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Editorial

Still on the Brazilian Response to the Microcephaly Epidemic: A Meta-analysis of 1,548 Pregnant Women from 13 Cohorts to Evaluate the Risk of Adverse Outcomes

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In 2015, the scientific community was surprised by an epidemic of microcephaly initially identified in some states in northeastern Brazil. The first observations of an unusual increase in the number of cases of microcephaly were made by physicians in their clinical practice. After confirming the occurrence of this new phenomenon, came the challenges in determining its etiology, characterizing the spectrum of clinical manifestations and estimating the risk of its occurrence. These stages were successively fulfilled through ecological studies, case reports and series, and epidemiological studies.[1] Clinicians were the first to raise the hypothesis that Zika virus infection during pregnancy was responsible for the adverse effects observed in children.[2] Subsequently, the virus was detected and sequenced in the amniotic fluid of two pregnant women whose fetuses had microcephaly[3] and specific IgM for Zika was detected in the cerebrospinal fluid of children with microcephaly.[4] A case-control study showed the association between the Zika virus and microcephaly and at the same time, ruled out the role of other factors that could be responsible for its occurrence.[5] The follow-up of cohorts of pregnant women allowed estimating the risk for microcephaly, abnormalities of the Central Nervous System (CNS) diagnosed by imaging, ophthalmologic and audiologic alterations and other birth defects in children born to Zika virus-infected mothers during pregnancy.[6–13] Although cohort studies have shown similar risks of microcephaly, estimates of the risk of other manifestations were diverse, indicating the need to use other analysis strategies with more robust estimates, such as meta-analysis.

In Brazil, cohort studies were developed by different groups of researchers. However, since the beginning of the microcephaly epidemic, Brazilian scientists were concerned about standardizing research protocols and collection instruments as far as possible to enable a joint data analysis in a later step. Several meetings were held to this end, initially involving Brazilian researchers and later researchers from different countries, with support of the Pan American Health Organization and the World Health Organization. In Brazil, the Zika Brazilian Cohorts (ZBC) Consortium[14] was formed. By performing a joint analysis of data from Brazilian studies, it overcomes the limitations of isolated studies, notably the small sample size and consequent inaccuracy of estimates and lower representativeness. Among the contributions of the ZBC Consortium is the recently published article: "Risk of adverse outcomes in offspring with RT-PCR confirmed prenatal Zika virus exposure: an individual participant data meta-analysis of 13 cohorts in the Zika Brazilian Cohorts Consortium."[15] Next, we will highlight some of its points.

Several factors reinforce the relevance of the results presented in this article. It is a meta-analysis of individual data that aggregates and analyzes data from different studies after a process of harmonization of results. Harmonization was performed through several meetings of researchers and enabled the formation of a single database and the analysis of information from all participants, differing from traditional meta-analyzes in which only aggregated data are reanalyzed. The Consortium included almost all cohorts of pregnant women developed in Brazil, totaling 13 studies performed in four Brazilian regions where the Zika virus epidemic occurred, namely the North, Northeast, Central West and Southeast. It is the study with the largest number of participants published so far, totaling 1,548 pregnant women and their respective gestational outcomes. All women had Zika virus infection during pregnancy confirmed through RT-PCR, the gold standard for diagnosing Zika virus infection.[16] Because of interpretation limitations, serological tests were not used to define exposure.

The results of this ZBC-Consortium meta-analysis provide more robust and accurate estimates of the risk of adverse

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events in children born to pregnant women who were infected with Zika virus during pregnancy. This study answers an important question for physicians and health professionals by informing the probability of occurrence of manifestations potentially associated with congenital Zika.

According to the study findings, although microcephaly is the most severe manifestation, it is not the most frequent, being observed in 1.5% of children at birth, and severe microcephaly is less frequent than mild/moderate microcephaly. Furthermore, even though some children are born with a normal head circumference for their age and sex, they may develop postnatal microcephaly, which implies the need to monitor these children and repeat head circumference measurements. It was also demonstrated that the risk of children being born small for gestational age was greater than the risk reported for the general population. Unlike what had been suggested by some authors, the risk of microcephaly did not vary in different regions of the country or with different socioeconomic conditions.

The risk of occurrence of structural changes in the CNS in children born to mothers who became infected during pregnancy was around 8%, and was observed even in children without microcephaly. The most frequent were calcifications, ventriculomegaly and diffuse cortical atrophy, in addition to other manifestations identified. Ultrasound imaging of the CNS after birth is a valuable tool for diagnosing structural alterations.

The risk of presenting at least one neurological alteration was around 20%, highlighting the occurrence of changes in tonus/trophism and convulsive crises. The risk of these alterations (20%) was greater than that of microcephaly and structural abnormalities in the CNS, showing the complementarity of this information and the need to integrate them for an adequate and long-term evaluation of these children.

The risks of audiological and ophthalmological adverse effects, especially changes in the optic nerve, were less than 5%.

Approximately one-third of infants born to mothers exposed to the Zika virus during pregnancy had at least one change, and less than 1% had concomitant changes.

The risks estimated in the ZBC-Consortium meta-analysis are relevant for planning care for pregnant women who become infected with the Zika virus during pregnancy and the care for children born to these mothers. Note that the possibility of a new Zika virus epidemic cannot be ruled out as the number of susceptible individuals increases. The study highlights the need for at least one comprehensive assessment of children by different groups of specialists during their follow-up for the early detection of abnormalities and definition of the necessary interventions. The study also indicates the need for long-term monitoring of children to identify the risk of late manifestations.

Conflicts of Interest
None to declare.

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The Use of Mid-Pregnancy Cervical Length to Predict Preterm Birth in Brazilian Asymptomatic Twin Gestations

O uso da medida do colo uterino no segundo trimestre de gestantes brasileiras como preditor de prematuridade na gestação gemelar

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Abstract

Objective To describe a reference curve for cervical length (CL) in mid-trimester twin gestations using transvaginal ultrasound (TVU) and to investigate whether short CL increases spontaneous preterm birth (sPTB) in asymptomatic twin pregnancies.

Methods This was a prospective cohort study performed at 17 outpatient antenatal facilities of Brazil with women at 18 0/7 to 22 6/7 weeks of gestation who participated in a randomized clinical trial screening phase (P5 trial) between July 2015 and March 2019. TVU was performed to provide CL measurement in all screened women. Almost all women with CL $\leq$ 30 mm received vaginal progesterone 200mg/day and they were also randomized to receive cervical pessary or not. We considered data from the CL distribution among asymptomatic twin pregnancies and analyzed CL and its association with PTB generating receiver operating characteristics (ROC) curves and Kaplan-Meier curves.

Results A total of 253 pregnant women with twins were included in the distribution curve. The mean CL was 33.7 mm and median was 35.5mm. The 10th percentile was 17.8mm. We identified a PTB rate of 73.9% (187/253) with 33.6% of sPTB $<$ 37 (85/253)

Keywords
- Cervical length measurement
- Preterm birth
- Prematurity
- Multiple pregnancy

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and 15% (38/253) of sPTB < 34 weeks. The best cutoff point to predict sPTB < 37 was 24.15 mm. However, the ROC curve showed a poor performance (0.64). The Kaplan-Meier survival curves identified that only CL values ≤ 20mm were associated to sPTB < 34 weeks.

Conclusion A cutoff point of CL ≤ 20 mm can be interesting point to identify short cervix in Brazilian twin pregnancies. However, in Brazilian asymptomatic twin pregnancies, CL does not show a good performance to predict PTB.

Resumo

Objetivo Descrever uma curva de referência da medida do colo uterino no Segundo trimestre de gestações gemelares através de ultrassonografia transvaginal (TVU) e investigar a correlação entre a medida do colo uterino (CL) e o parto prematuro espontâneo (sPTB) em pacientes assintomáticas.

Métodos Foi realizado uma coorte prospectiva multicêntrica em 17 centros de referência do Brasil com mulheres com gestação gemelar entre 18 0/7 a 22 6/7 semanas de gestação que participaram da primeira fase de um ensaio clínico randomizado (P5 trial) entre Julho/2015 a Março/2019. TVU foi realizada para obter a medida do colo uterino em todas as mulheres. A maioria das mulheres com CL ≤30 mm receberam progesterona por via vaginal 200mg/dia e estas foram randomizadas para receber ou não um pessário cervical. Este estudo considerou dados da medida do colo uterino entre mulheres assintomáticas, desenvolvendo uma curva de referência para gestantes gemelares e sua capacidade de predição do parto prematuro através de curva ROC (receiver operating characteristics) e curvas de sobrevida de Kaplan-Meyer.

Resultados O total de 253 gestantes foram incluídos no estudo, A média do CL foi 33.7mm e a mediana 35.5mm. O Percentil 10 do CL foi 17.8mm. A taxa de parto prematuro foi de 73.9% (187/253) com 33.6% de sPTB < 37 (85/253) e 15% (38/253) de sPTB < 34 semanas. O melhor ponto de corte para predizer sPTB < 37 foi 24.15 mm, entretanto a curva ROC demonstrou baixa performance (0.64). A curva de Kaplan-Meier para sPTB identificou que apenas CL ≤ 20 mm estavam associados a sPTB < 34 semanas.

Conclusão Colo uterino ≤20 mm pode ser um interessante ponto de corte para identificar colo curto entre gestações gemelares assintomáticas brasileiras. Entretanto, a medida do colo uterino não apresentou boa performance para predizer parto prematuro.

Palavras-chave

- Medida do colo uterino
- Parto prematuro
- Prematuridade Gestação gemelar

Introduction

Multiple gestations are at higher risk for preterm birth (PTB), and neonatal morbidity and mortality, and their incidence has been in a rising trend since many of them are associated with assisted reproduction treatments.[1–3] The largest cohort in Brazil focused on risk factors for prematurity demonstrated that twin pregnancies had higher chance of PTB than singletons (OR: 15.61; 95% confidence interval, CI: 6.24–39.04).[4]

The use of risk factors to identify women at higher risk of preterm delivery is part of the prevention strategies.[5,6] In this scenario, the cervical length (CL) measurement by transvaginal ultrasound (TVU) in singleton mid-trimester pregnancies has an important role to estimate the risk for spontaneous preterm birth (sPTB) associated with a short cervix.[7]

Studies involving singleton pregnancies have considered 25 mm as the most accepted cutoff to define a short cervix,[8] which represents women under the 10th percentile of an international reference curve.[7] Following this rationale, studies involving twin pregnancies also have focused on CL ≤ 25 mm as a short cervix.[9,10] However, this inference is highly questioned, since singleton and twin births present different CL distribution curves,[11] as well as different gestational outcome results.[2] So far, there is no consensus about the best cutoff point to define a short CL for twins, which makes clinical practice decisions regarding therapies for multiple gestations with short cervix even more difficult.[12]

To correctly identify the CL that is associated to sPTB, specific populational distribution curves are necessary to describe the range of CL and to suggest what should be considered a short cervix in Brazilian twins' pregnancies. Moreover, it is important to know if it is possible to use CL as

a predictor for sPTB in twin gestations. The main objective of this study was to describe a reference curve for CL in mid-trimester twin gestations using TVU and to identify the association between CL and gestational age at birth, and whether mid-pregnancy CL is a good predictor for PTB.

Methods

We performed an ancillary analysis using a cohort strategy analysis of all twin pregnancies included in the P5 Trial (Pessary Plus Progesterone to Prevent Preterm Birth Study – Trial registration RBR-3t8prz, approved by the Brazilian National Review Board/CONEP – number 1.055.555) to describe Brazilian populational curves.[13]

The P5 Trial was a multicenter, randomized, controlled trial involving 17 institutions (nine states in three regions: South, Southeast, and Northeast of Brazil) that compared the effectiveness of vaginal progesterone alone versus progesterone plus cervical pessary in women with short cervix. The study was coordinated by the University of Campinas from July 2015 to March 2019. A TVU screening program using a GE Logiq C5 (GE HealthCare. Chicago, IL, EUA) equipment or similar with a 5 to 9MHz transvaginal probe was offered as part of standard care for all women attending the ultrasound department during routine second trimester ultrasonographic examinations between 18 0/7 and 22 6/7 weeks. Women received information about the TVU technique and P5 study and all provided written informed consent. Sociodemographic characteristics, obstetric history, and current pregnancy information were previously collected.

Exclusion criteria for CL measurement were related to symptoms or pregnancy complications: painful contractions, vaginal bleeding, cerclage during current pregnancy before the screening, ruptured membranes diagnosed before screening, severe liver disease, cholestasis during this pregnancy, previous or current thromboembolism, placenta previa, cervical dilation greater than 1 cm, monoamniotic twin pregnancy, higher order multiple pregnancies (triplets or higher), major fetal malformation in at least one fetus, and stillbirth. For this analysis, we also excluded singleton gestations. The information on pregnancies was accessed using an online database from the screening phase of the P5 trial. Considering P5 trial interventions, 80 women had CL $\leq$ 30mm and 71 accepted to participate in the RCT, where 71 of the patients received progesterone and 43 also received a cervical pessary.

All participating sonographers received previous training in CL measurement according to the Fetal Medicine Foundation program, as well as additional training regarding the volume measurement developed by the University of Campinas's ultrasound department.

Describing the TVU technique briefly, after emptying the bladder, the woman was placed in the dorsal lithotomy position. The TVU probe was introduced until the anterior fornix region, avoiding extra pressure on the cervix, which can artificially increase the CL. A sagittal view of the cervix, showing the endocervical mucosa, was used to properly identify the internal and external ostium (os). Sludge and funneling were also evaluated and described, if present.

Descriptive statistical analysis was performed for demographic characteristics, expressed as means and percentages. Logistic regression was used to estimate odds ratio (OR) for baseline characteristics, gestational age, and CL measurements. Mean, median, and percentiles of CL (P5, P10, P25, P50, P75, P90, and P95) were obtained for the descriptive analysis. The receiver operating characteristics (ROC) curve analysis was performed to identify the most effective cutoff point to predict a sPTB ($<$ 37 weeks). We also used the ROC curve analysis to identify the most effective cutoff points to predict overall PTB ($<$ 37) and sPTB at different gestational ages ($<$ 37 and $>$ 34 weeks – later PTB; $<$ 34–PTB; and $<$ 28 weeks – extreme PTB). We calculated sensitivity, specificity, negative (NPV) and positive predictive values (PPV), and likelihood ratios (LR). The Kaplan-Meyer survival curves were used to analyze time to delivery, considering CL intervals ($\leq$ 10 mm, 10–15 mm, 15–20 mm, 20–25 mm, 25–30 mm, 30–35 mm, 35–40 mm, and $>$ 40 mm). A $p\neg$-value $<$ 0.05 was considered as statistically significant. All statistical analyses were performed using the R (R Foundation for Statistical Computing, Vienna, Austria) software, version 3.6.2.

Results

A total of 253 from 8,168 women were included in this analysis. We excluded 71 women due to missing information, and 7844 singleton women (►**Fig. 1**). Women with CL $\leq$ 30 mm received progesterone 200 mg/day (71 women) and part of them also received a cervical pessary (28).

The incidence of twin pregnancy in the P5 screening phase was 3.5%, with 157 dichorionic diamniotic twins (62%), and 96 monochorionic diamniotic twins (38%). Approximately 70.8% (179/253) of the women were between 20 and 34 years old, and 86.9% (220/253) had studied less than 11 years. Most of the women, 53.4% (135/253), were non-white, and 32.8% (83/253) were obese (body mass index, BMI $>$ 30). Considering obstetrical history, 58.5% (148/253) had at least one previous pregnancy, 7.5% (19/253) had at least one previous PTB, and 24.9% (63/253) had a previous abortion. Funneling was present in 10.7% (27/253), and 13.4% (34/253) presented sludge at measurement. The rate of PTB was 73.9% (187/253), with 33.6% of sPTB $<$ 37 weeks (85/253), and 15% (38/253) of sPTB $<$ 34 weeks (►**Table 1**).

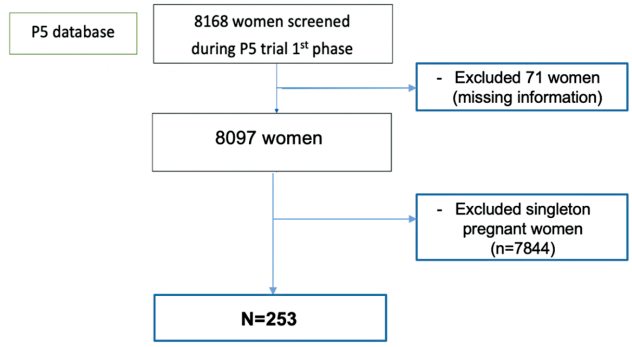

Fig. 1 Patient enrolment flowchart.

Table 1 Sociodemographic and baseline characteristics x gestational age at birth

	Total ($n = 253$)		Overall PTB < 37		≥ 37 weeks		OR (95% CI)	Spontaneous PTB < 37		≥ 37 weeks		OR (95% CI)	Spontaneous PTB < 34		≥ 34 weeks		OR (95% CI)
Characteristics	n or Mean	% or SD	n or Mean	% or ± SD	n or Mean	% or ± SD		n or Mean	% or ± SD	n or Mean	% or ± SD		n or Mean	% or ± SD	n or Mean	% or ± SD	
Maternal age at measurement (years)				±		±			±		±			±		±	
≤19	21	8.3	15	8	6	9.1	0.84 (0.32–2.47)	11	12.9	6	9.1	1.37 (0.49–4.25)	5	13.2	14	7.5	1.96 (0.59–5.68)
20–≤34	179	70.8	134	71.7	45	68.2		60	70.6	45	68.2		24	63.2	132	71	
>35	53	20.9	38	20.3	15	22.7	0.85 (0.43–1.73)	14	16.5	15	22.7	0.7 (0.3–1.6)	9	23.7	40	21.5	1.24 (0.51–2.8)
BMI (kg/m²)																	
≤18.5	4	1.6	4	2.1	0		NS	2	2.3	0	0	NS	2	5.3	2	1.1	NS
18.5–25	77	30.4	63	33.7	14	21.2		34	40	14	21.2		14	36.8	52	28	
25–30	89	35.2	59	31.6	30	45.5	0.44 (0.21–0.89)	25	29.4	30	45.5	0.34 (0.15–0.77)	12	31.6	68	36.6	0.66 (0.28–1.54)
>30	83	32.8	61	32.6	22	33.3	0.62 (0.28–1.3)	24	28.2	22	33.3	0.45 (0.19–1.04)	10	26.3	64	34.4	0.58 (0.23–1.4)
Ethnic origin (self-reported)																	
Non-white	135	53.4	96	51.3	39	59.1		53	62.4	39	59.1		21	55.3	102	54.8	
White	118	46.6	91	48.7	27	40.9	1.37 (0.78–2.43)	32	37.6	27	40.9	0.91 (0.47–1.76)	17	44.7	84	45.2	1.11 (0.54–2.28)
Schooling																	
Preschool, Elementary	163	64.4	123	65.8	40	60.6		56	65.9	40	60.6		27	71.1	116	62.4	
Middle school	57	22.5	38	20.3	19	28.8	0.65 (0.34–1.27)	19	22.4	19	10.6	0.74 (0.35–1.58)	6	15.8	45	24.2	0.61 (0.21–1.5)
Highschool and Higher education	33	13	26	13.9	7	10.6	1.21 (0.51–3.21)	10	11.8	7	13	1.06 (0.37–3.14)	5	13.2	25	13.4	0.91 (0.29–2.45)
Comorbidities																	
No comorbidities	201	79.4	147	78.6	54	81.8		71	83.5	54	81.8		36	94.7	148	79.6	
Hypertension	16	6.3	12	6.4	4	6.1	1.1 (0.37–4.07)	7	8.2	4	6.1	1.37 (0.39–5.45)	0		13	7	NS
Endocrinopathies[a]	14	5.5	10	5.3	4	6.1	0.92 (0.29–3.46)	3	3.5	4	6.1	0.59 (0.11–2.77)	1	2.6	10	5.4	0.43 (0.02–2.36)
Others[b]	22	8.7	18	9.6	4	6.1	1.65 (0.59–5.92)	4	4.7	4	6.1	0.78 (0.18–3.45)	1	2.6	15	8.1	0.29 (0.02–1.49)
Previous conization (yes)	3	1.2	3	1.6	0		NS	0		0		NS	0	2.6	3	1.6	NS
Obstetrical history																	
Nulliparous	105	41.5	77	41.2	28	42.4		34	40	28	42.4		14	36.8	74	39.8	
Parous with no previous PTB	129	51	93	49.7	36	54.5	0.94 (0.52–1.67)	38	44.7	36	54.5	0.92 (0.47–1.83)	16	42.1	102	54.8	0.96 (0.43–2.2)
Parous with at least one previous PTB	19	7.5	17	9.1	2	3	3.09 (0.81–20.28)	13	15.3	2	3	5.69 (1.41–38.41)	8	21.1	10	5.4	4.87 (1.58–15.01)
Previous abortion (yes)	63	24.9	43	23	20	30.3	0.69 (0.37–1.3)	19	22.4	20	30.3	0.64 (0.3–1.34)	7	18.4	48	25.8	0.58 (0.21–1.4)
Funneling at measurement	27	10.7	24	12.8	3	4.5	3.09 (0.99–13.33)	15	17.6	3	4.5	3.9 (1.19–17.58)	9	23.7	14	7.5	2.93 (1.04–7.7)

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; PTB, preterm birth; NS, not significant. **Notes:** [a]Diabetes Mellitus, gestational diabetes, thyroidopathy. [b]Asthma, autoimmune diseases, anemia, obesity, hepatitis.

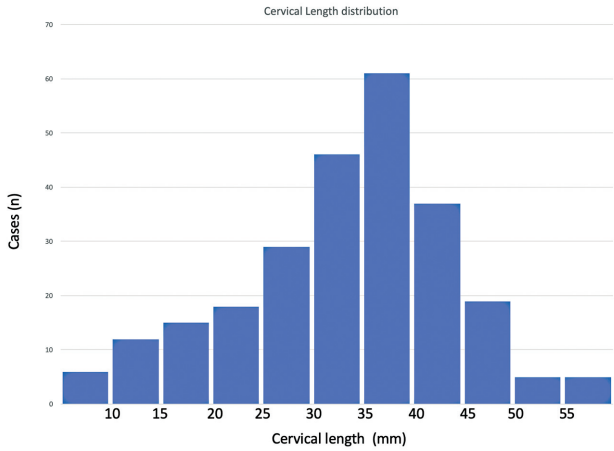

Fig. 2 Cervical length (mm) distribution between 18 and 22 weeks gestation.

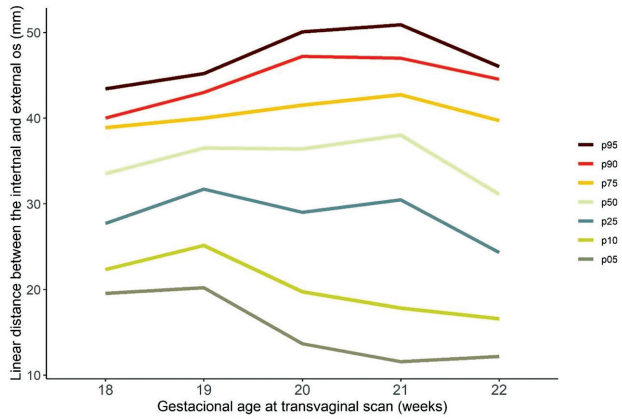

Fig. 3 Curve of percentile values for CL measurement.

The univariate logistic regression analysis for PTB at < 37 weeks did not identify specifically risk factors (►**Table 1**). There was a trend to protection for PTB and sPTB < 37 among overweight and obese women. When considering only sPTB, we identified that having a previous PTB was a risk factor for sPTB < 37 (OR: 5.69; 95% CI: 1.41–38.41) and sPTB < 34 weeks (OR: 4.87; 95% CI: 1.58–15.01). Moreover, funneling at measurement was associated with sPTB < 37 (OR: 3.9; 95% CI: 1.19–17.58) and sPTB < 34 weeks (OR: 2.93; 95% CI: 1.04–7.7). The mean CL was 33.7 mm, and the median was 35.4 mm. The CL was ≤ 25 mm in 51 women (20.2%), ≤ 20 mm in 33 (13%), ≤ 15 mm in 18 (7.1%), and ≤ 10 mm in 6 (2.4%). The CL percentiles were P5 = 12.7 mm, P10 = 17.8 mm, P25 = 27 mm, P50 = 35.4 mm, P75 = 40.7 mm, P90 = 46 mm, and P95 = 48.3 mm. The CL at measurement showed a non-normal distribution confirmed by the Shapiro-Wilk test ($p < 0.001$) (►**Fig. 2**).

Considering gestational age at measurement, there was a decrease in CL measure when gestational age increases (►**Table 2**).

As a presumable consequence, considering two gestational ages intervals at measurement (18–20 vs. 21–22 weeks), we identified an increase in sensitivity to predict sPTB < 37 during 21 to 22 weeks (►**Table 3**).

►**Fig. 3** illustrates the descriptive analysis of CL considering percentiles and gestational age at measurement.

Table 2 Values of percentile 5, 10, 25, 50, 75, 90, and 95 for the cervical length according to gestational age at measurement

Gestational age (weeks)	n	Mean	P05	P10	P25	P50	P75	P90	P95
Total	253	33.7	12.7	17.8	27	35.4	40.7	46	48.3
18	34	33.2	19.5	22.3	27.7	33.5	38.9	40	43.4
19	33	34.8	20.2	25.1	31.7	36.5	40	43	45.2
20	45	34.6	13.6	19.7	29	36.4	41.5	47.2	50.1
21	72	35.4	11.6	17.8	30.4	38	42.7	47	50.9
22	69	31.1	12.2	16.6	24.3	31.1	39.7	44.5	46

Table 3 TVU accuracy to predict sPTB < 37 considering gestational age intervals

Measurement	Cervix at 18–20 weeks				Cervix at 21–22 weeks			
	≤ 24.15 mm	≤ 15 mm	≤ 25 mm	≤ 30 mm	≤ 24.15 mm	≤ 15 mm	≤ 25 mm	≤ 30 mm
Sensitivity	15	10	15	30	42.2	20	44.4	60
Specificity	100	100	93.5	83.9	91.4	100	82.9	74.3
PPV	100	100	75	70.6	86.3	100	76.9	75
NPV	47.7	46.2	46	48.1	55.1	49.9	53.7	59.1
Positive Likelihood Ratio	–	–	2.3	1.7	4.9	–	2.6	2.3
Negative Likelihood Ratio	0.9	0.9	0.9	0.8	0.6	0.8	0.7	0.5

Abbreviations: NPV, negative predictive values; PPV, positive predictive values, sPTB, spontaneous preterm birth, TVU, transvaginal ultrasound.

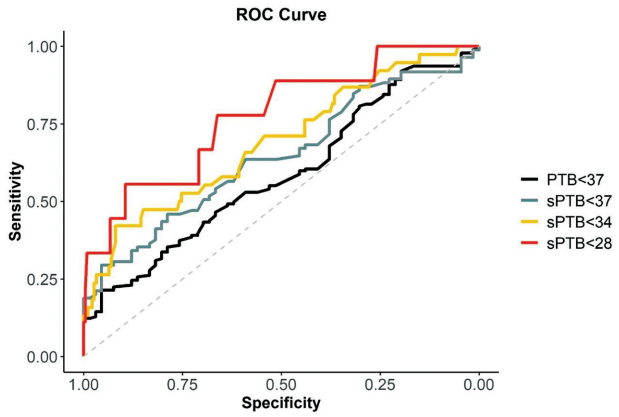

Fig. 4 The ROC curve analysis of PTB and sPTB at different gestational ages.

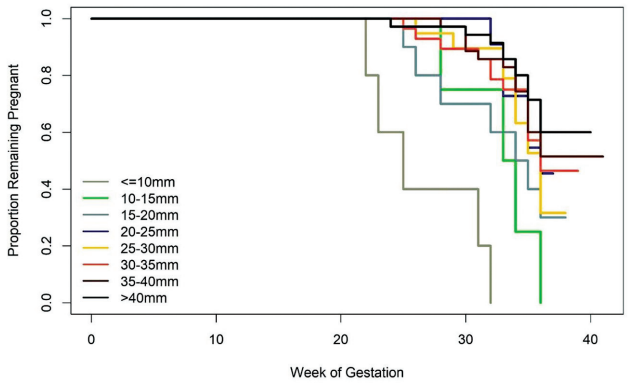

Fig. 5 The Kaplan-Meyer survival analysis for sPTB considering different ranges of cervical length.

The ROC curve analysis to predict sPTB at < 37 and < 34 weeks demonstrated a low performance, with area under the curve (AUC) 0.64 (0.56–0.73) and 0.69 (0.59–0.79), respectively. For sPTB at < 28 weeks the ROC curve demonstrated an AUC of 0.78 (0.60–0.95) (►**Fig. 4** and ►**Table 4**). ►**Table 4** illustrates CL performance tests results to predict prematurity. The best cutoff point to predict sPTB at < 37 weeks was 24.15 mm, with 24.9% sensitivity and 95.5% specificity.

The best cutoff points to predict sPTB at < 34 and < 28 weeks were 21.9 and 19.95 mm, respectively. The Kaplan-Meyer survival analysis demonstrated an association between extremely severe (< 28 weeks), severe (> 28–< 34 weeks) and late sPTB (> 34–< 37 weeks), as well as CL ≤ 20 mm (►**Fig. 5**).

Discussion

Our study provides Brazilian CL distribution curves from 18 to 22 + 6 weeks in asymptomatic twin gestations. The CL 10th percentile was 17.8 mm and when CL was ≤ 20 mm, there was an association with extremely severe, severe, and early sPTB. However, CL was a poor predictor for sPTB in twin gestations and CL measurement by TVU did not present good performance as a screening test for spontaneous PTB.

The mean CL identified in our study and the PTB rate are very similar to previous Brazilian studies focused on twin gestations. A prospective cohort involving 341 patients with CL measurement between 18 and 21 weeks, described CL mean (31.95–33.46 mm) with 68.2% of PTB < 37 weeks.[14] However, when compared with an Italian cohort study that involved 904 twin gestations with a slightly higher CL median (35.4 vs. 38 mm), our study presented a considerably higher incidence of PTB (PTB < 32 weeks, 14.6 vs. 8.3%), which raises the possibility that other factors could be more important to influence the preterm delivery rate in twins, especially when we consider different populations.[15]

Thus, before defining what is a short cervix (and its association with sPTB) in a Brazilian twin population it is crucial to know the CL distribution curve in this specific subset of women. If we consider short cervix as CL under P10, we demonstrated that in the Brazilian population CL ≤ 25 mm is not the best cutoff value for twin gestations. This way, a more interesting cutoff point would be CL ≤ 20 mm, since it is very close to P10 and demonstrated a clear association with early sPTB in the Kaplan-Meier curves.

Differently from a singleton gestation, where the maternal sociodemographic characteristics may influence the incidence of sPTB,[16] in our study, only previous PTB and funneling at measurement presented as risk factors for sPTB in twins. Our findings reinforce that, in twin gestations, maternal baseline characteristics do not influence prediction for sPTB. Additionally, the literature shows that combining CL and maternal characteristics does not seem to be the solution to increase sensitivity for screening.[17,18]

Implementing a screening test for prediction is the first step for prevention, offering possible therapies when risk factors are present. However, treatments such as progesterone and cerclage used for preventing sPTB in singleton with

Table 4 Cervical length performance for predicting PTB

	AUC	95% CI	*Cut-off*	Sensitivity	Specificity	PPV	NPV	LR+	LR-
PTB < 37	0.586	(0.509–0.663)	24.15	21.4%	95.5%	93.0%	30.0%	4.7	0.8
sPTB < 37	0.644	(0.557–0.732)	24.15	24.9%	95.5%	89.3%	51.2%	6.5	0.7
sPTB < 34	0.692	(0.594–0.79)	21.90	42.1%	91.9%	51.6%	88.6%	5.2	0.6
sPTB < 28	0.776	(0.607–0.946)	19.95	55.6%	89.6%	16.7%	98.1%	5.3	0.5

Abbreviations: AUC, area under the curve; CI, confidence interval; LR, likelihood ratios; NPV, negative predictive values; PPV, positive predictive values, PTB, preterm birth; sPTB, spontaneous preterm birth.

short cervix do not demonstrate promising results in twins.[10,19] Considering the possibility to predict sPTB and administer antenatal corticosteroids, routine CL measurement did not affect the rate of twins born before 34 weeks that received lung maturation intervention.[20] In our study CL measurement by TVU in mid-trimester to predict sPTB < 37 and sPTB < 34 weeks had a poor performance and this finding was very similar to a previous Brazilian cohort that identified an AUC of 0.64 (95% CI: 0.53–0.75) for sPTB < 34.[21] Thus, considering the lack of effective interventions for preventing PTB in twins, a routine CL measurement may not improve perinatal outcomes.[22] It could also increase hospital admission rates for false labor and antepartum length of stay, leading to stress and anxiety among patients and family. Moreover, it could potentially lead to unnecessary and risky interventions, such as prescription of tocolytic drugs and bed rest.[23]

A strength of our study is that our sample was composed by women from 17 different settings in Brazil, involving diverse population characteristics that can be found in a country with a continental territory.

One limitation is that almost all women with CL ≤ 30 mm received progesterone 200 mg/day and part of them also received a cervical pessary, which could have influenced the PTB's final result or even postponed PTB. However, the last studies did not show these two interventions as capable of causing a significant reduction in PTB for twins.[10,23] Also, considering that most of the participating centers were reference for high-risk pregnancies, it is possible that our distribution curve tended toward shorter CLs.

Finally, as CL does not show a good performance to predict PTB, and the available treatments for PTB in twins do not show a clear benefit, we believe that a universal screening program for twin gestation in Brazil, considering a panel with limited resources, would not be helpful or economically viable. When treatments for these high-risk populations show good efficacy, maybe a screening and treatment strategy [Q3] could be justified.

Conclusion

A cutoff point of CL ≤ 20 mm can be interesting to identify short cervix in Brazilian twin pregnancies. However, in Brazilian asymptomatic twin pregnancies, CL does not show a good performance to predict PTB. Furthermore, the available treatments for PTB in twins do not support a CL screening program in Brazil.

Contributions

TV Silva: design, investigation, data collection, data analysis, data curation, methodology, writing, and review & editing. AB Pinheiro: review & editing. MS França: investigation, data collection, and data analysis. KF Marquart: investigation, data collection, and data analysis. JP Argenton: statistics and data analysis. BW Mol: funding acquisition, writing, and review & editing. RC Pacagnella: conceptualization, design, data curation, funding acquisition, methodology, writing, and review & editing.

Conflict of Interests [Q2]

The authors have no conflict of interests to declare.

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Development of a Mobile Health Application Based on a Mixed Prenatal Care in the Context of COVID-19 Pandemic

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Abstract

Objective We describe the development and structure of a novel mobile application in a mixed model of prenatal care, in the context of the COVID-19 pandemic. Furthermore, we assess the acceptability of this mobile app in a cohort of patients.

Methods First, we introduced a mixed model of prenatal care; second, we developed a comprehensive, computer-based clinical record to support our system. Lastly, we built a novel mobile app as a tool for prenatal care. We used Flutter Software version 2.2 to build the app for Android and iOS smartphones. A cross-sectional study was carried out to assess the acceptability of the app.

Results A mobile app was also built with the main attribute of being connected in real-time with the computer-based clinical records. The app screens detail information about activities programmed and developed in the prenatal care according to gestational age. A downloadable maternity book is available and some screens show warning signs and symptoms of pregnancy. The acceptability assessment was mostly rated positively regarding the characteristics of the mobile app, by 50 patients.

Conclusion This novel mobile app was developed as a tool among pregnant patients to increase the information available about their pregnancies in the provision of a mixed model of prenatal care in the context of the COVID-19 pandemic. It was fully customized to the needs of our users following the local protocols. The introduction of this novel mobile app was highly accepted by the patients.

Keywords
- COVID-19
- Mobile application
- Telemedicine
- Prenatal care
- Acceptability

Introduction

Perinatal care is a public health strategy that has been thought to be one of the most effective means of reducing unfavorable perinatal outcomes.[1] However, the restrictions such as immobilization and lockdown to limit the spread of COVID-19 caused the health services to the outpatient clinics to be interrupted associated with an increased frequency of

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adverse maternal and perinatal outcomes.[2,3] Given this scenario and the need to assure the continuity of the provision of prenatal care, we introduced a new model of mixed prenatal with in-person visits and a teleconsultation program.[4,5] Telemedicine has been proven to be useful in the care of pregnant women in different scenarios to provide health outcomes comparable to the traditional methods of care.[6–9] Therefore, the major role of integrating electronic health technology into prenatal care is to provide broader healthcare in diverse manners and to create a lot of opportunities for patients and health providers.

Studies of women's general assessments of what they perceive as important aspects of antenatal care reported that sufficient information and explanation were so important.[10,11] We believe it is imperative to allow patients actively participation in their pregnancy care. The availability of more information about her health status and that of her baby allows the pregnant woman to be involved in the entire care process. This achieves feedback between the pregnant woman and the doctor that will improve maternal and perinatal outcomes. Mobile technology, a modality of telehealth, has been reported as a useful and reliable tool for monitoring clinical factors and treatment in different health conditions.[12] Thus, the introduction of new technology as a mobile application with data regarding their pregnancy could help our patients with this objective.

In this study, we describe the development and structure of a novel mobile application in mixed prenatal care in the context of the COVID-19 pandemic and tested its acceptability in a cohort of patients.

Methods

We introduced telemedicine and mobile technology considering recommendations from frameworks on the development of health-related interactive systems.[13,14] This study was part of a larger institutional study on COVID-19 (reference number: 063-2020-DG-N°20-OEAIDE/INMP) approved by the local institutional ethics board (reference number: 019-2020-CIEI/INMP).

Insights

We grouped a multidisciplinary team including TI people, OB/GYN doctors, statisticians, and external consultants supported by the hospital managers and the Ministry of Health to build a new model of prenatal care adapted to the new scenery of the COVID-19 pandemic. We followed 3 steps. First, we introduced a mixed model of prenatal care based on international recommendations,[15–17] which essentially considers a reduced number of in-person visits and some virtual phone consultations. A detailed description of this new care model was published in a previous article.[5] Second, we developed a comprehensive clinical computer-based patient record (Integrated Hospital Management System, SISGALEN PLUS®, INMP-MINSA, Peru), built on our standard model of prenatal care previously established in agreement with CLAP recommendations and other current international guidelines.[8,17,18] Third, we developed a mobile application to allow patients to actively participate in their pregnancy care.

Design and Build of the Mobile Application and Prototype Characteristics

In this context, our institution developed a mobile application to help provide comprehensive and personalized prenatal care. This technology was designed and developed by OB/GYN doctors and computer engineers based on the novel mixed model of prenatal care with continuous feedback from patients. We used Flutter Software version 2.2 to build the mobile application for Android and iOS smartphones. It took 6 months from design and construction to be introduced into the Google store. It will be soon introduced into the Apple store.

Acceptability Assessment

We assessed the app's acceptability using an instrument for evaluating a telehealth program proposed by Portz et al.[19] This survey is divided into 2 sections. The first one includes 8 questions measured on a 5-point Likert scale ranging from "extremely disagree" to "extremely agree," and the second section includes 3 open-ended questions. According to the technology acceptance model (TAM), our survey was applied to understand patients' adoption of new mobile application.[20,21] The 4 TAM constructs applied were 1) *perception of the app's usefulness* (1 question), 2) *perception of the app's ease of use* (5 questions), 3) *attitudes* about the app (2 questions), and 4) *intentions to use* the app (1 open question) (►**Supplemental 1**). We collected survey data in a cohort of patients with access to mixed prenatal care who were invited to participate in the study in a non-random fashion. Patients received comprehensive information on how to download and run the app, before the acceptability survey. Demographic characteristics were collected directly from the patients and electronic records. The acceptability was a paper questionnaire, carried out during the last in-person visit. Answers could be clarified at the time of the survey by the researchers.

We performed a descriptive analysis using MS Excel 2013. Results from the acceptability survey were summarized for each point of the Likert scale and represented in a stacked bar chart for the 9-item questions.[22] The open-ended responses were analyzed using magnitude coding, which quantifies participants' answers, highlighting the most frequent comments. Statistical analysis was performed using Stata Statistical Software 14.0 (Stata Corp. 2015, College Station, TX, USA).

Results

Design and Build of the Mobile Application and Prototype Characteristics

We built a mobile application with the main attribute of being connected in real time with the clinical computer-based record. The system was structured on a distributed architecture of microservices, then they are consumed by an app that is structured with a hybrid development through an

"API Gateway". This allows great versatility to be able to deploy it on Android and IOS cell phones. This mobile application can be delivered exclusively to patients with an electronic clinical record, accessed with a username defined by the national ID, and a protected password. The built app's main screens are shown in ►**Figures 1** and **2**, and additional screens are provided in ►**Supplementals**. The first screen of visualization (►**Figure 1**) shows the name, past medical history, and age of the patient, as well as the current gestational age.

It contains 5 options listed as follows: 1) *prenatal control schedule* including all the tasks for the corresponding gestational age, 2) *prenatal card* with the relevant clinical data and lab tests, 3) *information about the alarm signs* of the current pregnancy, 4) *list of symptoms* of COVID-19 disease, and 5) *notifications* about omitted tasks. By clicking on the prenatal control schedule, patients can visualize the prenatal protocol care summarized in 6 appointments (►**Figure 1**), each one corresponding to a specific period of pregnancy carried out either by virtual or in-person consultation. In addition, the gestational age of the patient at the time of the appointment can be visualized. Each completed visit is marked in orange, and the subsequent appointments are displayed in white (►**Figure 2**).

By clicking on each appointment, a screen is displayed with all the scheduled tasks for the corresponding gestational age (►**Figure 2**), such as clinical evaluation, obstetric ultrasound scan, lab tests, provision of medications, Pap smear test, vaccination, family planning counseling, and psychoprophylaxis. Tasks not carried out will be marked in red. The option of the maternity book enables the user to download a printable version of the updated information about clinical history and lab test results. Additionally, patients have access to information about the alarm signs of pregnancy, COVID-19 disease (►**Supplemental Figures**), and notifications about omitted activities and scheduled appointments (►**Figure 2**). We built several previous versions, which were modified according to patient feedback. A final version was tested for connectivity with the clinical computer-based record.

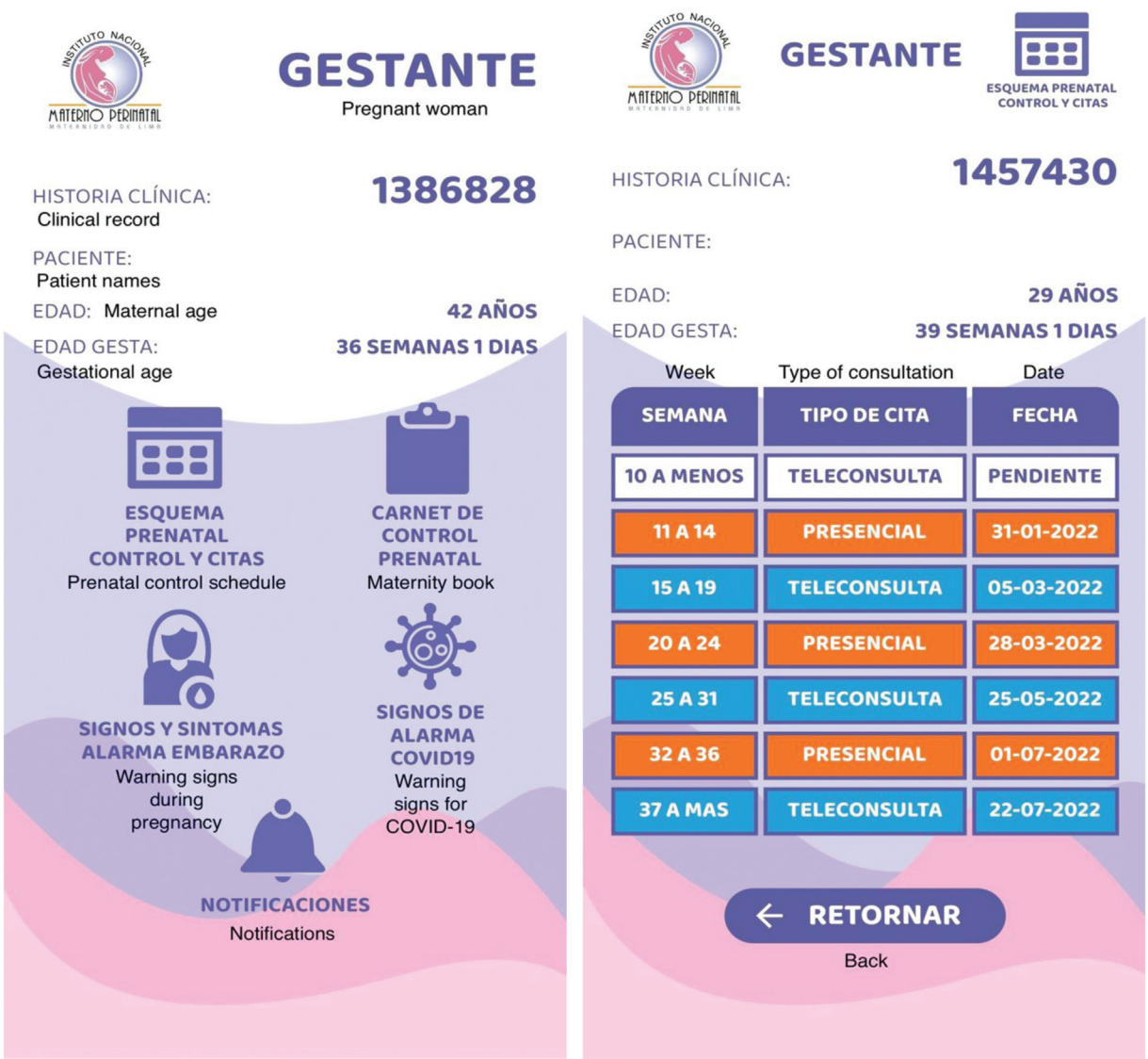

Fig. 1 Prototype's main screens and prenatal control schedule

Fig. 2 Scheduled tasks for the corresponding gestational age and notifications screen

Assessment of the Acceptability

Fifty patients were surveyed in the study period in our outpatient clinic. All gave written consent to participate in the survey. **Chart 1** details the characteristics of the study population. The mean maternal age was 30 years, and the mean gestational age at first contact with the mobile application was 27.8 weeks. Forty-three (86%) patients had national health insurance, and 11 patients (22%) reported having access to education beyond high school. All pregnant women had at least one risk factor, including overweight and obesity (n = 29, 58%) and previous cesarean sections (n = 20, 40%).

Regarding the type of mobile phone, 48 (96%) reported using the Android operating system. ►**Figure 3** shows the patients' acceptance of the mobile application. The 4 constructs of acceptability yielded the following results: 1) *perception of usefulness*: 96% (n = 48) agree that the mobile app is essential and will help with their prenatal care; 2) *perception of ease of use*: more than 94% of patients were able to enter, read, and navigate through the mobile app, but 46% (n = 23) still needed some orientation and help to use the application; 3) *attitudes about the app*: all patients were pleased with how the application works and looks; and 4) *intention to use*: 94% (n = 47) of patients reported the intention to use the app again. Regarding the open question asking "What do you like the most about the application," 62% of patients like the information about their pregnancy, visibility of lab test results, and subsequent appointment, and 22% of women like it because it is easy to use. Only 20% of patients gave some suggestions to improve the application. Six patients recommended that the app be available to all pregnant women, 2 of them suggested including notifications a day before the appointment, and 1 patient suggested the possibility to contact doctors online anytime.

Chart 1 Demographic and maternal characteristics (n = 50)

	n	%
Mean maternal age, years (range)	**30.0 (17.8–41.2)**	
Mean gestational age at first contact with the mobile app, weeks (range)	27.8 (12.1–37.1)	
Human Development Index		
Stratum I	2	4.0
Stratum II	22	44.0
Stratum III	21	42.0
Stratum IV	5	10.0
Insurance modality		
National health insurance	43	86.0
Not national health insurance	7	14.0
Education level		
Primary	3	6.0
High school	36	72.0
Technical or University	11	22.0
Nulliparous	15	30.0
Risk factors		
Obesity (BMI≥30)*	29	58.0
Previous cesarean section	20	40.0
Mother Rh negative	11	22.0
Fetus with structural abnormalities	10	20.0
Diabetes	7	14.0
Hypothyroidism/Hyperthyroidism	6	12.0
History of hypertension/preeclampsia	6	12.0
Anemia	5	10.0
Multiple pregnancy	3	6.0
Placenta previa	2	4.0
Asthma	2	4.0
Short interpregnancy interval	1	2.0
Mother with HIV** infection	1	2.0
Previous perinatal death	1	2.0
Others	6	12.0
Operating system used by the patients		
iOS	2	4.0
Android	48	96.0

*BMI: Body mass index
**HIV: Human immunodeficiency virus

Discussion

This study details the development and structure of a novel mobile application in a mixed model of prenatal care in the context of the COVID-19 pandemic. The assessment of the app's acceptability was mostly positive.

There are several mobile applications commercially available dedicated to some aspect of pregnancy care,[23] however, not all have an impact on improving maternal health. Cawley et al.[24] reported using a mobile application based on information tips to enhance healthy behaviors among pregnant women but with no impact on clinical health outcomes. Innovative solutions are recommended to closely manage, monitor, and empower pregnant women to actively participate in the management of their pregnancy.[25,26] A mobile health app that targets pregnant women may facilitate the integration of prenatal care into other aspects of their family and professional life. Thus, women who are highly engaged with their healthcare decisions during pregnancy might be more receptive to educational programs and recommendations.[27] Our new mobile application allows patients to access some aspects of the clinical record, enhancing personalized care. In our scenario, patients have a prenatal card as proof of compliance with the traditional prenatal care protocol summarizing the main achieved activities. Therefore, the new app described here still allows patients to view an updated printable card anytime and anywhere. Thus, if the app can communicate prenatal care information and basic alarm signs of pregnancy, the in-person visits may allow for more individualized discussion. Ultimately, health managers and providers must ensure the privacy and security of patients' information when using telemedicine.[28] Therefore, we adhered to a strict security protocol when developing this app, allowing access exclusively to patients with a valid ID card and an encrypted password.

This mobile application was tested with a considerable number of high-risk pregnant women and showed an acceptable perception regarding the characteristics of the application in 3 of the 4 constructs evaluated: perception of usefulness, attitudes toward the app, and intention to use. However, some aspects of the ease of using the app among the patients could dampen the usability of this new technology. These difficulties probably occur due to the inexperience of patients with mobile applications that provide health care information despite 94% of them having an educational level higher than high school. Several improvements to the app should be incorporated for future use, and instructions for use should be provided to future users. Because the inexperience was associated with a need for assistance to use the app, instructions, and support from health providers will be important to engage pregnant patients with the app. Final changes to our app should also include improvements in mobile platform capability to support the number of patients in prenatal care.

Conclusion

To our knowledge, this is the first study to introduce a mobile application among pregnant patients during the COVID-19 pandemic scenery as a tool to increase the information available about their pregnancies in a mixed prenatal care program in a low-resource country. Our results provide evidence of the high acceptability of this mobile application among users, which is an essential step to massifying this tool in routine prenatal care. However, further studies are needed to test the impact of this novel application among perinatal outcomes.

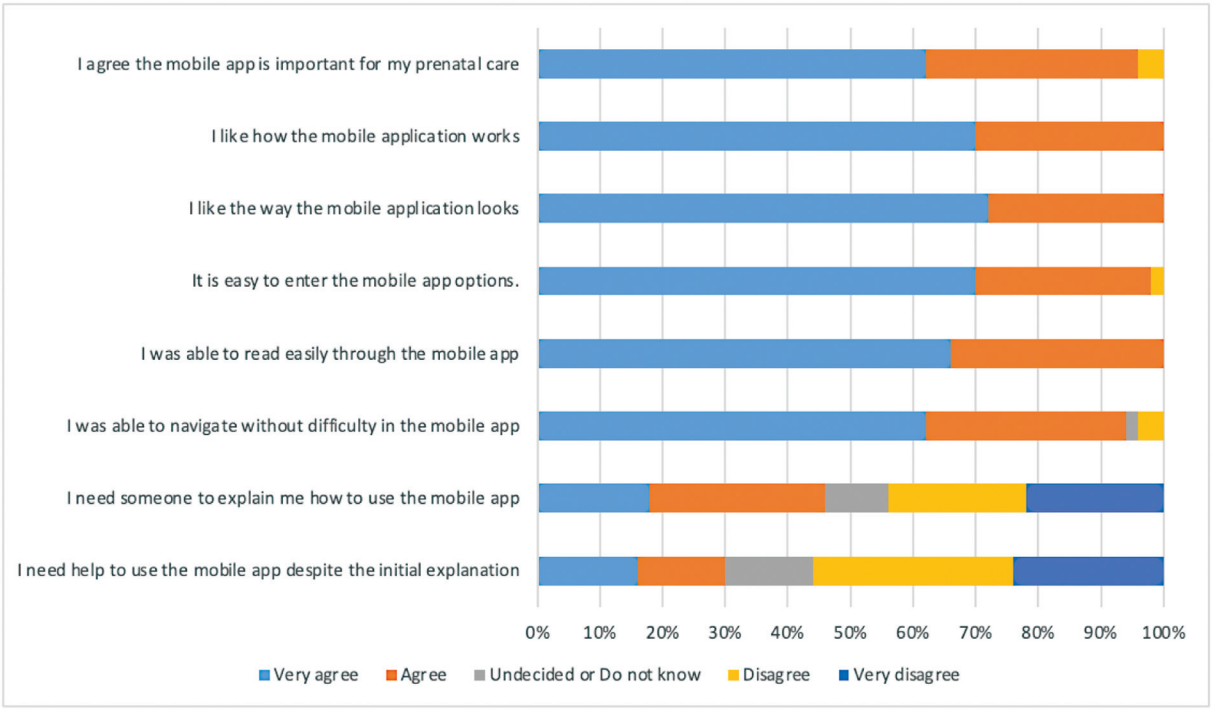

Fig. 3 Acceptability survey of the mobile app among pregnant women (n = 50)

Contributions

Rommy Helena Novoa, Walter Ventura, Luis Meza-Santibañez, conceived of the study and planned the methodology. Xin Huang Yang, Wilder Eduardo Melgarejo, Juan Carlos Bazo-Alvarez contributed to search strategy development and mobile app acceptability assessment. Rommy Helena Novoa, Luis Meza-Santibañez, Juan Torres-Osorio, Vladimir Jáuregui-Canchari, Noe Rodríguez-Hilario contributed to the development of the mobile app. All authors contributed to the manuscript.

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Conflicts to Interest

None to declare.

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Psychiatric Symptoms in Women with High-risk Pregnancy in the Postpartum Period: A Case-control Study

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Abstract

Objective: Psychiatric symptoms are common mental issues in pregnancy and the postpartum period. There is limited information regarding the psychiatric symptoms of women with high-risk pregnancy in the postpartum period. This study aimed to compare the severity of psychiatric symptoms and psychological distress in women with high-risk and low-risk pregnancies in the postpartum period.

Methods: This case-control study examined 250 women in the postpartum period in two groups with low-risk (n = 112) and high-risk (n = 138) pregnancies. Women completed the Brief Symptom Inventory-53 (BSI-53) and the Risk Postnatal Psychosocial Depression Risk Questionnaire (PPDRQ).

Results: The mean severity of psychiatric symptoms in women with high-risk pregnancies was significantly higher than that in women with low-risk pregnancies (39.34 ± 17.51 vs. 30.26 ± 17.08). Additionally, the frequency of psychological distress in women with high-risk pregnancies was approximately twice higher than that in women with low-risk pregnancies (30.3% vs. 15.2%). Furthermore, the risk factors for depression in women with high-risk pregnancies were almost 1.5 times (59.8% vs. 39.8%) higher than the factors in women with low-risk pregnancies. The results of the logistic analysis indicated that high-risk pregnancies could be twice the odds ratio of developing postpartum psychological distress (ß = 2.14, 95% CI 1.4-6.3, p= 0.036).

Conclusion: Psychiatric symptoms and the psychological distress index are higher in postpartum women with high-risk pregnancies than in postpartum women with low-risk pregnancies. The study suggests that obstetricians and pregnant women's health care providers should strongly consider screening of psychiatric symptoms in women with high-risk pregnancies both during pregnancy and after delivery as the women's routine care priorities.

Keywords
- Psychological disorders
- High-risk pregnancy
- Postpartum
- Psychological distress

Introduction

Pregnancy and childbirth are important stages of a woman's life that increase the chance of mental disorders.[1,2] Numerous studies have confirmed a higher risk of psychiatric symptoms during the first months after delivery compared to the risk of the out-of-postpartum period.[3] Severe psychiatric disorders are events putting mothers and fetuses at risk

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for suicide and/or infanticide and are among developmental growth disorders for fetus or child.[4,5]

Approximately 10 to 13% of women experience postpartum depression,[6] and among them, 20 to 60% also experience anxiety.[7,8] Delivery is an important life event accompanied by profound and usually stressful changes in all aspects of daily life, causing women to be vulnerable to psychiatric disorders.[9] The risk of severe postpartum psychological disorders may be related to hormone fluctuation rather than their concentration.[10]

Although various risk factors have been identified for perinatal psychiatric illnesses, a review study indicates that medical complications during pregnancy are associated with postpartum psychiatric disorders.[11] The medical complications include preeclampsia,[3,12] hyperemesis gravidarum,[13] gestational diabetes,[14,15] gestational hypertension,[16] postpartum hemorrhage,[17] cesarean section,[18] and preterm delivery.[19] A meta-analysis study also reported preeclampsia as a risk factor for postpartum depression.[20]

Further understanding of the relationship between high-risk pregnancy and postpartum psychiatric disorders is significant for the development of targeted screening and treatment approaches. Few studies have examined the range of psychiatric illnesses in the postpartum period, and most have focused on a disorder. To the best of our knowledge, the present research was the first case-control study comparing the severity of psychiatric symptoms to nine subscales and risk of postpartum depression in two groups of women with high-risk and low-risk pregnancies. Therefore, this study had three objectives: 1) comparison of the severity of nine symptoms of psychiatric disorders, and the psychological distress index in postpartum women with low-risk and high-risk pregnancies, 2) comparison of the scores of psychosocial risk factors in postpartum women with low-risk and high-risk pregnancies, 3) exploration of the determinants of psychological distress in women with psychological distress in the postpartum period.

Methods

The present case-control study examined pregnant women who visited public or private midwifery clinics in Babol city from November 2020 to September 2021 to receive postpartum care. The initial inclusion criteria for both groups were as follows: age over 18 years, education level higher than primary school, vaginal delivery, the first 6 weeks after delivery, and consent to enter the study. Women, who experienced "traumatic birth" like an operative birth, large perennial lacerations, and infant malformation or death, were excluded from the study.

Inclusion criteria for the case group included having a high-risk pregnancy in a recent delivery so that the person should have at least one of the high-risk pregnancy criteria according to the pregnancy risk questionnaire. This questionnaire determines high-risk pregnancy based on several important factors, including demographic (age under 18, age over 35, low/high body mass index), history of medical diseases (cardiovascular, pulmonary, renal, and thyroid diseases), current status of high-risk pregnancy (gestational diabetes, hypertension, preterm delivery, fetal distress, and medical diseases, pregnancy following in vitro fertilization, and multiple pregnancy), and high-risk behaviors (substance abuse, alcohol, and smoking).[21]

Inclusion criteria for the control group included low-risk pregnancies with no high-risk pregnancy symptoms. The participants in the low-risk pregnancy group were selected by matching them to the high-risk group. The matching method was based on the frequencies of age and education characteristics.

This study had a convenience sampling method. The sample size was obtained equal to 243 based on the clinical difference of 10 units in the score of the Brief Symptom Inventory using the sample size formula (considering the test power of 80%, $\alpha = 0.05$, $\mu_1 = 17$, and $\mu_2 = 12$) with the PASS15 software.

One midwife outside the research team explained the purpose of the study to the patients. She interviewed the women during postpartum visits, while the women waited to visit a doctor. She examined the initial inclusion criteria by studying the medical record and obtaining a history from the patient. If the woman were eligible to include in the case group (high-risk) or control group (low-risk), she would tell her the research purpose. A high-risk pregnancy was considered when a person had one of the criteria for diagnosing a high-risk pregnancy according to the checklist.[21] If the person did not have any of the high-risk pregnancy criteria, she was assigned to the low-risk group. If the pregnant woman were willing to participate in the study, she would complete the informed consent form. Then, the women in both groups (112 with high-risk pregnancies and 138 with low-risk pregnancies) responded to the questionnaires of the study. The participants completed the following questionnaires:

Brief Symptom Inventory-53 (BSI-53): This questionnaire consists of 53 questions covering 9 domains of psychological symptoms, including depression (symptoms of mood swings and influences as well as lack of motivation and loss of interest in life), anxiety (restlessness and stress as well as panic attacks and feelings of fear), somatization (suffering from the perception of bodily dysfunction), obsessive-compulsive (thoughts and impulses experienced are incessant and irresistible but undesirable in nature), interpersonal sensitization personal (feeling of personal inferiority and inferiority to others), phobic anxiety (persistent fear response to a place, object, or situation that is not reasonable), paronid [Q4]ideas (disordered thinking characteristics of projective thoughts and hostility), hostility (thoughts, feelings, or actions characteristic of anger), and psychoticism (withdrawal, isolation, schizophrenia lifestyle as well as the leading symptoms of schizophrenia).Top of Form[Q5]

Bottom of Form[Q6] Psychological distress, Global Severity Index (GSI), was calculated with the sum of the scores of 53 questions divided by 53 questions.[22] The reliability of the Persian version of BSI-53 showed a Cronbach's alpha coefficient of 0.95 for all subscales. The cut-off point of the psychological distress index was obtained 1 based on the scores.[23]

Postnatal Psychosocial Depression Risk Questionnaire (PPDRQ): This questionnaire has 12 questions some of which are scored from 0 to 6. The score range of the questionnaire is from 8 to 82. Higher scores indicate a higher risk.[24] The Persian validity of the questionnaire was used in this study. The cut-off point of psychosocial risk was considered 23 based on the total scores.[25]

The study data were statistically analyzed using SPSS 22. To compare the variables of the two groups, the independent t-test, chi-square test, and Fisher's exact test were used according to the type of variable and the assumptions of the tests. Furthermore, multivariate models were also used to control the effects of other confounding variables in the data analysis. Moreover, the Multiple Logistic Regression test was used. In this model, GSI >1 was included as a dependent variable, while the psychosocial risk score $\geq$23, age, and education level were included as independent variables. The results were calculated and reported as an adjusted odds ratio with a confidence level of 95%. P values less than 0.05 were considered statistically significant.

Results

The mean age of all women was 29.71 ± 5.42 years (minimum age of 17, and maximum age of 44). In terms of education level, 62 (24.8%) women had under-high-school-diploma degrees, 75 (30.0%) had high-school diplomas, and 113 (45.2%) had academic degrees and higher. ►**Table 1** shows that the highest frequency belongs to the risk factor of age of women under 18 years or over 35 (26.8%) in women with high-risk pregnancies. Furthermore, the lowest frequency of pregnancy risk is related to renal diseases (1.1%).

►**Table 2** compares the mean psychological symptoms with 9 subscales, the GSI, and the psychosocial risk score in the groups. The normal data distribution was measured using the Kolmogorov-Smirnov test. Based on the results, not all variables followed the normal distribution; hence, the nonparametric Mann-Whitney test was used. The results indicated that the mean scores of severe symptoms of obsession-compulsion, depression, anxiety, hostility, paranoid ideation, and psychoticism were significantly higher in postpartum women with high-risk pregnancies than in those with low-risk pregnancies ($P < 0.05$). Furthermore, the psychological distress index and high-risk factors were significantly higher in women with stillbirths and high-risk pregnancies than in those with low-risk pregnancies ($P < 0.05$). However, the two groups were not significantly different in terms of mean physical complaints, interpersonal sensitivity, and phobic anxiety. We also compared the frequencies of psychological distress and psychosocial risk in women with high-risk and low-risk pregnancies. According to the study of psychosocial risk based on the cut-off point 23, 59.8% (67.112) of women with high-risk pregnancies compared to 39.8% (55.138) of women with low-risk pregnancies had high psychosocial risk in terms of depression,

Table 1 Frequency of maternal complications in women with high-risk pregnancy

Factors	n(%) (n = 112)
Maternal age of upper 35 year or	30 (26.9)
Hyperemesis gravid	10 (8.9)
Hypertension	7 (6.7)
Diabetes	16 (14.4)
Kidney disease	2 (1.1)
Treated abortion	9 (8.2)
Hemorrhage placenta previa or abruption	3 (2.8)
Pyelonephritis	10 (8.9)
Peterman labor	15 (13.5)
Intrauterine growth retardation	10 (8.9)

Table 2 The comparison of the mean of psychological symptoms in women with high-risk and low-risk pregnancy

	Low- risk pregnancy Mean (SD)	High-risk pregnancy Mean (SD)	P-value	Total population Mean (SD)
Somatization	5.16(3.99)	5.75(4.55)	0.283	5.42(4.25)
Obsession-computation	3.77(3.62)	4.66(4.51)	0.091	4.17(4.06)
Interpersonal Senility	2.71(2.84)	3.09(3.24)	0.326	2.88(3.03)
Depression	2.96(3.56)	4.27(5.08)	0.022	3.54(4.35)
Anxiety	3.77(3.95)	4.75(4.51)	0.072	4.21(4.23)
Hostility	2.17(2.19)	3.21(3.21)	0.004	2.64(2.75)
Phobic anxiety	1.63(2.26)	2.54(3.15)	0.011	2.04(2.73)
Paranoid ideation	3.73(3.65)	4.80(4.01)	0.028	4.21(3.84)
Psychoticism	1.83(2.53)	3.17(3.35)	0.001	2.43(3)
Total score BSI-53	30.17(26.08)	39.17(34.51)	0.022	24.14(9.29)
*GSI	0.56(0.49)	0.73(0.65)	0.022	26.42(9.29)
Risk of depression	25.57(8.38)	28.20(9.66)	0.022	0.54(0.57)

*GSI: Global Severity Index; BSI-53: Brief Symptom Inventory-53.

Table 3 The results of multiple logistic regression* for determinates of psychological distress of women in postpartum period

Variable	OR	CI 95%	P- value
High-risk pregnancy	2.14	1.06-4.30	0.036
Psychological risk > 23	22.46	6.68-74.42	<0.001
Age	1.04	0.98-1.11	0.148
Educational level	1	–	0.316
Primary school	1.41	0.49-4.06	0.517
University	0.75	0.29-1.92	0.556

*In this model, Psychological distress (GSI > 1) as a dependent variable, the psychosocial risk score ≥23, age, and education level as independent variables.

and the difference was statistically significant (P= 0.04). The level of psychological distress (with GSI > 1) was 30.3% in women with high-risk pregnancies, and it was significantly higher than that in women with low-risk pregnancies (15.2%) (P= 0.004).

►**Table 3** presents the results of multiple logistic regressions, indicating that high-risk pregnancies could be twice the odds ratio of developing postpartum psychological distress (ß = 2.14, 95% CI 1.4-6.3, p= 0.036). The results also showed that high-risk pregnancy could almost double the odds ratio of developing postpartum psychological distress (ß = 2.14, 95% CI 1.4-6.3; p = 0.036). Moreover, it was noticed that pregnant women at high risk for mental health problems (scores above 23) had odds ratios of 22.5 times higher than those at low risk in terms of experiencing psychological distress in the postpartum period (ß= 22.46, 95% CI 6.74-42.68; p< 0.001). However, factors such as age and education level were not risk factors for postpartum psychological distress.

Discussion

The present research was the first study comparing the severity of psychiatric symptoms and psychological distress in postpartum women with high-risk and low-risk pregnancies. The results confirmed the effect of high-risk pregnancy on the increase in the severity of psychiatric symptoms in the postpartum period.

This study also indicated that the mean scores of severe symptoms of obsession-compulsion, depression, anxiety, hostility, paranoid ideation, and psychoticism were significantly higher in postpartum women with high-risk pregnancies than in those with low-risk pregnancies. The frequency of the psychological distress index (GSI > 1) in postpartum women with high-risk pregnancies was twice as likely as that in postpartum women with low-risk pregnancies. To the best of our knowledge, no study has ever compared postpartum psychiatric problems (9 disorders) of pregnant women with low-risk and high-risk pregnancies; hence, we succeeded in comparing the means of the two groups in the present study to the ones in previous studies. However, few studies have reported one of the symptoms of 9 postpartum psychiatric disorders in either low-risk or high-risk groups. Consistent with the results, Chen et al.[26] concluded that the odds ratio of developing psychological disorders was higher in women with high-risk pregnancies. They also reported that postpartum depression in preeclampsia patients was twice (26.67%) as prevalent as in women with low-risk pregnancies. Another study reported that high-risk pregnancies were associated with an increased risk of postpartum psychological disorders.[27] One study also concluded that women with gestational diabetes had an increased risk of postpartum depression.[28] Contrary to the current report, another study did not report the severity of nine disorders and compare low-risk pregnancies.[29]

Our results indicated that the frequency of risk factors for depression was approximately 1.5 times (59.8% vs. 39.8%) higher in women with high-risk pregnancies than in women with low-risk pregnancies. In line with the results, one study reported that women, who experienced high-risk pregnancy, had an increased risk of acute postpartum stress and depression in the postpartum period.[27] In that study, 16% of women with high-risk pregnancies needed hospitalization in the postpartum period due to psychiatric disorders. Among all patients admitted to the hospital,42, 6.30, 1.4, and 6.11% had anxiety disorders, depressive disorders, psychosis, and substance abuse, respectively.[30]

The results of this study indicated that high-risk pregnancies and high scores of the risk factors for depression could increase the odds ratio of postpartum psychological distress twice and 22 times, respectively; however, age, education level, and numbers of pregnancies were not effective. Although no study was found on the risk factors for postpartum mental distress, some studies had examined the risk factors for postpartum psychological disorders. One study on 122 pregnant women with high-risk pregnancies reported that the scores of psychological distress in postpartum women were significantly correlated with their psychological distress scores during pregnancy (r = 0.67). Furthermore, the psychological distress of women with high-risk pregnancies increased significantly after delivery.[31] One study reported that low birth weight and lack of social support were the risk factors for psychological disorders in such women.[32] In one prospective study on 167 Chinese women with high-risk pregnancies, high scores of depression in the third trimester of pregnancy were considered a risk factor for postpartum depression.[33] In some studies with inconsistent results, women, who had their first pregnancy, were at a high risk of developing psychological disorders in the first month after delivery.[30]

The results of the present study have many clinical implications in maternal care centers. The results suggest that all maternity healthcare providers, including obstetricians, midwives, and nurses should pay special attention to the identification and treatment of psychiatric problems in women with high-risk pregnancies, not only during pregnancy but also after delivery. In women with high-risk pregnancies, not only the risk of psychiatric problems is not eliminated after childbirth, but also it is more likely to

increase. All healthcare providers of pregnant women should consider risk factors for psychiatric problems during pregnancy and after delivery. Identification and treatment of pregnant women with high-risk pregnancies, suffering from psychiatric problems, not only positively affect pregnancy outcomes, but also make the postpartum period less risky in terms of developing or exacerbating psychiatric problems.

The present study had several limitations. First, it was a case-control study, which cannot assess causation. Additionally, despite all the attempts made to control (by matching) important confounding variables, some effective factors like socioeconomic status were not controlled due to the patients' incorrect responses to income status. Second, in the study, high-risk pregnancy was not limited to one type of medical problem or risk factor, and each person was included in the study even with one factor. Therefore, there were 112 women with different causes of high-risk pregnancies. Owing to the small number of causes of high-risk pregnancy, it was impossible to conduct a supplementary analysis of subgroups and compare the severity of psychiatric symptoms in high-risk pregnancies with various causes. Thus, it is recommended that further studies be conducted as a prospective cohort on a population with a high number of high-risk pregnancies to compare the severity of psychiatric symptoms in two groups of women with low-risk and high-risk pregnancies from pregnancy to the postpartum period.

Conclusion

The severity of numerous psychiatric symptoms and the psychological distress index were at higher levels in postpartum women with high-risk pregnancies than in those with low-risk pregnancies. Pregnant women with high-risk pregnancies or risk factors for psychological disorders were more likely to experience postpartum psychiatric distress. The study suggests that obstetricians should pay more attention to the identification and treatment of psychiatric symptoms in pregnant women with high-risk pregnancies, particularly those at high risk of developing psychological disorders, from pregnancy to the postpartum period.

Contributions

ZB, FR, MF designed and conducted the project. MK conducted review literature. MS analyzed the data. MF wrote the primary draft of the paper. ZB reviewed the paper. FR collected the data. All authors read and approved the final manuscript.

Conflicts to Interest[Q3]

None to declare.

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Changing Paradigms in the Initial Treatment of Ectopic Pregnancy at a University Hospital in Brazil

Mudança de paradigmas do tratamento inicial de gravidez ectópica em um hospital universitário no Brasil

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Abstract

Objective To evaluate the use of different treatment options for ectopic pregnancy and the frequency of severe complications in a university hospital.

Methods Observational study with women with ectopic pregnancy admitted at UNICAMP Womeńs Hospital, Brazil, between 01/01/2000 and 12/31/2017. The outcome variables were the type of treatment (first choice) and the presence of severe complications. Independent variables were clinical and sociodemographic data. Statistical analysis was carried out by the Cochran–Armitage test, chi-square test, Mann–Whitney test and multiple Cox regression.

Results In total 673 women were included in the study. The mean age was 29.0 years (±6.1) and the mean gestational age was 7.7 (±2.5). The frequency of surgical treatment decreased significantly over time ($z = -4.69$; $p < 0.001$). Conversely, there was a significant increase in the frequency of methotrexate treatment ($z = 4.73$; $p < 0.001$). Seventy-one women (10.5%) developed some type of severe complication. In the final statistical model, the prevalence of severe complications was higher in women who were diagnosed with a ruptured ectopic pregnancy at admission (PR = 2.97; 95%CI: 1.61–5.46), did not present with vaginal bleeding (PR = 2.45; 95%CI: 1.41–4.25), had never undergone laparotomy/laparoscopy (PR = 6.69; 95%CI: 1.62–27.53), had a non-tubal ectopic pregnancy (PR = 4.61; 95%CI: 1.98–10.74), and do not smoke (PR = 2.41; 95%CI: 1.08–5.36).

Conclusion there was a change in the first treatment option for cases of ectopic pregnancy in the hospital during the period of analysis. Factors inherent to a disease that is more difficult to treat are related to a higher frequency of severe complications.

Keywords

- Pregnancy complications
- Pregnancy
- Tubal
- Pregnancy trimester first
- Uterine hemorrhage

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Resumo

Objetivo Avaliar as diferentes opções de tratamento para gravidez ectópica e a frequencia de complicações graves em um hospital universitário.

Métodos Estudo observacional com mulheres com gravidez ectópica admitidas no Hospital da Mulher da UNICAMP, no Brasill, entre 01/01/2000 e 31/12/2017. As variáveis de desfecho foram o tipo de tratamento (primeira escolha) e a presença de complicações graves. As variáveis independents foram dados clínicos e sociodemográficos. A análise estatística foi realizada pelo teste de Cochran–Armitage, teste de qui-quadrado, teste de Mann–Whitney e Regressão de Cox Múltipla.

Resulados No total, 673 mulheres foram incluídas no estudo. A idade médica foi de 29.0 anos ($\pm$ 6.1) e a idade gestacional media foi de 7.7 ($\pm$ 2.5). A frequencia de tratamento cirúrgico diminuiu significativamente ao longo dos anos($z = -4.69$; $p < 0.001$). Simultaneamente, houve um aumento da frequencia do tratamento clínico($z = 4.73$; $p < 0.001$). Setenta e uma mulheres (10.5%) desenvolveram algum tipo de complicação grave. No modelo estatístico final, a prevalência de complicações graves foi maior nas mulheres que tiveram diagnóstico de gestação ectópica rota à admissão (PR = 2.97; 95%CI: 1.61–5.46), que não apresentaram sangramento vaginal (PR = 2.45; 95%CI: 1.41–4.25), sem antecedentes de laparotomia/laparoscopia (PR = 6.69; 95%CI: 1.62–27.53), com gravidez ectópica não-tubária (PR = 4.61; 95%CI: 1.98–10.74), e não tabagistas (PR = 2.41; 95%CI: 1.08–5.36).

Conclusão Houve uma mudança na escolha do primeiro tratamento indicado nos casos de gravidez ectópica durante o período analisado. Os fatores inerentes a doença relacionados a maior dificuldade de tratamento foram associados a maior frequencia de complicações graves.

Palavras-chave

- Complicações na gravidez
- Gravidez tubárea
- Gravidez primeiro trimester
- Hemorragia uterina

Introduction

An ectopic pregnancy is one in which the blastocyst is implanted in a location other than the uterine cavity. In most cases of ectopic pregnancy, the fallopian tube is the most common site of implantation, although it can occur at other sites, such as the ovaries, uterine scar, intestinal loops, cervix, and uterine horn.[1,2] Ectopic pregnancy accounts for 2% of all pregnancies and is one of the main obstetric emergencies.[3–5] It is one oh the main causes of maternal death in the first trimester of pregnancy. This is an indicator of poor quality of health care services provided to women because most of those deaths are preventable.[6,7]

Advances in early diagnosis can help in the adoption of less invasive treatments and reduce death rate.[8] Ectopic pregnancy can be treated with methotrexate, a folate antagonist, using different protocols. It can also be treated by different surgical techniques, such as laparotomy or laparoscopy. Tubal ectopic pregnancy is generally treated either by salpingostomy or salpingectomy.[8,9] Laparoscopy is currently considered the best approach for cases in which surgical intervention is indicated as well as non-tubal cases, that fulfill two preconditions: hemodynamically stable and the availability of a team of experienced laparoscopist.[3,8,10]

What makes the difference in managing ectopic pregnancy is the ability to provide high-quality, cost-effective treatment that will yield maximum patient satisfaction. However, this might not be possible in some locations. In low- and middle-income countries where early diagnosis is not possible, careful selection of treatment is often difficult because most patients are usually brought to the hospital facility in emergencies.[11,12] Brazil, which is considered a middle-income country, has a relatively high maternal mortality rate, which is still far from the United Nation targets. Concomitantly, there is a scarcity of studies evaluating the morbidity and mortality associated with ectopic pregnancy as well as the treatments provided.[7–9] Considering the importance of this disease in the establishment of a fundamental index for women's health and the scarcity of data specific to Brazil, we sought to compare the rates of methotrexate, surgical, and expectant management in a university hospital in the south eastern region of the country. We also evaluated the laparoscopic rate and the frequency of severe complications.

Methods

This was an observational study involving all women admitted at the University of Campinas (UNICAMP) Women's Hospital, Campinas, Brazil, between January 1, 2000 and December 31, 2017, who had a confirmed diagnosis of ectopic pregnancy, registered either at admission or at discharge. The University of Campinas (UNICAMP) Women's Hospital is a tertiary-level hospital, located in the south eastern region of Brazil. It usually receives cases of pregnancy-related complications from several cities in the region. The hospital handles an average of 250 deliveries and 20 first trimester pregnancy complications per month. Ectopic pregnancy cases were identified using the following International

Classification of Diseases (ICD), 10th revision codes: O00 (ectopic pregnancy), O00.0 (abdominal pregnancy), O00.1 (tubal pregnancy), O00.2 (ovarian pregnancy), O00.8 (other ectopic pregnancy), and O00.9 (ectopic pregnancy, unspecified). Data was collected by the researchers in charge of the Medical Archive and Statistics Service of the hospital after careful analysis of the medical records. Data containing cases other than ectopic pregnancy were excluded from the study. The project was approved by the UNICAMP Research Ethics Committee (CAAE 53019116.6.0000.5404). It was a convenience sample. To calculate the power of the sample, the proportion estimate was used in a study descriptive with a categorical qualitative variable, in this case the estimate of surgical treatment of 64.34%, the clinical treatment estimate of 25.85%, the expectant treatment estimate of 9.81%, and an estimated presence of severe complications of 10.55% in a sample of n = 673 women, and setting the alpha significance level or type I error at 5% (alpha = 0.05) (or confidence interval of 95%) and the sampling error of 5% (d = 0.05). According to results, a power of 75.4% was obtained for surgical treatment, of 86.4% for clinical, 99.8% for expectant treatment and 99.8% for the presence of complications severe (►**Table 1**).

As this was a retrospective study based on database review, not compromising the privacy of subjects, the University of Campinas Research Ethics Committee waived the signing of informed consent. This article was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

We considered as outcome variables: the type of treatment, administered as first choice after the diagnosis of ectopic pregnancy was made, which could be methotrexate, expectant or surgical management, the surgical approach (laparotomy or laparoscopy), and the presence of severe complications, defined as the presence of any of the following conditions during hospitalization: blood transfusion necessity, ICU (Intensive Unity Care) admission, surgical reassessment, hysterectomy, or death due to ectopic pregnancy.

We considered as independent variables: the year of occurrence of ectopic pregnancy, ectopic pregnancý s location, diameter of the gestational sac, serum quantitative β-hCG at diagnosis (measured in mUI/ml), fetal heartbeat on ultrasound, ectopic pregnancy integrity at diagnosis and during evolution, gestational age at diagnosis (calculated by the date of the last menstruation and by ultrasound analysis when available), woman's age, weight, height, body surface area, body mass index, skin color, schooling, marital status, parity, previous ectopic pregnancy history, history of tubal ligation, history of pelvic inflammatory disease, surgical history such as laparotomy or laparoscopy, history of intrauterine device as a contraceptive method as well as use during the diagnosis of ectopic pregnancy, symptoms reported when seeking emergency care—abdominal pain, vaginal bleeding, absence of symptoms, or other symptoms reported, smoking and current pregnancy resulting from in vitro fertilization, short or long methotrexate administration protocol,[13] and methotrexate dose administered. We defined the integrity of ectopic pregnancy at hospital presentation based on ultrasound and clinical features. In cases of unsuccessful methotrexate treatment, we evaluated the number of days from methotrexate treatment to the surgery and the reason for the indication of secondary treatment: pain, rupture of the gestational sac, and absence of biochemical response of β-hCG. In cases of methotrexate treatment was replaced by surgical treatment justified by the rupture of ectopic pregnancy during the follow-up, the rupture was defined by clinical and ultrasound findings. The methotrexate protocols used was short and long protocols. The short protocol consists of administering a dose of 50-mg/m^2 of body surface and repeat the dose if β-hCG levels does not drop by at least 15% between days 4 and 7 after treatment. The long protocol consists of administering 1-mg/kg/day in days 1, 3, 5 and 7, alternating with the administration of folinic acid in dose 0,1mg/kg/day – the protocol can e interrupted before 8 doses as long as β-hCG levels drops 15% or more between days.[1] Once the surgical approach was chosen as the initial treatment, we analyzed the: reason for the indication (described as absolute contraindication to methotrexate treatment, relative contraindication to methotrexate treatment, or option of medical staff), access route (Pfannenstiel laparotomy, median laparotomy, laparoscopy), type of surgery (salpingectomy, salpingophorectomy, salpingostomy), and the integrity of the contra lateral tube.

First, we performed a descriptive analysis of the data. Continuous variables were expressed as mean, standard deviation, median, minimum, and maximum. Categorical variables were expressed as relative frequencies. In order to compare the frequency of the types of treatment first indicated after the diagnosis of ectopic pregnancy, the surgical access route and the presence of serious complications between the years analyzed, the Cochran–Armitage test

Table 1 Results of calculating the power of the sample to estimate the prevalence of the type of treatment of 1st choice and the presence of severe complications in women with ectopic pregnancies

Variables	n	Prevalence	Power of the sample	Sample Size for 80% power
Surgical treatment	n = 673	64,34%	0.754	n = 747
Methotrexate treatment	n = 673	25,85%	0.864	n = 543
Expectant management	n = 673	9,81%	0.998	n = 180
Presence of severe complications	n = 673	10.55%	0.998	n = 201

*Calculation of sample power considering proportion values of the current sample size, setting the alpha significance level at 5% (tipe I error) Calculation of sample size considering sample power at 80% (type II erro ror 20% beta), according to Hulley et al. (2007)[13] and Cohen (1988)[14]

(trend test) was performed. Subsequently, bivariate analysis was performed to verify the association between the dependent variable "severe complication in cases of ectopic pregnancy" and the independent variables. For categorical independent variables, the chi-square test or Fisher's exact test was performed; for continuous variables, the Mann–Whitney test was performed. Multiple analysis by Cox regression was then performed. The level of significance was assumed to be 5%. The Statistical Analysis System for Windows version 9.2 (SAS Institute Inc., 2002-2008, Cary, NC, USA) was used.

Results

During the evaluation period, the total number of cases identified with an ICD code of admission or discharge corresponding to ectopic pregnancy was 673. The mean age of women was 29.0 ± 6.1 years and the mean BMI was 25.44 (±4.9), including minimum BMI 16.23, q1 BMI 22.04; median BMI 24.46, q3 BMI 27.82, and maximum BMI 43.87. Three hundred and eighty-two women (73.5%) had a partner .and 70.1% were white. Of the patients evaluated: 23.9% were primiparous, 29.8% had undergone at least one cesarean section, 40.4% had previously had at least one abortion, 15.6% had previously had an ectopic pregnancy, 3.5% had undergone tubal ligation, and 23.3% had undergone laparotomy or laparoscopy. The main clinical and socioeconomic characteristics are described in ►**Table 2**.[Q4]

The majority (94%) of the ectopic pregnancies were located in the fallopian tube. The mean gestational age was 7.4 ± 2.8 weeks when counted from the first day of the last menstrual period and 7.7 ± 2.5 weeks when determined by ultrasound. The mean diameter of the gestational sac was 37.2 ± 20.1 mm, and the mean serum β-hCG level was 5,783.2 ± 11,585.0. A visible fetal heartbeat was identified in 13.9% of cases, and 59.6% of the ectopic pregnancies were not ruptured at diagnosis. At admission, 87.0% of the women were symptomatic, 74% had abdominal pain, while 71.0% had vaginal bleeding. Twenty women (2.98%) had an ectopic pregnancy while using an intrauterine device, and seven (1.0%) had an ectopic pregnancy after an assisted reproduction procedure. Most of the treatments initially indicated, were surgical, (salpingectomy by Pfannenstiel laparotomy). When opting for methotrexate treatment, in the vast majority, a short protocol was performed with a mean methotrexate dose of 86.9 ± 22.1 mg (►**Table 3**).

The frequency of surgical treatment for ectopic pregnancy decreased significantly over time. In the year 2000, 70.9% of the women underwent surgical treatment, compared with only 41.5% in 2017 ($z = -4.69$; $p < 0.001$). Conversely, there was a significant increase in the frequency of methotrexate treatment, from 29.0% in 2000 to 45.2% in 2017 ($z = 4.73$; $p < 0.001$). As for expectant management, we did not observe a trend toward a change over time ($z = 0.58$; $p = 0.561$). These data are shown in detail in ►**Figure 1**.

Once clinical methotrexate treatment was indicated, we have successful in 47.4% of the treatments. 33.5% need surgery after methotrexate treatment, and the reasons were increased β-hCG and detection of tubal rupture during follow-up. For 18.9% of methotrexate treatment it was not possible do determine success due to lack of follow-up. When assessing the frequency of the use of surgical access routes over the years, we observed a significant trend towards an increase in the use of laparoscopic access and a reduction in laparotomy ($z = 2.09$; $p = 0.03$) (►**Figure 2**).

Of the women in our sample, 71 (10.55%) developed some type of severe complication associated with ectopic pregnancy. The most common complication was the need for blood transfusion (8.1%), followed by admission at the intensive care unit (4.3%). During the 17-year study period: only 6 (0.8%) of the women required reoperation, 5 (0.7%) underwent hysterectomy as a consequence of ectopic pregnancy, and no deaths due to ectopic pregnancy were registered. When assessing the frequency of severe complications over

Table 2 The main clinical and socioeconomic characteristics

Characteristics	n	%
Age (y)		
< 20	39	5.79
20–29	308	45.77
30–39	303	45.02
40–49	23	3.42
Years of schooling*		
≤ 9	110	44.5
≤ 12	111	44.5
> 12 (college)	26	11.0
Marital status*		
With partner	382	73.5
Without partner	138	26.5
Skin color*		
White	420	70.1
Brown	129	21.6
Black	47	7.8
Yellow	2	0.3
Indigenous	1	0.2
Previous pregnancies*		
0	161	23.96
1	187	27.83
2	141	20.98
≥ 3	183	27.23
Previous cesarean sections*		
0	471	70.19
1	136	20.27
≥ 2	64	9.54
Previous abortions*		
0	400	59.52
1	187	27.83
≥ 2	85	12.65

Table 3 Treatments indicated for ectopic pregnancy (n = 673)

Treatments	Frequency (%)
Type of treatment (first choice)	
Surgical	64.64
Methotrexate	25.85
Expectant	9.81
Methotrexate protocol	
Short	98.32
Long	1.68
Surgery access route	
Pfannenstiel	64.24
Laparoscopy	21.22
Median incision	13.56
Laparoscopy followed by Pfannenstiel	0.98
Type of surgery	
Salpingectomy	77.57
Salpingophorectomy	4.30
Salpingostomy	8.01
Other	10.16

the years, we did not notice any significant difference (z = -0.95; p = 0.342) (►**Figure 3**).

We found that severe complications were significantly more common among white women (p = 0.01), who had a ruptured ectopic pregnancy (p <0,01), cases with a non-tubal location (p <0.01), those who did not present with vaginal bleeding (p < 0.01), with abdominal pain (p < 0.01), without previous ectopic pregnancy (p <0.01), those who had no history of abdominal surgery (p = 0.01), and non-smokers (p = 0.02). Among the women who developed severe complications, the initial treatment was surgical in 90% (p < 0.01) and 29.4% underwent median laparotomy (p < 0.01) (►**Table 4**).

As can be seen in ►**Table 5**, the occurrence of severe complications was also correlated with some quantitative variables, such as higher levels of β-hCG (p < 0.01), larger

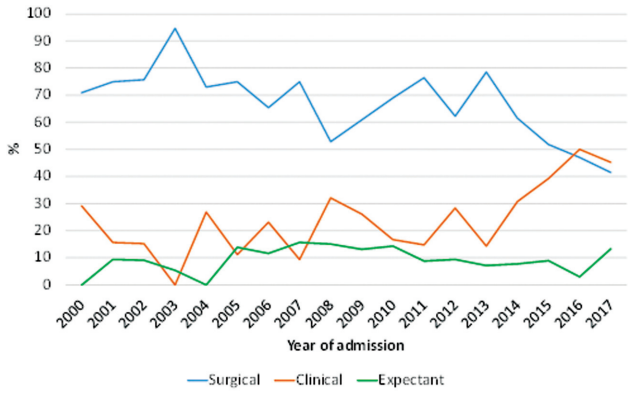

Fig. 1 Type of treatment (first choice) between 2000 and 2017*
Cochran-Armitage test: Clinical: z = 4.73; p < 0.001; Surgical: z = -4.69; p < 0.001; Expectant: z = 0.58; p = 0.561

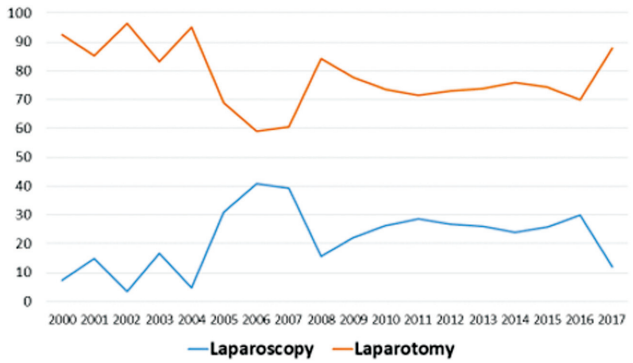

Fig. 2 Surgical access routes between 2000 and 2017*
Cochran-Armitage test: z = 2.09; p = 0.03

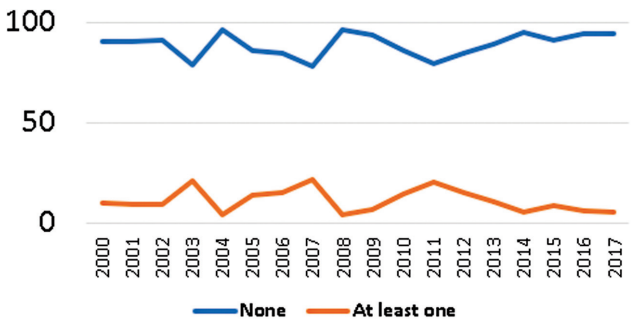

Fig. 3 Severe complications between 2000 and 2017*
Cochran-Armitage test: z = -0.95; p = 0.342

diameter of ectopic pregnancy (p = 0.01), shorter stature (p = 0.049), higher gestational age determined by ultrasound (p = 0.019), and longer hospital stay (p < 0.01).

In the final statistical model, the prevalence of severe complications was found to be higher in women who: were diagnosed with a ruptured ectopic pregnancy at admission (PR = 2.97; 95% CI: 1.61–5.46) did not present with vaginal bleeding (PR = 2.45; 95% CI: 1.41–4.25), had never undergone laparotomy or laparoscopy (PR = 6.69; 95% CI: 1.62–27.53), had a non-tubal ectopic pregnancy (PR = 4.61; 95% CI: 1.98–10.74), and do not smoke (PR = 2.41; 95% CI: 1.08–5.36) (►**Table 6**).

Discussion

Ectopic pregnancy has significant repercussions on women's health, in terms of morbidity and mortality, and there have been few studies evaluating the treatments and factors associated with a worse prognosis among them in Brazil. The main objective of this study was to compare the rates of methotrexate, surgical, and expectant management and to evaluate severe complications of ectopic pregnancy in a university hospital in the south eastern region of Brazil over a period of 17 years.

Some studies have suggested that the use of methotrexate in the clinical treatment of ectopic pregnancy, in cases that meet the eligibility criteria (gestational sac diameter < 4 cm, serum β-hCG ≤ 5,000 IU, absence of a fetal heartbeat, hemodynamic stability, and no contraindications), has the same

Table 4 Factors associated with severe complications in patients diagnosed with ectopic pregnancy (categorical variables)

Variables	Severe complication		n	p-value
	Yes (%)	No (%)		
Location				0.004[b]
Tubal	85.92	95.35	635	
Nontubal	14.08	4.65	38	
Abdominal pain				< 0.001[a]
Yes	83.10	62.17	432	
No	16.90	37.83	239	
Vaginal bleeding				< 0.001[a]
Yes	43.66	64.17	416	
No	56.34	35.83	255	
Previous ectopic				0.002[a]
Yes	2.82	17.11	105	
No	97.18	82.89	568	
Previous laparotomy				0.011[a]
Yes	11.27	24.75	157	
No	88.73	75.25	516	
Smoking				0.029[a]
Yes	15.63	28.52	156	
No	84.38	71.48	420	
Skin color				0.015[a]
White	83.61	68.59	420	
Non-white	16.39	31.41	179	
Ectopic pregnancy integrity				< 0.001[a]
Non-ruptured	27.94	63.23	399	
Ruptured	72.06	36.77	270	
Type of treatment (first choice)				< 0.001[a]
Surgical	90.14	61.30	433	
Methotrexate	8.45	27.91	174	
Expectant	1.41	10.80	66	
Surgical access route				< 0.001[b]
Laparoscopy	2.94	24.04	108	
Laparoscopy followed by Pfannenstiel	1.47	0.91	5	
Median laparotomy	29.41	11.11	69	
Pfannenstiel	66.18	63.95	327	
Median laparotomy	29.41	11.11	69	
Pfannenstiel	66.18	63.95	327	

[a]Chi-square test.
[b]Fisher's exact test.

success rate as surgical treatment.[8] In addition, in well-selected patients, treatment with methotrexate had a better cost-benefit ratio than surgery.[3,8,11,15] Because ectopic pregnancy is being diagnosed earlier and treatment protocols based on methotrexate have been developed, there is a trend toward an increase in the number of methotrexate treatments, in comparison with that of surgical treatments, in several countries.[3,9,11,16–18] In line with worldwide standards, the trends over the years at the university hospital studied were toward an increase in the rates of methotrexate treatment, possibly due to earlier diagnosis. Some studies point to an increase in expectant management rates in recent years,[18] which was not observed in our study. The inevitable question, however, is whether all health care facilities in Brazil show similar trends or whether it is a peculiarity of university, tertiary and private care centers.

In the present study, 40.3% of the patients were diagnosed with a ruptured ectopic pregnancy at admission. Among the surgical access routes available for the surgical treatment of ectopic pregnancy, laparoscopy has less morbidity than laparotomy, provided that a trained team is available.[1] Some studies have also suggested that patients undergoing laparoscopy require less blood transfusion and will have fewer pelvic adhesions than those who undergo laparotomy, which minimizes the impact on the reproductive future.[19–23] During the period of analysis, we observed a significant increase in the use of laparoscopy, which may be related to a greater availability of surgical instruments and a better adaptation of the team to the surgical technique. However, it is possible that the same does not happen in other health services in the country.

We found that 10.55% of the sample developed some type of serious complication associated with ectopic pregnancy. The most common complication was the need for blood transfusion, followed by admission to the intensive care unit. This frequency remained stable throughout the period of analysis, despite the increased use of methotrexate treatment and laparoscopy. The non-fatal complications of ectopic pregnancy are poorly studied.[24] Some observational studies have reported surgical complications in 23.4% of cases[25] and blood transfusion rates of 4.8% regardless of the type of treatment.[18]

As for the factors that were most associated with the severity of the cases, we noticed that women who had a ruptured EP at admission, who did not have vaginal bleeding, had non-tubal EP, had never undergone laparotomy or laparoscopy, and who did not smoke had a higher prevalence of complications. Clearly, delayed diagnosis tends to have an impact on the evolution of the disease, increasing the risk of rupture prior to admission and of an unfavorable evolution. During the study period, there were 270 cases in which the ectopic pregnancy had already ruptured prior to diagnosis, accounting for 40.3% of all cases. Although we have the means of early diagnosis and clinical treatment in the hospital, we are also a reference for other cities in the region, from where we usually receive many cases at advanced evolution that do not warrant other ways of management than surgery.

It is possible that the absence of vaginal bleeding can decrease the chance of early diagnosis because health professionals are looking for the classic triad of positive β-hCG, abdominal pain, and vaginal bleeding. It is possible that women, who seek emergency care for abdominal pain,

Table 5 Distribution of continuous variables according to the presence of severe complications after ectopic pregnancy

Variables	Severe complication		p-value*
	Yes	No	
	Mean ± SD	Mean ± SD	
Serum β-hCG at diagnosis (mIU/mL)	16,325 ± 24,529	5,300.9 ± 10,459	0.005
Gestational sac diameter (mm)	43.20 ± 21.40	36.73 ± 19.96	0.016
Methotrexate dose (mg)	93.50 ± 32.89	86.7 ± 21.76	0.921
Height (cm)	159.46 ± 7.50	161.11 ± 6.52	0.049
Body surface area (m^2)	1.69 ± 0.19	1.69 ± 0.16	0.833
Gestational age at diagnosis (ultrasound-weeks)	9.91 ± 4.33	7.46 ± 2.06	0.019
Number of previous pregnancies	1.61 ± 1.52	1.72 ± 1.51	0.452
Number of previous cesarean sections	0.40 ± 0.75	0.43 ± 0.77	0.660
Length of hospital stay (days)	3.85 ± 2.23	3.14 ± 1.94	< 0.001

Table 6 Variables associated with severe complications – Multiple Cox Regression (n = 548)

Variables	p-value	P.R.*	95% CI PR*
Ectopic pregnancy integrity at diagnosis			
Non-ruptured (ref)	–	1,00	–
Ruptured	<0,001	2,97	1,61–5,46
Vaginal bleeding			
Yes (ref)	–	1,00	–
No	0,002	2,45	1,41–4,25
Surgical history such as laparotomy or laparoscopy			
Yes (ref)	–	1,00	–
No	0,009	6,69	1,62–27,53
Smoking			
Yes	–	1.00	–
No	0.031	2.41	1.08–5.36
Ectopic pregnancý́s location			
Tubal (ref)	–	1,00	–
Non-tubal	<0,001	4,61	1,98–10,74

without vaginal bleeding, are misdiagnosed, and the diagnosis is only made during the second consultation. In addition, irregular or unexpected vaginal bleeding tends to be an early warning sign that prompts patients to seek immediate emergency care. Another hypothesis to explain this association is related to the notion of the evolutionary nature of pregnancy; that is, pregnancies in which there is a greater amount of trophoblastic tissue (i.e., those with longer evolution) will have an ascending curve and higher levels of β-hCG. Consequently, they will have higher levels of progesterone and less vaginal bleeding due to endometrial desquamation.[20] Ectopic pregnancy that does not present with vaginal bleeding tends to be characterized by delayed diagnosis with a potential for greater severity.

Non-tubal ectopic pregnancies also tend to be diagnosed later and present a greater degree of difficulty in the surgical approach. Unusual sites for trophoblast implantation include the cervix, cornual, and ovaries as well as abdominal scars from previous cesarean sections, the frequency of the latter being on the rise due to an increase in cesarean delivery.[25–27] When trophoblast implantation occurs in the uterine cornus and surgery is required, the rates of associated bleeding are often higher, due to the thickness of the myometrium in this region, together with the abundant vascularization resulting from trophoblastic implantation.[28] The difficulty in repairing it, associated with bleeding, can lead to an emergency hysterectomy.[29,30] The ovaries are irrigated by the ovarian artery, an arterial branch of the aorta. Therefore, in addition to the risk of oophorectomy and impaired reproductive future,[31] ovarian ectopic pregnancy carries a great risk of hemorrhage. When trophoblast implants in a cesarean scar, the risk of uterine rupture and shock is a considerable possibility, and this type of ectopic pregnancy is associated with placenta percreta in more advanced pregnancies.[32] Cervical ectopic pregnancy presents difficulties in surgical access due to the proximity of the uterine arteries and ureters, and can present with postoperative complications such as: hemorrhage, the need for hysterectomy, and urinary tract injury.[33] Abdominal pregnancy also presents serious risks as it can occur close to the liver, spleen, and intestinal loops, which evolve with difficulty in controlling hemorrhage and fecal peritonitis.[34] In our study, we observed an association between the absence of abdominal surgery, no smoking and a higher occurrence of serious complications. We are not aware of any study that has previously found similar associations, and we have no hypothesis that can explain these findings. Possibly, as several associations were made between variables, there may have been multiple comparison bias. Therefore, further studies are needed to assess these possible associations.

This study illustrates 17 years of monitoring cases of ectopic pregnancy in a university hospital, permitting not only the description of the variables related to the diagnosis and management of cases, but also the observation of trends.

However, it has some limitations. Due to the retrospective characteristics and the cross-sectional analysis of the data, it was not possible to establish cause-and-effect relationships. Additionally, due to the large number of variables analyzed, there may have been multiple association biases. We believe, however, that the results are valid, since we analyzed a considerable number of cases over a long period of time, thereby contributing to the discussion and analysis of the management of ectopic pregnancy cases in Brazil.

Conclusion

In conclusion, we observed that there was a change in the first treatment option for cases of ectopic pregnancy in the hospital during the period of analysis. There was a change in management of ectopic pregnancy with reduced surgeries and increased methotrexate treatment. This is possibly related to the development of treatment protocols based on methotrexate, in addition to the earlier diagnosis of the disease. We also observed an increase in the use of laparoscopy, which represents an improvement in the quality of care for women. Factors inherent to a disease that is more difficult to treat, such as non-tubal ectopic location together with conditions related to late diagnosis, are related to a higher frequency of serious complications. The results obtained may contribute to the reduction of maternal morbidity and mortality in our country and improve the quality of care for women.

Contributions

BVGT and LFB contributed to data collection, study conception and design, and drafting the manuscript. LSD and ISI contributed to project development, data collection, and study conception and design. All authors reviewed and approved the final manuscript.

Conflicts of Interest[Q3]

Q3

The authors have no conflicts of interest.

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Q4: AU: Tables has been renumbered for sequences [Second citation of Table 1 has been changed to Table 2; Table 2 becomes Table 3; Table 3 becomes Table 4; Table 4 becomes Table 5; Table 5 becomes Table 6]. Please check for correctness.

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Conservative Treatment of Stage IA1 Cervical Carcinoma Without Lymphovascular Space Invasion: A 20-year Retrospective Study in Brazil

Tratamento conservador do câncer do colo do útero IA1 sem invasão linfovascular: estudo retrospectivo no Brasil

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Abstract

Purpose: To evaluate recurrence rates and risk factors among women with stage IA1 cervical cancer without lymph vascular space invasion managed conservatively.

Methods: retrospective review of women with stage IA1 squamous cervical cancer who underwent cold knife cone or loop electrosurgical excision procedure, between 1994 and 2015, at a gynecologic oncology center in Southern Brazil. Age at diagnosis, pre-conization findings, conization method, margin status, residual disease, recurrence and survival rates were collected and analyzed.

Results: 26 women diagnosed with stage IA1 squamous cervical cancer without lymphovascular space invasion underwent conservative management and had at least 12 months follow-up. The mean follow-up was 44.6 months. The mean age at diagnosis was 40.9 years. Median first intercourse occurred at age 16 years, 11.5% were nulliparous and 30.8% were current or past tobacco smokers. There was one Human immunodeficiency virus positive patient diagnosed with cervical intraepithelial neoplasia grade 2 at 30 months after surgery. However, there were no patients diagnosed with recurrent invasive cervical cancer and there were no deaths due to cervical cancer or other causes in the cohort.

Conclusion: Excellent outcomes were noted in women with stage IA1 cervical cancer without lymphovascular space invasion and with negative margins who were managed conservatively, even in a developing country.

Keywords
- Uterine cervical neoplasms
- Conization
- Conservative treatment
- Recurrence
- Squamous cell carcinoma

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Resumo

Objetivo: Avaliar recidiva e seus fatores de risco em mulheres com câncer do colo do útero estádio IA1 sem invasão do espaço linfovascular tratadas conservadoramente.

Métodos: Estudo de coorte retrospectivo de pacientes com câncer do colo do útero IA1 escamoso submetidas a cone do colo do útero, entre 1994 e 2015, em um centro de ginecologia oncológica do sul do Brasil. Foram revisados e analisados idade no diagnóstico, achados pré-conização, método de conização, margens, doença residual, recorrência e sobrevida.

Resultados: 26 mulheres diagnosticadas com câncer do colo do útero estádio escamoso sem invasão do espaço linfovascular foram submetidas a tratamento conservador, com seguimento mínimo de 12 meses. O tempo médio de seguimento foi 44,6 meses. A média de idade no diagnóstico foi 40,9 anos. A primeira relação sexual ocorreu aos 16 anos (mediana), 11,5% eram nulíparas e 30,8% eram tabagistas atuais ou passadas. Houve um caso de recidiva de neoplasia intraepitelial cervical grau 2 aos 30 meses em uma paciente com vírus da imunodeficiência humana. Não houve pacientes diagnosticados com câncer de colo do útero invasor recorrente, e não houve mortes por câncer do colo do útero ou outras causas.

Conclusão: Os resultados observados após tratamento conservador em mulheres com câncer cervical escamoso IA1 sem invasão do espaço linfovascular com margens negativas foram excelentes, mesmo em um país em desenvolvimento.

Palavras-chave

- Neoplasias do colo do útero
- Conização
- Tratamento conservador
- Recorrência
- Carcinoma de células escamosas

Introduction

Cervical cancer (CC) is the fourth cancer in global incidence and the fourth leading cause of death due to cancer in women. Greater than 85% of cervical cancer deaths occur in low- and middle-income countries (LMICs) where it is the first or second leading cause of cancer-related deaths.[1] CC is the third most common cancer and the fourth most common cause of cancer-related death among women in Brazil.[2] The highest incidence occurs among women in reproductive ages, which reinforces the need for safe oncologic outcomes as well as fertility-sparing approaches.[2]

Micro-invasive cervical cancer was initially described in 1947 by Mestwerdt[3] and extensively revised. According to the 2018 *International Federation of Gynecology and Obstetrics* (FIGO) new definition, stage IA disease is defined as invasive carcinoma diagnosed only by microscopy with a depth of invasion up to 5mm.[4,5] The horizontal dimension (up to 7mm extension) is no longer considered. Stage IA1 disease has stromal invasion up to 3mm, and stage IA2 has stromal invasion greater than 3mm and up to 5mm. Lymphovascular space invasion (LVSI) does not modify the stage, but it may impact prognosis and therapeutic approach.[4,6]

FIGO proposes extrafascial hysterectomy or conization with negative margins as treatment options for stage IA1 CC without LVSI, but the studies that evaluated stage IA1 treatment options have a lack of homogeneity regarding variables such as LVSI, depth of invasion, histologic type, and surgical margin status.[4,7–17] In addition, risk factors for cervical cancer have been extensively studied, but not in this specific population.[18]

There are limited reports from LMIC on cervical micro-invasive cancer. The purpose of this study was to analyze recurrence rates after conservative treatment for stage IA1 squamous cell CC without LVSI and with negative cone margins. In addition, we sought to describe the population characteristics.

Methods

A retrospective cohort study of patients diagnosed with stage IA1 squamous cell CC without LVSI who underwent loop electrosurgical excision procedure (LEEP) or cold knife cone biopsy (CKC), between June 1994 and December 2015, at the Gynecology of the Federal University of Health Science of Porto Alegre (UFCSPA)/Hospital Irmandade Santa Casa de Misericórdia de Porto Alegre (ISCMPA), was performed after Ethics and Research Committee ISCMPA approval (No. 2.606.2990, Irmandade Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, Brazil). All methods were performed in accordance with the relevant guidelines and regulations as well as in compliance with the requirements of the Declaration of Helsinki. The need for informed consent was waived by Ethics Committee ISCMPA, due to the retrospective nature of the study.

The study population included stromal invasion up to 3mm, with surface extension no greater than 7mm (previous FIGO staging guidelines). Exclusion criteria included positive surgical margins, non-conservative surgery, and less than 12 months of follow-up. The following variables were analyzed: age at diagnosis, age at first intercourse, parity, comorbidities related to the immunosuppressive status, tobacco use, contraceptive method, menopausal status,

pre-conization cytology results, biopsy pathologic results, conization method, conization pathologic results, margin status, residual disease, follow-up, and recurrence. A negative margin was defined as the absence of cervical intraepithelial neoplasia or carcinoma at the surgical margins of the CKC/LEEP specimen. Risk factors for CC were defined as age at first intercourse below 15 years, parity, immunosuppression, current or past smoking, and use of oral contraceptives.[19–23]

All the surgical procedures were performed by UFCSPA/ISCMPA gynecologic oncology team, and experienced pathologists analyzed the samples. Follow-up included pelvic examination with cytology and colposcopy for the following 5 years after the first treatment. Patients were evaluated every 3 months for the first 2 years and, every 6 months thereafter. The presence of a high-grade squamous intraepithelial lesion (HSIL)/ cervical intraepithelial neoplasia (CIN) 2/3 or carcinoma after 6 months post-treatment defined recurrence; before 6 months, findings were considered disease persistence.

Continuous variables were expressed as mean and standard error of mean (± SEM), or by median and 95% Confidence Interval [95%CI]. Categorical variables were described as absolute (n) and relative (n%) frequencies. The Shapiro-Wilk test was used to determine the normality of data distribution. Spearman's correlations were carried out among all variables. Statistical analysis was performed using SPSS, version 18.0. [SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.].

Results

A total of 50 patients had the diagnosis of stage IA1 CC without LVSI. Twenty-six patients underwent conservative treatment with CKC or LEEP and were included in the study. Demographic and clinical characteristics are shown in ►**Table 1**.

The mean age at diagnosis was 40.9 years (23 to 59), 4/26 (15.4%) participants were younger than 30 years, 4/26 (15.4%) were 50 years or older, and 8/26 (30.8%) were menopausal status. The median age at first intercourse was 16 (range 15-17) years. The Mmean parity was 2.8 ± 0.3; 3/26 (11.5%) were nulliparous and 3/26 (11.5%) had five or more children. One patient (3.8%) was Human immunodeficiency virus (HIV)-positive. Previous or current use of tobacco was reported in 8/26 (30.8%) women. The contraceptive method used by 12/26 patients (46.2%) was oral contraceptive pills ($p < 0.01$). Only two women (7.7%) did not have at least one of the CC risk factors. Among 15/26 (57.7%) had one risk factor, 5/26 (19.2%) had two risk factors and 4/26 (15.4%) had three risk factors. Pre-conization cytology was low-grade squamous intraepithelial lesion (LSIL) in 2/26 (7.7%), atypical squamous cells of undetermined significance (ASC-US) in 1/26 (3.8%), HSIL in 18/26 (69.2%), atypical squamous cells cannot exclude a higher-grade lesion (ASC-H) in 2/26 (7.7%) and invasive carcinoma in 1/26 cases (3.8%). In the other 2/26 cases (7.7%) cytology was negative. Cervical biopsies prior to cone showed CIN 1 in 2/26 (7.7%), CIN 2 or CIN 3 in 14 of 26 (53.8%) cases, and micro-invasive carcinoma was identified in six of 26 (23.1%) women. In the remaining four out of 26 cases, (15.4%) a cervical biopsy was negative or not performed, and diagnostic conization was recommended (►**Table 2**).

Table 1 Demographic and clinical characteristics

Characteristic	Total (n = 26)
Age (years) (mean ± SEM)	40.9 ± 2
Parity (mean ± SEM)	2.8 ± 0.3
Age of first Intercourse (years) (median [CI95%][a])	16 [15.2–17.3]
Parity – n (n%)	
0	3 (11.5)
1-4	20 (76.9)
≥ 5	3 (11.5)
HIV positive serology n (n%)	
Yes	1 (3.8)
No	25 (96.2)
Tobacco use n (n%)	
Current smoker	5 (19.2)
Former smoker	3 (11.5)
Non-smoker	18 (69.2)
Contraceptive method – n (n%)	
Oral contraceptive pills	12 (46.2)
Barrier	2 (7.7)
Tubal ligation	2 (7.7)
None	10 (38.5)

Table 2 Pap Test and pathology report previous conization

Variable	Total (n = 26)
Pre-surgery Pap test – n (n%)	
LSIL	2 (7.7%)
HSIL	18 (69.2%)
ASC-US	1 (3.8%)
ASC-H	2 (7.7%)
Invasive carcinoma	1 (3.8%)
Negative results	2 (7.7%)
Pre-surgery cervical biopsy – n (n%)	
CIN 1	2 (7.7%)
CIN 2/3	14 (53.8%)
Invasive carcinoma	6 (23.1%)
Negative results or not performed	4 (15.4%)

The surgical treatment was CKC in 23 out of 26 (88.5%) and LEEP in three of 26 (11.5%) patients. The depth of the CKC pieces ranged from 0.7 to 4.8 centimeters. The three LEEP procedure comprised type 1 and 2 excisions. The cone results were CIN 1 in 1/26 cases (3.8%), CIN 2/3 in 2/26 (7.7%), and micro-invasive carcinoma in 23/26 (88.5%). Three of 26 cases (11.5%) were diagnosed with micro-invasive carcinoma only in the cervical biopsy performed prior to the cone (►**Table 3**). Stromal invasion depth up to 1mm was found in 11 of 26 patients (42.3%). As soon as the cone biopsy was performed, 5/26 (19.2%) required a repeat intervention due to positive endocervical margins with CIN 3. In the remaining 21/26 (80.8%) patients, the surgical margins were negative. Only

Table 3 Surgical and pathologic findings

Surgical and Pathological findings	Total (n = 26)
Technique – n (n%)	
CKC	23 (88.5)
LEEP	3 (11.5)
Conization anatomopathological results cone – n (n%)	
CIN 1	1 (3.8)
CIN 2/3	2 (7.7)
Micro-invasion	23 (88.5)
Cone biopsy negative margins (CIN 3) – n (n%)	
Yes	21 (80.8)
No	5 (19.2)
Reconization results – n (n%)*	
Negative	3 (60)
CIN 3	2 (40)
Follow-up period (months) – mean ± SEM	44.6 ± 4.6

*n=5.

two of the five cases with positive margins (40%) showed residual disease with CIN 3, and none with invasion (an = 5 in ►**Table 3**). All five women that underwent a second cone had negative margins in the second procedure.

One patient recurred at 30 months with CIN 2 in an HIV-positive woman, and she was retreated with CKC. None of the patients developed recurrent invasive carcinoma and no patients died of cervical cancer. The studied variables did not correlate with recurrence ($p > 0.05$). The mean follow-up was 44.6 months (12 to 98). Sixteen of 26 (61,5%) women were followed for more than 36 months.

Discussion

The primary finding from our study confirms that CKC or LEEP are an alternative and effective treatment in conservative management of women with IA1 squamous CC without LVSI and negative margin, even in low- and middle-income countries. This conservative management resulted in only one (3.8%) recurrence of CIN 3 in a 50-year-old woman with HIV.

The main risk factor for the development of CC is the persistent infection of carcinogenic types of Human papillomavirus (HPV), especially the subset of HPV16.[21] It happens in a small percentage of women and becomes more prevalent after 30 years.[21,24–30] The current study identified the mean age at CC diagnosis at 40 years, similar to other studies.[6,15–17,31] As far as age is concerned in stage IA1 CC, 4/26 patients were 50 years or older and it was not correlated to recurrence in this study, but it was associated with a greater chance of recurrence in previous studies.[6,10,32] Elliot and collaborators studied 476 stage IA CC and they found there was a tendency for more recurrences in older women in a univariate analysis.[10] Hartman et al.,[32] in a large and recently published study involving 562 women treated by cervical conization or hysterectomy found recurrence twice as frequent in women over 40 years of age.

Another important risk factor for CC is HIV co-infection, which is linked to accelerated progression of pre-cancerous lesions and more frequent recurrences. Immunosuppression is associated with prevalence of HPV infection and viral persistence. However, HIV-infected but well-controlled with high-activity antiretroviral therapy presents a similar evolution to other women.[22] Although in this study the only CIN recurrence was in an HIV patient, this data is not enough to draw conclusions.

Studies have shown that the risk of cervical cancer increases with the increasing time of use of oral contraceptive pills.[20] But the use of oral contraceptive pills, the most common contraceptive method in this population, did not correlate with recurrence. Early age at first intercourse, high parity, and use of tobacco, risk factors for cervical cancer, also did not correlate with cervical cancer recurrence in this study.[21–23,33]

Previous studies about CC stage IA recurrence rates range between 1.7% to 9.6% and include CIN 2, CIN 3, intraepithelial vaginal neoplasia (VAIN) 3, and invasive cancer.[10,12,14–17,31,32] The variation in recurrence frequencies may be explained by the heterogeneity in the use of different definitions of recurrence and different methodologies. Hartman et al.[16] described a study performed in Brazil that showed a 7% (3/41 cases) recurrence rate and included one case that recurred with CIN 3/VAIN 3, one case with micro-invasive carcinoma and one with invasive carcinoma IB1 at 6, 9 and 104 months after completion of treatment respectively. Lee et al.[17] described a retrospective study with 22 conservative management in 75 stage IA1 CC patients, performed in three affiliated hospitals in South Korea, that showed two cases, out of the 6 recurrence cases, with micro-invasive carcinoma. The low recurrence rate found in our study can be attributed to the effects of the surgical technique used in which the surgical margins of the remaining cervix were cauterized during hemostasis which may eliminate residual neoplastic cells; this technique was not described by Hartman et al.[16] Xiang et al.,[31] described that maybe the cautery used for hemostasis was related to their recurrence reduction.[31] However, their recurrence rate was still higher (9.7%), but they included cases in which very early recurrence happens (3 months after conization) potentially representing persistent disease.

The low recurrence rate in our cohort may be also attributed to the high number (42%) of cases with stromal invasion ≤ 1mm. Costa et al.[34] evaluated 230 CC IA1-2 women primarily conservatively treated and they detected seven recurrences (3%) for invasive lesion closely related to the depth of stromal invasion (0/110 tumors with stromal invasion ≤1mm, 2/63 in tumors with invasion of 1.1 to 3.0 mm and 5/57 among tumors with stromal invasion between 3.1 and 5.0 mm). The case with recurrence in our study had stromal invasion of 3mm, similar to studies that describe recurrences only in patients with stromal invasion between 1 and 3mm.[9,14,35] The recurrence was observed at 30 months and falls according to other studies that report the risk of recurrence peaking up to 36 months.[11,14,16,31] Some authors reported that subsequent recurrences (many years later) are possibly related to inadequate follow-up (unsatisfactory colposcopies, scar changes, or stenosis) or new lesions (new cancer), not correlated with progression.[9,10,12,16]

All patients in the current study had negative margins and an absence of LVSI. According to some studies, the higher recurrence risk occurs in cases with LVSI and positive margins.[9,13,14,31,35] Wong et al.[35] reported positive surgical margins in CKC or LEEP as an independent risk factor for residual disease in early invasive cervical cancer stage. They reviewed the pathology reports of 108 hysterectomy specimens. Only two patients were treated with conservative fertility-sparing surgery and there was no recurrence on follow-up (mean follow-up: 63.5 months). Östör and Rome[9] found recurrence only in cases with positive margins. Kim et al.[13] showed that only cases with endocervical positive margins recurred in their study. Qian et al.[14] included 280 patients with stage IA1 cervical cancer within epidermoid, glandular, and clear cell histological types, regardless of LVSI. They found a recurrence rate of 2.4% in patients treated with conization.[14]

The findings from our study concur with the standard management even in a developing country.[4,5,7,8] This practice has been reassured by similar studies comparing conization and hysterectomy outcomes for stage IA1 CC.[14,16,32] Since we had only one recurrence, it is not possible to make a direct correlation with the known risk factors for CC. This study is limited by retrospective data collection and data from a single institution with possible referral bias. Another potential limitation is the absence of a control group, which could add relevance to the data. The strengths of this study include a homogeneous group of patients from a developing country within the perspective of surgical treatment, a strict follow-up routine, and a long period of follow-up.

Conclusion

This study was conducted in Brazil, a developing country with high rates of cervical cancer, and we found patients with stage IA1 CC without LVSI and with negative margins treated by conservative treatment resulting in excellent outcomes since it was found no recurrences of invasive cancer or any cancer-related deaths.

Contributions

Authors D.L.A., S.A.P. and M.P.S. conducted all aspects of conception, design and provision of study materials or patients. Authors D.L.A. and R.P.Z. conducted collection and assembly data. D.L.A., C.F.F., S.A.P. and M.P.S. conducted analysis and interpretation. D.L.A. wrote the manuscript with input from all other authors. Authors S.A.P., M.P.S. and K.M.S. collaborated with the critical revision of the article. All authors approved the final manuscript.

Conflicts to Interest:[Q3]

None to declare.

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Impact of Maternal Folic Acid Supplementation on Descendants' Kidney in Adulthood

Impacto da suplementação materna com ácido fólico no rim dos descendentes na vida adulta

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Abstract

Supplementation with folic acid (FA) during gestation has been recommended by medical society all over the world, but some studies have shown that intake of high folic acid diet may unleash damages to the descendants. Objectives: Describing the effects of maternal supplementation with FA during gestation on offspring's kidney at late life stages. Data Source: It is a systematic review by which were consulted the following databases: Medline, through Pubmed, Lilacs, and SciELO. The research was performed using the keywords "Folic acid", "Gestation" and "Kidney". Study Selection: Eight studies were regarded for this systematic review. Data Collection: Only studies that evaluated folic acid consumption during gestation and its effects exclusively on descendants' kidney at several phases of life were regarded. Results: Gestational FA intake did not change the renal volume, glomerular filtration rate and the expression of some essential genes in the kidney of puppies whose dams were supplemented with FA. Maternal consumption of double FA plus selenium diet was effective in preserving antioxidant enzymes activity in the kidney of descendants from mothers exposed to alcohol. FA supplementation decreased some gross anomalies in the puppies caused by teratogenic drug despite of had not been effective in preventing some renal architectural damages. Conclusion: FA supplementation did not cause renal toxicity; it exerted an antioxidant protective effect and mitigated some renal disorders caused by severe aggressions.

Keywords
- Folic acid
- Gestation
- Kidney
- Descendant
- Adulthood

Resumo

A suplementação com ácido fólico (AF) durante a gestação tem sido recomendada pela sociedade médica em todo o mundo, mas alguns estudos têm mostrado que a ingestão de altas quantidades de ácido fólico na dieta pode desencadear danos aos descendentes. Objetivos: Descrever os efeitos da suplementação materna com AF durante a gestação no rim da prole em fases tardias da vida. Fonte de Dados: Trata-se de uma revisão sistemática realizada através da consulta das seguintes bases de dados: Medline, através da Plataforma Pubmed, Lilacs e Scielo. A pesquisa foi realizada

Palavras-chave
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- Gestação
- Rim
- Descendentes
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utilizando-se as palavras-chave “Ácido Fólico”, “Gestação” e “Rim”. Seleção dos Estudos: Oito estudos foram considerados para esta revisão sistemática. Coleta de Dados: Foram incluídos estudos que abordaram o consumo de ácido fólico durante a gestação e seus efeitos exclusivamente no rim dos descendentes em diferentes fases da vida. Resultados: O consumo gestacional de AF não alterou o volume renal, a taxa de filtração glomerular e a expressão de alguns genes essenciais no rim dos filhotes de mães suplementadas com AF. A associação de AF e selênio na dieta materna foi eficaz na preservação da atividade de enzimas antioxidantes no rim da prole de mães expostas ao álcool. O consumo de AF diminuiu algumas anomalias importantes nos filhotes causadas por drogas teratogênicas, apesar de não ter sido eficiente na prevenção de alguns danos a arquitetura renal. Conclusão: A suplementação com AF não causou toxicicdade renal, exerceu efeito protetor antioxidante e mitigou algumas desordens renais causadas por agressões severas.

Introduction

Folic Acid Characterization

Folic acid (AF) is a water-soluble B (B9) vitamin, poorly stored in the body. The term “folic” comes from the Latin *folium*, leaf, due to its presence in leafy green vegetables such as spinach, cabbage, and broccoli besides viscera such as liver and kidney, milk, and egg. It is found in more than 90% as polyglutamates, which must be converted into monoglutamate before being absorbed.[1] FA is synthesized by microorganisms and higher plants, but not by mammals for which it is an essential nutrient needing to be ingested through food.[2,3] It can be also found in monoglutamate as a drug supplement, being quickly absorbed.[4] It has a pivotal role in purine and pyrimidine biosynthesis and consequently, in DNA and RNA formation.[5] It is also essential to specific metabolic reactions in the cell environment besides the growth and functioning of the organism.[1] FA works as coenzymes in the transport of simple carbon fragments and in the metabolism of amino acids.[6]

Absorption and Transport of Folic Acid

Polyglutamates of folates obtained from the diet are hydrolyzed into monoglutamate in the small intestine and absorbed by the intestinal mucosa. The enzyme named gamma-glutamyl hydrolase (γ-GH or glutamate carboxypeptidase II) is responsible for the hydrolysis of folylpolyglutamate and it is present on the villi of the small intestine epithelial cells characterized by brush shape. After hydrolysis, folate crosses basolateral membrane of intestinal mucosa cells, which contain their specific transporters, being released into the portal circulation.[7] FA is absorbed mainly in jejunum by passive transport, following a concentration gradient and by active transport when folate binds to reduced folate transporter 1 and 2 (RFT-1 and RFT-2) and folate binding protein (FBP). It can also be absorbed in the ileum just by passive transport. Folate is absorbed in a neutral pH environment (pH 7,4), with such a process being facilitated by the neutralization of gastric content by the alkaline pancreatic juice. The main form of circulating endogenous folate is 5-methyltetrahydrofolate, which is transported through plasm by low-affinity bindings with specific proteins, such as albumin and a soluble form of folate receptors (FR).[8] However, its concentrations are higher in red cells than in plasm due to its binding to hemoglobin.[9] Liver is able to absorb much of the folate from the portal circulation. The hepatic cells metabolize it into polyglutamate derivatives, retaining or releasing it in the blood or bile.[10,11] The folate excretion occurs mainly through bile in an approximate concentration of 100μg daily,[10,12] but it is reabsorbed in the small intestine. FA is filtered in the renal glomerulus and reabsorbed in the proximal contorted tubule. No FA is found in the urine, only its cleavage products.[13]

Gestation and Folic Acid

FA or B9 vitamin is spontaneously ingested in proper amounts by food in balanced diets. However, its deficiency becomes greater in women of childbearing age who intend to become pregnant, a period in which it is common to prescribe a drug supplement.[14,15] During gestation, the amount of FA ingested is insufficient to supply the daily needs that are increased in the pregnant.[16] Such vitamin has a fundamental role on cell proliferation, interfering in erythrocyte increasing, uterus enlargement, and development of both placenta and fetus,[17] becoming indispensable during pregnancy. According to Rangel-Rivera and Osma-Zambrano,[18] FA is essential for suitable formation and maintenance of several structures of the central nervous system, reducing the risk of severe language and attention disorders, schizophrenia, pre-eclampsia, low birth weight and premature birth. Meroanencephaly and spina bifida are the most common severe congenital malformations and both stem from defects of neural tube closure, can be prevented by FA intake in early gestation and immediately before such period.[19] Both periconceptional supplementation and during the first trimester of pregnancy has reduced the risk of recurrence of such defects in about 50 to 70%.[20] Due to this fact, the supplementation of pregnant with such nutrient has been recommended by medical societies all over the world both to

prevent the first occurrence and the recurrence of those defects.[21] In China, for example, there was a significant decline in the number of congenital hydrocephalus cases after 2009, when it was applied a massive program of FA supplementation during gestation.[22] In Bangladesh also its prenatal intake decreased significantly the probability of myelomeningocele occurrence.[23] In Brazil, in 2002 the Ministry of Health regarded the folic acid as an essential medicine during prenatal care, recommending 400 µg (0,4mg) as daily dose 30 days before conception until the first trimester of gestation as a way of to prevent the occurrence of neural tube defects and maternal anemia.[8] This institution also recommends a dose of 5mg per day of FA for women who have congenital malformations history.[14] Nowadays, some studies have evaluated the impact of FA maternal intake besides those related to nervous system disorder prevention. Previously our group reported by systematic review that such supplementation during gestation exerted protective effects on liver of offspring in adulthood,[24] avoiding deleterious epigenetic changes and improving the cell defenses, especially in hostile maternal conditions, such as, alcohol exposition and deprivation of protein. Several studies agree about the importance of FA intake during gestation as a way of to prevent congenital malformations, but, some of them have questioned what would be the ideal doses and proposed that the ingestion of high quantities could trigger of some damages to descendants. Recent researches suggest that selective excessive intake of a type of vitamin can change negatively the metabolic activities and it is also applied to this supplementation.[25] Morakinyo et al.,[26] for instance, demonstrated that high doses of FA during pregnancy or lactation decreased insulin sensitivity and adiponectin expression in offspring, predisposing to dyslipidemia and changes in glucose metabolism. Barua et al.[27] also report that FA high doses changes genomic function and affect the offspring's behaviour in mice. Leeming and Lucock[28] ponder that clinical and experimental studies are based on the fact such vitamin can prevent some malformations, but they do not consider the long-term effects, which can be deleterious. These authors suggest that high-dose supplementation can predispose to autism disorder and be associated to the increase in the number of children with such pathology. Other works corroborate it by reporting that ingestion throughout pregnancy may be associated with negative results in the development of the offspring's nervous system.[29,30]

Fetal Programming

Gestation is featured by physical and psychological changes, as result of body adaptations,[31] becoming the nutritional needs increased during such period.[16] Maternal nutritional state is pivotal to determine both metabolic and hormonal profile of descendants and stablish conditions which can remain throughout life. Waterland e Garza[32] defined this relationship as fetal programming, expression which associates nutritional changes in early life to diseases in adulthood, such as diabetes, obesity and arterial hypertension. Maternal nutrition is the main factor to determine intrauterine environment, due to its potential to change the expression of fetal genome and lead to development adaptations. Thus, the suitable nutrition may reduce the risks of developing chronic diseases in late life.[33] Several experimental models have been set up in order to evaluate the impact of maternal feeding on offspring development. Protein restriction, for example, is a widely used one and has been harmful to descendants inducing decrease in the number of nephrons in both adult male[34] and female rats[35] when it occurs during entire gestation. Exposure to prenatal undernutrition in human beings is also associated with premature brain aging in young adults.[36] In rats the protein shortage during gestation and lactation triggered some changes in male and female offspring's behaviour in a period equivalent to adolescence. According to the authors, both stereotyped behaviour and decreased social interaction observed can be associated with autism spectrum disorder.[37] Inappropriate amounts of micronutrients in the maternal diet can also cause some disorders in kidney development, such as both reduction in offspring's number of nephrons whose dams were submitted to vitamin A deprivatio[38] and renal glomeruli in descendants from dams that received iron deficient diet.[39] Regarding FA, some works have demonstrated that its deficiency during pregnancy changes cell division, which is more meaning in tissues with a high proliferation rate.[40] Cell multiplications, as well as rapid growth, which are central aspects of fetal development require a suitable folate supply. Meher et al.[41] found reduction of liver absolute weight in offspring from dams fed on low quantities of it during gestation and lactation, besides changed hepatic transcription factors expression. The hepatic protein levels involved with metabolism and neutralization of toxic products were also altered in male offspring from rats submitted to similar restriction during gestation.[42] Those changes remained until both six months and one year old, reinforcing the fetal programming concept. Due to some studies' question about the ideal quantity of FA that should be consumed during gestational period, this work intended to gather different experimental models and doses as well as its absence in order to report the impact in these situations. Besides it, few works have evaluated the effects of such supplementation in the kidney at late life. Because of its important role on homeostasis, this work goals to evaluate the supplementation effects exclusively during gestation in the offspring's kidney by current literature.

Methods

It was performed research in the following databases: MedLine (Medical Literature Analysis and Retrieval System Online), through Pubmed, LILACS (Literatura Latino- Americana e do Caribe em Ciências da Saúde) and SciELO (Scientific Electronic Library Online). It was carried out through advanced research with the descriptors together: "folic acid", "gestation" and "kidney" in English and Portuguese. In this way, we obtained 107 articles in the PubMed platform, two in LILACS, and none in Scielo. The word "offspring" was not included to enable a wide and comprehensive research. After

preliminary reading, the articles that met the inclusion criteria were regarded: (1) studies with rats, mice, and human beings (2) studies that approached the effects of maternal folic acid consumption during gestation and lactation, and (3) studies that evaluated the offspring's kidney in several phases of life. The exclusion criteria were: (1) studies that performed FA supplementation in any other period than pregnancy and (2) articles that evaluated the effect on the mother.

Results

The works regarded used different experimental models and evaluated several parameters. Thus, the results were separated into categories according to the evaluated criteria.

Gestational Supplementation[Q4] in Normal Conditions

Effects on Glomerular Filtration Rate

Lee et al.[43] followed children whose mothers received micronutrient supplementation during pregnancy and evaluated the long-term effects. These authors showed that maternal supplementation during early gestation was associated with a reduction of diastolic pressure in childhood despite the systolic pressure not being altered in those children. Also, the renal volume and glomerular filtration rate were not changed by such supplementation. Children whose mothers received high doses of iron (60mg) and folate (400μg) during gestation presented higher glomerular filtration rate when compared to offspring from supplemented mothers with half the quantity of iron. Lee et al.[43] performed a systematic review in order to comprehend the relationship between maternal nutrition and renal development exclusively in human beings, evaluating its structure and function in some nutritional situations. Among the works cited in such study, one of them reported a significantly lower risk to develop microalbuminuria in children six to eight years old whose mothers consumed FA during pregnancy.[44] Another study did not show any relation between such supplementation and change in the kidney of descendants at six years old. However, it suggested that higher maternal serum folate concentrations at early gestation were positively correlated with an increase in renal volume in childhood, but not with albuminuria risk.[45]

Molecular Level Effect

One of the studies regarded in this manuscript analyzed both FA supplementation in specific organs and gestational period, investigating its impact at the first, second and third weeks singly or throughout pregnancy.[46] Folate plasmatic levels were higher in 30 to 42% in the pups from supplemented dams, meanwhile, its concentrations in the kidney and colon were not affected because of maternal intake. The intervention time did not cause difference about such parameters. Global DNA methylation was also observed in different organs. Relation to kidney, liver, and colon, was not observed any change in descendants whose dams received FA, regardless of supplementation time. The gene expression levels of essential genes for fetal development, such as α estrogen receptor (Er-α), glucocorticoid receptor (Gr), peroxisome proliferator-activated receptor alfa (Ppar-α), insulin-like growth factor 2 (Igf2) and peroxisome proliferator-activated receptor gamma (Ppar-γ) were not changed in the kidney of puppies from dams FA supplemented at any time of gestation. Similar results have been found in the brain and colon of those animals. Among the evaluated organs, only in the liver the expression of Er-α, Gr, Ppar-α genes was decreased in 15 to 25% in puppies whose mothers received FA in late gestation or throughout it. Based on results, the authors comment that the effects depend on the evaluated organ and the period in which it is applied.

Gestational Supplementation in Hostile Conditions

Maternal Exposure to Alcohol

This study also selected articles that reported the impact of FA maternal intake associated with conditions which can predispose the descendants to diseases in long-term, such as, alcohol. Ojeda et al.[47] have investigated if such vitamin could reverse the damages from oxidative stress due to alcohol consumption during pregnancy and lactation in the offspring. They found out that the addition of FA and selenium (Se) on maternal diet mitigates the puppies' growth retardation, which is one of the harmful effects of alcohol exposure. The supplementation did not exert any effect on kidney relative weight; however, it prevented the reduction of protein content in renal tissues, found in those animals whose mothers consumed ethanol. The same puppies also had a decrease by 50% in creatinine clearance not improved by FA and Se. On the other hand, the supplemented diets were effective to preserve glutathione reductase enzyme activity in the kidney, which was decreased in descendants of dams exposed to alcohol. The double supplementation increased the superoxide dismutase (SOD) activity only in control animals and not in those whose mothers consumed alcohol. Catalase activity was preserved in the litter of dams that received Se and FA as well as. Another work published by the same authors reported that maternal alcohol intake during lactation caused reduction on litter body growth despite of did not alter the weight of any specific organ. Such disorder was reversed by double supplementation. Ethanol exposure also depleted Se in some organs as kidney, liver and brain, meanwhile the diet recovered this pattern.[48]

Maternal Protein Restriction

Król et al.[49] have evaluate if FA combined with normal and hypoprotein diets during gestation could reverse the harmful effects from protein deprivation about minerals content in different tissues. Renal copper (Cu) content was reduced by maternal FA intake, but such levels were significantly lower in the offspring whose mothers received the vitamin associated with hypoprotein diet. Neither the protein-deficient nor FA supplemented diet affected iron (Fe) levels in the descendants' kidney. Maternal protein-defficient diet enriched by high quantity of FA (5mg) also was associated with higher renal levels of zinc (Zn). The gender was an

important factor to determine Cu, Zn and Fe contents in the liver and kidneys, with female offspring having higher levels of such minerals than males.

Maternal Exposure to Other Drugs

Some studies have questioned if FA is able to prevent the disorders induced by genotoxic and teratogenic drugs during pregnancy. El-Ashmawy and Bayad[50] administered this vitamin together with azathioprine (AZA) between sixth and fifth days of gestation in rats and observed changes that happened to dams and fetuses. Despite not being the object of our study, some findings should be highlighted. Maternal weight gain, implantation sites and number of fetuses were close to control group. On the other hand, the dams which received only AZA presented higher number of dead fetuses and the living ones had marked reduction in body weight and growth, besides gross visceral and skeletal anomalies. The groups treated with FA displayed similar results to the control group, with significant decrease of those anomalies. The administration of FA and AZA during four weeks in a successive experiment became urea and creatinine serum levels close to the control group (**Chart 1**). Otherwise, FA was not effective in reducing renal malondialdehyde (MDA) levels in those animals and preventing the architectural damages in the kidney, such as degeneration and tubular necrosis, swollen glomeruli, and infiltration of lymphocytes triggered by AZA.[50–64]

Discussion

The literature indicates that gestation is a critical period to determine the concept's future metabolic status and many factors can affect such development. In this review, we have found that FA maternal supplementation was not capable to change the DNA global methylation in the kidney, which seems to be beneficial, even though this result has not been observed in all organs. The supplementation performed throughout pregnancy is associated with such alteration in the brain and liver, with the first one being more susceptible. These organ-specific effects are probably related to the differences in both metabolism and folate demand in each of them.[51] The literature reports that changes in DNA methylation due to FA maternal intake vary according to the tissue, specific genes, interaction with other vitamins, among others.

Gestational supplementation did not change the expression of some genes, such as Igf2, Ppar-α e Ppar-γ in the kidney. Igf2 promotes fetal growth,[52] meanwhile Er-α is an estrogen nuclear receptor which allows the action of such hormone on reproductive development in embryo and fetus.[53] Ppar-α regulates lipid metabolism[54] and Ppar-γ regulates both glucose metabolism and storage of fatty acids.[55] The conservation of those genes expression is a relevant finding due to they are essential to several aspects of fetal development, such as growth and cell metabolism.

During embryogenesis, a new pattern of DNA methylation is set up[56] and is vulnerable to environmental factors such as maternal diet. Any alteration is likely to predispose disorders in long-term since aberrant or deregulated models of DNA methylation are associated with many diseases in human beings.[57]

Organogenesis is a complex process that is under the influence of harmful conditions and drugs during the gestational period. FA seems to be effective to mitigate the disorders caused by teratogens or prevent some complications from such exposure in the kidney and other organs. Its protective effect observed in the offspring's kidney of dams exposed to AZA is corroborated by Ojeda et al.[58] when showing that FA administered with alcohol to pregnant rats avoided hepatic damages in the puppies at late life.

One of the ways to protection performed by FA is antioxidant activity. Its intake during pregnancy was able to preserve the glutathione reductase and catalase activity in the kidney of puppies whose mothers consumed alcohol. Catalase is related to superoxide dismutase in the removal of hydrogen peroxide and folate conjugated to catalase increases the ability of this enzyme to neutralize these reactive oxygen-derived species (RODS) being produced during some cell process that are potentially harmful.[59]

Lipid and protein peroxidation is one of the damage mechanisms triggered by free radicals and RODS and occurs when there is imbalance between generation and capacity to eliminate it, which features oxidative stress.[60] The kidneys are susceptible organs due to plenty of polyunsaturated fatty acids in renal lipid composition[61] FA associated with selenium also reestablished the protein overall content in the kidney of puppies from dams exposed to ethanol, reinforcing its effectiveness in preventing the protein peroxidation caused by oxidative molecules.

According to Dennery,[62] the embryo development may be rather affected by such molecules due to the reduced capacity to neutralize them, since the embryo develops in an environment with relatively low oxygen levels. Oxidative stress can trigger off failure in embryo implantation, abortions, and congenital malformations.[60]

Despite its protective properties, FA cannot be enough to suppress completely the impact of some acute and important aggressions during the gestational period, for instance, changes in renal ions transport unleashed by maternal deprivation of protein,[49] as well as the reduced glomerular filtration observed in the litter of ethanol-exposed dams during gestation was not prevented by FA + Se supplementation.[47] Hostile conditions can compromise embryonic nephrogenesis and in turn, alter the glomerular filtration rate.[63] Albeit FA has not reverted some disorders associated with nephrogenesis, it is suggested that folate deficiency might impact this process through epigenetic modulation.[43] There are hypotheses that little availability of folate, B12 vitamin, and other nutrients affects the volume of the kidneys and decreases the nephrons number of the offspring, predisposing to chronic renal disease in adulthood,[45,64] it reinforcing the concept of fetal programming.

In short, because of the large variety of maternal factors which may exert influence on fetal organogenesis and the intrinsic vulnerability of this process, studies that evaluate the supplementation with this one and other nutrients, as

Chart 1 General characteristics of the included studies

Author/Year	Sample	Intervention	Follow-up	Settings & participants	Objective	Assessment methods	Results
Lisle et al. (2003)[39]	Control (153 mg Fe/kg diet, n 7) or low-Fe (3 mg/kg diet, n 6)	Experimental study	18 months	Offspring rats (n = 28)	Investigated the renal morphology of adult rats born to mothers who were Fe-deficient during pregnancy.	Kidney weight; Glomerular number and size; Systolic blood pressure	Maternal Fe restriction causes hypertension in the adult offspring that may be due, in part, to a deficit in nephron number.
Miliku et al. (2017)[45]	Folic acid supplement (0.4–0.5 mg)	Population-based prospective cohort study from fetal life onwards	From pregnancy to 6 years of the child	Pregnant women and their (n = 4.226)	Examined the associations of folate, vitamin B12, and homocysteine concentrations during pregnancy with kidney outcomes in school-aged children.	Folate, vitamin B12 and homocysteine blood concentrations measured in early pregnancy and at birth (cord blood).	Folate, vitamin B12 and homocysteine concentrations during fetal life are associated with offspring kidney development.
Ly et al. (2016)[46]	Folic acid supplement (2 mg and 5mg)	Experimental study	8 weeks	Sprague-Dawley Rats (n = 10)	This study evaluated whether maternal folic acid supplementation might change the offspring's. metabolism.	Brain, liver, kidney and colon of puppies were assessed about folate concentrations, global DNA methylation and expression. of Igf2, Er-α, Gr, Ppar-α e Ppar-γ genes.	Folic aid supplementation at late pregnancy or throughout gestation reduced the expression of Er-α, Gr and Ppar-α genes in the liver.
Ojeda et al. (2012)[47]	(Se) (0.5 ppm) or with Se (0.5 ppm) + folic acid (8 ppm) administered to EtOH-exposed (20% v/v	Experimental study	8 weeks	Winstar rats (n = 6) female (n = 6) male	Diet supplemented with selenium or with Se + folic acid administered to EtOH-exposed dams during gestation and lactation prevents the oxidative EtOH-provoked effects in their offspring's kidneys.	Serum, urine and kidney, Se levels, creatinine clearance, antioxidant enzyme activities and lipid and protein peroxidation in the kidney.	Dietary supplementation improve renal development, Se deposits, and protein content while decreasing lipid and protein oxidation and modifying antioxidant enzymes' activity.
Ojeda et al. (2010)[48]	Se (0.5 ppm) or with Se (0.5 ppm) plus folic acid (8 ppm) to ethanol-exposed (20% v/v)	Experimental study	8 weeks	Winstar rats (n = 6) female (n = 6) male	Supplemented diet with Se or with Se plus folic acid to ethanol-exposed dams prevents the ethanol-provoked effects in their offspring's Se deposits.	Selenium levels in the liver, kidney and testes.	Results show that ethanol decreases Se deposits in pups' heart, liver, kidney and testes. However Se levels in both pancreas and serum were increased by ethanol; it also compromised the weight and length of the offspring at the end of lactation.
Król et al. (2011)[49]	(1) normal protein, normal folic acid (FA) diet (0.002-g FA); (2) protein-restricted, normal folic acid diet (0.002-g); (3) protein restricted, folic acid-supplemented diet (0.005 g FA); (4) normal protein, folic acid-supplemented diet (0.005 g FA).	Experimental study	6 weeks	Offspring (n = 48)	The aim of the study is investigate the influence of maternal diet during gestation on Fe, Zn, and Cu levels in the liver and kidney of adult rats.	The levels of Fe, Zn, and Cu in the livers and kidneys; Offspring's tissue mineral levels.	The results of this study show that maternal dietary folic acid and protein intake during pregnancy, as well as the type of postweaning diet, affect Fe, Zn and Cu levels in the offspring.
El-Ashmawy and Bayad (2016)[50]	(1) AZA (25 mg/kg) (2) AZA, simultaneously with grape seed extract at the dose of 75 mg/kg (3) AZA, simultaneously with folic acid at the dose of 5 mg/kg;	Experimental study	4 weeks	Adult Wister rats (n = 40)	Investigate the influence of AZA on the fetal development and renal function and its co-administration with either folic acid (FA) or grape seed extract (GSE).	Kidney histology; Glutathione level (GSH); Lipid per oxidation content as malondialdehyde in the kidney tissue.	Maternal administrations of both FA and GSE protect against AZA-induced fetal malformations. Grape seed extract was more active than FA in potentiating the antioxidative defenses for controlling AZA-induced oxidative renal damages.
Hawkesworth et al. (2013)[64]	(1) Fe30F: 30 mg iron and 400 µg of folate (2) Fe60F: 60 mg of iron and 400 µg of folate (3) MMS: Multiple micronutrient supplement	A trial follow-up study	Between November 2001 and October 2003 (recruited early in pregnancy) Between May 2007 and February 2009 when the descendants were 4.5 years old (children born)	Women were recruited early in pregnancy (n = 3.560) children (n = 3.267)	Assess the association between prenatal food and micronutrient supplementation and childhood blood pressure and kidney function. Women received either iron and folate or multiple micronutrient tablets daily.	Blood pressure; Kidney function.	Limited evidence for long-lasting impacts of pregnancy supplementation on offspring markers of kidney function.

well as their absence, can enlighten the benefits and ensure the safe use in order to maintain the descendants' health.

Conclusion

Gestational FA supplementation did not cause renal toxicity; it exerted antioxidant protective effect and mitigated some renal disorders unleashed by severe aggressions.

Q3

Conflicts to Interest[Q3]
None to declare.

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Federação Brasileira das Associações de Ginecologia e Obstetrícia

FEBRASGO POSITION STATEMENT

Accurate diagnosis of breast lesions

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The National Specialized Commission on Breast Imaging of the Brazilian Federation of Gynecology and Obstetrics Associations (Febrasgo) endorses this document. Content production is based on scientific evidence on the proposed theme and the results presented contribute to clinical practice.

Key points

- Breast lesions comprise a wide variety of diagnoses with different manifestations.
- Breast lesions can be classified as benign, of uncertain malignant potential (B3), carcinoma in situ, and invasive carcinoma.
- In the era of personalized medicine, individualizing and getting an accurate diagnosis makes a big difference in the patient's final outcome, especially in the case of breast cancer.
- Targeted and quality imaging exams, properly selected biopsy methods and conventional anatomopathology, immunohistochemistry and even molecular analyzes are crucial in the diagnosis and management of patients.

Recommendations

- The minimal imaging propaedeutics indicated in the assessment of breast lesions is mammography and ultrasound of the breasts and armpits, which are sufficient in most cases.
- The diagnosis of patients with palpable lesions of suspicious characteristics on clinical examination should not be delayed; therefore, core biopsy should be indicated, preferably ultrasound-guided core biopsy.
- For suspicious lesions detected by imaging tests, the choice of biopsy method should consider the presentation and size of the lesion and in which imaging methods the lesion is visualized.
- Whenever the lesion is visualized on ultrasound, this will be the method of choice to guide the minimally invasive procedure.
- When the lesion is visible on magnetic resonance imaging (MRI) of the breasts, a second look ultrasound should be performed in an attempt to find the lesion. Mammography with localized compression and magnification can also be performed, especially in the case of non-mass enhancements in an attempt to localize the lesion. Second look tomosynthesis considerably increases lesion localization rates. If no other method can visualize the suspicious finding, the biopsy should be MRI-guided.
- Every service that proposes to offer MRI as a screening option must have means for performing MRI-guided biopsy in its own service or in a referenced service. Alternatively, preoperative marking methods for performing a surgical biopsy can be performed. However, performing therapeutic procedures without prior knowledge of the nature of the lesion is not allowed.
- In the case of suspicious mass lesions (nodules) larger than 1 cm, core biopsy should be the preferred method of biopsy. In nodules smaller than 1 cm, both core biopsy and vacuum biopsy may be indicated, depending on the individual case.
- In complex solid-cystic lesions with a solid component smaller than 1 cm, vacuum-assisted biopsy (VAB) should be indicated preferably. In lesions with an extensive solid component, core biopsy or VAB can be used, depending on availability and the degree of suspicion.
- In polypoid intraductal lesions (suspected papilloma), VAB should be indicated as a diagnostic method, if available.
- For lesions that present as architectural distortion and probable radiating scar, VAB is more accurate than core biopsy.
- For microcalcifications seen only on mammography, stereotactic vacuum biopsy should be the method of choice whenever available.
- In lesions of uncertain malignant potential (B3) or in cases of inconclusive core biopsy, vacuum-assisted excision (VAE) is indicated.

- The recommendation for probably benign BI-RADS category 3 lesions is the biannual follow-up in the first year, and annual follow-up thereafter. In patients younger than 30 years old with BI-RADS category 3 nodules, simple or complicated cysts, fine needle aspiration biopsy (FNAB) is indicated if desired by the patient or when indicated by the clinician.
- In the case of suspected axillary lymph nodes, the evaluation can be performed by FNAB or core biopsy according to the indication and evaluation of the case. The location of these lymph nodes and the expertise of the physician performing the examination should also be considered.
- A pathologist experienced in breast pathology is imperative for pathological evaluation and accurate diagnosis.
- Immunohistochemical panel should be mandatory for all cases of ductal carcinoma in situ and invasive carcinoma.
- Immunohistochemistry should be performed whenever the pathologist deems it necessary, being essential in cases of malignant breast lesions.
- Immunohistochemical panel of breast carcinoma is prognostic, predictive and should include estrogen receptor, progesterone receptor, HER2/neu and Ki 67.
- Molecular exams and prognostic genetic panels have specific indication and are tools that can contribute in selected cases.
- Clinical, imaging and pathology agreement is essential for the accurate diagnosis. It is the role of the physician who performs outpatient diagnostic procedures to be aware of the results, both for audit purposes and to exchange information with requesting physicians, if necessary.

Background

Breast lesions comprise a wide variety of diagnoses with different behaviors and presentations. The broad aspect of suspicious breast lesions ranges from proliferative lesions without atypia to carcinomas. Breast lesions can be grouped into three categories that present different risks and management: benign lesions of uncertain malignant potential (pathological classification B3), in situ carcinomas and invasive carcinomas.[1-3] A specific diagnosis is the goal of all investigation, but it is important to confirm malignancy or exclude it. In the era of personalized medicine, individualizing makes a big difference in case management. Targeted and high-quality imaging exams, properly selected biopsy methods and conventional anatomopathology, immunohistochemistry and even molecular analyzes can be decisive for the diagnosis and management of patients. The investigation of breast lesions can result from two different situations: screening or diagnosis. The interpretation of imaging findings, the indication of the biopsy technique, the interpretation of results and the correlation of clinical, imaging and pathology may vary depending on whether the finding is due to screening in asymptomatic patients or patients with complaints, signs or symptoms on physical examination in a diagnostic situation.[4-5]

Imaging propaedeutics

Anamnesis and complete clinical examination should be performed in patients with complaints and clinical alterations resulting from screening. In the case of clinically suspicious lesions, core biopsy should be indicated immediately, preferably ultrasound-guided core biopsy. Mammography and ultrasound are the minimum propaedeutics for the evaluation of breast lesions.[6] Mammography is not necessary in patients under 30 years of age, especially in those under 25 years of age with nodules suggestive of benign BI-RADS category 3. Tomosynthesis can be particularly useful in the assessment of breasts lesions with density pattern B (sparse areas of fibroglandular tissue) and C (heterogeneously dense) according to the BI-RADS classification.[6,7] Magnetic resonance imaging of the breasts can be used in selected cases and in patients at high risk for breast cancer; in its absence, contrast-enhanced mammography can be used. Thermography and other alternative imaging methods are still in the experimental phase, have not demonstrated any additional benefit in the diagnosis of breast lesions and currently have no indication in the investigation or diagnosis of breast lesions. The Ministry of Health and the National Cancer Institute (Inca) strongly recommend not incorporating thermography into the line of breast diagnostic care.[8-12]

What is the imaging method of choice to guide the biopsy procedure?

Although biopsies can be performed manually without an associated imaging method, this association improves the results, so it should always be used when available. Whenever the lesion is visualized on ultrasound, this is the method of choice to guide the procedure. For calcifications seen only on mammography, the method of choice is stereotaxis. For architectural distortions and focal asymmetries seen on mammography, methods of choice are tomo biopsy (tomosynthesis-guided biopsy) and in its absence, stereotaxis. Lesions seen only on tomosynthesis should be approached by tomo biopsy.[13] Lesions seen only on MRI should be biopsied using this method. Contrast-

enhanced mammography biopsy is not available in our country.[14-15]

Is it a minimally invasive procedure?

The preferred biopsy method for solid lesions should be histological.[8] BI-RADS category 3 nodules and changes should be followed up every six months for one year and annually thereafter, except for probably benign BI-RADS category 3 lesions in patients younger than 30 years and simple or complicated cysts, in which cytology is well indicated when, for clinical reasons or patient concern, an invasive procedure has been requested.[15] Fine needle aspiration biopsy is performed to obtain cytological material in mastology. Core biopsy is performed using tru-cut mechanisms (elastic potential energy, spring) and 14 G to 18 G needles. Most lesions are satisfactorily diagnosed with core biopsy.[16] Vacuum biopsy rescues a fragment of the lesion by means of vacuum suction using 7G to 12G needles.[17] Both core biopsy and vacuum biopsy can be used in lesions smaller than 1.0 cm according to the individual case.[4-6,14,18-19] Vacuum-assisted biopsy is preferred in complex solid-cystic lesions with a solid component smaller than 1 cm, and core biopsy or VAB may be used in those with a solid extensive component, depending on availability and degree of suspicion. In polypoid intraductal lesions (suspected papilloma), VAB should be indicated as the diagnostic method, if available.[20] For microcalcifications seen only on mammography, stereotactic vacuum biopsy should be the method of choice, whenever available.[14] Diagnostic vacuum-assisted excision (VAE) is defined as the complete percutaneous excision of the lesion or the salvage of more than 4 g of tissue.[21] In lesions of uncertain malignant potential or cases of inconclusive core biopsy, VAE is indicated.[1,16,18,21] Incisional or excisional surgical biopsy is currently reserved for cases of clinical-imaging-pathological disagreement or situations in which percutaneous methods cannot be performed because of unavailability or technical contraindication, such as risk of pneumothorax.[14]

What is the pathology?

Breast pathology is a concentration field and requires targeted training. A pathologist experienced in cytopathology and breast pathology is imperative for cytological and pathological evaluation and accurate diagnosis. Most diagnoses can be confirmed in established tissue analysis using hematoxylin-eosin staining. Diagnostic immunohistochemistry should be performed whenever the pathologist deems it necessary and may be essential to confirm the diagnosis in some situations. The immunohistochemical panel is prognostic and predictive, and should be performed for all in situ or invasive breast carcinomas, as it allows approximating the molecular classification of invasive breast cancer, classifying breast tumors as luminal-like (tumors with hormone receptors, estrogen and progesterone positive), HER2-like (with expression of the HER2 membrane protein) and basal-like (tumors lacking hormone receptors and the HER2 membrane protein). Currently, immunohistochemical panel is used for decisions regarding all breast cancer therapy, since, in addition to being prognostic, it has predictive value for endocrine therapy, anti-HER2 therapy, chemotherapy and immunotherapy.[22-23]

Molecular tests

Molecular tests and prognostic genetic panels have a specific indication and should not be performed in a generalized way for all cases of malignancy.

However, doing these tests can optimize the treatment of many patients, either by adding or removing systemic treatments. Molecular tests allow individualizing each patient according to their specific risk and directing the best treatment.

Final considerations

In the era of precision medicine and personalization of procedures, the accurate diagnosis of breast lesions is essential. The clinical situation of the patient (screening versus diagnosis), imaging tests, the biopsy technique used, the imaging method to guide the procedure, the cytological-histological-immunohistochemical diagnosis and eventually the molecular diagnosis must be taken into account for the proper diagnosis of breast lesions. Although all this arsenal is available, clinical agreement with imaging and pathology are essential as well. In the occurrence of any disagreement of findings, the case should be reviewed and a new biopsy should always be considered.

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Instructions to Authors

About the journal

Basic information

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

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

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

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

Subareas of knowledge of interest GO:

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

Indexing sources:

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

Intellectual property

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

Responsibilities of the Editorial Board

Responsibilities of the Editor-in-Chief

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

- Maintain impartiality and clarity in the publication of sponsored supplements and/or with any other type of sponsorship/funding.
- Ensure open access and describe in all articles the Creative Commons license modality adopted by the journal.
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- Inform the registration number referring to the research approval report at the National Council for the Control of Animal Experimentation (Concea). Studies involving animal experiments must comply with Law No. 11.794, of October 8, 2008, which establishes procedural rules for the scientific use of animals in Brazil. International manuscripts must submit local ethical documentation to proceed with the submission process. Any manuscript involving animal or human experiments submitted without proof of approval by institutional or local research committees will not be reviewed and will be returned to authors.
- Inform potential conflicts of interest in a written statement signed by all authors.
- Inform the journal editor when a major error is found in the study and provide all necessary information for publication correction, errata and retraction.
- Provide data records associated with the study when requested by the editor.
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Scientific misconduct

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

Investigation of scientific misconduct

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

Retraction policy

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

Editors will consider a publication retractable in case:

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

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- It has been published solely based on a compromised or manipulated peer review process;
- The author(s) have not disclosed a major conflict of interest which, in the Editor's opinion, may have unduly affected the interpretations of the work or the editors' and reviewers' recommendations.

Retraction notices must:

- Be linked to the retracted article in all versions printed or online;
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- Be clearly identified as a retraction (i.e. distinct from other types of correction or comment);
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- Authors' conflicts of interest were reported to the journal after publication, but in the editor's opinion, they likely did not exert influence in interpretations, recommendations or conclusions of the article;

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

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

Instructions to authors for manuscript submission

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

Evaluation of manuscripts

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

Preparing a manuscript for submission

Mandatory documents for submission

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

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

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Manuscript

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

- **Original articles:** full prospective, experimental or retrospective works.
- **Case reports:** They are of interest if well documented from a clinical and laboratory point of view and should contain new or unexpected aspects in relation to cases already published. Authors should indicate this information in the referral letter. The text of **Introduction** and **Discussion** sections must be based on an up-to-date literature review.
- **Review articles:** Spontaneous contributions are accepted, including integrative, scoping, or systematic reviews with or without meta-analyses. Narrative reviews will only be accepted exceptionally, given the questionable scientific evidence they represent. The methods and procedures adopted to obtain data inserted in the text must be described and based on recent references, including the current year. As this is still subject to controversy, the review should discuss trends and lines of investigation in progress. In addition to the review text, the synthesis and conclusions must be presented.
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OBS. Manuscripts containing results of original clinical or experimental research have priority for publication

Manuscript structure

Title

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

Abstract

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

1. Abstract: for original articles

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

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

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

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

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

2. Abstract: for systematic review articles

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

Objective: State the main objective of the article.

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

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

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

Conclusions: State the main conclusions and their clinical utility.

3. Abstract: for integrative/scoping reviews

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

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

Keywords

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

Manuscript body

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

Introduction

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

Methods

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

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

Randomized clinical trial:

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

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Results

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

Discussion

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

Conclusion

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

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