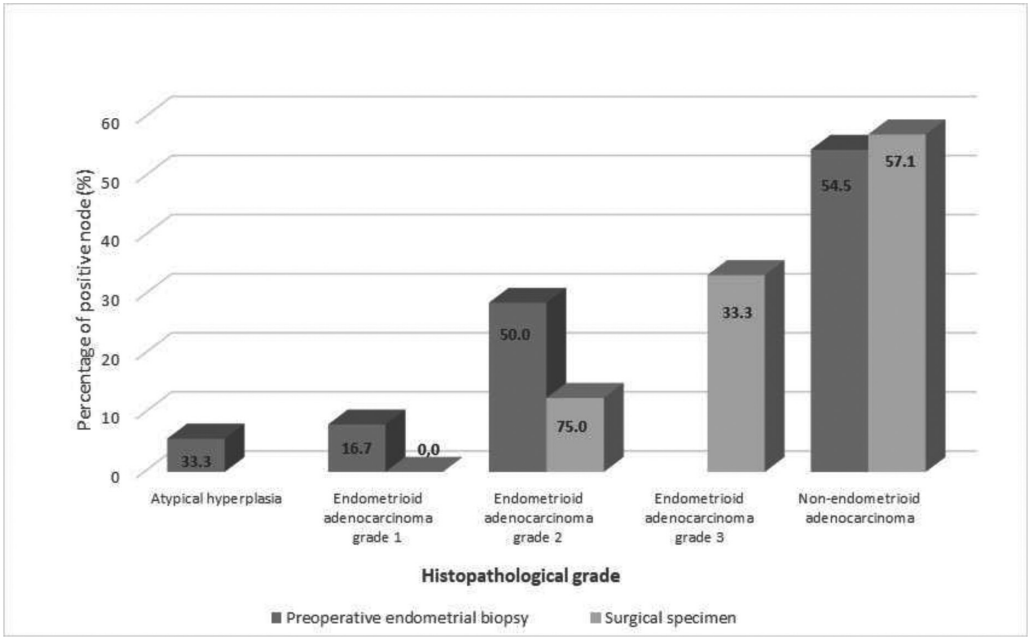

Fig. 1 Percentage of patients with positive nodes according to histopathological grade of the preoperative endometrial samples and surgical specimens.

histopathological review of the preoperative endometrial samples and surgical specimens. The general agreement between the preoperative endometrial samples and surgical specimens was 46.8% (Kappa: 0.279, $p < 0.001$). However, we noted that the agreement varied significantly by tumor type and grade, so that a reasonable concordance occurred at endometrioid adenocarcinoma grade 1 (64.0%) and grade 2 (50.0%) and non-endometrioid adenocarcinoma (81.8%). It is interesting to note that there were 18 patients diagnosed with atypical hyperplasia in the preoperative sample and none confirmed in the surgical sample. Moreover, no women were diagnosed with endometrioid adenocarcinoma grade 3 in the preoperative samples, and we observed 3 in the surgical specimens. Those data demonstrate that higher discordances occur in the extremes of classifications.

During the hysterectomy, the lymph nodes were excised in 61 patients and were affected in 10 patients (19.2%). ►**Fig. 1** describes the percentage of patients with positive lymph nodes according to the histopathological grades of the preoperative endometrial samples and surgical specimens.

We obtained the follow-up data of 49 patients for a period that varied from 1 to 121 months (median: 41; Q25:9; Q75: 66 months/mean ± SD: 45.6 ± 31.9 months). Of those, 20 were considered cured (32.7%), 20 had disease remission (40.8%), 2 had active disease or suffered disease recurrence (4.8%), and 11 died (22.4%). The percentage of patients with disease remission or cure according to the histopathological grade of the surgical specimens are described in ►**Table 2**.

We also evaluated the rates of disease remission or cure among the 49 patients with follow-up data, according to agreement or not with the histopathological classifications determined from the preoperative endometrial samples and surgical specimens. The percentage of patients with disease remission or cure was similar between those who had a correct diagnosis (15/22, 68.2%) on preoperative endometrial sampling and those with a misdiagnosis (21/27, 77.8%; $p = 0.450$). Then, ►**Fig. 2** shows the Kaplan-Meier curve for survival function in subgroups of women with correct diagnosis or misdiagnosis on preoperative endometrial sampling. This shows that the estimated mean of survival time was similar between patients with correct diagnosis in the preoperative samples (85.6%) and those with misdiagnosis (93.7%, $p = 0.487$). Those data showed that even though misdiagnosis in preoperative samples is frequent (53.2% of cases), it does not affect the survival rates of patients.

Table 2 Percentage of patients with disease remission or cure according to the histopathological grade of the surgical specimens

Histopathological grade of the surgical specimens	Disease remission or cure n(%)
Endometrioid adenocarcinoma grade 1	19/21 (90.5)
Endometrioid adenocarcinoma grade 2	13/15 (86.7)
Endometrioid adenocarcinoma grade 3	2/2 (100.0)
Non-endometrioid adenocarcinomas	2/11 (18.2)
Total number of patients	36/49 (73.5)

$P < 0.001$.

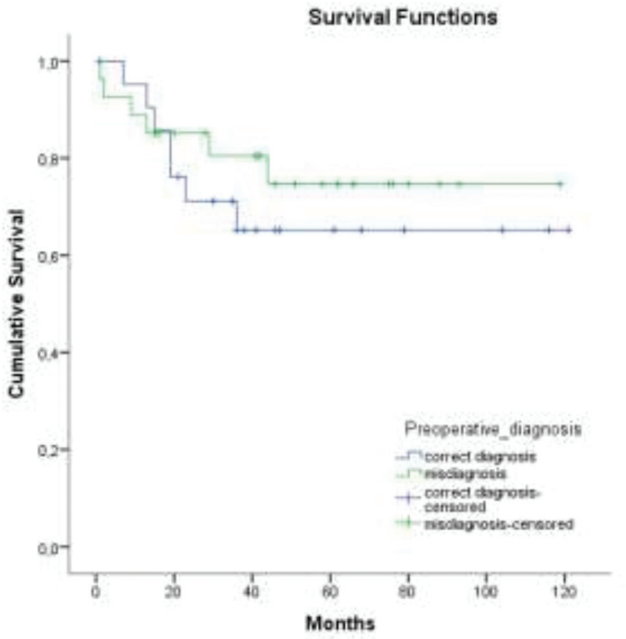

Fig. 2 Kaplan-Meier plots showing the cumulative survival function in subgroups of women with correct diagnosis or misdiagnosis on preoperative endometrial sampling.

Discussion

Pathological information of preoperative sampling is often used to stratify endometrial cancer based on low and high risk for lymphatic dissemination and prognosis, which guides decision-making for surgical planning. Thus, the accuracy of the preoperative histopathological assessment is imperative. Our findings showed that the agreement between the histopathological diagnoses based on the preoperative endometrial samples and those based on the surgical specimens is fair, and the vast majority of samples that were misdiagnosed had a lower grade classification based on preoperative endometrial sampling. Our findings corroborate those of other studies that also showed fair agreement between the histopathology assessment of preoperative and surgical specimens in endometrial cancer,[20,25,26] suggesting that the preoperative histological grade is not a good predictor of definitive diagnosis. Our findings and those outcomes suggest that patient treatment planning can be underestimated and may impair the patient's prognosis.

On the other hand, the samples classified as non-endometrioid adenocarcinoma had higher agreement between the diagnoses based on the preoperative endometrial samples and the surgical specimens. Hence, at least for the patients with the worst prognosis, a higher accuracy of histopathology for the preoperative endometrial sample gives us the correct information for the decision-making on surgical planning for most cases.

Despite some authors[9,27] and FIGO[11] recommending that the surgical treatment of endometrial cancer include hysterectomy plus lymph node dissection of the pelvis and paraaortic areas for all histological grades and types of endometrial cancer, there are other authors[12,13,28,29] who did not find benefits of lymph node dissection for patients with early disease. In our study, most patients underwent lymph node dissection, and we found $\sim$ 20% of cases with lymph node involvement, which represents a higher percentage than that in other studies.[9,30,31] However, those with early disease presented a lower incidence of lymph node involvement, and higher grade tumors had a higher incidence of lymph node involvement, corroborating the literature findings.[28]

It is well established that patient prognosis and survival are directly associated with tumor staging and lymph node involvement. We considered those patients without disease recurrence after 60 months of follow-up to be cured, and those patients without disease recurrence before completing 60 months of follow-up to have disease remission. We found a significantly lower disease remission/cure for patients presenting with non-endometrioid adenocarcinoma, similar to the literature findings.[32,33] A limitation of our data are the small number of patients presenting endometrioid adenocarcinoma grade 3, who had 100% of remission/cure, which is not consistent with this tumor type. Additionally, the under staging of endometrial cancer did not affect the survival rates, probably due to the higher grades and, consequently, a worse prognosis patients, in whom there was a greater agreement between the histopathological assessments of the preoperative and surgical specimens. Another pitfall is that the follow-up until 60 months was missed for most patients and the survival analysis can be compromised, although Kaplan-Meier plots do not show any difference between subgroups.

The retrospective design of our study is also a limitation. Additionally, although all surgeries were performed in the same hospital, the surgeons were not the same, and there was no clear rule to perform lymph node dissection in early-stage tumors, which can be considered a bias.

Faced with our results and literature findings demonstrating the under staging of endometrial cancer on preoperative endometrial samples, other parameters can be considered for surgical planning. Magnetic resonance imaging to evaluate myometrial invasion,[34] tumor volume,[35] and intraoperative staging estimation by the analysis of cryopreserved specimens[36] can also contribute to surgical planning.

Conclusion

In summary, our findings corroborate the literature results and confirm the under staging of preoperative endometrial samples by histopathological assessment, especially for lower grade endometrial tumors. Therefore, we suggest that the preoperative diagnosis should be complemented with other methods to better plan the surgical management strategy.

Contributions

Mario Augusto Silveira Bueno Piotto contributed to study design, execution, manuscript drafting, critically revising and discussing of the article and final approval of the version to be published. Gustavo Rubino de Azevedo Focchi contributed to study execution, sample analysis,

revising and final approval of the version to be published. Renato Moretti Marques contributed to data collection and final approval of the version to be published. Andressa Melina Severino Teixeira contributed to data collection and final approval of the version to be published. Wagner José Gonçalves contributed to critically revising and discussing of the article and final approval of the version to be published. Sergio Mancini Nicolau contributed to study design, execution, manuscript drafting, critically revising and discussing of the article 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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Use of GnRH Analogues in the Reduction of Submucous Fibroid for Surgical Hysteroscopy: A Systematic Review and Meta-Analysis

Uso de análogo de GnRH na redução de mioma submucoso na histeroscopia cirúrgica: Revisão sistemática e meta-análise

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Abstract

Objective Gonadotropin-releasing hormone analogues (GnRH-a) have been used preoperatively before hysteroscopic myomectomy to decrease the size and vascularization of the myomas, but evidence to support this practice is weak. Our objective was to analyze the use of GnRH-a in the reduction of submucous fibroid as a facilitator for surgical hysteroscopy from published clinical trials.

Data sources Studies from electronic databases (Pubmed, Scielo, EMBASE, Scopus, PROSPERO), published between 1980 and December 2018. The keywords used were *fibroid*, *GnRH analogue*, *submucous*, *histeroscopy*, *histeroscopic resection* and their correspondents in Portuguese.

Study selection The inclusion criteria were controlled trials that evaluated the GnRH-a treatment before hysteroscopic resection of submucous myomas. Four clinical trials were included in the meta-analysis.

Data collection Two review authors extracted the data without modification of the original data, using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third person.

Data synthesis The present meta-analysis included a total of 213 women and showed no statistically significant differences in the use of GnRH-a compared with the control group for complete resection of submucous myoma (relative risk [RR]: 0.94; 95% confidence interval [CI]: 0.80–1.11); operative time (mean difference [MD]: - 3.81; 95% CI : - 3.81–2.13); fluid absorption (MD: - 65.90; 95%CI: - 9.75–2.13); or complications (RR 0.92; 95%CI: 0.18–4.82).

Keywords
- GnRH analogue
- fibroid
- hysteroscopy
- myoma resection
- submucous fibroid

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Conclusion The present review did not support the routine preoperative use of GnRH-a prior to hysteroscopic myomectomy. However, it is not possible to determine its inferiority when compared with the other methods due to the heterogeneity of existing studies and the small sample size.

Resumo

Objetivo Análogos de hormônio liberador de gonadotrofina (GnRH-a) têm sido usados no pré-operatório de miomectomia histeroscópica para reduzir o tamanho e vascularização dos miomas, mas a evidência que suporta essa prática é fraca. Nosso objetivo foi analisar o uso de GnRH-a na redução do mioma submucoso como um facilitador de histeroscopia cirúrgica em ensaios clínicos publicados.

Fonte de dados Estudos de bases de dados eletrônicas (Pubmed, Scielo, EMBASE, Scopus, PROSPERO), publicados entre 1980 e dezembro de 2018. As palavras-chave usadas foram *fibroid*, *GnRH analogue*, *submucous*, *histeroscopy*, *histeroscopic resection* e seus correspondentes em português.

Seleção dos estudos Os critérios de inclusão foram ensaios clínicos controlados que avaliaram o tratamento com GnRH-a antes da ressecção histeroscópica de miomas submucosos. Quatro ensaios clínicos foram incluídos na meta-análise

Coleta de dados Dois autores revisores extraíram os dados, sem modificarem os dados originais, usando a forma acordada. Nós resolvemos as discrepâncias através de discussão ou, se necessário, consultando um terceiro autor.

Síntese dos dados A meta-análise incluiu um total de 213 mulheres e não demonstrou diferença estatisticamente significativa no uso de GnRH-a comparado com o grupo controle para ressecção completa de mioma submucoso (risco relativo [RR]: 0.94. índice de confiança [IC] 95%: 0.80–1.11); tempo cirúrgico (diferença de média [MD]: - 3.81; IC95%: -3.81–2.13); absorção de fluidos (MD: - 65.90; IC95%: - 9.75–2.13); ou complicações (RR 0.92; IC95%: 0.18–4.82).

Conclusão A presente revisão sistemática não suporta o uso pré-operatório rotineiro de GnRH-a antes de miomectomia histeroscópica. No entanto, não é possível determinar sua inferioridade quando comparado aos outros métodos devido à heterogeneidade dos estudos existentes e ao pequeno tamanho da amostra.

Palavras-chave
- mioma
- análogo GnRH
- submucoso
- histeroscopia
- ressecção histeroscópica

Introduction

Uterine myomas are the most common benign tumor of the female genital tract.[1] Myomas could be classified into subserous, intramural, and submucous types according to their location in the uterus. Clinical presentation of the submucous myoma includes menorrhagia, metrorrhagia, dysmenorrhea, infertility, and repeated abortion.[2,3]

The surgery goal is the complete removal of the fibroid – reducing the chance of recurrence and regrowth.[3] Submucous fibroids distort the endometrial cavity and typically cause heavy or irregular menstrual bleeding.[4] The advantages of hysteroscopic resection of submucous myomas are reduced trauma, shorter hospitalization and recovery times, as well as decreased risk of adhesion formation. Gonadotropin-releasing hormone analogues (GnRH-a) have been used preoperatively before hysteroscopic myomectomy to decrease the size and vascularization of the myomas (therefore rendering surgery faster), but robust evidence to support this practice is weak.[5]

Fibroid growth is stimulated by estrogen. Gonadotropin-hormone releasing analogues induce a state of hypoestrogenism that shrinks fibroids, but has undoubtedly unpleasant side effects such as hot flushes and night sweats.[6,7]

The available literature on the issue of medical treatment before hysteroscopic resection is scanty, mainly consisting of uncontrolled and relatively small and nonrandomized trials, which are in contrast with each other and possibly biased.[7]

A Cochrane review evaluated the role of preoperative medical therapy before surgery for uterine fibroids. They compared GnRH-a, progestin, selective progesterone receptors modulators (SPRMs), selective estrogen receptor modulators (SERMs), dopamine agonists, estrogen receptor antagonists and placebo before myomectomy and hysterectomy. They did not specifically compare GnRH-a and placebo prior to hysteroscopic resection of submucous fibroid.[6]

In 2014, a systematic review comparing GnRH-a and no treatment before hysteroscopic resection of submucous fibroids found no significant benefit of preoperative GnRH-a before hysteroscopic resection of submucosal myomas. It used two

randomized controlled trials (RCTs) for the meta-analysis.[8,9] Since then, other trials were conducted.

As the majority of previous studies of use of GnRH-a preoperatively for hysteroscopic resection of submucous fibroids have been relatively small and not randomized, our objective was to analyze the use of GnRH-a in the reduction of submucous fibroid as a facilitator for surgical hysteroscopy from published clinical trials and to compare its efficacy with other methods.

Methods

Search Strategy

The review protocol was established by two investigators (Corrêa T. H. and Caetano I. M.) prior to commencement and two authors (Corrêa T. H. and Caetano I. M.).identified trials by searching independently the literature in electronic databases. We used the following sources for the identification of trials: Pubmed, Scielo, LILACS, EMBASE, Scopus, the PROSPERO International Prospective Register of Systematic Reviews and Cochrane Central Register of Controlled Trials, between 1980 and June 2019. We also screened the reference lists of identified articles for additional studies, according to the review eligibility criteria.

The review was based only on published literature. The following Medical Subject headings (MeSH terms) and all combinations of these words were used: *fibroid*, *GnRH analogue*, *submucous*, *histeroscopy*, *histeroscopic resection* and their correspondents in Portuguese, *mioma*, *análogo GnRH*, *submucoso*, *histeroscopia* and *ressecção histeroscópica*. We restricted our search to papers published in the English and Portuguese languages. Agreement regarding potential relevance was reached by discussion with a third reviewer (Santos Filho A. S.) and the full text of all relevant trial reports identified through the searching activities described above was reviewed.

Primary and secondary outcomes were defined before data extraction. The primary outcome was complete resection of the fibroid. The secondary outcomes were operating time, complications (excessive intraoperative bleeding, uterine perforation, bowel injury), fluid absorption and adverse effects.

Study Selection

The review was undertaken by two reviewers (Corrêa, T.D and Saraiva, P. H. T.). The search strategy described previously was employed to obtain titles, and, where possible, abstracts of studies that were potentially relevant to the review. The titles and abstracts were screened by Corrêa, T.D and Saraiva, P. H. T., who discarded studies that were clearly ineligible but aimed to be overly inclusive rather than risk losing relevant studies. Copies of the full articles were obtained. Both reviewers independently assessed whether the studies met the inclusion criteria. Disagreements were resolved by referring to a third reviewer (Santos Filho A. S.) for discussion. Further information was sought from the authors whose papers contained insufficient information to make a decision about eligibility.

The inclusion criteria were: controlled trials that evaluated the GnRH-a treatment before hysteroscopic resection of submucous myomas. The exclusion criteria were: observational studies, review or retrospective studies, articles published outside the period described and those with non-hysteroscopic myomectomy.

Data Extraction and Risk of Bias Assessment

We designed a form to extract data. For eligible trials, the two reviewers independently abstracted data for each eligible study using a standardized electronic data abstraction form. Data elements included the following: trial identifiers; study methods (including enrollment and withdrawal numbers); patient characteristics; interventions; outcomes; and comments. We reported the results of trial selection using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (►**Fig. 1**).

We performed an assessment of all RCTs using the Cochrane 'risk of bias' tool according to the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[10] Two review authors (Corrêa, T.D and Saraiva, P. H. T.) worked independently to assess each element of potential bias listed below as high (any nonrandom process), low (any truly random process), or unclear risk of bias. Disagreements were resolved by discussion or by involving a third assessor.

The Cochrane tool for assessing risk of bias was used, which included the following domains: selection bias (random sequence generation and allocation concealment); performance bias (blinding of participants and personnel); detection bias (blinding of outcome assessment); attrition bias (incomplete outcome data); reporting bias (selective reporting); other bias (checking for bias due to problems not covered by others above).

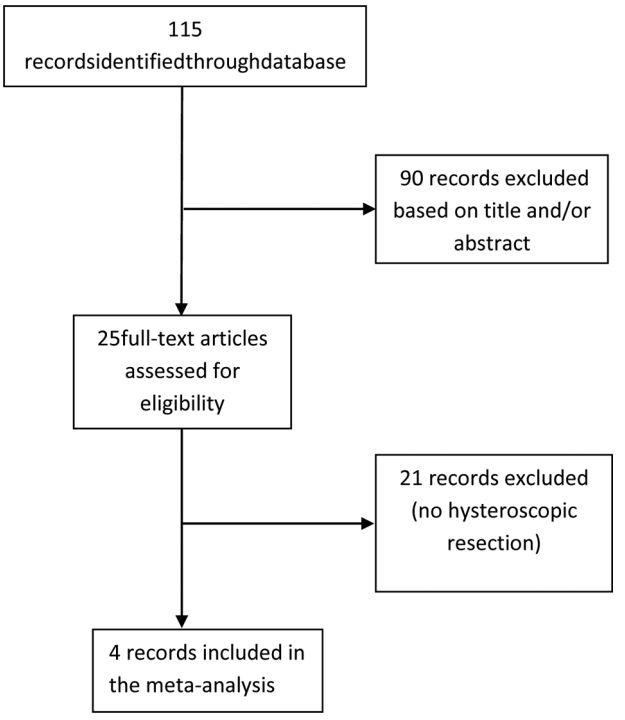

Fig. 1 Flow diagram of identified studies.

Data Analysis

Data was entered into Review Manager 5.3 software (The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark)[11] and checked for accuracy. For continuous outcomes, we recorded the mean, standard deviation (SD) and total number of participants in both the treatment and control groups and performed analyses using the mean difference (MD) with 95% confidence intervals (CIs). For dichotomous outcomes, we recorded the number of events and the total number of participants in both the treatment and control groups and reported the pooled risk ratio (RR) with a 95% CI. We used the Mantel–Haenzel method for combining dichotomous variables and inverse variance method for continuous variables.

The meta-analysis was reported following the PRISMA statement. The comparisons made among these publications were between GnRH-a and no-GnRH-a or placebo.

Heterogeneity between studies was tested with the I^2 Index. An $I^2 > 50\%$ was interpreted as moderate heterogeneity, and $I^2 > 80\%$ was considered considerable. A random-effects model was used for this meta-analysis to produce an overall summary, when we detected a substantial statistical heterogeneity, sufficient to expect that the underlying treatment effects differed between trials and an average treatment effect across trials was considered clinically meaningful. When heterogeneity was $< 50\%$, we used the fixed-effects model.

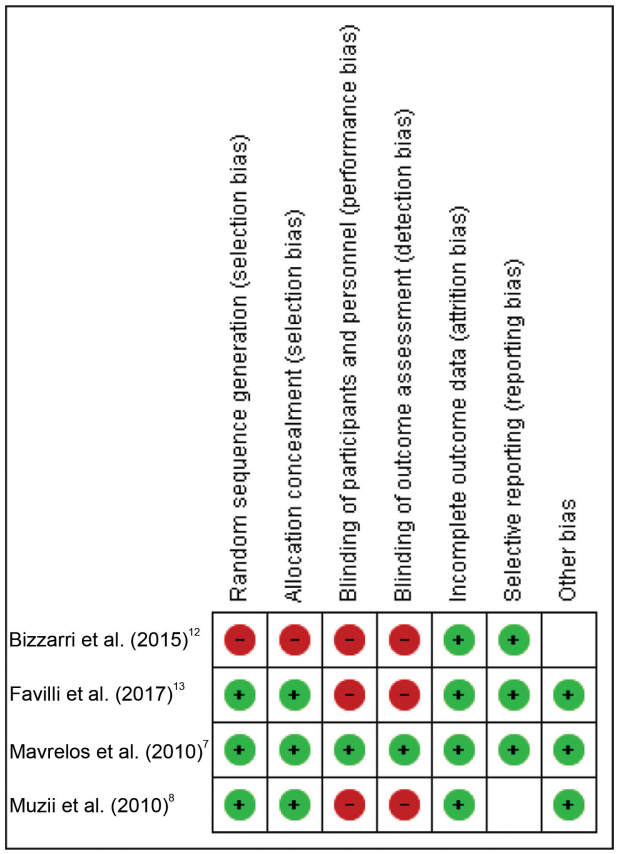

Fig. 3 Summary of risk of bias for each trials. Minus sign: high risk of bias; plus sign: low risk of bias; blank space or question mark: unclear risk of bias.

Results

Study Selection and Study Characteristics

►**Fig. 1** shows the flow diagram (PRISMA template) of information through the different phases of the review.

A total of 115 articles were found, and the ones which did not meet the criteria of the present study were excluded. A total of 25 studies were screened; 21 including nonhysteroscopic resection were excluded. Four clinical trials were therefore included in the meta-analysis. Two studies are unpublished, planned or ongoing. At least 10 trials for inclusion in a meta-analysis were not identified, so we did not explore potential publication bias (small trial bias) by generating a funnel plot and using a linear regression test. The overall risk of bias is shown on ►**Figs. 2** and **3**.

Muzii et al[8] is a multicenter randomized controlled trial of 39 women with abnormal uterine bleeding caused by submucous fibroids (1 or 2 submucous fibroids and size between 10 mm and 35 mm) and scheduled for hysteroscopic resection. The recruited women were randomized into two groups: women who received GnRH-a (triptorelin 3.75 mg) for 8 weeks prior to surgery, and women who received no

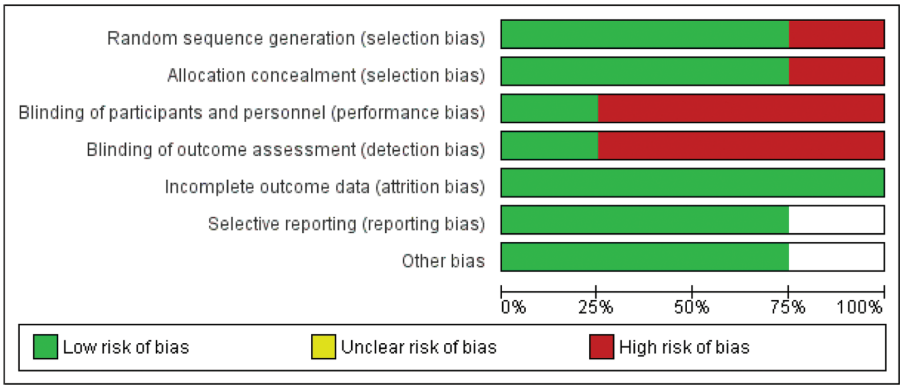

Fig. 2 Summary of risk of bias for all trials. Risk-of-bias graph about each risk-of-bias item presented as percentages across all included studies.

treatment prior to surgery. The authors followed up women at 1, 3, 6 and 12 months. In that cohort, no patients presented G2 myomas, but only G1 and G0, and the main outcome was the duration of the procedure in minutes.

Mavrelos et al[7] performed a double-blinded placebo-controlled trial at a single center in London and 47 women were analyzed with submucous fibroids (single or multiple fibroids of any size) on ultrasound requiring hysteroscopic resection. They were randomized in two groups: women who received preoperative GnRH-a (3.6 mg goserelin) for 12 weeks prior to planned surgery, and women who received placebo (identical injections; 5 ml of 1% lignocaine) for similar duration prior to surgery. After resection of the fibroid, women of both groups were reviewed in the clinic 6 weeks after the procedure.

Bizzarri et al[12] is a single-center nonrandomized controlled trial involving 46 subjects with premenopausal women with FIGO type 0, 1 or 2 myomas with diameter between 20 and 35 mm conducted in Genova.[13] Treatment allocation was decided on the basis of patient preferences, who were informed of the potential benefits and adverse effects of each hormonal therapy. Patients underwent either direct surgery (group S) or received a 3-month preoperative treatment with: triptorelin (3.75 mg intramuscular injection every 28 days; group T), letrozole (2.5 mg/day; group L) or ulipristal acetate (UPA) (5 mg/day; group U). For our meta-analysis, we considered only data of groups S and T.

Favilli et al[14] performed a single-center randomized controlled trial at Rome with 99 participants, who had the diagnosis of a single submucous myoma without any other intracavitary pathology. Patients were analyzed according to the type of myoma, G0, G1 or G2, according to the European Society for Gynecological Endoscopy classification.[14,15] Women were randomly assigned to

Box 1 Descriptive Data of the Included Trials

	Muzii et al. (2010)[8]	Mavrelos et al. (2010)[7]	Bizzarri et al. (2015)[12]	Favilli et al. (2017)[14]
Study location	Rome	London	Genova	Rome
Number of centers	3	1	1	1
Sample size	39	47	46	99
Lost to follow-up	0	7	3	15
Intervention	Preoperative GnRH analogues for 8 weeks Control: no preoperative GnRH	Preoperative GnRH analogues for 12 weeks Control: placebo (5ml of 1% lignocaine)	Preoperative GnRH analogues for 12 weeks Control: no preoperative GnRH	Preoperative GnRH analogues for 12 weeks Control: no preoperative GnRH
Medication and route of administration	Triptorelin 3.75 mg intramuscular injection	Goserelin 3.6 mg Subcutaneous injection	Triptorelin 3.75 mg intramuscular injection	Triptorelin 375 mg intramuscular injection
Outcomes	Duration of the procedure in minutes, fluid absorption, difficulty of the operation, surgeon satisfaction with the procedure, intra- and postoperative complications, postoperative pain, patient satisfaction	Completeness of fibroid resection. Duration of the TCRM, fluid deficit recorded at TCRM, resolution of symptoms postoperatively, number of subsequent fibroid related operations.	Assess the incidence of incomplete resection in the study groups. Surgical and hysteroscopy time, volume of absorbed fluid, complications, operative difficulty, postoperative patient pain and satisfaction, changes in myoma volume caused by hormonal therapies.	Assess if cold loop hysteroscopic myomectomy in a single surgical procedure was facilitated by preoperative GnRH analogue administration. Distension liquid absorption, duration of the procedure
Inclusion criteria	Submucous myomas diagnosed by transvaginal ultrasonography, with a diameter between 10 and 35 mm, and a grade G0 or G1 according to the European Society for Gynecological Endoscopy classification	History of heavy and/or irregular menstrual periods and diagnosis of a Type I or Type II submucous fibroid on ultrasound	Premenopausal women with FIGO type 0, 1 or 2 myomas with diameter between 20 and 35 mm.	Women with a diagnosis of a single submucous myoma without any other intracavitary pathology and a grade G0, G1 or G2 according to the European Society for Gynecological Endoscopy classification
Exclusion criteria	Present or past history of cancer, preoperative clinical suspicion of associated multiple or large polyps (sonographic estimate being $>$ 20 mm in largest diameter), planned associated nonhysteroscopic surgical procedures, or $>$ 2 myomas requiring hysteroscopic resection.	Not reported	Associated polyps or other pathologies requiring hysteroscopic treatment (such as uterine septa), previous incomplete myoma resection, associated nonhysteroscopic surgical procedures, $>$ 2 myomas requiring hysteroscopic resection.	Patients with multiple myomas, endometrial polyps, scheduled combined surgical procedures (hysteroscopy with laparoscopy), a present or past history of cancer, ongoing pregnancy, and a postmenopausal status.

Abbreviation: TCRM, transversal resection of myoma.
Data are presented as total number (number in the GnRH analogue group versus number in the control group).

Table 1 Primary and secondary outcomes

	Muzii et al. (2010)[8]	Mavrelo et al. (2010)[7]	Bizzarri et al. (2015)[12]	Favilli et al. (2017)[14]	Total	I^2	RR or MD (95% CI)
Sample size	39 (20 vs 19)	47 (24 vs 23)	43 (20 vs 23)	84 (42 vs 42)	213	–	–
Complete resection of the fibroid	20/20 (100%) vs 19/19 (100%)	14/24 (58.3%) vs 16/23 (69.5%)	20/20 (100%) vs 22/23 (95.6%)	31/42 (73.8%) vs 39/42 (92.9%)	85/106 (80.2%) vs 96/107 (89.7%)	74%	0.90 (0.81 to 1.00)
Operating time	M 15.9 (SD 3.1) vs M 21.3 (SD 4)	M 30.1 (SD 11.7) vs M 33.8 (SD 22.7)	M 26.4 (SD 6.4) vs M 36.7 (SD 8.4)	M 26.62 (SD 15.308) vs M 20.71 (SD 15.052)	–	82%	−3.81 [−9.75 to 2.13]
Complications*	2/20 (10%) vs 1/19 (5.2%)	1/21 (4.8%) vs 2/19 (10.5%)**	0/20 (0%) vs 0/23 (0%)	0/42 (0%) vs 0/42 (0%)	3/103 (2.9%) vs 3/103 (2.9%)	0%	0.92 [0.18 to 4.82]
Fluid absorption	M 378 (SD 137) vs M 566 (SD 199)	M 662.5 (SD 668.3) vs M 568.75 (SD 785.8)	M 340 (SD 112) vs M 457 (SD 139)	M 135.85 (SD 217.2) vs M 62.44 (SD 130.66)	–	85%	−65.90 [−207.79 to 75.99]

Abbreviations: CI, confidence interval; M, mean; MD, mean difference; RR, relative risk; SD, standard deviation.
Data are presented as total number (number in the GnRH analogue group versus number in the no-GnRH analogue group) with percentage.
*Complications (excessive intraoperative bleeding, uterine perforation, bowel injury).
**1 woman in the placebo group had abdominal myomectomy and 3 women were not operated. In the GnRH analogue group, 1 woman had abdominal myomectomy, 1 had allergic reaction and 1 was not operated.

nonpharmacologic treatment or preoperative GnRH-a treatment, where three injections of triptorelin 3.75 mg were given 28 days apart. Afterwards, they were submitted to a cold loop hysteroscopic myomectomy. Further details are provided in ►**Box 1**.

Synthesis of Results

►**Table 1** shows the pooled results for the primary and the secondary outcomes.

Although the studies have similar outlines, their results were different. Muzii et al[8] demonstrated that the use of medical treatment before hysteroscopic resection of G0–G1 10–35 mm myomas is associated with shorter operative times, less fluid absorption, and better surgeon satisfaction, with similar patient satisfaction and reduction of symptoms, compared with no preoperative medical treatment. According to these findings, Bizzarri et al[12] presented that preoperative treatment with triptorelin decreases the hysteroscopy time and the volume of fluid absorbed during hysteroscopic resection of uterine submucosal myomas with diameter between 20 and 35 mm (FIGO type 0, 1 or 2). On the other hand, Mavrelos et al[7] do not support routine administration of GnRH-a before transcervical resection of fibroid as they did not identify any benefit in such treatment (Complete resection: 58.3% in the GnRH-a group versus 69.5% in the no-GnRH-a; relative risk [RR]: 0.79; 95% confidence interval [CI]: -0.55–1.13). Favilli et al[14] showed that GnRH-a administration does not facilitate the completion of cold loop hysteroscopic myomectomy in a single surgical procedure in G2 myomas (according to the European Society for Gynecological Endoscopy classification), and it is correlated with a longer duration of the surgery.[14,15] Considering side effects, in the trial by Muzii et al,[8] patients in the GnRH pretreatment group experienced hot flushes (80% mild and 20% moderate), which were, in any case, well tolerated. Bizzarri et al[12] demonstrated that three patients interrupted the hormonal therapy because of adverse effects and requested to undergo immediate surgery, and patients treated with triptorelin and letrozole reported some adverse effects. However, they did not specify the side effects or the group to which they belong.

Meta-Analysis

The meta-analysis was done as specified in the protocol. The meta-analysis showed no statistically significant differences in the use of GnRH-a compared with the control group (RR: 0.94; 95%CI: 0.80–1.11) for complete resection of submucous myoma, as exposed in ►**Fig. 4**.

Considering the secondary outcomes, the meta-analysis showed no statistically significant difference in the use of GnRH-a compared with the group that did not use the GnRH-a when considering operative time (mean difference [MD]: -3.81; 95%CI: -3.81–2.13), fluid absorption (MD: - 65.90; 95%CI: - 9.75–2.13) or complications (RR 0.92; 95%CI: 0.18–4.82), as exposed in ►**Figs. 5**, **6** and **7**.

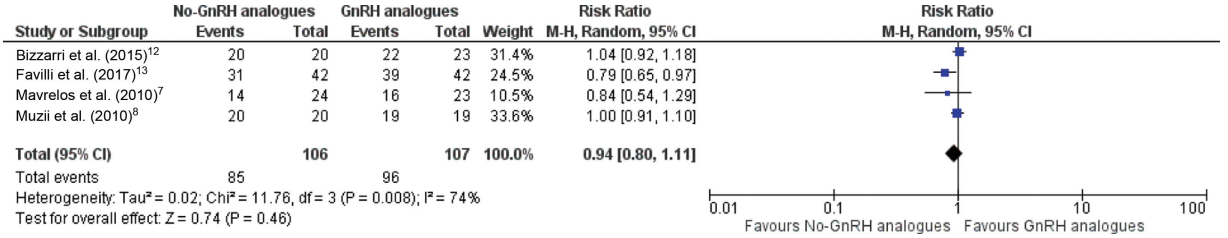

Fig. 4 Meta-analysis of included studies, for complete resection of submucous myoma.

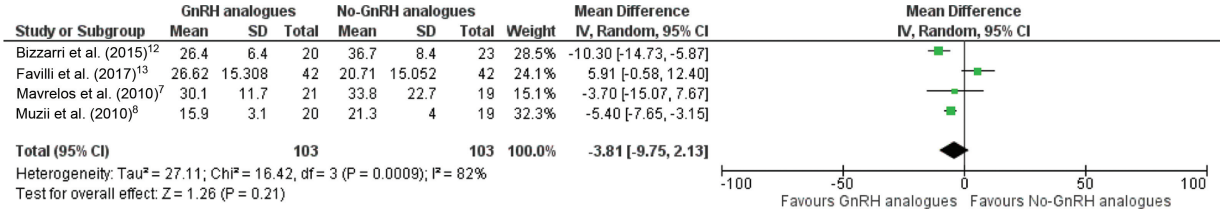

Fig. 5 Meta-analysis of included studies, for operative time (in minutes).

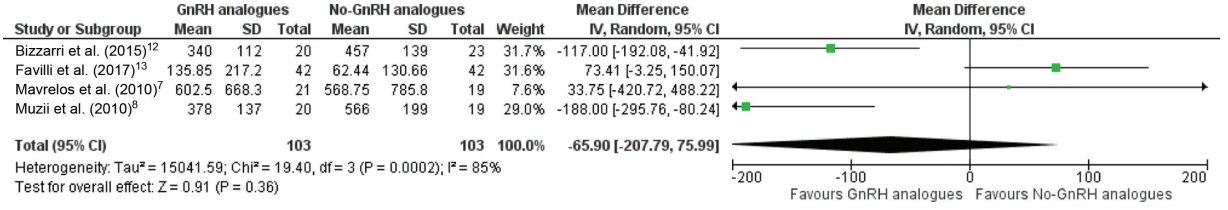

Fig. 6 Meta-analysis of included studies, for fluid absorption (in mL).

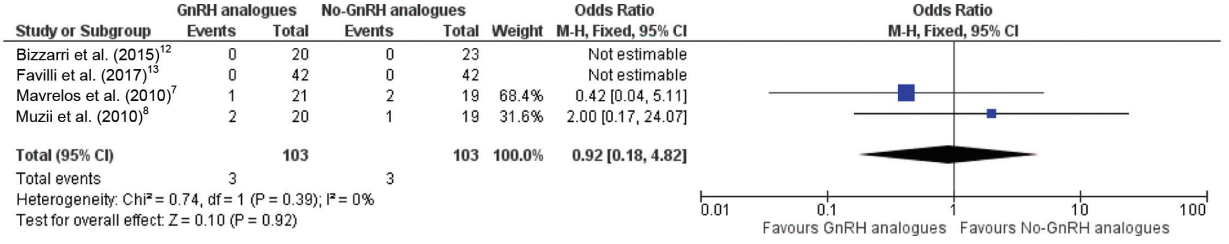

Fig. 7 Meta-analysis of included studies, for complications (excessive intraoperative bleeding, uterine perforation, bowel injury).

Discussion

Main Findings

The meta-analysis obtained after analysis and comparison of results from 4 clinical trials – Mavrelos et al,[7] Muzii et al,[8] Bizzarri et al[12] and Favilli et al[14]–including a total of 213 women, showed that there was no statistically significant difference between the group that used GnRH-a and the group that did not use it. Therefore, with regard to the primary outcome evaluated, that is, complete resection of submucous myoma, the use of GnRH-a was not effective. Our meta-analysis included level 1 data from 4 appropriately powered, well-designed clinical trials. Pooled data available to date point to a lack of efficacy of the GnRH-a pretreatment before myomectomy resection.

We also searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports and found 2 studies.

Comparison with the Existing Literature

The present meta-analysis showed no advantage of administering GnRH-a preoperatively before hysteroscopic resection of fibroids over no GnRH-a preoperatively, in accordance with Mavrelos et al,[7] Muzii et al[8] and Bizzarri et al.[12] Favilli et al[14] revealed a significantly longer duration of surgery and a greater number of repeated procedures in the GnRH-a group when compared with the control group. It is possible that Favilli et al[14] found a different result because they used electrical powered loop for the resection of the intracavitary component of the myoma and a cold loop for the cleavage plane between the myoma and the pseudocapsule and the detachment of the intramural portion of the myoma from its pseudocapsule. The other clinical trials used exclusively electrical powered loop.

Our data supports earlier findings of a meta-analysis of 2 trials, including 86 women with submucous fibroids, when preoperative GnRH-a were not more effective than placebo/no treatment in terms of symptom relief, complications and ease

of surgery. However, our study did not show benefit of GnRH-a therapy in terms of reduction in both operating time and fluid absorption, as shown in the previous meta-analysis.[9]

Fluid volume depends directly on the duration of the procedure. Another rationale for the administration of preoperative GnRH-a is a reduction of fluid deficit. A study found that preoperative administration of GnRH-a is associated with reduced fluid deficit. However, the criteria for GnRH-a administration were not listed and the operating surgeon was not blinded to the treatment, which may have introduced an element of bias.[16] Muzii et al[8] and Bizzarri et al[12] revealed that the procedure was faster in the intervention group. Therefore, they also revealed that the intervention group had less fluid absorption.

The four clinical trials had different criteria used to establish the end of the procedure.[7,8,12,14] Favilli et al[14] conducted the only clinical trial that used clearly vision of the pseudocapsule in the uterine cavity as the criterium to stop the procedure. The use of GnRh-a decreases myoma size, but at the same time causes an alteration to the structure of the pseudocapsule, masking the correct cleavage plan between the myoma and its pseudocapsule.[17] It is possible that it prolonged the procedures in the intervention group conducted by Favilli et al.[14]

As we already know, theoretically, GnRH-a pretreatment may render surgery easier, by means of a reduction of the myoma size and vascularization and possibly a thinning of the endometrium. Additional advantages of a preoperative treatment are the correction of anemia, if present, and the possibility of performing surgery at any time, because the patient is amenorrheic, with clear organization benefits.[5] A meta-analysis of RCTs comparing GnRH-a administration before abdominal myomectomy showed that women in the treatment group had significantly higher preoperative hemoglobin concentration compared with the control group. Similar benefits are also likely to occur in women scheduled for hysteroscopic surgery.[6]

On the other hand, a retrospective study affirmed that the preoperative treatment with GnRH-a can be associated with a prolonged operative time, because the step of the cervical dilation can be more uncomfortable in a hypoestrogenic patient.[18]

In contrast, a controlled study of 53 patients found that preoperative GnRH reduced operative time and the volume of distension medium used.[19] However, it is unclear from the published paper whether the treatment and control groups were balanced in terms of the morphological characteristics of the fibroids submitted to hysteroscopic resection. Moreover, they did not include women with fibroids > 3 cm in diameter, which is the group of women that we would expect to derive the maximum benefit from preoperative GnRH-a.[19]

Considering surgery complications, the meta-analysis revealed that there was no statistic difference in patients who received GnRH-a preoperatively when compared with patients who did not, in accordance with Mavrelos et al[7] and with Muzii et al.[8] The other two clinical trials used for the meta-analysis did not use the complication rates as an outcome of the study.

In the RCT conducted by Mavrelos et al,[7] one procedure was abandoned because of excessive bleeding and one was abandoned because of a fluid deficit of 1.5 L.[7] One woman who received GnRH-a suffered a uterine perforation and bowel injury that necessitated laparotomy and repair. Two women in the placebo group suffered excessive intraoperative bleeding, which was controlled by the insertion of a Foley catheter in one and by cervical suture in the other case. In the RCT conducted by Muzii et al,[8] no cases of uterine perforation or fluid overload occurred in either group. Minimal complications recorded were three cases of minor cervical tears (not requiring any suture placement), two of which occurred in the GnRH-a group.

Strengths and Limitations

One of the strengths of the present review is that we followed the Cochrane Handbook of Systematic Review for Intervention closely in conducting the present review.[10] Our meta-analysis included all studies published to date on the topic and included > 200 women. Intent-to-treat analysis was used and publication bias could not be assessed given the small (< 10) number of studies included.

We encountered a high heterogeneity in the meta-analysis of the primary outcome for complete resection of submucous myoma (74%), operative time (82%) and fluid absorption (85%). On the other hand, for complications, heterogeneity was low (0%).

Only 4 trials were included in the meta-analysis. The small number of available studies and the variation of their sample size could have decreased the forcefulness of the meta-analysis with an increased chance of bias. Other limitations of our study are intrinsic to the limitations of the included RCTs. Just one of the included studies was double-blind – Mavrelos et al.[7] Bizzarri et al[12] was a non-randomized controlled trial. Since the patients and the surgeons were not blinded, performance and detection biases could possibly creep in.

Furthermore, the outcome assessment for intraoperative parameters, such as complete resection of fibroid, depends on the experience of the surgeon. Ideally, a total resection should be confirmed by ultrasound and by the symptomatology of the patients during follow-up visits. Thus, studies should include and report ultrasound findings and follow-up of the patients to avoid biases. In our review, the included studies did not give ultrasound details in the postoperative period and long-term follow-up in descriptive manner, but Favilli et al[14] reported an outpatient diagnostic hysteroscopy 2 months after the surgical procedure. Taking in consideration that the visualization of the myoma fovea could be "subjective" and at risk of bias, a diagnostic hysteroscopy has more diagnostic power than ultrasound regarding the follow-up of residual myomas.[14]

Muzii et al[8] and Bizzarri et al[12] evaluated, respectively, myomas between 10 and 35 mm and 20 and 35 mm. Hysteroscopic resection of large fibroids may involve increased perioperative complications and/or require more than one procedure for symptomatic relief.[20]

The size of the submucous myoma may contribute to determine if the myomectomy is preferable through hysteroscopy or laparotomy. As discussed above, GnRH-a reduces

the size of the myoma. A potential use of GnRH-a is to reduce the size of larger myomas and change the access way of the myomectomy – from laparotomy to hysteroscopy – reducing trauma, hospitalization and recovery times, as well as decreasing the risk of adhesion formation.

Implications

From the data obtained by the present meta-analysis, it is observed that the GnRH-a is not effective as a pretreatment in the hysteroscopic resection of submucous fibroid, as the proportion of patients undergoing complete resection of fibroids was not affected by preoperative administration of GnRH-a. Thus, there is still insufficient evidence to support the use of this tool in practice as an attempt to reduce the incidence of surgical complications. Moreover, it might be beneficial when administered preoperatively in anemic patients.

Conclusion

From the analyzed studies, we can conclude that the preoperative use of GnRH-a seems to show a lack of efficacy to support a routine use prior to hysteroscopic resection of submucous fibroids. However, it is not possible to determine its inferiority when compared with the other methods due to the heterogeneity of existing studies and the small sample size. Future studies should preferably be blinded and define the completeness of fibroid resection – assessment of the surgeon, clinical profile of the patient pre- and postsurgery, preoperative and intraoperative effects, ultrasound follow-up and reduction in the size of larger myomas, which could possibly change the access way of the myomectomy - from laparotomy to hysteroscopy. More studies are necessary to evaluate the use of GnRH-a with this specific purpose.

Contributors

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

Conflict of Interests

The authors have no conflict of interests to declare.

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Clinical Procedures for the Prevention of Preeclampsia in Pregnant Women: A Systematic Review

Procedimentos clínicos para a prevenção de pré-eclâmpsia em gestantes: Uma revisão sistemática

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Abstract

Objective To identify the most effective procedures recommended for the prevention of preeclampsia.

Data Sources A systematic review was performed in the following databases: Pubmed/MEDLINE, CINAHL, Web of Science, Cochrane and LILACS via the Virtual Health Library (VHL). A manual search was also performed to find additional references. The risk of bias, the quality of the evidence, and the classification of the strength of the recommendations were evaluated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.

Selection of Studies In the initial search in the databases, the total number of articles retrieved was 351, and 2 were retrieved through the manual search; after duplicate articles were removed, 333 citations remained. After a thorough review of the titles and abstracts, 315 references were excluded. Accordingly, 18 articles were maintained for selection of the complete text (phase 2). This process led to the exclusion of 6 studies. In total, 12 articles were selected for data extraction and qualitative synthesis.

Data Collection The articles selected for the study were analyzed, and we inserted the synthesis of the evidence in the online software GRADEpro Guideline Development Tool (GDT) (McMaster University and Evidence Prime Inc. All right reserved. McMaster University, Hamilton, Ontário, Canada); thus, it was possible to develop a table of evidence, with the quality of the evidence and the classification of the strength of the recommendations.

Data Synthesis In total, seven studies recommended the individual use of aspirin, or aspirin combined with calcium, heparin or dipyridamole. The use of calcium alone or in combination with phytonutrients was also highlighted. All of the studies were with women at a high risk of developing preeclampsia.

Keywords
- pregnant women
- preeclampsia
- prevention and control
- maternal health
- pregnancy complications

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Conclusion According to the studies evaluated, the administration of aspirin is still the best procedure to be used in the clinical practice to prevent preeclampsia.

Resumo

Objetivo Identificar quais são as condutas recomendadas para a prevenção de pré-eclâmpsia em gestantes.

Fontes de Dados Foi feita uma revisão sistemática da literatura, e foram desenvolvidas estratégias detalhadas de busca individual nas bases de dados PubMed/MEDLINE, CINAHL, Web of Science, Cochrane e LILACS pela Biblioteca Virtual em Saúde (BVS). Uma pesquisa manual também foi realizada para encontrar referências adicionais. O risco de viés, a qualidade da evidência, e a classificação da força das recomendações foram avaliadas usando a abordagem Classificação de Recomendações, Avaliação, Desenvolvimento e Análises (*Gradings of Recommendations, Assessment, Development and Evaluations*, GRADE).

Seleção dos Estudos No total, foram encontrados 351 artigos na busca inicial nas bases de dados consultadas e 2 na busca manual; após exclusões por duplicidade, 333 artigos permaneceram. Após a leitura de títulos e resumos, 315 referências foram excluídas. Portanto, 18 artigos foram mantidos para a seleção do texto completo (fase 2); esse processo levou à exclusão de 6 artigos. Após as exclusões por incompatibilidade com os critérios de inclusão, 12 artigos compuseram a amostra.

Coleta de Dados Os artigos selecionados para o estudo foram analisados, e a digitação da síntese das evidências foi realizada no *software online* GRADEpro Guideline Development Tool (GDT) (McMaster University and Evidence Prime Inc. Todos os direitos reservados. McMaster University, Hamilton, Ontário, Canadá), o que possibilitou a elaboração de uma tabela de evidências, com a qualidade das evidências e a classificação da força das recomendações.

Síntese dos Dados No total, sete estudos recomendaram o uso individual de aspirina, ou aspirina combinada com cálcio, heparina ou dipiridamol. O uso de cálcio isolado ou em combinação com fitonutrientes também foi destacado. Todos os estudos foram realizados com mulheres com alto risco de desenvolver pré-eclâmpsia.

Conclusão De acordo com os estudos avaliados, a administração de aspirina ainda é a melhor conduta a ser utilizada na prática clínica para prevenir a pré-eclâmpsia.

Palavras-chave
- gestante
- pré-eclâmpsia
- prevenção e controle
- saúde materna
- complicações na gravidez

Introduction

Preeclampsia (PE) is a systemic disease, and much of its etiology is unknown. Evidence suggests that it is characterized by angiogenic imbalance, exaggerated inflammation and endothelial dysfunction, leading to clinical manifestations of pregnancy-specific hypertension, which usually occurs in the second half of pregnancy.[1,2]

It is one of the main causes of maternal and perinatal death, affecting 3% to 5% of pregnancies worldwide, and accounting for 25.7% of all maternal deaths in Latin America and the Caribbean.[3,4] The risk of these complications is greater when the disease has an early onset (before 34 weeks of gestation), and it is serious, as it causes restricted intrauterine growth (RIG) or fetuses that are small for the gestational age (SGA), severe maternal morbidities, and it also causes women to become more prone to develop cardiovascular risk factors. The costs for each birth with the presence of preeclampsia have been shown to increase by US$ 6,583.[5–8]

One of the major challenges for modern obstetrics is the early identification of women at a high risk of developing preterm preeclampsia (before 37 weeks of gestation). Thus, the prediction of preeclampsia is paramount in performing appropriate procedures to reduce the prevalence of the disease by modifying antenatal care and pharmacological interventions in a timely manner.[9,10]

Several clinical, biochemical and biophysical tests have been proposed to predict PE; however, none of them have proved to be useful in isolation to classify the preexisting maternal risk for PE with sufficient specificity and sensitivity for clinical use. Ideally, the predictive model should be simple, inexpensive, and easy to apply, so that it can be widely used in the clinical practice.[11]

Researchers developed a predictive model that is able to predict the risk of developing PE in the first trimester (11 weeks, 0 day - 13 weeks, 6 days), based on a combination of maternal factors that includes the mean arterial pressure (MAP), the pulsatility index (PI) of the uterine artery, and the serum placental growth factor (PlGF). This model can predict

75% (95% confidence interval [95%CI]: 70–80%) of preterm preeclampsia and 47% (95%CI: 44–51%) of term preeclampsia, with a false-positive rate (FPR) of 10%, with these data being superior to the respective values of 49% and 38% achieved by screening with maternal factors only.[12]

Accordingly, strategies to reduce the risk of pregnancy-related hypertension disorders are a global priority, and screening only makes sense if there is an effective intervention available to prevent the disease and control the unfavorable outcomes.[13,14] Therefore, the present study sought to answer the following question: what are the most up-to-date and effective procedures to prevent PE? The aim of the present review was to identify the most effective procedures recommended for the prevention of PE.

Methods

Type of Study

A systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15]

Eligibility Criteria

The inclusion criteria were 1) randomized controlled trials (RCTs), systematic reviews/meta-analyses, and prospective or retrospective cohort studies 2) that included pregnant women of all ages, with a single pregnancy and without preeclampsia in the current gestation, 3) which reported the outcome of interest (prevention and control of PE). There were no language restrictions. Articles published between the years of 2013 and 2018 were included. Studies were excluded due to the following reasons: they did not cover the topic; and studies that were letters, abstracts of congresses, personal opinions, chapter of books, descriptive studies, case reports, or case series, study protocols and qualitative studies.

Information Sources and Search Strategy

The studies were identified through a search strategy adapted for each electronic database: PubMed/MEDLINE, CINAHL, Web of Science, Cochrane and LILACS via the Virtual Health Library (VHL). All of the electronic database searches were performed on December 14, 2018. In a complementary way, a manual search was performed on the reference lists of the selected articles, to ensure that any additional references that might not have been retrieved in the electronic search were duly found. To perform the searches in the electronic databases, the following medical subject headings (MESH) were used: *pregnant women*, *preeclampsia*, *prevention and control*; we also used the AND Boolean operator to search for the combination (*pregnant women AND preeclampsia AND prevention and control*).

Selection of the Studies

After collecting all of the references, duplicate articles were deleted using a free online bibliographic reference manager (EndNote Web). The selection of the studies was performed in phases. In phase 1, two investigators independently examined the titles and abstracts of potentially relevant studies and selected articles that appeared to meet the inclusion criteria based on their abstracts. In phase 2, the same reviewers read the full text of all of the independently-selected articles and excluded studies that did not meet the inclusion criteria. Any disagreements, whether in the first or second phases, were solved through discussions between the two investigators. In the event of failure to reach a consensus, a third reviewer was called to make a final decision.

The studies that were excluded and the reasons for exclusion are presented in ►**Fig. 1**.

Data Collection Process

Two investigators independently collected data from the articles, including: study characteristics (references, year of publication, objective), population characteristics (sample size, gestational age), procedure characteristics (study design, follow-up period) and main results.

Summary of the Measures

The primary outcome of interest in the study was the prevention of PE. In addition, fetal outcomes (preterm delivery, premature rupture of membranes, restricted intrauterine growth, Apgar score, and fetal/neonatal death) were also considered as secondary outcomes.

Risk of Bias in the Studies and Classification of the Strength of the Recommendations

The quality of the evidence and the classification of the strength of the recommendations were evaluated through the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.[16] The synthesis of the evidence was digitalized using the online software GRADEpro Guideline Development Tool (GDT) (McMaster University and Evidence Prime Inc. All right reserved. McMaster University, Hamilton, Ontário, Canada), which made it possible for us to develop the evidence table. The criteria for this evaluation were study design, risk of bias, inconsistency, indirect evidence, inaccuracy, possible publication bias, whether the study had a large effect size, the potential confounding factors, and the dose–response gradients of the procedures. With this, the quality of the evidence was characterized as high, moderate, low or very low.

Results

Selection of the Studies

In phase 1 of the study selection, 351 citations were identified in the 5 databases consulted. The manual search from the reference lists of the identified studies provided two additional studies. After duplicate articles were removed, 333 citations remained. After a thorough review of the titles and abstracts, 315 references were excluded. Accordingly, 18 articles were maintained for selection of the complete text (phase 2). This process led to the exclusion of six studies (►**Fig. 1**). In total, 12 articles were selected for data extraction and qualitative synthesis.

Characteristics of the Studies

Of the twelve studies selected for the present review, three of them used only aspirin, four used aspirin combined with

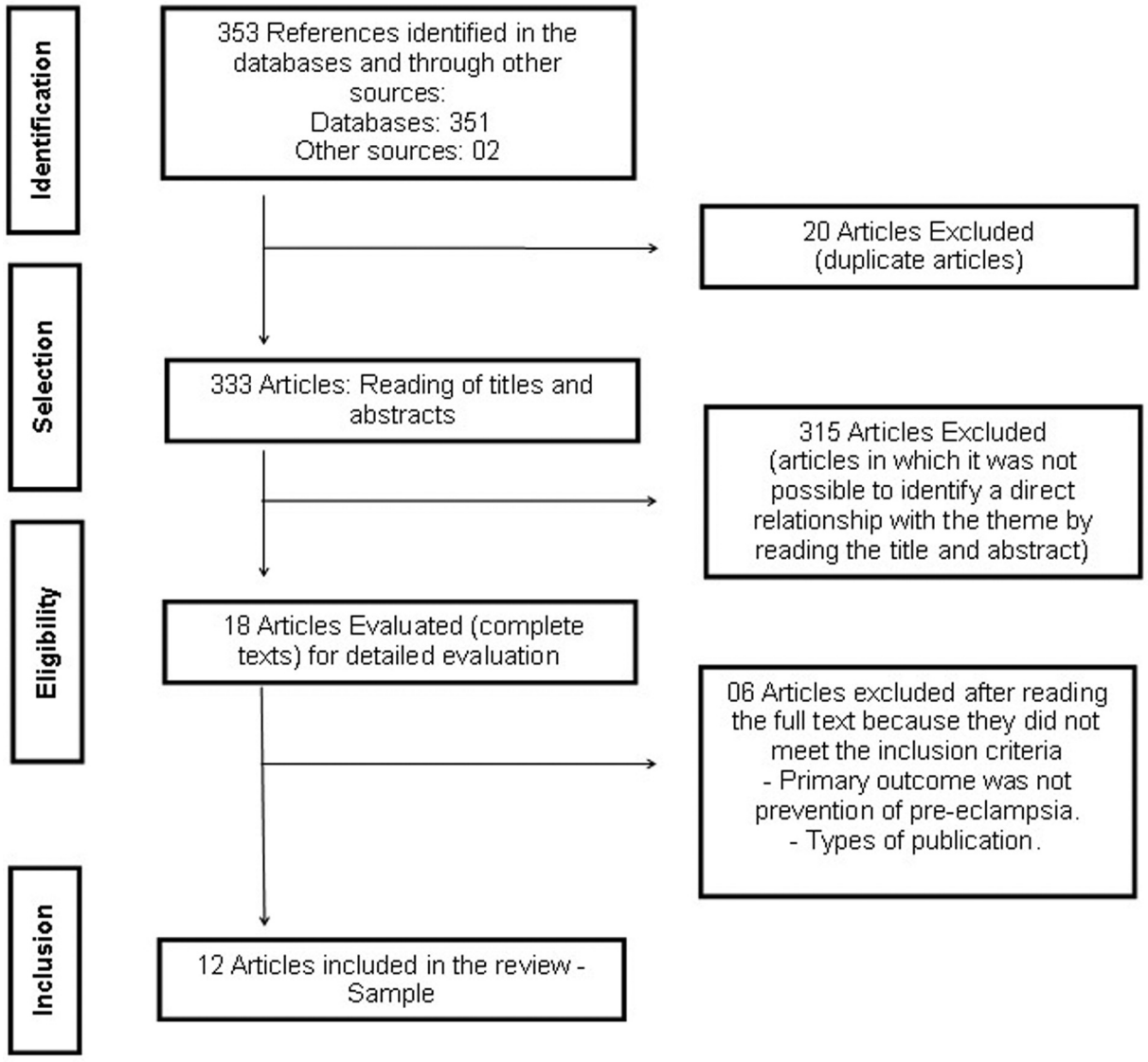

Fig. 1 Flowchart showing the results of the database search, the selection, and the inclusion of original articles in the systematic review.

calcium, heparin or dipyridamole, while the others used only calcium or calcium combined with phytonutrients, L-arginine, heparin or pravastatin as procedures for the prevention of PE. Most studies included women at a high risk of developing PE in their samples; for this, those who had at least one risk factor for the disease were considered at a high risk of developing PE; one of the risk factors analyzed was pregnant women with systemic hypertension before pregnancy, aiming to evaluate superimposed PE.

The descriptive characteristics of the studies are summarized in **Chart 1**.

Risk of Bias in the Studies and Classification of the Strength of the Recommendations

The quality of the evidence of the results evaluated through the GRADE system was classified as high certainty, moderate certainty, low certainty and very low certainty (**Chart 2**).

Most of the studies classified as high-certainty were those that used the administration of aspirin individually as the procedure. The other high-certainty studies used L-arginine, phytonutrients and aspirin with calcium, and they demonstrate that further studies are unlikely to change the confidence in the estimate of the effect of these findings, which allows us to have confidence in these results. Among the high-certainty studies, the use of phytonutrients was not statistically significant in the reduction of the risk of developing PE, a fact that discourages their isolated use as a preventive measure.

One study[20] involving the addition of low-molecular-weight heparin (LMWH) or unfractionated heparin to a low dose of aspirin and one[21] that used a low dose of aspirin (75 mg) were moderately certain, indicating that additional studies should be performed, and are likely to have an impact on the confidence in the estimate of the effect, and may

Chart 1 Characteristics of the included articles

Reference	Study Design	Objective	Sample	Procedure	Main results
Rolnik et al (2017)[5]	Randomized controlled trial	To evaluate whether low-dose aspirin during pregnancy reduces the risk of developing preeclampsia (PE) before 37 weeks of pregnancy in high-risk women according to an individual-risk calculation algorithm.	798 participants in the aspirin group; 822 in the placebo group.	Aspirin at a dose of 150 mg per day, administered from the 11th to the 14th gestational weeks until the 36th week.	Preterm PE occurred in 13 out of the 798 participants (1.6%) in the aspirin group, compared with 35 out of 822 (4.3%) participants in the placebo group, a 62% reduction (adjusted odds ratio [OR] in the aspirin group: 0.38; 95% confidence interval (95%CI): 0.20–0.74; $p = 0.004$).
Camarena Pulido et al (2016)[10]	Randomized controlled trial	To estimate the effectiveness and safety of L-arginine to prevent PE in high-risk patients.	L-arginine group ($n = 50$); placebo group ($n = 50$).	L-arginine 3 g once daily orally in 600 mg capsules. Beginning at the 20th week of gestation with follow-up every 3 weeks during pregnancy and 2 weeks after birth.	The incidence of severe PE was higher in the placebo group ($n = 7$) than in the L-arginine group ($n =$;, $p = 0.02$; 95%CI: 0.001–0.031)
Costantine et al (2016)[3]	Randomized controlled trial	To evaluate the maternal-fetal safety and pharmacokinetic parameters of pravastatin when used in pregnant women at high risk of developing PE.	Pravastatin group ($n = 11$); placebo group ($n = 10$).	Pravastatin 10 mg, 1 capsule orally per day until birth. Beginning in the 1st trimester (weeks 12 to 16) and follow-up until birth.	There were 4 cases of PE in the placebo group and none in the pravastatin group, with 5 preterm births before 37 weeks in the placebo group compared with 1 in the pravastatin group.
Talari et al (2014)[9]	Randomized controlled trial	To determine whether the treatment with acetylsalicylic acid (ASA) reduces the incidence of PE among pregnant women with abnormal uterine artery flow.	Aspirin group ($n = 40$); placebo group ($n = 40$).	Aspirin 80 mg, 1 tablet daily after lunch. Beginning between 12 and 16 weeks of gestation, with no clear follow-up time.	The aspirin group presented an $\sim$ 11-fold reduced risk of developing PE. There was a significant difference between the aspirin and placebo groups in the incidence of PE (2.5% versus 22.5% respectively).
Souza et al (2014)[14]	Randomized controlled trial	To test the hypothesis that the administration of a combination of low-dose aspirin and calcium would reduce the risk of superimposed PE in women at a high risk of developing this condition due to chronic hypertension and abnormal uterine artery Doppler in the second trimester.	Aspirin and calcium group ($n = 23$); placebo group ($n = 26$).	Pills containing 100 mg of aspirin and clear plastic envelopes containing 2 g of elemental calcium in the form of calcium carbonate. The placebo and powder pills were combined with the study supplements for taste, color, and size. Follow-up since the patient's hospital admission (between weeks 20 to 27) up to 6 weeks postpartum.	The rate of superimposed PE was 28.6% lower among women receiving aspirin and calcium than in the placebo group (52.2% versus 73.1% respectively); however, this difference did not reach statistical significance ($p = 0.112$).
Parrish et al (2013)[27]	Randomized controlled trial	To provide daily dietary supplements containing antioxidants and phytonutrients to pregnant women to reduce the incidence of PE.	Supplement group ($n = 349$); placebo group ($n = 335$).	Phytonutrient (the contents of the antioxidant supplement capsule consisted of a blend of fruit and vegetable juice powder concentrate). Each capsule contained 7.5 mg of β-carotene, 234 mg of vitamin C, 30 mg of vitamin E, 420 mg of folate, and 60 mg of calcium. From the 12th week of gestation until birth.	No difference was observed in the incidence of PE between the phytonutrient and placebo groups: 15.9% versus 16.3%, respectively (relative risk [RR]: 0.97; 95% CI: 0.56–1.69).
Roberge et al (2018)[25]	Systematic review with meta-analysis	To examine the effect and the dose of aspirin on the prevention of preterm and term PE in relation to the gestational age at the beginning of the treatment.	16 studies (18,907 participants).	Aspirin alone or in combination with dipyridamole with another group receiving placebo or no treatment. Gestational age at the start of aspirin use: $\leq$16 and $>$ 16 weeks of gestation. Daily dose of the drug: $<$ 100 mg and $\geq$100 mg.	The administration of aspirin was associated with a reduction in the risk of developing preterm PE (RR: 0.62; 95%CI: 0.45–0.87); however, there was no significant effect on term PE (RR: 0.92, 95%CI: 0.70–1.21). The reduction in preterm PE was confined to the subgroup in which aspirin was initiated before or at 16 weeks gestation, and at a daily dose of $\geq$100 mg. There was no significant reduction in the risk of developing

(*Continued*)

Chart 1 (*Continued*)

Reference	Study Design	Objective	Sample	Procedure	Main results
					preterm PE in the subgroup in which aspirin was started before or at 16 weeks gestation and at a daily dose < 100 mg (RR: 0.59; 95%CI: 0.29–1.19) or in the subgroup in which aspirin was initiated after 16 weeks of gestation, regardless of whether the dose was ≥100 mg (RR: 0.88; 95%CI: 0.54–1.43) or < 100 mg (RR: 1.00; 95%CI: 0.80–1.25).
Roberge et al (2017)[19]	Systematic review with meta-analysis	To estimate the impact of aspirin dosing on the prevention of PE, severe PE and restricted fetal growth (RFG).	45 studies (20,909 participants).	Aspirin with or without dipyridamole. The dose of aspirin ranged from 50 mg to 150 mg per day, including 2 studies that combined 300 mg of dipyridamole with aspirin. The follow-up period was not clear.	Aspirin, when started before the 16th gestational week, was associated with a significant reduction in the prevalence of PE, severe PE, and RFG, with a significant dose–response relationship.
Roberge et al (2016)[20]	Systematic review with meta-analysis	To estimate the impact of low-molecular-weight heparin (LMWH) or unfractionated heparin on the low dose of aspirin initiated before or at16 weeks of gestation in relation to the prevalence of PE and birth of newborns small for gestational age (SGA).	8 studies (885 participants).	Three RCTs used dalteparin, two used enoxaparin, another two did not specify the type of LMWH, and one used unfractionated heparin. The dose of aspirin ranged from 75 mg to 100 mg/day. The follow-up period was not made clear.	In women with a history of PE, the addition of LMWH or unfractionated heparin to a low dose of aspirin reduced the risk of developing PE (3 RCTs, $n = 379$; RR: 0.54; 95% CI: 0.31–0.92; $p = .03$), and SGA (2 RCTs, $n = 363$; RR: 0.54; 95%CI: 0.32–0.91; $p = .02$).
Gan et al (2016)[21]	Systematic review with meta-analysis	To comparatively evaluate the efficacy of low-dose aspirin in the prevention of PE and related fetal complications in East Asian and non-East Asian pregnant women at risk of developing PE.	21 high-quality RCTs were included in the meta-analysis, 3 studies from East Asia, and 18 non-East Asian studies.	Aspirin in low doses (75 mg). The follow-up period was not made clear.	Low-dose aspirin significantly reduced the risk of developing PE in East Asian (OR = 0.20; 95%CI: 0.11–0.35) and non-East Asian women (OR = 0.84; 95%CI: 0.77–0.92).
Rodger et al (2014)[26]	Systematic review with meta-analysis	To compare LMWH *versus* non-LMWH for the prevention of recurrent placental-mediated pregnancy complications.	6 studies (848 participants).	LMWH *versus* non-LMWH. The follow-up period was not made clear.	The primary outcome, being a composite of PE, birth of a an SGA newborn (percentile < 10), placental abruption, or termination of pregnancy > 20 weeks, was significantly reduced by LMWH, with an RR reduction of 0.52 (95%CI: 0.32–0.86; $p < 0.01$)
Hofmeyr et al (2014)[13]	Systematic review	To determine the lowest effective dose of calcium supplementation to reduce the effects of preeclampsia.	9 studies.	Low-dose calcium. The follow-up period was not made clear.	The 4 trials with low risk of bias, all with women at a high risk of developing PE, showed a consistent reduction in PE (365 women; RR: 0.25; 95% CI: 0.12–0.50). However, in three of these trials there was co-intervention with linoleic acid (two trials) or antioxidants.

change the estimate. The study[13] that used calcium for the prevention of PE presented low certainty, even though this drug is already used for this purpose, and is well accepted in populations with calcium deficiency in the diet. This indicates that further studies are likely to have a significant impact on the confidence in the estimate of the effect, and may change the estimate.

Finally, only two studies[3,23] were classified as very-low-certainty, suggesting that the estimation of the effect of the administration of pravastatin and heparin as the procedure for the prevention of PE is very uncertain. Perhaps this was due to the fact that these studies had small samples, but statistically significant results, and due to the fact that these procedures are still not used much for this purpose.

Chart 2 Risk of bias in the studies and classification of the strength of the recommendations

Reference	Outcomes	Potential absolute effects* (95%CI)		Relative effect (95%CI)	Number of participants (studies)	Certainty in evidence (GRADE)
		Comparison group - risk	Intervention group – risk			
Rolnik et al (2017)[5]	Preterm preeclampsia occurred in 13 out of the 798 participants (1.6%) in the aspirin group, compared with 35 out of 822 (4.3%) in the placebo group, when aspirin was started between the 11th and 14th gestational weeks and continued until the 36th week.	4 per 100	2 per 100 (1 to 3)	OR: 0.38 (0.20 to 0.74)	1620 (RCT)	⊕⊕⊕⊕ HIGH
Camarena Pulido et al (2016)[10]	The incidence of severe preeclampsia was greater in the placebo group ($n = 7$) than in the L-arginine group ($n = 1$; $p = 0.02$; 95%CI: 0.001–0.031). Follow-up: since 1st trimester until birth.	23 per 100	0 per 100 (0 to 1)	Not estimable	96 (RCT)	⊕⊕⊕⊕ HIGH
Costantine et al (2016)[3]	Four subjects in the placebo group developed pre-eclampsia (3 out of 4 with severe illness) compared with none in the pravastatin group. Follow-up: variation from the 1st week to the 40th week.	40 per 100	0 per 100 (0 to 0)	Not estimable	21 (RCT)	⊕○○○ VERY LOW[a,b]
Talari et al (2014)[9]	There was a significant difference between the aspirin and placebo groups in the incidence of preeclampsia (2.5% versus 22.5% respectively). The aspirin group presented an ∼ 11-fold reduced risk of developing preeclampsia.	25 per 100	79 per 100 (31 to 97)	OR: 11.323 (1.360 to 94.248)	80 (RCT)	⊕⊕⊕⊕ HIGH
Souza et al (2014)[14]	The rate of superimposed preeclampsia was 28.6% lower among women receiving aspirin and calcium when compared to the placebo group (52.2 versus 73.1% respectively); however, this difference did not reach statistical significance ($p = .112$). Follow-up: variation from hospital admission to birth.	73 per 100	0 per 100 (0 to 0)	Not estimable	49 (RCT)	⊕⊕⊕⊕ HIGH[a,b]
Parrish et al (2013)[27]	No difference was observed in the incidence of preeclampsia between the phytonutrient and placebo groups (15.9% versus 16.3% respectively). Follow-up: variation from the 12th week to birth.	33 per 100	32 per 100 (18 to 55)	OR: 0.97 (0.56 to 1.69)	267 (RCT)	⊕⊕⊕⊕ HIGH
Roberge et al (2018)[25]	The administration of aspirin was associated with a reduction in the risk of developing preterm pre-eclampsia (RR: 0.62; 95%CI: 0.45–0.87); however, there was no significant effect on term preeclampsia (RR: 0.92; 95%CI: 0.70–1.21).	0 per 100	0 per 100 (0 to 0)	OR: 0.62 (0.45 to 0.87)	(16 RCTs)	⊕⊕⊕⊕ HIGH
Roberge et al (2017)[19]	Aspirin was associated with a significant reduction in the prevalence of preeclampsia, severe preeclampsia and fetal growth restriction, with a significant dose–response relationship when initiated before the 16th week of gestation.	0 per 100	0 per 100 (0 to 0)	OR: 0.57 (0.43 to 0.75)	(45 RCTs)	⊕⊕⊕⊕ HIGH
Roberge et al (2016)[20]	The addition of low-molecular-weight heparin or unfractionated heparin to low dose aspirin reduced the risk of developing preeclampsia.	0 per 100	0 per 100 (0 to 0)	OR: 0.54 (0.31 to 0.92)	(8 RCTs)	⊕⊕⊕○ MODERATE[c]
Gan et al (2016)[21]	The low dose of aspirin (75 mg) significantly reduced the risk of developing preeclampsia in East Asian and non-East Asian women.	0 per 100	0 per 100 (0 to 0)	OR: 0.20 (0.11 to 0.35)	(21 RCTs)	⊕⊕⊕○ MODERATE
Rodger et al (2014)[26]	The primary outcome, being a composite of pre-eclampsia, birth of a newborn small for gestational age (percentile < 10), placental abruption, or termination of pregnancy > 20 weeks, were significantly reduced by low-molecular-weight heparin, with an RR reduction of 0.52 (95%CI: 0.32–0.86; $p < .01$)	0 per 100	0 per 100 (0 to 0)	OR: 0.52 (0.32 to 0.86)	(6 RCTs)	⊕○○○ VERY LOW[a,b]
Hofmeyr et al (2014)[13]	The four trials with low risk of bias, all in women at a high risk of developing preeclampsia, showed a consistent reduction in the incidence of pre-eclampsia, even with calcium started at the end of the pregnancy.	0 per 100	0 per 100 (0 to 0)	RR: 0.38 (0.28 to 0.52)	(9 RCTs)	⊕⊕○○ Low

Abbreviations: 95%CI, 95% confidence interval; GRADE, Gradings of Recommendations, Assessment, Development and Evaluations; OR, odds ratio; RCT, randomized controlled trial; RR, risk ratio.

Notes: *The risk in the intervention group (and its 95% confidence interval) is based on the risk assumed for the comparison group and the relative effect of the intervention (and its 95% confidence interval).

[a]Inaccurate due to not presenting confidence interval.

[b]Highly suspicious due to sample size, form of sample selection, and for presenting statistically significant results.

[c]Due to the heterogeneity of the selected studies.

Discussion

The present review included 12 studies that addressed different procedures for the prevention of PE, and they were published in the previous 5 years. Most studies used the administration of aspirin as the procedure to prevent PE. Three of them used only aspirin[5,9,21], and another four[14,19,20,25] used aspirin combined with calcium, heparin or dipyridamole. These findings are in line with the international recommendations for women at a high risk of developing PE.[17,18]

In all of the studies, the expected outcome, the prevention of PE, was achieved. This fact confirms the efficacy of aspirin when administered to pregnant women at a high risk of developing PE when it is started prior to the 16th week of pregnancy, preferably between weeks 11 and 14. Regarding the ideal dose, the studies have administered doses between 50 mg and 150 mg, and most suggest that the dose should be higher than 100 mg in order to achieve satisfactory effects.[5,9,14,19–21]

The recommendation for the use of aspirin is associated with uteroplacental underperfusion due to impaired placentation, placental vascular lesions, and incomplete transformation of the spiral uterine arteries.[14] Approximately 30 thousand women have already participated in RCTs with aspirin, thus making this one of the most intensely studied drugs in obstetrics.[22] Physiologically, reduced placental blood flow is thought to lead to the activation of the coagulation cascade, platelet aggregation and endothelial dysfunction, which may be partially mediated by prostacyclin and thromboxane A2, so that aspirin selectively reduces thromboxane A2 without significantly affecting prostacyclin levels and also inhibiting placental aggregation.[21]

The low dose of aspirin inhibits the biosynthesis of platelet thromboxane A2 by altering the imbalance between thromboxane A2 and prostacyclin, and is therefore thought to favor vasodilation, which assists in the reduction of blood pressure and the prevention of PE.[23] This mechanism has achieved good results in practice, more in reducing the incidence of PE in high-risk women than in those of low and moderate risk.[14]

It is recommended that antiplatelet agents be administered to pregnant women at a high risk of developing PE or to those with chronic hypertension, as they lead to a wide reduction in adverse pregnancy outcomes for both the mother and the newborn.[24] The results of the systematic reviews showed that antiplatelet agents are associated with a reduction in the risk of developing preterm PE (relative risk [RR]: 0.62; 95%CI: 0.45–0.87), when initiated before the 16th gestational week, and they are also associated with a significant reduction in the prevalence of PE, severe PE, and restricted intrauterine growth.[19,25]

For LMWH, a meta-analysis showed that heparin alone reduced the risk of: severe or early onset of PE (1.7% versus 13.4%; RR: 0.16; 95%CI: 0.07–0.36), preterm birth (< 37 weeks; 32.1% versus 47.7%; RR: 0.77; 95%CI: 0.62–0.96) and SGA newborns (10.1% versus 29.4%; RR: 0.42; 95%CI: 0.29–0.59), without a significant effect on gestational termination (> 20 weeks) (1.9% versus 5.3%; RR: 0.41; 95% CI: 0.17–1.02).[26]

The second most frequent procedure in the selected studies was the prescription of calcium, although administered alone it obtained low certainty.[13] In the other studies[14,27], calcium was combined with other medications, such as phytonutrients and aspirin, both of which obtained high certainty.

Calcium is also used for the prevention of PE because there is epidemiological, clinical and laboratory evidence that indicates the association of dietary calcium deficiency with hypertensive disorders of pregnancy.[13] Like aspirin, calcium is recommended by international societies, and the doses range from 1.5 g to 2.0 g of elemental calcium daily for pregnant women residing in areas with low dietary intake of calcium.[17,18]

One systematic review[28] highlighted calcium supplementation (1 g to 2 g/day) for the prevention of PE, and found that calcium supplementation significantly reduces the risk (between 55% and 64%) in women with low dietary calcium intake. In addition, calcium supplements have a significant protective effect on maternal mortality and severe morbidity and premature delivery, with a tendency to reduce the risks of low birth weight and stillbirth.[24]

Another procedure found in one study[27] was the use of phytonutrients for the prevention of PE. The contents of the antioxidant supplement capsule consisted of a blend of fruits and vegetable juice powder concentrate derived from acerola, cherry, apple, beetroot, broccoli, cabbage, carrot, blackberry, kale, orange, peach, papaya, parsley, pineapple, spinach and tomato, with each capsule providing 7.5 mg of β-carotene, 234 mg of vitamin C, 30 mg of vitamin E in the form of RRR-α-tocopherol, 420 mg of folate, and 60mg of calcium. It was initiated in the 12th week of gestation, and the use was maintained until birth.[27] This study,[27] even with high certainty, found no difference between the phytonutrient and placebo groups in the prevention of PE, discouraging its use in the clinical practice.

In relation to the administration of pravastatin and L-arginine, both are innovative procedures that are little used in the prevention of PE. However, their real benefits are still unclear, as studies are still incipient. In the present review, the studies[3,10] regarding their administration were classified as very-low-certainty and high-certainty respectively. Pravastatin (10 mg) is a hydrophilic statin used to lower serum cholesterol and prevent cardiovascular disease. Some of the main characteristics of PE are angiogenic imbalance, exaggerated inflammation, and endothelial dysfunction, which lead to clinical manifestations of hypertension, proteinuria and target-organ damage. Furthermore, although PE is a disease exclusive to pregnancy, it has pathogenic similarities and is associated with many risk factors for cardiovascular disease in adults.[3]

The use of statins in the treatment of PE has taken a leading role in recent years. In particular that of pravastatin, with many studies and strong scientific evidence supporting its use as the statin of first therapeutic option for the treatment of early and

severe forms, which is in disagreement with the findings of the present review.[29] The ability of statins to reverse the angiogenic imbalance that is characteristic of PE, and to restore endothelial dysfunction in animal models, demonstrates the need for clinical trials that further assess the efficacy of pravastatin.[29,30]

Unlike pravastatin, L-arginine (3 g) was classified as high-certainty. L-arginine is a basic amino acid nitric oxide precursor that has the ability to dilate vessels and improve blood flow and circulation.[10]

In a study[10] included in the present review, the number of pregnant women with severe PE was higher in the placebo group; in addition, the systolic blood pressure, the diastolic blood pressure and the mean arterial pressure were significantly lower in the L-arginine group compared with the placebo group. This demonstrates that the oral treatment with 3 g per day of L-arginine has a significant effect on the prevention of PE in high-risk patients, as well as on the ability to avoid more severe outcomes.

The cost of L-arginine is high compared with that of aspirin; however, the benefits of L-arginine in the prevention of PE exceed the cost of treating PE. Furthermore, L-arginine showed good results when administered to patients with 19 to 20 weeks of gestation. L-arginine therapy may be important because many patients with PE have their first consultation with a physician when it is too late for other treatments, such as the one with aspirin, to be effective.

Although there was no limit to the type of conduct for the prevention of PE, to obtain more publications on the subject, none of the studies verified the relationship between non-medicated treatment and the prevention of PE. Moreover, we found no studies that evaluated women classified as low risk for PE, and the conduct for this population.

Conclusion

Based on the studies included in the present review, the administration of aspirin is considered the best procedure for the prevention of PE in high-risk women, which corroborates the results of several studies published in recent years. Further studies are needed to identify and test other medications and their benefits during pregnancy in the prevention of adverse maternal and perinatal outcomes.

Conflict of Interests

The authors have no conflict of interesst to declare.

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Coronavirus 2019, Thrombocytopenia and HELLP Syndrome: Association or Coincidence?

Coronavírus 2019, trombocitopenia e síndrome HELLP: Associação ou coincidência?

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Abstract

The present report describes the case of a 31-year-old primigravida, with dichorionic twins at 31 weeks. She presented with history of myalgia, jaundice, and abdominal discomfort. No flu-like symptoms as fever or cough. She was not aware of exposure to COVID-19. Normal blood pressure and O_2 saturation. Laboratory tests showed platelet count of 218,000 mm^3, alanine aminotransferase (ALT) 558 IU and serum creatinine 2.3 mg/dl. Doppler ultrasound in one twin was compatible with brain sparing. Partial hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome was the hypothesis, and a cesarean section was performed. On day 2, the white-cell count reached 33,730, with decreased consciousness and mild respiratory distress. Tomography revealed both lungs with ground-glass opacities. Swab for COVID-19 polymerase chain reaction (PCR) was positive. Thrombocytopenia in patients with COVID-19 appears to be multifactorial, similar to what occurs in preeclampsia and HELLP syndrome. We assume that the synergism of these pathophysiological mechanisms could accelerate the compromise of maternal conditions and could be a warning to the obstetric practice.

Keywords

- preeclampsia
- HELLP syndrome
- thrombocytopenia
- coronavirus infections
- pregnancy complications

Resumo

O presente relato descreve o caso de uma gestante de 31 anos, gemelar dicoriônica com 31 semanas, com queixa de mialgia, icterícia e desconforto abdominal. A paciente não apresentava sintomas gripais como febre ou tosse e não tinha conhecimento de exposição ao COVID-19. Pressão arterial e saturação de oxigênio normais. Os exames laboratoriais apresentaram contagem de plaquetas de 218,000 mm^3, ALT 558 IU e creatinina 2.3 mg/dl. Doppler compatível com centralização de um dos fetos. Síndrome

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Palavras-chave
- pré-eclâmpsia
- síndrome HELLP
- trombocitopenia
- infecções por coronavírus
- complicações na gravidez

de *hemolysis, elevated liver enzymes, low platelet count* (HELLP) parcial foi a hipótese diagnóstica inicial e a cesariana foi realizada. No segundo dia, a paciente apresentou leucócitos de 33.730 com queda do nível de consciência e desconforto respiratório leve. A tomografia revelou opacidade pulmonar em vidro fosco bilateralmente. A pesquisa de COVID-19 por *polymerase chain reaction* (PCR)/swab teve resultado positivo. Trombocitopenia em pacientes com COVID-19 é multifatorial, semelhante ao que ocorre na pré-eclâmpsia e na síndrome HELLP. Acreditamos que o sinergismo da fisiopatologia das doenças em questão pode acelerar o comprometimento materno e deve servir de alerta para a prática obstétrica.

Introduction

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), produces a respiratory and systemic illness. It can progress to a severe form of pneumonia in 10 to 15% of patients and lead to critical illness, with acute respiratory distress, multi-organ failure and eventually intravascular coagulopathy. To identify these patients and optimize care, biomarkers are urgently needed for actively monitoring illness severity.[1]

Lippi et al[1] showed that platelet count is a simple and readily available biomarker, which is independently associated with disease severity and risk of mortality in the intensive care unit (ICU). Besides, thrombocytopenia correlates with higher disease severity scores, and it was reported to occur in up to 55% of patients and was identified as a significant risk factor for mortality.[1]

Preeclampsia is a complex medical disorder; worldwide, each year, it is responsible for $>$ 500,000 fetal and neonatal deaths and $>$ 70,000 maternal deaths. Preeclampsia can deteriorate rapidly and without warning.[2] Proteinuria is not mandatory for a diagnosis of preeclampsia. Rather, this is diagnosed by the presence of de novo hypertension after 20 weeks' gestation accompanied by proteinuria and/or evidence of maternal acute kidney injury, liver dysfunction, neurological features, hemolysis or thrombocytopenia, or fetal growth restriction. Preeclampsia may develop or be recognized for the first time intrapartum or early postpartum in some cases.[2]

Hemolysis, elevated liver enzymes, low platelet count (HELLP) is the combination of all or some of hemolysis, elevated liver enzymes and thrombocytopenia and is often referred to as the HELLP syndrome. For clinicians familiar with the management of preeclampsia, this constellation of abnormalities signifies a more serious part of the spectrum of this disorder.[2]

Case Report

A 31-year-old primigravida from Guarulhos, SP, Brazil, with dichorionic twins at 31 weeks, presented at the emergency room with 1-day history of general body pain (myalgia), jaundice, darkening of the urine and diffuse abdominal discomfort. She had no medical history, normal prenatal visits, and had received aspirin and calcium. She had no flu-like symptoms, including fever and cough, nor difficulty breathing and was not aware of exposure to COVID-19. She was afebrile. Her respiratory rate was 16/minute, blood pressure of 110×60 mm Hg and O_2 saturation of 98%. Uterine activity was absent.

The heart rate in antepartum cardiotocography tracings was abnormal (category III—recurrent late decelerations) in both fetuses. For the male fetus, Doppler ultrasound was abnormal with reducing cerebrovascular impedance, compatible with brain sparing.

Laboratory tests showed a white-cell count of 17,170 and platelet count of 218,000 mm^3. The C-reactive protein level was 2,5 and the liver function tests showed alanine aminotransferase (ALT) 558 IU and total bilirubin 9.28 mg /dl. Lactate dehydrogenase was 1,000 UI/l, serum creatinine was 2.3 mg/dl, and urine dipstick showed negative. Preeclampsia (PE) and partial HELLP syndrome was the hypothesis at that moment, associated to impairment of the twins. A cesarean section was performed without complications. Four hours after the procedure, a spike in blood pressure (220×120 mmHg) was detected associated to a hematoma of the abdominal wall that needed a surgical repair. The hypertensive emergency was controlled with MgSO4 and sodium nitroprusside. From then on, conditions have remained stable.

On day 2, the white-cell count reached 33,730, with decreased consciousness and mild respiratory distress. With the hypothesis of an infectious site, examinations were performed. Chest tomography revealed both lungs with ground-glass opacities and pleural effusion (►**Fig. 1**). An oropharyngeal swab for COVID-19 polymerase chain reaction (PCR) testing was positive. The patient was admitted to the intensive care unit (ICU) with O_2 saturation 94% and maintained adequate saturation just with face mask oxygen. In the following days, the patient remained stable with improvement in laboratory tests, except for platelets, which reached the worst level on the day 9 (49,000 mm^3). Thereafter, the exams returned to normal, with discharge from the ICU on day 14 with platelets of 121,000 mm^3, ALT 58, total bilirubin 2.9 mg /dl and creatinine 0.8 mg/dl. On day 21, she was discharged from the hospital.

The male fetus, who was born weighing 1,350 g, died on the 16th day due to intracranial hemorrhage. The female fetus, who was born weighing 1,190 g (NGA), remains in the neonatal care unit with good evolution. The macroscopic appearance of the placentas was normal, but no microscopic

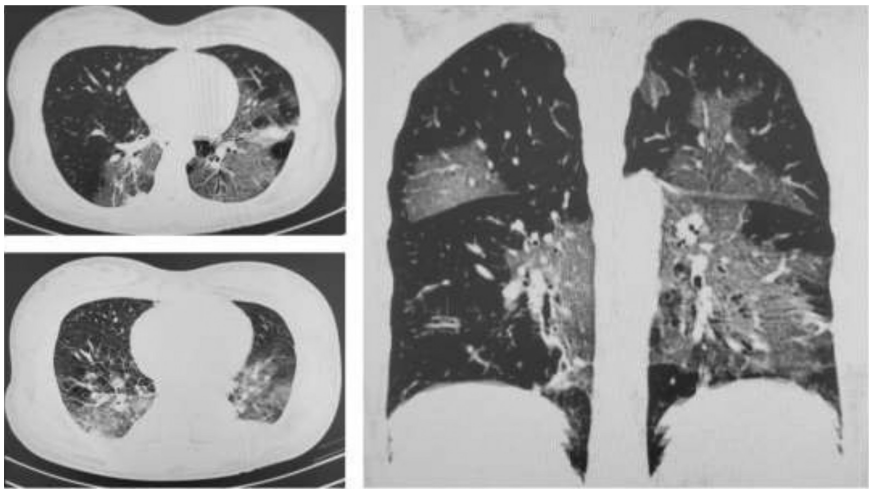

Fig. 1 Chest tomography showing extensive pulmonary involvement.

study was performed. The COVID-19 tests were negative in both newborns.

Discussion

Given the initial set of maternal clinical and laboratory information added to the fetal conditions, the diagnosis of HELLP syndrome seemed plausible, and the decisions followed recommendations in the face of an unsafe condition for mothers and babies. However, the sequence of events in this case suggests, although without strong evidence, that COVID-19 may have been a factor associated with hemolysis and thrombocytopenia. Many clinical and laboratory aspects of this new emerging infection are not yet fully understood, and several clinical expressions are observed, from asymptomatic conditions to critical and rapidly lethal situations.

Thrombocytopenia in patients with COVID-19 appears to be multifactorial, including endothelial damage, platelet activation with aggregation and thrombosis, impairment of bone marrow and megakaryocyte activity. It may also be due to changes in the pulmonary capillary bed morphology, which may lead to platelet defragmentation.[1,3] Endothelial damage, platelet activation, and thrombosis are similar to what occurs in preeclampsia and HELLP syndrome.

This is an intriguing case of a pregnant woman with risk factors for preeclampsia (twin pregnancy and first pregnancy), admitted with the hypothesis of partial HELLP syndrome, having received appropriate treatment for this situation. However, subsequent events led to the COVID-19 diagnosis. Hemolysis, elevated liver enzymes, low platelet syndrome is a serious obstetric disease with general inflammatory activation, and it can progress to extensive endothelial damage and thrombocytopenia, with a high rate of maternal and fetal problems.[2] It would be reasonable to assume that the synergism of these pathophysiological mechanisms could accelerate the compromise of maternal conditions. In addition, prophylactic administration of low-dose aspirin to pregnant women is common.

Despite the uncertainties, based on this case, we assume that the synergism of these pathophysiological mechanisms could accelerate the compromise of maternal conditions and could be a warning to the obstetric practice.

Given the current scenario, it is reasonable to assume that COVID-19 infection may be one of the causes of thrombocytopenia in pregnant women and with a high risk for serious problems. Fortunately, in the present case, the patient had a good response to treatment.

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

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Wernicke Encephalopathy as a Complication of Hyperemesis Gravidarum: Case Report

Encefalopatia de Wernicke como complicação de hiperêmese gravídica: Relato de caso

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Abstract

Wernicke encephalopathy (WE) is an acute neurological disorder resulting from vitamin B1 deficiency, which is common in chronic alcoholism. We report a rare case of WE due to hyperemesis gravidarum in a 25-year-old pregnant patient at 13 weeks and 5 days of gestation. Initially, the disease manifested as weakness, mental confusion, anterograde amnesia, and visual and auditory hallucinations. The diagnosis was established after the detection of suggestive findings of WE in the thalamus by magnetic resonance imaging (MRI) and a rapid improvement in the patient's clinical status subsequent to treatment with thiamine. Hyperemesis is a rare cause of WE, which makes the reported case important in the literature and reinforces the need for attention in clinical practice to rare but important complications of this common condition (hyperemesis gravidarum).

Keywords
- pregnancy
- Wernicke encephalopathy
- hyperemesis gravidarum
- thiamine
- case report

Resumo

A encefalopatia de Wernicke (EW) é uma condição neurológica aguda resultada da deficiência de vitamina B1, muito comum em etilistas crônicos. Relatamos um caso de EW secundário a um quadro de hiperêmese gravídica em uma gestante de 25 anos de idade e 13 semanas e 5 dias de idade gestacional. Inicialmente essa desordem se manifestou como fraqueza, confusão mental, amnésia anterógrada, e alucinações auditivas e visuais. O diagnóstico foi estabelecido depois da detecção de achados sugestivos de EW na ressonância nuclear magnética e da melhora do quadro clínico com reposição de tiamina. A hiperêmese gravídica não é uma causa comum de EW, o que faz com que o presente relato de caso tenha importância na literatura e reforça a necessidade de atenção na prática clínica para complicações raras mas importantes desse quadro tão comum (hiperêmese gravídica).

Palavras-chave
- gravidez
- encefalopatia de Wernicke
- hiperêmese gravídica
- tiamina
- relato de caso

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Introduction

Nausea and vomiting are very common during pregnancy (NVP), affecting up to 80% of pregnancies.[1–3] Hyperemesis gravidarum (HG), which can be described as severe NVP, affects up to 3% of all pregnancies and frequently leads to weight loss, dehydration, and electrolyte imbalance.[2,4] Hyperemesis gravidarum is the most common indication for hospitalization in the first half of pregnancy.[4] Maternal complications include dehydration, malnutrition and vitamin deficiencies, peripheral neuropathy, and more serious neurological complications, including central pontine myelinolysis and Wernicke encephalopathy (WE).[2,4–8]

The relation between WE and HG was described in 1939 by Sheehan.[9] As this complication is rare, there is not much data about it in the literature. However, as it is a serious and rare complication, it deserves attention as a case report.

Here, we describe the case of a 25-year-old pregnant female with WE due to HG.

Case Report

A 25-year-old pregnant patient at 13 weeks and 5 days of gestational age, in her third pregnancy, presented to our emergency department with symptoms of weakness, mental confusion, anterograde amnesia, and visual and auditory hallucinations.

One month before this first visit, the patient reports having presented hypoxia and vomiting. On examination, the patient was awake, disoriented, responding to commands, with isochoric and photoreactive pupils, absence of relative afferent pupillary defect, preserved visual acuity, exhaustible horizontal nystagmus, atypical gait, with slight dysbasia.

Laboratory tests showed the following changes: drop in hemoglobin levels (7.0 mg/dl, reference: 11–16 mg/dl), albumin (3.0 g/dl, reference: 3.5–4.8 mg/dl) and potassium (3.3 mmol/l, reference: 3.5–5.5 mmol/l), seric iron (43.5 mcg/dl, reference: 50–170 mcg/dl), seric magnesium (1.4 mg/dl, reference; 1.7–2.5 mg/dl) and increased liver enzymes glutamate pyruvate (129 U/L, reference $<$ 41 U/L) and transaminase glutamate oxaloacetate transaminase (61 U/L, reference $<$ 31 U/L). Transient hyperthyroidism was also observed, with TSH (0.04 mU/L, reference 0.3–4.0 mU/L) below normal limits. Other complementary exams did not show alterations. Ultrasound showed single alive intrauterine fetus.

Magnetic resonance imaging (MRI), on T2/FLAIR sequence, showed symmetrically increased signal intensity in the dorsomedial thalami (►**Figs. 1** and **2**). This finding may suggest injury to the medial portion of the thalamus.

Due to the main diagnostic suspicion of WE, thiamine replacement was initiated with a 500 mg intravenous loading dose every 8 hours for 3 days, and then maintained with 100 mg orally for another 14 days. The patient also received potassium replacement orally, and 3 blood concentrates were transfused, after which she presented a slow improvement in her neurological condition, being discharged after 7 days of hospitalization for prenatal follow-up at our service.

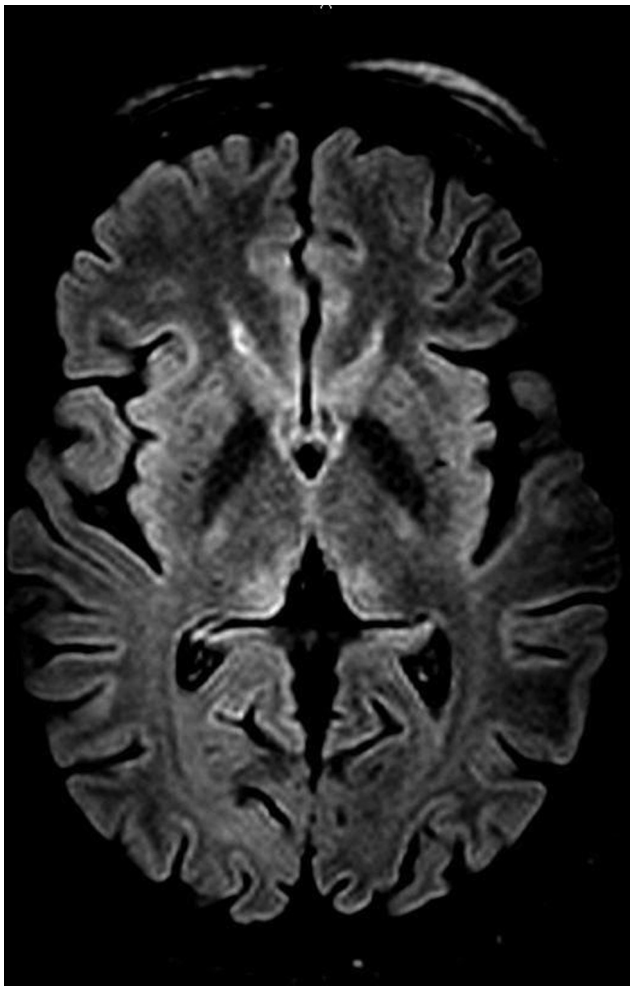

Fig. 1 Dorsomedial thalami.

During prenatal care, the patient evolved with improved thyroid function, and presented normal exams in 2 months. She was diagnosed with gestational diabetes mellitus but obtained good control with diet.

The fetus was diagnosed with ventriculomegaly (dilation of the cerebral ventricles) and intrauterine growth restriction during the morphological ultrasound in the second trimester.

The patient evolved to cesarean delivery at term due to altered fetal vitality. The newborn is being followed-up with genetics and neurology, with a probable diagnosis of Dandy-Walker malformation (DWM).

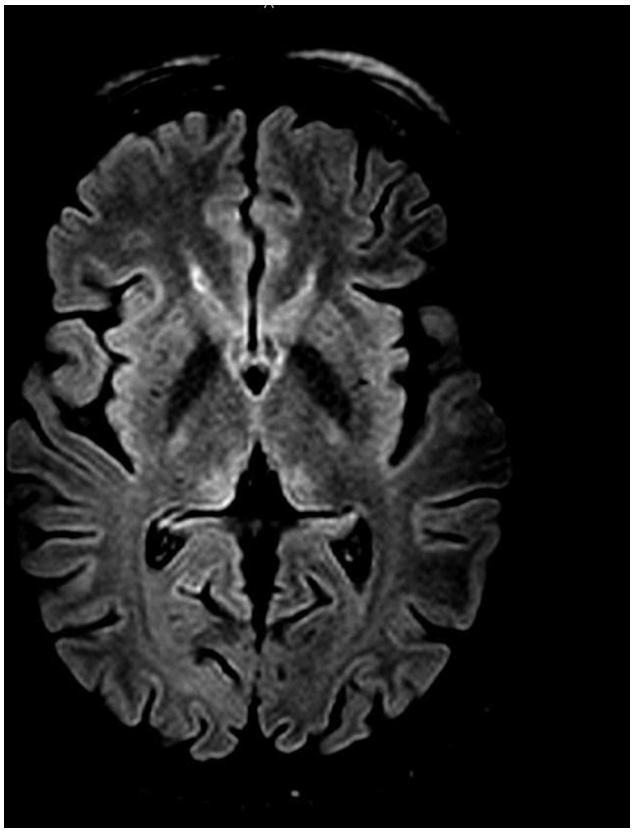

Fig. 2 Dorsomedial thalami (white arrows).

Discussion

The patient has presented neurological changes (nystagmus, disorientation) as well as a previous history of HG. The laboratory tests reinforced the finding of malnutrition (low levels of albumin and minerals), and the MRI showed alterations in the thalamus region. All these findings were suggestive of WE.

Wernicke encephalopathy is an acute neuropsychiatric syndrome characterized by the classic triad of ataxia, eye movement disorders, and mental status change. It is the result of a thiamine deficiency.[4]

The majority of patients that develop WE have a history of chronic alcoholism and accompanying malnutrition.[2,8] Before the onset of WE, prodromal characteristics of severe thiamine deficiency are present, such as nausea and vomiting, and blurred or double vision.[2,8,10] Inadequate treatment often results in additional characteristics of the classic triad consisting of oculomotor abnormalities, cerebellar dysfunction, and an altered mental state. The more symptoms of WE, the more likely chronic Korsakoff syndrome will develop: a cognitive disorder characterized by severe amnesia, executive problems, and confabulation, which leads to lifelong impairment.[8,10] It is relatively unknown that HG can lead to WE.

Wernicke encephalopathy is better diagnosed by the Caine's operational criteria, since not all patients have the classic triad. Caine's operational criteria for WE are: Wernicke's classic triad; autopsy evidence of WE; or clinical response to thiamine.[11] The defining signs and symptoms for WE were: dietary deficiencies, oculomotor abnormalities (reported as nystagmus or ophthalmoplegia), cerebellar dysfunction (reported as falling or imbalance), and an altered mental state (reported as delirium, confusion, and problems in alertness, or cognition).[11]

The body stores $\sim$ 25 to 30 mg of water-soluble vitamin thiamine (B1), which is good for $\sim$ 18 days. The daily requirement is 0.4 mg/1,000 kcal per day, which increases in pregnancy to 1.5 mg/day.[12] Deficiency of thiamine pyrophosphate, which is an important co-factor for enzymes in the pentose phosphate pathway, affects multiple tissues, particularly those with high thiamine turnover that include neural parenchyma resulting in cell necrosis or apoptosis.[13]

Wernicke encephalopathy in pregnancy generally occurs in women who are malnourished, due to the increased demands of pregnancy. Hyperemesis further depletes thiamine stores.[14] However, WE is uncommon in pregnancy but HG is pretty common. Wernicke encephalopathy generally occur at 14 to 18 weeks gestation after 2 to 3 weeks of vomiting, which was the case with our patient who presented at 13 weeks and 5 days gestation with history of vomiting for 1 month.[13]

The diagnosis of WE is primarily clinical. In his operational criterion for the identification of WE, Caine et al[11] proposed that WE is diagnosed if any two of the following four signs exist: ophthalmoplegia, ataxia, altered mental status, and malnourishment. Nystagmus is the most common ocular sign and confusion is the most common presenting symptom.[11]

The diagnosis may be reinforced by a brain MRI, which shows symmetric high T1, T2, and T2 flair signal intensities in the mammillary body, medial thalamus, periventricular, and periaqueductal regions. The sensitivity and specificity of brain MRIs are 53% and 93% for the diagnosis of WE, respectively.[15]

The gold-standard treatment is to replace thiamine, which results in the resolution of symptoms in a few hours to a few days depending on the severity of the disease. If untreated, WE can progress to Wernicke-Korsakoff syndrome (WKS), resulting in more chronic symptoms such as anterograde amnesia, which takes more time to resolve after treatment.[16] Therefore, diagnosis and treating as fast as possible will result in less severe disease.

Dandy-Walker malformation (DWM) or syndrome is a posterior fossa anomaly characterized by agenesis or hypoplasia of the vermis and cystic enlargement of the fourth ventricle causing upward displacement of tentorium and torcula.[17] DWM may be isolated or associated with chromosomal abnormalities, Mendelian disorders, syndromic malformations, congenital infections, and various other comorbidities.[18] There is no description in the literature of cases of DWM in pregnant women complicated with HG or WE. And we cannot infer that thiamine deficiency or nutritional changes lead to brain formation.

Conclusions

Wernicke encephalopathy is an uncommon and life-threatening neurological disease complicating pregnancy in the setting of hyperemesis. Timely and serious management of vomiting in pregnancy and replacement of thiamine stores help treat acute neurological symptoms and can prevent both maternal and fetal morbidity.

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

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What is the Role of OBGYN Residents during COVID-19 Pandemics?

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Dear Editor,

We have read with great interest the Special Article from Romão et al.,[1] with recommendations from the Brazilian Federation of Gynecology and Obstetrics Associations (FEBRASGO, in the Portuguese acronym) regarding medical residency training during the coronavirus disease (COVID-19) pandemic. While it is clear in considering aspects of theoretical activities, it is less conclusive of how practical workload should be accomplished: can we participate in COVID-19 care while practicing obstetrics and gynecology (OBGYN)?

We agree that there are major concerns of how the COVID-19 pandemic will impact the apprenticeship of the residents and, especially, women's health care. We are aware of and respectful to all the necessary arrangements in dealing with the COVID-19 pandemic.[2] In Brazil, at least a third of OBGYN residents were relocated to deliver care to suspected or confirmed COVID-19 patients.[3] Although it may represent OBGYN interrupted regular activities, it comes to our attention that the relocation of residents was simultaneous to important modifications in women's health care in Brazil.

First, women are afraid of seeking medical care and exposing themselves to SARS-CoV-2, therefore tending to underestimate their health condition and to delay arrival to medical facilities; they presume there is a great risk of viral infection. Second, quarantine and lockdown measures have restricted health care to essential services, decreasing access to on-time diagnosis. Health personnel were deviated from women's health facilities, including antenatal clinics, to help emergency services. Ultrasound and laboratory tests, which were never adequate, are now restricted to a bare minimum. Therefore, women are admitted to hospitals in worsened medical conditions; it seems that 10% of maternal deaths in Brazil this year are related to COVID-19.[4] Third, other health issues arise during the pandemic. To cite just a few, domestic violence, anxiety, and perinatal depression are rising in times of social isolation and emotional constraints.[5,6] We understand that OBGYN are the leading professionals in women's integral health care, and residents must take part on it. Finally, and of the uttermost importance, we still do not know how SARS-CoV-2 behaves in specific conditions of our field, such as in pregnancy[7] or oncology.[8] Therefore, we can still afford COVID-19 care while offering OBGYN care.

In our view, the role of OBGYN personnel in taking care of women's health is irreplaceable. In times of pandemics, our role is to provide a safe environment for the continuity of our species, which is not a lesser endeavor. In this context, program directors and institutions should focus the efforts of OBGYN residents on activities for which they have the best training for, and in sectors where they can really help. For example, emergency obstetrical care, which is historically overburdened in terms of resource personnel. Many lessons can be learned from the pandemic as a whole, but in our field, we have a clear picture of how essential our work really is. Antenatal care, labor wards, OBGYN emergency rooms, and gynecological oncology procedures are still places for assistance and residency training. If there is less gynecological training during the pandemic,[3] residents must be replaced to obstetrics or oncology, which is in accordance with the FEBRASGO statement.[1]

The pervasive feeling among some institutions that OBGYN is a common specialty is unequivocally wrong. We have a unique set of abilities which are simply indispensable. Obstetrics and gynecology personnel cannot be relocated without considerable impact on the quality of care. It is a waste of precious human resources to use the OBGYN workforce in the frontline of COVID when we have pressing needs in attending obstetrics emergencies and oncologic cases. Perhaps more lives will be wasted – or an increase of long-term sequelae for both mother and newborn[9,10]– with this shift of personnel from where they are most effectively used to performing general COVID-19 care. Gynecological and perinatology health care must be seen as essential areas of medical assistance and education.

Residency training in 2020 has been challenging for residents, program directors, institutions and policy makers. Obstetrics and gynecology residents are skilled professionals and need to work as such. In Brazil, women's health is marked by inequalities of access and deliver of care, which impairs

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the maternal morbidity and mortality rate. Residency programs need to be in line with women's needs.

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

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Authors' response

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Dear Editor,

We are grateful to the authors for their comments about our recently published manuscript outlining the recommendations from the Brazilian Federation of Gynecology and Obstetrics Associations (FEBRASGO, in the Portuguese acronym) in medical residency training during the coronavirus disease (COVID-19) pandemic. We read with interest their comments and agree that the COVID-19 pandemic has affected both the quality of postgraduate training and the quality of care in non-COVID conditions.

The obstetrics and gynecology (ObGyn) residency training program is indeed heterogeneous, since acquisition of clinical, surgical and emergency management skills is mandatory. Daily practice, along with an adequate theoretical preparation, plays a fundamental role in achieving autonomy. Regarding the comments of the authors about the practical workload of ObGyn residents, we recommended that it should be mainly performed in time-sensitive care activities such as prenatal, childbirth, postpartum, gynecological oncology, family planning, sexually transmitted infections and assistance for victims of sexual violence. For the activities that have been suspended or postponed during the pandemic, such as non-COVID inpatient or outpatient care and elective surgeries, decisions must be made locally between health managers and those responsible for residency programs. It includes providing proper resident supervision.

The need to move ObGyn residents to combat the COVID-19 pandemic will depend on epidemiological conditions in each region. In the largest hospital complex in South America, the Hospital das Clínicas of the School of Medicine, Universidade de São Paulo (HCFMUSP, in the Portuguese acronym), almost 500 volunteer residents from 40 different residency programs were recruited to work in the frontlines of the COVID-19 pandemic.[11] All residents of this multispecialty team received personal protective equipment (PPE) and appropriate training in individual protection and orotracheal intubation, with a maximum weekly workload of 48 hours. The team of supervisors was composed of working physicians in intensive care units (ICUs), wards, and in the emergency department. A total of 132 residents of this group reported their opinions through a

survey. Although many of them have expressed fear of becoming ill and concerns about the possible deficits in their professional training, important positive aspects were also reported, such as the quick growth in professionalism, altruism and communication in the healthcare field.

In other countries severely affected by the pandemic, such as the United States, trainees in different clinical and surgical areas have also been moved to provide care for COVID-19 patients.[12]

In Brazil, medical residency is essentially time-based and not competency-based.[13] Consequently, after a period of 3 years of training, the ObGyn resident is considered fit to practice, even if the quality of the training of a resident or of a group of residents has been compromised. As the competencies are not systematically assessed throughout the program, it is difficult to objectively measure the damage resulting from the lack of training during the COVID-19 pandemic.

In 2010, the Carnegie Foundation's report on the reform for postgraduate programs proposed a model with "fixed standards and flexible paths."[14] This model was adopted in many countries where the readiness of the residents for unsupervised activities is formally assessed through the Entrustable Professional Activities (EPAs).[15]

Currently, the FEBRASGO is preparing and validating the Brazilian ObGyn EPAs, which will serve as a reference to ensure that the resident is able to carry out the activities properly without supervision, bridging the gap between well-designed competency structure and clinical practice with the patient.

Note

Text prepared by the members of the National Specialized Commission on Medical Residency and endorsed by the Scientific Board and Presidency of the Brazilian Federation of Gynecology and Obstetrics Associations (FEBRASGO).

Conflict of Interests

The authors have no conflict of interests to declare.

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FEBRASGO POSITION STATEMENT

Surgical management of postpartum hemorrhage

Number 4 - October 2020
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The National Specialty Commission for Obstetric Emergencies of the Brazilian Federation of Gynecology and Obstetrics Associations (FEBRASGO) endorses to this document. The content production is based on scientific studies on a thematic proposal and the findings presented contribute to clinical practice.

Key-points:

- Postpartum hemorrhage is the world's leading cause of peripartum hysterectomy, even among women with a desire for future fertility.
- Vascular ligation and uterine compression sutures must precede hysterectomy in the surgical treatment of postpartum hemorrhage.
- The main technique of vascular ligation is bilateral uterine artery occlusion, although progressive devascularization techniques may optimize the surgical control of postpartum hemorrhage.
- Uterine compression sutures are heterogeneous and the choice of technique to be applied must correlate with the hemorrhage etiology and the topography of the hemorrhagic focus.
- The combination of uterine compression suture and vascular ligation increases the effectiveness of surgical treatment of postpartum hemorrhage.
- Surgical techniques for controlling postpartum hemorrhage should be used immediately after failure of drug therapy, preferably within the "golden hour".
- All pregnant women with placenta previa and previous cesarean section must have assisted birth in a tertiary service.
- Damage control surgery is indicated when the patient with postpartum hemorrhage is already in the lethal triad and definitive interruption of bleeding was not possible or requires excessive time.

Recommendations:

- In the surgical treatment of postpartum hemorrhage, when choosing vascular ligation and/or uterine compression sutures, the technique option must correlate with the topography of the hemorrhagic focus and the surgeon's skill and experience.
- If uterine atony occurs during cesarean section and drug therapy fails, uterine compression sutures of B-Lynch and Hayman and/or bilateral ligation of the ascending branches of the uterine arteries are excellent surgical options.
- In hemorrhage from placenta accreta that affects the uterine body, the Cho compression suture is an excellent surgical option. In placenta accreta of the uterine segment, both the Cho compression suture and low selective vascular ligations show excellent results in hemorrhagic control.
- If surgical techniques for uterine preservation fail, hysterectomy is indicated and should be performed as early as possible, before coagulopathy is installed. Unless there is concomitant infection or the hemorrhagic etiology is an invasive central placenta previa, subtotal hysterectomy should be preferred.
- The spectrum of placenta accreta in its previous increta and percreta varieties can be treated by means of hysterectomy or uteroplacental segmental excision followed by restoration of the uterine anatomy. Hysterotomy and fetal extraction should be performed outside the invaded uterine area, usually in the uterine fundus. Vascular neoformation must be carefully and selectively ligated and hysterectomy must be performed with the placenta in situ. In the face of bladder invasion by the placenta, partial cystectomy and/or reimplantation of the ureters may be necessary.
- In damage control surgery, the incisions must be large to facilitate technical execution. Open pelvic packing techniques with drainage reduce intestinal fistulas and increase the rate of primary closure. In patients undergoing total hysterectomy, damage control can be achieved through closed packing by adapting an intrauterine balloon in the pelvis.
- Skill training programs and simulations should be implemented in order to optimize the safety of care teams when applying surgical techniques to control postpartum hemorrhage.

Background

Postpartum hemorrhage (PPH) is the world's leading cause of peripartum hysterectomy, even among women with a desire for future fertility.[1] The main etiologies are uterine atony, birth canal trauma, ovarian tissue retention and coagulation disorders. Uterine atony is the etiology with the highest incidence and placenta accreta is the one with the highest lethality. The placenta accreta spectrum shows its higher incidence that correlates with the contemporary increase in cesarean section rates. Undoubtedly, the placenta percreta is the etiology of PPH that imposes greater surgical difficulty, especially when neighboring organs are affected.[2]

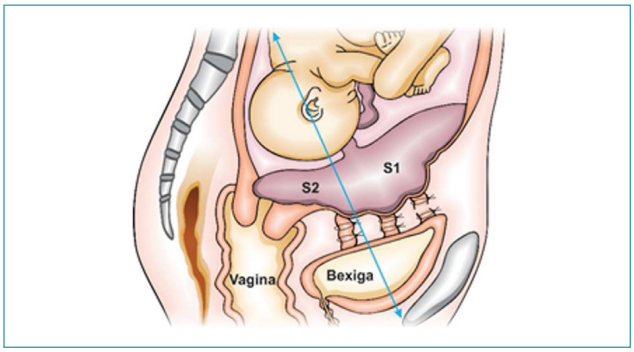
In recent decades, several techniques have been developed to preserve the uterus in PPH. Vascular ligation (VL), uterine compression suture (UCS), intrauterine balloons (IUBs), arterial embolization (AE) and intravascular balloons stand out. When well applied, surgical techniques (VL and UCS) can provide faster hemorrhagic control and potentially preserve fertility.[3]

When and how to apply surgical techniques for uterine preservation?

Vascular ligation and UCSs are surgical techniques for controlling PPH that provide uterine preservation, and may or may not be applied in combination. The main indication for these techniques is uterine atony with failure of drug therapy, especially during caesarean section. Other indications include placenta accreta, uterine inversion after repositioning the uterus and uterine rupture that can be preserved. These techniques stand out for their low cost, fast learning curves, high percentage of success in hemorrhagic control, fertility preservation, and for avoiding the additional loss of two or more liters of blood linked to hysterectomy. Therefore, they are indicated prior to hysterectomy.[4]

The chosen technique must correlate with the topography of the hemorrhagic focus, since the genital vascular region S1 (uterine fundus and body) is irrigated by the uterine and ovarian arteries, while region S2 (segment and cervix) receives blood supply from the internal pudendal, inferior vesical and middle, upper and lower vaginal arteries (Figure 1). Another important criterion when choosing the technique is the surgeon's skill, knowledge and experience with the techniques.[5]

The main VL technique is the bilateral uterine artery occlusion (O'Leary technique). Bilateral sutures are done in the ascending branches of the uterine arteries. Alternatively, "high" ligations can be added by using sutures in the utero-ovarian connections bilaterally located in the mesosalpinx.[6] This technique is excellent for uterine atony of the genital vascular region S1, good for S1 accretism, but inefficient for hemorrhages in region S2. Very similar to the O'Leary technique, the Posadas technique consists of flexing the uterus



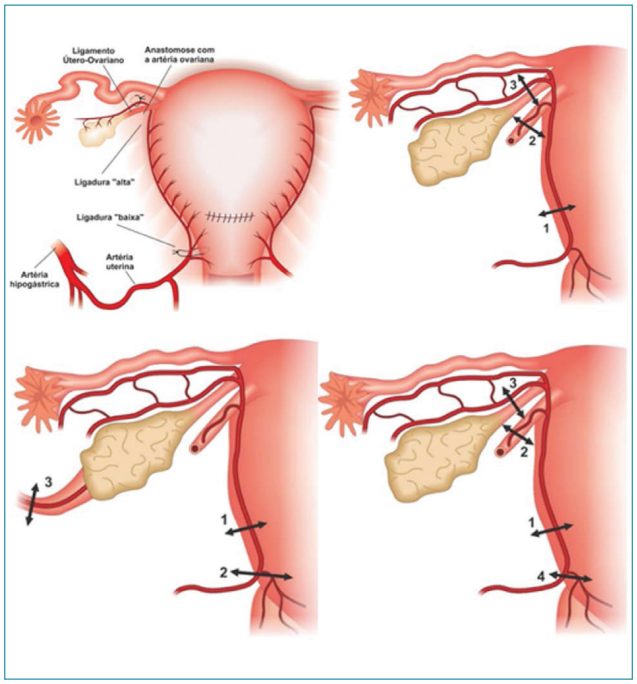
Source: Illustration by Felipe Lage Starling (authorized).

Figure 1. Sagittal scheme of the division of S1 and S2 genital vascular regions

towards the pubic bone, visualizing, palpating and ligating the ascending branches of the uterine arteries in their path in the posterior wall of the uterus. In addition, it is complemented by the occlusion of utero-ovarian connections in the mesosalpinx.[7] In the triple ligation of Tsirulnikov, in addition to the sutures described above, sutures in the round ligament are added by obstructing the flow of the round ligament arteries. In step-by-step ligation techniques, sutures are progressively applied at 10-minute intervals. The hemorrhagic control after the application of a certain step is what determines the interruption in the application of sutures. In the AbdRabbo technique, the sutures are progressively applied to the ascending branches of the uterine arteries, to cervicouterine pedicles and to the ovarian arteries (infundibulopelvic ligaments). In the Morel technique, sutures are progressively applied to the ascending branches of the uterine arteries, round ligament arteries, utero-ovarian connections in the mesosalpinx and cervicouterine pedicles (Figure 2).[8]

In the presence of invasive placenta previa, low selective ligations applied in region S2 with the use of suture passer are the ideal techniques for hemorrhagic control from vascular neoformation associated with accretism.[5] As the ligation of the internal iliac arteries (hypogastric) is performed far from the uterus and its annexes, it is less efficient than the other techniques when used alone. Its most accurate indications in PPH are severe lacerations of the birth canal and as a supporting procedure in the control of damage in patients already hysterectomized and in coagulopathy.[8,9] In association with other uterine preservation techniques (IUB and UCS), this technique reduces hysterectomy rates.[10]

Uterine compression sutures provide mechanical compression in the uterine vascular sinus with simultaneous occlusion or not of the uterine arteries and other points of genital irrigation. The techniques are heterogeneous and what differentiates them is the figure in which the suture is applied, the number of



Source: Illustrations by Felipe Lage Starling (authorized).
Upper left: bilateral ligation of the ascending branches of uterine arteries and utero-ovarian connections in the mesosalpinx (O'Leary technique); upper right: Tsirulnikov's triple ligation (1 - ascending branch of the uterine artery; 2 - round ligament artery; 3 - utero-ovarian connections in the mesosalpinx); lower left: step-by-step AbdRabbo ligation (1 - ascending branch of the uterine artery; 2 - cervicouterine pedicle; 3 - ovarian artery); lower right: Morel step-by-step ligation (1 - ascending branch of the uterine artery; 2 - round ligament artery; 3 - utero-ovarian connections in the mesosalpinx; 4 - cervicouterine pedicle).

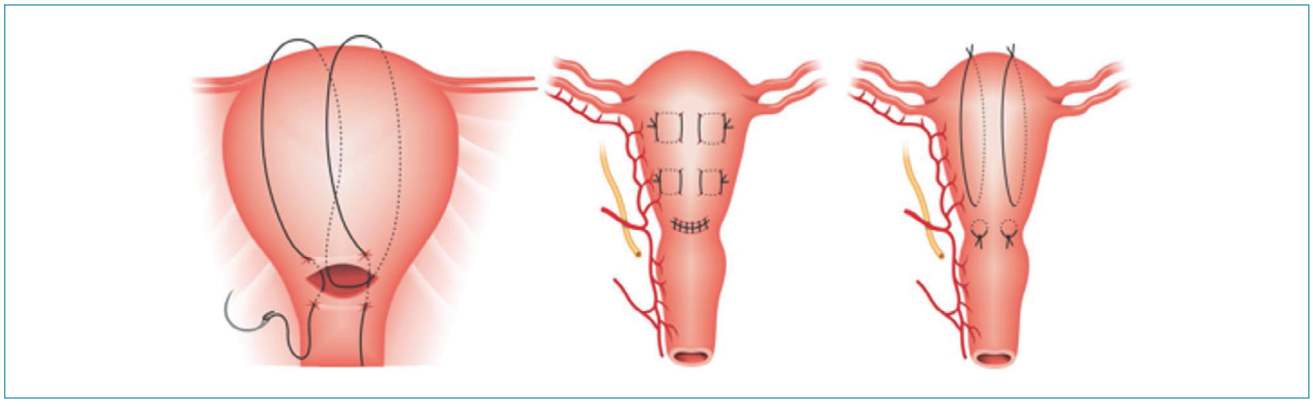
Figure 2. Vascular ligation techniques

vertical and/or horizontal suture sets and the penetration/occlusion or not of the uterine cavity. To predict the success of the technique, the uterus must be compressed bimanually before the sutures are applied, while the vaginal blood loss is checked simultaneously. The main UCSs are those of B-Lynch, Cho and Hayman. The mechanism of action of the B-Lynch suture is the compression of the uterine fundus on the segment, simulating the effect of a uterine compression maneuver. The Cho suture promotes obliteration of the uterine cavity and can be selectively applied to hemorrhagic topographies. The Hayman's technique, on the other hand, has a mixed action mechanism, with compression of the uterine fundus on the segment, associated or not with the obliteration of the segmental uterine cavity. After exteriorization of the uterus, two loops are applied to the uterine segment in the anteroposterior direction, each at a 3-4 cm distance from the lateral border of the uterus, ending with the knots in the uterine fundus.[11] Thus, the B-Lynch suture is excellent for uterine atony in the S1 region, good for accretion in S1 and ineffective for the S2 region. The Cho's technique is good for uterine atony in S1 and excellent for accretism both in S1 and S2. The Hayman suture is an excellent option for uterine atony in S1 and good for accretism both in S1 and S2 (Figure 3).

The effectiveness of UCSs increases when they are associated with VL.[12] A simple and efficient option is to associate bilateral ligation of the ascending branches of the uterine arteries with Hayman's upper vertical compressive loops.[13] This strategy provides an association of techniques performed with only four needle passages in the uterus and is highly effective for the hemorrhagic control of uterine atony and accretism in the S1 region (Figure 4).

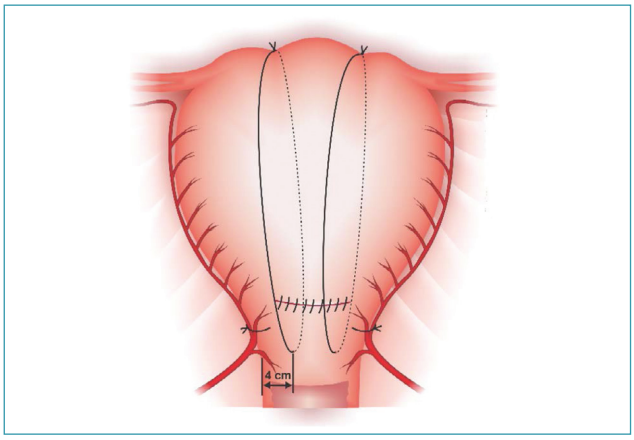
Another association that optimizes hemorrhagic control is the "uterine sandwich" technique, in which the UCS is associated with uterine balloon tamponade. In this situation, the balloon is inserted through the hysterotomy and the suture is applied under direct vision, preventing the needle from passing through the balloon. The balloon infusion should be limited to only 100 mL of saline and performed at the end of the surgery, after closing the UCS and laparorrhaphy.[14]

In order to prevent associated complications, the current trend is towards the development of removable UCSs.[15,16] The main techniques already described are the Aboulfalah and Zhang USCs (removable B-Lynch and Hayman) (Figure 5).



Source: Illustrations by Felipe Lage Starling (authorized).

Figure 3. B-Lynch, Cho and Hayman uterine compression sutures



Source: Illustration by Felipe Lage Starling (authorized).
Ligation of the ascending branches of the uterine artery and vertical loops of the uterine compression suture

Figure 4. Technique of uterine devascularization and uterine compression suture

The main complications related to VL and UCSs are infections (pyometrium, endometritis and endomyometritis), ischemic partial necrosis, erosions, sulcus and defects in the uterine wall, synechiae, hematometrium, Asherman's syndrome and uterine rupture in subsequent pregnancy.[4] Both VLs and UCSs must be made only with absorbable thread sutures. Polyglecaprone is the suture material of choice, with polyglactin and polydioxanone as second options. For the application of some techniques, straight needles may be necessary.[17]

When and how to perform hysterectomy in uterine atony?

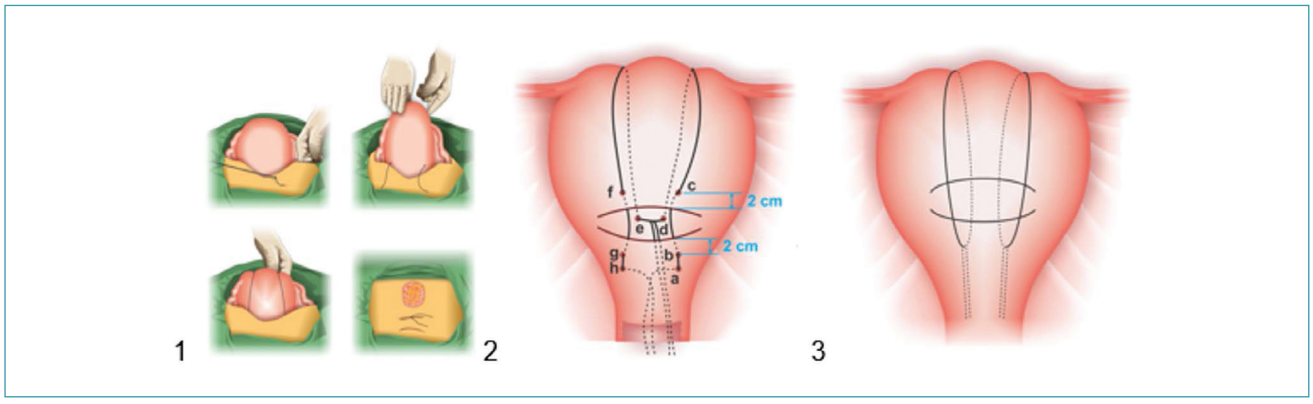
Currently, hysterectomy should be the last stage of the surgical approach to PPH due to uterine atony and performed without delay before the installation of the lethal triad (coagulopathy, acidosis and hypothermia). Since the removal of the puerperal uterus imposes an additional loss of two to three liters of blood, its late performance can worsen the hemorrhagic shock. In the absence of a central placenta previa or infection, subtotal hysterectomy should be preferred.[2]

How to treat placenta accreta surgically?

Every pregnant woman with placenta previa and prior cesarean section must have assisted birth in a tertiary service, because the treatment, especially of placenta percreta that invades neighboring organs (bladder, abdominal vessels), requires a multidisciplinary team.[18]

The surgical approach must be properly planned (reserve of blood components, definition of the anesthetic technique and laparotomy incision), performed by an experienced team and guided according to the invaded genital vascular region (S1 or S2). Since placental blood flow at gestational term is 600 to 700 mL/min, elective interruption between 35 and 38 weeks is consensus.[5,19]

Starting with spinal anesthesia until fetal extraction, then proceeding to general anesthesia is a good strategy in the face of prolonged surgical time often imposed by the need for extensive dissection of vascular neoformations. After wide laparotomy (longitudinal incisions may be necessary) and adequate uterine exposure, hysterotomy and fetal extraction should be performed outside the invaded uterine area. Thus, fundal hysterotomies should be preferred. After clamping and removal of the umbilical cord, hysterorrhaphy is performed with the placenta in situ. The ureters and internal iliac arteries (hypogastric) should be located and the surgical technique defined. The exeresis by segmental excision followed by restoration of the uterine anatomy may be preferable to hysterectomy. Both require experience and dexterity from the surgeon to perform the low selective ligation (using suture passer) of vascular neoformations, especially in the uterine segment. In hysterectomy performed by means of high vascularization and uterovesical adhesion, mobilization and bladder dissection (Pelosi by-pass) performed in zones of adhesion are useful in preventing urinary tract injuries (Figures 6, 7, 8 and 9). In the face of bladder invasion by the placenta, one of



Source: Illustrations by Felipe Lage Starling (authorized).
1 – Aboulfalah; 2 – Removable B-Lynch by Zhang; 3 – Removable Hayman by Zhang.

Figure 5. Removable uterine compression sutures

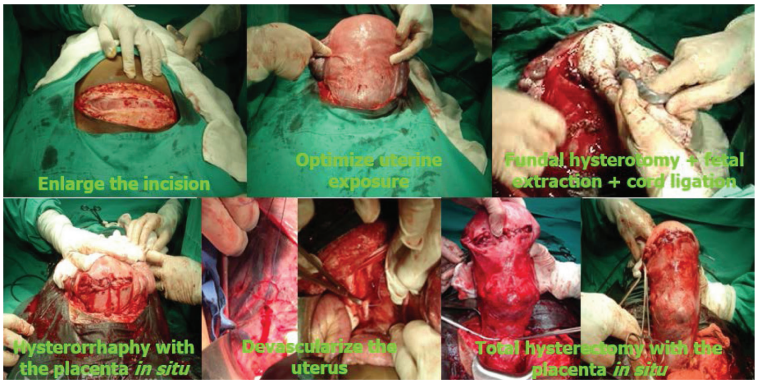
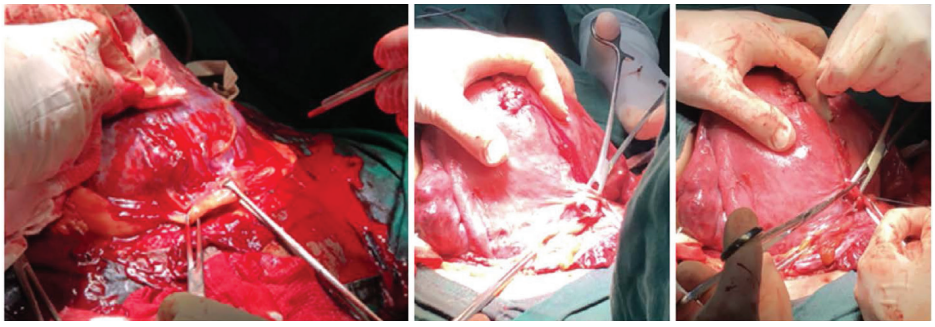
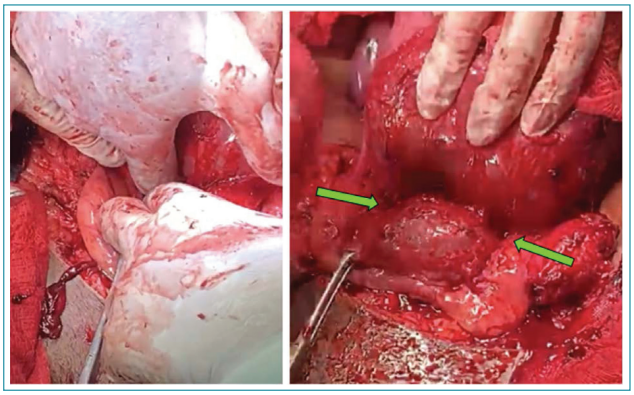


Figure 6. Steps of the cesarean-hysterectomy technique in the surgical treatment of placenta accreta



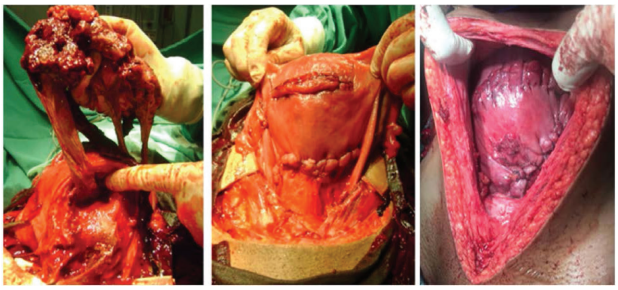
Exposure of vascular neoformations present in vesicouterine reflection by means of traction with Allis forceps. Double ligation performed with a suture passer.

Figure 7. Low selective ligation of vascular neoformations present in the uterine segment in the surgical treatment of placenta accreta



After performing the low selective ligation of vascular neoformations, mobilization and blunt dissection of the vesicouterine space are performed.

Figure 8. Mobilization and bladder dissection (Pelosi by-pass) performed in the areas of vesicouterine adhesions in the surgical treatment of placenta accreta



Left: exeresis of the uterine segment affected by invasion of placental cotyledons and ovular membranes. Center and right: final result of restoration of the uterine anatomy with hysterorrhaphy in the uterine fundus and suture between the uterine body and the lower residual portion of the segment.

Figure 9. Exeresis with segmental uteroplacental excision followed by restoration of uterine anatomy in the surgical treatment of placenta accreta

the options is to perform partial cystectomy and "one-piece" hysterectomy (Pelosi technique).[20] As an alternative to partial cystectomy, and especially in the face of invasion of the bladder trigone (rare), embolization of the uterine and internal pudendal arteries is a good option for sites with this technical availability. Eventually, ureteral reimplantation is necessary. An alternative for the control of hemorrhage in the genital vascular region S2 is the application of segmental UCSs. The most suitable techniques for this purpose are the Cho UCSs (adapted by Palacios-Jaraquemada),[5,19] Dedes and Zioga or the transverse segmental figure-of-8 UCS (Figure 10). The strategies described above offer the advantage of one-step surgical resolution.

In exceptional situations, such as in extrauterine placental implantations (in large vessels or adjacent

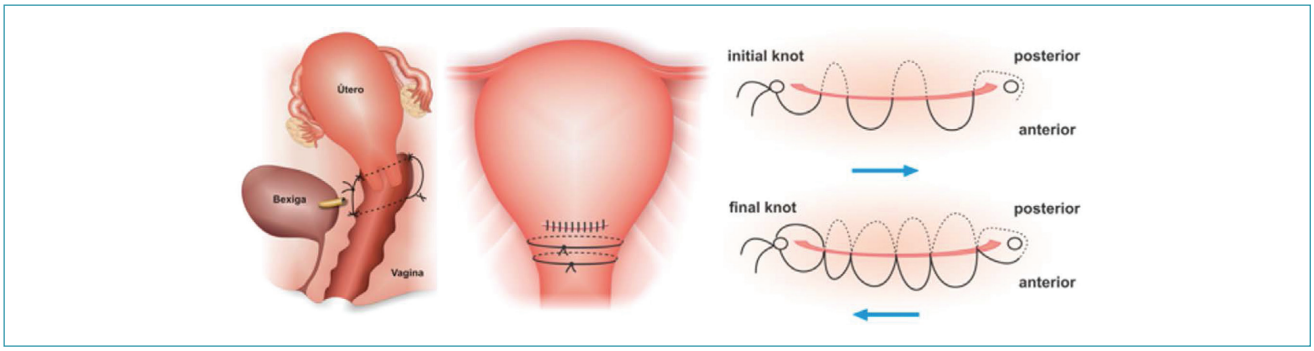


Figure 10. Cho uterine compression sutures (adapted by Palacios-Jaraquemada),[19] Dedes and Zioga and transverse segmental figure-of-8

organs), maintaining the placenta in situ associated or not with methotrexate or arterial embolization may be the safest resource.[19]

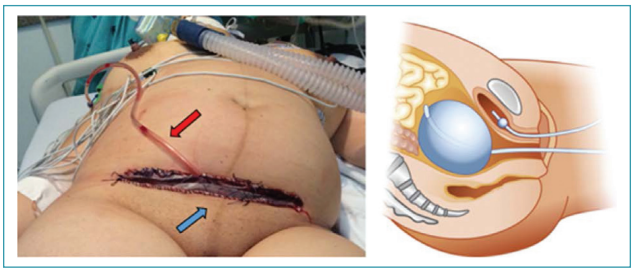
In the face of prenatal diagnostic failure followed by perioperative diagnosis in non-ideal surgical conditions (lack of experience of the team and/or blood components), the surgical procedure must be restricted to hysterotomy and fetal extraction outside the invaded uterine area, followed by hysterorrhaphy with the placenta in situ and laparorraphy. In these situations, the definitive re-approach (hysterectomy or excision with uteroplacental segmental exeresis followed by restoration of the uterine anatomy) is performed after the reorganization of the care conditions (two step).[5,19]

When and how to perform damage control surgery?

Damage control surgery (pelvic packing and laparostomy, with or without concomitant ligation of the internal iliac arteries) is indicated when definitive bleeding control was not possible or when it demands excessive time and the patient is already in the lethal triad. The goal is to temporarily control the hemorrhagic focus and allow the restoration of the patient's physiology in intensive care. The surgery is temporary. The control of the remaining hemorrhagic foci and the permanent laparorrhaphy should be performed two to five days later.[20,21]

Open pelvic packing techniques with drainage reduce intestinal fistulas and increase the rate of primary closure. Longitudinal incisions may be necessary for good technical execution. A good option for open packing (laparorrhaphy) includes the insertion of 7 to 10 compresses in the pelvis and a fenestrated pouch above the package that will not be sutured, being loose and below the parietal peritoneum. Above this first bag, two compresses are allocated. Above these, one or two drains, plus two compresses for top drain protection are placed. The technique is completed with the insertion of a second, non-fenestrated pouch sutured directly to the skin. As alternative to this second pouch, an adherent dressing involving the entire abdominal circumference can be applied. The drains must be adapted to the suction system at a negative pressure between -100 and -150 mmHg.[22,23]

In patients undergoing total hysterectomy, damage control can be achieved through closed packing. In this technique, an intrauterine balloon is inserted into the pelvis and its axis is directed to the vaginal cavity, before the approach to the vaginal dome. After laparorraphy and the balloon infusion, a weight is connected to its axis and adapted to the bedside in order to optimize pelvic compression (Figure 11). In this technical option, surgical re-approach is not necessary. After physiological restoration, the balloon is deflated and removed through the vagina.[24,25]



Left: open pelvic packing; the red arrow indicates aspiration; the blue arrow indicates the protective pouch of the pelvic pack made with compresses. Right: closed packing with an intrauterine balloon adapted to the pelvis.

Figure 11. Pelvic packing damage control surgery

Still in the context of care to puerperal women in critical situation due to severe PPH, such as imminent cardiopulmonary arrest and extra-hospital care, the external manual compression of the infrarenal aorta can be performed as a life-saving maneuver. Compression should be temporary (maximum 90 minutes) with the application of a force of approximately 45 kg and performed until the arrival of support and/or the start of correction of coagulopathy and shock.[26]

Finally, the evolution of the HPP assistance flowcharts with incorporation of several more recent surgical idealization and evaluation techniques imposed on care teams the need to acquire new skills and competences. These can be obtained through skills training programs and simulations aimed at optimizing the safety and technical quality of the care teams.[27]

Final considerations

Since HPP is the major cause of maternal mortality worldwide, health care teams' ability to institute surgical treatment, preferably within the "golden hour", becomes essential in the event of drug treatment failure. The contemporary development of invasive techniques that preserve the uterus and have high rates of success in hemorrhagic control has changed the sequencing of surgical treatment for PPH. These techniques, including IUB, UCS, VL, AE and their associations must precede hysterectomy and their choice must correlate with the mode of delivery, PPH etiology, topography of the hemorrhagic focus and valuably, with the skill and experience of professionals. However, in view of the failure of surgical techniques that preserve the uterus, hysterectomy should be performed as early as possible, before the installation of coagulopathy. Hysterectomy is also frequently required as a primary treatment in the face of the spectrum of placenta accreta, especially in increta and percreta varieties associated with unfavorable conditions for uteroplacental segmental exeresis and restoration of uterine anatomy. In these situations, the complexity of the operative tactic and severity of the risks demand adequate surgical conditions and a qualified and experienced multidisciplinary team. Since it is a cause of high lethality, high incidence and complex and specialized surgical treatment, its current impact on the planning and reorganization of care teams is significant.

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