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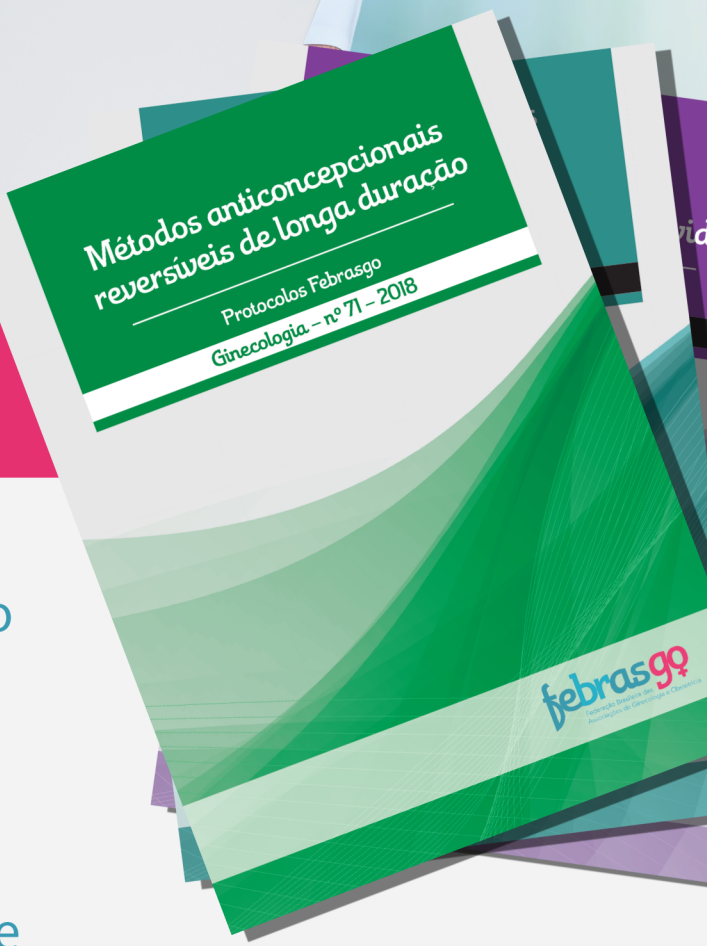

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Editorial

'Missing Adenocarcinomas': Are They a Real Problem in Cervical Cancer Screening in Brazil?

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Screening and human papillomavirus (HPV) vaccine are the most critical strategies for cervical cancer control.[1] The impact of vaccine programs has not been fully demonstrated yet due to the long natural history of the neoplasia. Regions that have implemented organized screening had efficiently reduced their incidence and mortality rates. Even in Brazil, where screening is opportunist, the cervical cancer rate is going down, dropping to the fourth most common female cancer.[2–4]

The acquired knowledge about the pathogenesis of cervical cancer has proved that HPV DNA test is more efficient than cytology in detecting precursor lesions and reducing the incidence of cervical cancer. In screening programs, the HPV DNA test anticipates the diagnosis with a higher sensitivity.[5,6] The most robust evidence comes from the systematic review by Ronco et al,[6] who analyzed four randomized trials that enrolled 176,464 women aged 20–64 years, who were randomly assigned to the HPV DNA intervention group or the cytology control group. The authors showed a benefit with the HPV DNA test for the detection of invasive squamous cell carcinoma (0.78, 0.49–1.25) that was even higher for adenocarcinoma (odds ratio [OR]: 0.31; 95% confidence interval [95% CI]: 0.14–0.69).[6]

This finding might be related to the limitations of cytology in detecting endocervical lesions: endocervical glands are harder to sample and, given the rarity of these lesions, reading and interpreting abnormal findings is more difficult.[7–9] Although invasive adenocarcinomas are usually detected in more advanced stages, cytology screening is associated with the downstaging of these lesions.[9]

However, as cervical cancer rates are expected to fall, a new debate emerges regarding cancers not related to HPV infection, like some rare endocervical adenocarcinomas.

Invasive endocervical adenocarcinoma is a difficult histological type for pathologists. Recently, attempts are being made to switch to a different endocervical adenocarcinoma classification that would more precisely reflect the different prognosis observed in the various subtypes.[10,11] Currently, misclassification is common. One of the proposals is the classification based on the morphologic features linked to HPV: HPV-associated (HPVA) and HPV-unassociated (NHPVA) features. The NHPVA includes such subtypes as endometrioid, gastric, minimal deviation, clear cell, serous and mesonephric tumors, and is related to a worse prognosis than that of the HPVA subtypes.[11]

The pathogenesis of NHPVA subtypes is poorly understood. The minimal deviation and gastric subtypes may share the same precursor lesion, which is called lobular endocervical glandular hyperplasia, and some are associated with Peutz-Jeghers syndrome.[12,13] Serous tumors are associated with *p53* gene mutations, as serous endometrial adenocarcinoma and endometrioid tumors might represent endometrial cancers in origin that have spread to the cervix.[14]

The positivity of HPV in adenocarcinomas is high, usually around 90%. A recent study by Pirog et al[15] has provided comprehensive data on the genotype distribution of 760 adenocarcinomas cases from 38 countries between 1940 and 2009. The overall HPV prevalence was of 62.8%, raising the concern about the possibility of missing almost 1/3 of adenocarcinomas with HPV DNA test screening. Although those cases were reviewed through three-level pathology, the authors considered two main reasons for this low HPV prevalence: aging of the paraffin-embedded tissues (older samples showed lower positivity than recent ones), and differences in regional tissue-fixation protocols within countries. Another relevant result was that HPV-negative samples were more common in older women. It is not clear if HPV could be lost during a slow progression tumor or if it is a non-HPV pathogenesis.

Irrespective of the differences in prevalence rates, HPV detection is harder to be demonstrated due to the relative low viral load in the glandular epithelium. The thin epithelium does not support a productive infection, as it is observed in the squamous epithelium. The HPV life cycle involves the infection of a dividing cell and a reservoir in the basal layer. The ability to drive cancer progression is related to the expression of different proteins that may vary according to the position or level of maturity of the cells. The less dynamic scenario of the

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glandular epithelium and the low number of integrated virus copies observed in glandular lesions are barriers to understand how these precursor lesions develop.[15–17]

Brazil and other Latin-American countries have demonstrated some effect of the cytology opportunist screening in reducing the incidence of cervical cancer in the last few decades.[4] However, this effect is much more discreet than the one observed in countries that have implemented organized screening, with a high-complexity quality control program and a population-based strategy of invitation (call and recall system).[18–20] For those countries, the shift to the HPV DNA test will improve the efficiency of the programs, but the impact of the superiority of the HPV DNA test may not result in a significant reduction in rates since they already have reached low incidence rates. For those countries, the question of the 'missing adenocarcinomas' seems to be more relevant, as it may correspond to around 3% to 4% of the total of cervical cancers, as claimed by Pirog et al.[15] Even if this estimation is correct, it should be considered that these rare cancers are challenging to be found through cytology or HPV DNA tests.

In regions with moderate to high incidence of cervical cancer, as in Brazil, this shift to the HPV DNA test may cause a more pronounced impact on decreasing rates, particularly if accompanied by an effort to implement organized screening programs. The question of how to prevent and diagnose rare adenocarcinoma subtypes (or the 'missing adenocarcinomas') is currently not as relevant as the necessity to reduce the incidence of squamous cell cancer, irrespective of the test used. Only in the near future, as the incidence of cervical cancer drops, could the 'missing adenocarcinomas' emerge as a critical problem in the screening program in Brazil.

Conflict of Interests

The authors have none to declare.

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Do We Know How to Avoid OASIs in Non-Supine Birth Positions? A Retrospective Cohort Analysis

Sabemos como evitar as LOEAs em posições de parto não supinas? Uma análise de coorte retrospectiva

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Abstract

Objective To evaluate the association between the upright and supine maternal positions for birth and the incidence of obstetric anal sphincter injuries (OASIs).

Methods Retrospective cohort study analyzed the data of 1,728 pregnant women who vaginally delivered live single cephalic newborns with a birth weight of 2,500 g. Multiple regression analyses were used to investigate the effect of the supine and upright positions on the incidence of OASIs after adjusting for risk factors and obstetric interventions.

Results In total, 239 (13.8%) births occurred in upright positions, and 1,489 (86.2%) in supine positions. Grade-III lacerations occurred in 43 (2.5%) patients, and grade-IV lacerations occurred in 3 (0.2%) women. Supine positions had a significant protective effect against severe lacerations, odds ratio [95% confidence interval]: 0,47 [0.22–0.99], adjusted for the use of forceps 4.80 [2.15–10.70], nulliparity 2.86 [1.44–5.69], and birth weight 3.30 [1.56–7.00]. Anesthesia ($p < 0.070$), oxytocin augmentation ($p < 0.228$), shoulder dystocia ($p < 0.670$), and episiotomy ($p < 0.559$) were not associated with the incidence of severe lacerations.

Conclusion Upright birth positions were not associated with a lower rate of perineal tears. The interpretation of the findings regarding these positions raised doubts about perineal protection that are still unanswered.

Keywords
- birth position
- delivery
- episiotomy
- labor
- perineal trauma
- risk factors

Resumo

Objetivo Avaliar a associação entre as posições maternas verticais e supinas ao nascimento e a taxa de incidência de lesões obstétricas do esfíncter anal (LOEAs).

Métodos Estudo coorte retrospectivo que analisou os dados de 1.728 gestantes que tiveram parto vaginal cefálico simples com peso ao nascer de 2.500 g. Análises de regressão múltipla foram usadas para investigar o efeito de posições supinas ou verticais sobre a taxa de incidência de LOEAs após o ajuste para fatores de risco e intervenções obstétricas.

Resultados No total, 239 (13,8%) nascimentos ocorreram nas posições verticais, e 1,489 (86,2%), nas posições supinas. Lacerações graves de grau III ocorreram em

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43 (2,5%) pacientes, e de grau IV, em 3 (0,2%) mulheres. As posições supinas tiveram um efeito protetor significativo contra lacerações graves, razão de probabilidades [Intervalo de Confiança de 95%]: 0,47 [0.22–0.99], ajustado para o uso de Fórceps 4.80 [2.15–10.70], nuliparidade 2.86 [1.44–5.69], e peso ao nascer 3.30 [1.56–7.00]. Anestesia ($p < 0.070$), aumento de ocitocina ($p < 0.228$), distocia de ombro ($p < 0.670$), e episiotomia ($p < 0.559$) não estiveram associados à incidência de laceração grave.

Conclusão As posições de parto verticais não estiveram associadas a uma menor taxa de ruptura perineal. A interpretação dos achados referentes a essas posições levantou dúvidas sobre a proteção perineal que ainda aguardam respostas.

Palavras-chave
- posição do parto
- parto
- episiotomia
- trabalho de parto
- trauma perineal
- fatores de risco

Introduction

The best maternal position adopted during the pelvic phase to avoid perineal damage is an issue that is still controversial, depending on a set of multifactorial predictors and specific subgroups of analysis.[1–3] High rates of obstetric anal sphincter injuries (OASIs) among women giving birth in the lithotomy position were reported in a population-based study[1] in Sweden on term non-instrumental births without episiotomy. However, another population-based research[2] in Austria, including primiparous term births, did not prove any effect of the birth positions on OASIs. It has been supported that the traditional lithotomy position favors fetal assistance, enabling interventions such as episiotomy and surgical vaginal delivery.[4] Meanwhile, balancing risks and benefits during the second stage of labor is the current practice, as the occurrence of severe perineal lesions is multifactorial, and no single factor is responsible for the increased incidence of OASIs.[5]

The present study reports the frequency and the profile of births occurred in upright positions in a teaching maternity. The main objective was to evaluate the association between upright maternal positions for birth and the rate of OASIS, with a comprehensive view, using a multifactorial analysis. Additionally, we compared the rate of OASIs found in the present study with that of our previous report.[6]

Methods

An observational cohort study retrospectively evaluated vaginal births from July 2016 to February 2018 based on eligibility criteria. The Ethics Review Board of our institution approved the study under registry number CAAE-Brazil 10286913.3.0000.5149, with a waiver for written consent.

The primary hypothesis was that the maternal position during birth, be it upright or supine, did not affect the incidence of OASIs. The Maternal and Neonatal Healthcare Information System (Sistema de Informação em Saúde Materna e Neonatal, SISMater) platform, which was developed by Universidade Federal de Minas Gerais, provided the structured database. Physicians and obstetric nurses used the electronic register consistently to collect data in real time. Birth positions have a specific interface, with structured entries: upright positions (including sitting, kneeling, knee-elbow/all fours, squatting and standing), and supine positions (including recumbent, semi-recumbent, lateral, and lithotomy). The eligibility criteria were cephalic vaginal single births of live newborns with birth weights $\geq$2500 g.

A collaborative team of obstetric specialists, resident physicians, obstetric nurses, and doulas managed the women in labor, but the physicians were directly responsible for the delivery. The staff encouraged the practice of women-centered care to improve the mother's experience during labor and childbirth. The clinical protocol of the university has recommended best practices for delivery and maternal care, including maternal mobility, companion during a hospital stay, non-pharmacological pain relief or epidural analgesia, partograph, and effective communication. Mediolateral episiotomies and operative delivery followed restrictive protocols, indicated only for interrupted progression or suspicion of fetal distress. There was no institutional recommendation for perineal massage or warm compresses during pushing, or data related to antenatal perineal massage. The birth position during the second stage of labor was chosen by the women taking into account the comfort of the position or following the medical recommendation based on the facilities where the birth took place. The birth positions registered by the midwives, grouped as upright or supine, were the predictive variables for severe perineal lacerations. A detailed classification of the positions was approved by consensus among the physicians and the nursing staff. They were proposed according to the report by Soong and Barnes.[7] The difference between the recumbent and semi-recumbent positions was the inclination of the surgical table. Sitting was the position adopted when the woman gave birth on the stool. The primary outcome, OASIs, was classified as severe grade-III (laceration extending to the anal sphincter) and grade-IV (laceration reaching the rectal mucosa, exposing its lumen) lacerations.[8] Episiotomy, as an intentional laceration, was considered a grade-II laceration.[9]

We performed a descriptive analysis of the characteristics of the cohort concerning the frequency, variability, and measures of central tendency and the births in upright positions. The univariate analysis evaluated the statistical

association between severe perineum lacerations (dependent variable) and birth positions. The Chi-squared test was used for the independence hypothesis, and the odds ratio (OR) and 95% confidence interval (95%CI) were calculated to estimate the strength of the association. The Mann–Whitney test compared the numerical variables between the groups. Logistic multiple regression analyses were used to investigate the effect of birth positions on OASIs, adjusted for non-modifiable risk factors (maternal age, nulliparity, gestational age, shoulder dystocia, and birth weight) and obstetric interventions (induced labor, delivery with analgesia, oxytocin use in the second stage of labor, episiotomy, and use of forceps). The set of independent variables was obtained using the stepwise-backward method, setting the input value of 0.20 and output *p*-value of 0.10, and biological plausibility. The fit of the models and the calibration, specifically the Hosmer–Lemeshow goodness-of-fit test, and the coefficients of determination (adjusted R^2) were evaluated. The Statistical Package for the Social Sciences (SPSS, IBM Corp., Armonk, NY, US) software, version 22.0, was used for the analyses. The significance level, adjusted for the hypothesis test, was ≤ 0.05, and the bootstrap CI was set to 95%, calculated over 1,000 samples.

Results

During the period evaluated, 3,473 women gave birth to 3,529 newborns. The rate of cesarean sections was of 37.5% ($n = 1{,}304$). Out of 2,169 vaginal deliveries, 1,754 were of live newborns with a birth weight $\geq$2500 g. After an analysis of database consistency, 26 (1.2%) of the vaginal births were excluded due to incomplete registration. The overall group selected for the present analysis consisted of 1,728 women, as presented in ►**Fig. 1**.

The positions adopted for delivery in the second phase were supine and upright for 1,489 (86.2%) and 239 women (13.8%) respectively. Based on the characteristics of the birth, 707 out of of 1,728 (40.9%) had high-risk pregnancies, and 95 out of 1,727 (5.5%) had major malformations. Around 1/3 (506 out of 1,728; 29.3%) of the women delivered after induced labor. Concerning labor management, the doulas participated in 387 out of 1,728 (22.4%) births, ambulation was frequent in 1,280 out of 1,728 (74.1%) patients, and the episiotomy rate was of 18.3% (317 out of 1,728; ►**Table 1**). The women who preferred upright positions were also observed to adhere to other newly-introduced practices of labor management, such as ambulation ($p = 0.011$), non-pharmacological analgesia ($p = 0.019$), bath to relieve labor pain ($p = 0.015$), and birth ball ($p = 0.001$). The episiotomy rate was significantly lower in the subgroup that preferred supine positions ($p < 0.001$). The immediate outcome after the delivery was classified as good in both subgroups.

Perineal lacerations occurred in 1,402 (81.1%; 95%CI: 79.3–83.0%) births, and they were classified as follows: grade I (624 [36.1%]; 95%CI: 33.7–38.4), grade II (732 [42.4%]; 95%CI: 39.9–44.7), grade III (43 [2.5%]; 95%CI: 1.7–3.2), and grade IV (3 [0.2%]; 95%CI: 0.0–0.4). The occurrence of OASIs was of 2.7% in this cohort (95%CI: 2.0–3.5%). Grade-IV lacerations occurred in the lithotomy ($n = 1$), semi-recumbent ($n = 1$), and sitting ($n = 1$) positions. The semi-recumbent position was the most frequent position, which was adopted in 917 out of 1,728 (53.1%) births. No significant association was found between any specific birth position and the occurrence of OASIs

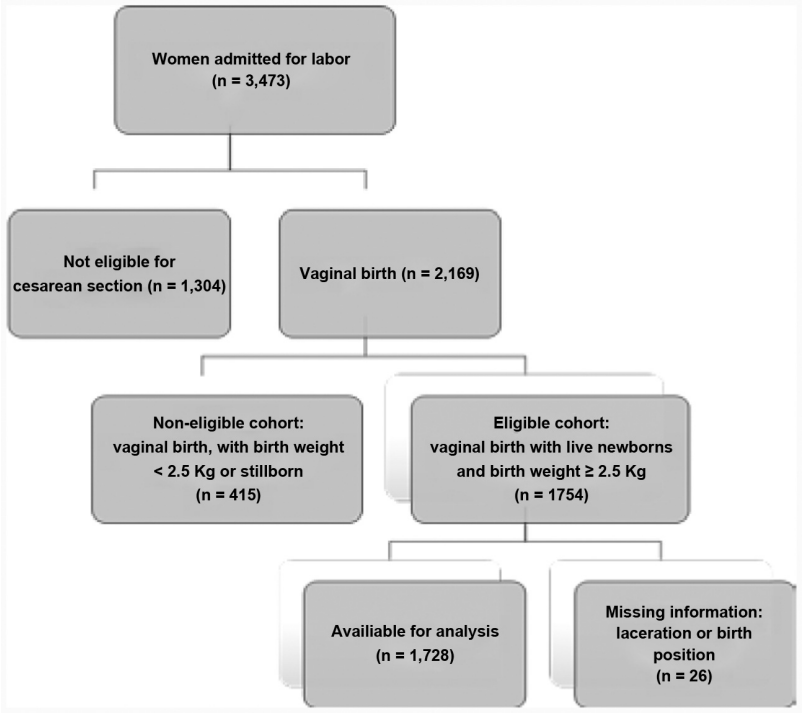

Fig. 1 Flowchart of patient allocation according to the selection criteria.

Table 1 Clinical and obstetrical characteristics of the births in upright positions during the second phase of labor

Clinical and obstetric characteristics	Descriptive statistics			*p*-value
	Upright* n = 239	Supine* n = 1,489	Total cohort n = 1,728	
Maternal age, years (median, interquartile range)	25.0 (10)	26.0 (10)	26.0 (10)	0.177[a]
Nuliparous, n (%)	116 (48.5)	628 (42.2)	744 (43.1)	0.065[b]
Doula, n (%)	57 (23.8)	330 (22.2)	387 (22.4)	0.561[b]
Induced labor (%)	61 (25.5)	445 (29.9)	506 (29.3)	0.169[b]
Ambulation, n (%)	193 (80.8)	1087 (73.0)	1280 (74.1)	0.011[b]
Non-pharmacological analgesia, n (%)	66 (27.6)	311 (20.9)	377 (21.8)	0.019[b]
Bath to relieve labor pain, n (%)	171 (71.5)	944 (63.4)	1115 (64.5)	0.015[b]
Birth ball, n (%)	71 (29.7)	304 (20.4)	375 (21.7)	0.001[b]
Analgesia, n (%)	76 (31.8)	496 (33.3)	572 (33.1)	0.645[b]
Oxytocin augmentation, 2nd period	61 (25.5)	411 (27.6)	472 (27.3)	0.503
Birthweight (median, interquartile range)	3.1 (0.5)	3.2 (0.5)	3.2 (0.5)	0.464[a]
Episiotomy, n (%)	14 (5.9)	303 (20.3)	317 (18.3)	< 0.001[b]
Forceps, n (%)	2 (0.8)	70 (5.3)	81 (4.7)	0.002[b]
Shoulder dystocia, n (%)	5 (2.1)	25 (1.7)	30 (1.7)	0.650[b]

Notes: *Birth position during delivery; [a]Mann–Whitney test; [b]Chi-squared test.

($p = 0.458$, ►**Table 2**). Cord prolapse did not occur in any of the groups, and only 1 out of 30 (4.5%) fetuses with shoulder dystocia was delivered using the Gaskin maneuver.

According to the univariate analysis, the rate of occurrence of OASIs was similar in the upright or supine groups ($p = 0.120$). The individual analyses of cofactors did not present evidence of any differences between the birth position subgroups, with or without OASIs, with respect to maternal age ($p = 0.615$), gestational age ($p = 0.745$), induced labor ($p = 0.419$), oxytocin augmentation during the second stage ($p = 0.072$), vacuum extraction ($p = 0.554$), and shoulder dystocia ($p = 0.187$) (►**Table 3**). However, the incidence of OASIs was higher in births with nulliparity ($p < 0.001$), epidural labor anesthesia ($p < 0.001$), episiotomy ($p = 0.013$), and the use of forceps ($p < 0.001$). Moreover, the median birth weight was higher in this particular group ($p = 0.004$).

The multivariate analysis revealed novel findings regarding the association between the occurrence of OASIs and the final birth position when the data was adjusted for the cofactors. Statistical evidence showed a protective effect of the supine positions against OASIs in contrast to the upright positions, reducing the chance of the incidence of severe lacerations by

Table 2 Clinical and obstetrical characteristics of pregnancies stratified by grade of perineal laceration

Position during the second stage		Women with severe lacerations (OASIs, *n* = 46)	Women with grade-I and -II lacerations (*n* = 1,356)	Women without lacerations (*n* = 326)
Supine				
Lithotomy, n (%)	528	12 (2.3)	418 (79.3)	98 (18.6)
Recumbent, n (%)	39	0 (0)	28 (71.8)	11 (28.2)
Semi-recumbent, n (%)	917	24 (2.6)	715 (78.0)	178 (19.4)
Lateral, n (%)	5	0 (0)	4 (80.0)	1 (20.0)
Upright				
Sitting, n (%)	188	7 (3.7)	152 (80.9)	29 (15.4)
Kneeling, n (%)	0	0 (0)	0 (0)	0 (0)
Gaskin, n (%)	22	2 (9.1)	17 (77.3)	3 (13.6)
Squatting, n (%)	18	1 (5.6)	15 (83.3)	2 (11.1)
Standing, n (%)	11	0 (0)	7 (63.6)	4 (36.4)

Abbreviation: OASIs, obstetric anal sphincter injuries.
Note: Chi-squared test: $p = 0.513$.

Table 3 Clinical and obstetric risk factors and association with severe perineum lacerations

Clinical and obstetric characteristics	Women with severe lacerations (OASIs) n = 46	Women without severe lacerations (OASIs) n = 1,682	OR (95%CI)	*p*-value[a]
Birth position (upright) n (%)	36 (78.3)	1,453 (86.4)	0.58 (0.28–1.16)	0.115
Maternal age, years (median, interquartile range)	24.0 (10)	26.0 (10)	0.99 (0.95–1.03)	0.615
Birthweight, Kg (median, interquartile range)	3.34 (0.57)	3.15 (0.54)	2.82 (1.40–5.67)	0.004
Nulliparity, n (%)	33 (71.7)	711 (42.3)	3.47 (1.81–6.63)	< 0.001
Induced labor, n (%)	11 (23.9)	495 (29.4)	0.75 (0.38–1.50)	0.419
Oxytocin augmentation, 2nd period	18 (39.1)	454 (27.0)	1.74 (0.95–3.17)	0.072
Labor anesthesia, n (%)	28 (60.9)	544 (32.3)	3.25 (1.78–5.93)	< 0.001
Episiotomy, n (%)	15 (32.6)	302 (18.0)	2.2 (1.18–4.15)	0.013
Forceps, n (%)	11 (23.9)	70 (4.2)	7.23 (3.53–14.85)	< 0.001
Shoulder dystocia, n (%)	2 (4.3)	28 (1.7)	2.7 (0.620–11.63)	0.187

Abbreviations: 95%CI, 95% confidence interval; OASIs, obstetric anal sphincter injuries; OR, odds ratio.
Note: [a]Univariate logistic regression.

Table 4 Clinical and obstetric risk factors and association with severe perineum lacerations (OASIs) in cephalic live births of newborns with birth weight ≥ 2.5 Kg

Clinical and obstetric characteristics	n	OR (95%CI)	*p*-value[a,b]
Birth position: supine, n (%)	1,428/1,728	0.47 (0.22–0.99)	0.047
Birth weight, Kg (interquartile range)	...	3.30 (1.56–7.00)	0.002
Forceps, n (%)	81/1728	4.80 (2.15–10.70)	< 0.001
Labor anesthesia, n (%)	572/1728	1.84 (0.95–3.54)	0.070
Nulliparous, n (%)	744/1728	2.86 (1.44–5.69)	0.003
Episiotomy, n (%)	317/1728	...	0.559
Oxytocin augmentation, 2nd period	472/1728	...	0.228
Shoulder dystocia, n (%)	30/1728		0.670

Abbreviations: 95%CI, 95% confidence interval; OASIs, obstetric anal sphincter injuries; OR, odds ratio.
Notes: Constant of the model = −7.6 ($p < 0.001$). Model coefficients: $p < 0.001$. Calibration of the model: −2 Log likelihood: 375.2. Hosmer–Lemeshow test: $p = 0.359$.

63%: 0.47 (95%CI: 0.22–0.99; $p = 0.047$; ►**Table 4**). Nulliparity ($p = 0.003$) and birth weight ($p = 0.002$) were non-modifiable risk factors associated with OASIs. The use of forceps increased the probability of occurrence of OASIs 4.80 (95%CI: 2.15–10.70; $p < 0.001$) times. Labor anesthesia ($p = 0.070$), oxytocin augmentation during the second stage ($p = 0.228$), shoulder dystocia ($p = 0.670$), and episiotomy ($p = 0.559$) had no significant effect on the rate of occurrence of OASIs.

Discussion

The main contribution of the present study was to provide a comprehensive view of the risk factors associated with OASIs in a transitional scenario of care that endorses less intervention in labor. The university centers in Brazil play an essential role in the revival of vaginal delivery supported by good practices to reduce the highest rates of cesarean delivery in the world.[10] The analysis is part of the continuous monitoring of the new evidence-based practices implemented to reduce unnecessary cesarean deliveries.

Our results seem to conflict with previous studies that reported higher rates of sphincter injuries associated with the lithotomy position.[1] In our analysis, the main supine position was the semi-recumbent position, with 53.1% of all births, and not the lithotomy position. On the other hand, Marschalek et al,[2] analyzing a national database, reported that the birth position had no effect on OASIs. Our interpretation has raised questions that range from a long history of births in the horizontal position to the effective approaches for perineal protection in upright positions. Added to this, there is the complexity of the factors involved in the occurrence of sphincter injuries and the diversity of its occurrence in different birth scenarios around the world.

Interestingly, the rate of episiotomy was significantly reduced in the present cohort, in contrast to the cohort analysis previously reported.[9] In both analyses, in the same setting of delivery in different periods, episiotomy did not contribute to reduce the incidence of OASIs events. In the present study, the incidence of restrictive episiotomy was lower in the upright position subgroup than in the supine position subgroup (►**Table 1**). Other studies have also observed a reduction in the rate of episiotomy in upright positions, a slight decrease in the duration of the second stage of labor, reduction of pain, and a decrease in the number of births requiring surgical intervention.[4] However, these studies reported a possible increase in the rate of grade-II perineal tears, and no clear difference in the number of perineal tears of grades III and IV.[4]

Regarding the low OASIs incidence in the cohort (2.7%), we speculate that it is probably due to the maintenance of and adherence to good practices during intrapartum care,[11] and to the quality of the computerized registry in the maternity.[12] For the purpose of comparison, Marschalek et al,[2] in a national population-based study including only term single cephalic deliveries, reported a 2.6% incidence of OASIs. Similarly, a lower incidence, of 2.1%, was recently reported in an Indian tertiary healthcare center when the data was adjusted for birth weight $>$ 500 g.[3] However, previous studies have reported higher rates of severe perineal tears in the group including term births only, ranging from 4.5 to 5.9%.[13,14]

In the multivariate analysis, supine positions were associated with 53% of reduction in the rate of OASIs, whereas induced labor, analgesia, oxytocin use in the second stage of labor, and episiotomy did not have a significant effect. Although these findings corroborate the previous report, revealing a relative risk of 4.41 (95%CI: 3.15–6.17) for any perineal trauma,[15] one must be cautious when interpreting this outcome because of our preliminary data concerning upright positions. Only physicians performed the final stage of birth and, in this teaching scenario, perineal protection in upright positions is a new challenge. In our maternity department, upright positions have been recently preferred by women during the second stage of labor. However, limitations in the facilities still restrict its adoption. This practice has been stimulated by a national program to reduce cesarean sections and by the inclusion of obstetric nurses into the team performing the delivery.

The limitations of a retrospective design have to be taken into account, mainly those concerning the accuracy of OASIs diagnosis in cases that were not monitored or were evaluated by different physicians. Concerning the number of subjects, our sample covered 8 predictor variables with at least 30 events per variable in a binary regression model, which is more than what is recommended by the rule of ten.[16] Type-II error was still avoided with a comprehensive analysis of variables prospectively collected in the electronic health record system.[12] Nevertheless, the use of forceps in upright positions occurred two times, both without OASIs, a situation that seems a register error. The generalizability of the risk factors associated with severe perineal trauma is possible among tertiary healthcare centers, considering cephalic and single deliveries with birth weight $\geq$2,500 g.

For the interpretation of the results, it is important to acknowledge that there is no consensus regarding the risk factors or improvements in diagnosis that can explain the observed increase in the rate of grade-III and grade-IV tears in many settings, even in the populational analysis.[13] The perineum naturally stretches during the second stage of labor. However, the threshold of physiological efforts to stretch the perineum needs to be determined, with particular attention to perineal muscle injury and its negative impact on the pelvic floor, resulting in pelvic floor dysfunction.[17,18] Upright positions would be more physiologically appropriate because they promote effective uterine contractions, significantly reducing the risk of aortocaval compression, and they facilitate fetal expulsion directed by gravity.[19] Besides, it has been reported that when women freely adopt a comfortable position, they feel in control of the parturition process, which results in a better experience when compared with the experience with pre-established positions.[7] Moreover, the classification of upright positions is not unanimous. According to Walker et al,[20] *the knee-elbow (all fours) position is considered recumbent because the axis of the trunk is horizontal.*

Birth weight, a positive factor for OASIs in the present study and in many others,[14] is presumed to be an antenatal factor that can be controlled and depends on maternal health conditions and prenatal healthcare quality. Although it is not modifiable at delivery, adequate prenatal maternal healthcare favors satisfactory fetal weight gain and interventions that can promote perineal distensibility, thus potentially preventing the occurrence of perineal tears. Clinical or instrumental approaches involving the antenatal determination of risks using pelvic floor distensibility measurements,[18] perineal massage,[21] and the proper training of healthcare professionals concerning perineal protection methods[22] are strategies to reduce severe obstetric perineal trauma. Regarding instrumental delivery, we have reinforced the use of forceps as a critical predictor of severe perineal trauma in the present analysis. A previous systematic review reported that the incidence of OASIs was higher with the use of forceps than with the vacuum extractor, regardless of episiotomy.[23] The vacuum-extraction method is relatively recent in our department, and its use remains limited due to its high cost.

Women-centered healthcare practices offer the opportunity to take collaborative decisions during labor assistance. The psychological benefits of upright positions include reduced perception of pain, increased feeling of being in control, and active involvement of the woman's partner.[24] Changes in obstetric practice, such as the restricted practice of episiotomy, better management of perineal support, and the choice of birth position on the part of the woman, are potentially modifiable factors associated with perineal trauma.[14] Well-informed women can make better choices and guarantee the full exercise of individual autonomy. The encouragement to adhere to new scientific evidence gains worldwide focus, reducing the excessive use of medication during labor, and opening a dialog about the preferences of the mother concerning delivery methods.[25]

Conclusion

Being in an upright position in the second stage of birth was not associated with a lower rate of perineal tears. Episiotomy was not found to be protective. Maternal and fetal factors, such as nulliparity, birth weight, and the use of forceps, should be taken into account before adopting a non-supine birth position. The interpretation of the findings regarding this position raised doubts about perineal protection that are still unanswered.

Contributors

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

Conflicts to Interest

The authors have none to declare.

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Contribution of Ultra-processed Food to the Daily Food Intake of HIV-positive and HIV-Negative Women during Pregnancy

Contribuição dos alimentos ultraprocessados no consumo alimentar diário de mulheres soropositivas e soronegativas para o HIV durante a gestação

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Abstract

Objective To assess the daily dietary intake and energy contribution of ultra-processed foods among women who are positive and negative for the human immunodeficiency virus (HIV) during pregnancy.

Methods This case–control study included 77 HIV-positive and 79 HIV-negative puerperal women between 2015 and 2016. The socioeconomic and maternal demographic data were assessed, and a food frequency questionnaire (FFQ) adapted for pregnant women was applied. The Fisher exact test and the Mann-Whitney test were applied to detect differences between the groups. Linear regression was used to assess the associations between the intake of ultra-processed food and energy, macro- and micronutrients, with values of $p < 0.05$ considered significant.

Results The HIV-positive group was older ($p < 0.001$) and had lower income ($p = 0.016$) and level of schooling ($p < 0.001$) than the HIV-negative group. Both groups presented similar average food intake: 4,082.99 Kcal/day and 4,369.24 Kcal/day for the HIV-positive and HIV-negative women respectively ($p = 0.258$).The HIV-positive group consumed less protein ($p = 0.048$), carbohydrates ($p = 0.028$) and calcium ($p = 0.001$), and more total fats ($p = 0.003$). Ultra-processed foods accounted for 39.80% and 40.10% of the HIV-positive and HIV-negative groups' caloric intake respectively ($p = 0.893$). The intake of these foods was associated with a higher consumption of carbohydrates ($p < 0.001$), trans fat ($p = 0.013$) and sodium ($p < 0.001$), as well as lower protein ($p < 0.001$) and fiber intake ($p = 0.022$).

Keywords
- HIV
- pregnancy
- micronutrients

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Conclusion These findings demonstrate that the energy consumption and ultra-processed food intake were similar in both groups, which reinforces the trend toward a high intake of ultra-processed food in the general population. The intake of ultra-processed food was positively associated with the consumption of carbohydrates, trans fat and sodium, and negatively associated with the consumption of protein and fiber.

Resumo

Objetivo Avaliar o consumo alimentar diário e a contribuição dos alimentos ultraprocessados na dieta de gestantes soropositivas e soronegativas para o vírus da imunodeficiência humana (HIV).

Métodos Estudo de caso–controle com 77 puérperas soropositivas e 79 soronegativas entre 2015 e 2016. Analisaram-se dados socioeconômicos e demográficos maternos, e aplicou-se um questionário de frequência alimentar (QFA) adaptado para gestantes. Utilizou-se o teste exato de Fisher e o teste de Mann-Whitney para detectar diferenças entre os grupos. A regressão linear avaliou a associação entre o consumo de ultraprocessados e de energia, macro e micronutrientes. Valores de $p < 0,05$ foram considerados significativos.

Resultados O grupo de puérperas soropositivas foi mais velho ($p < 0,001$), com menor renda familiar ($p = 0,016$) e escolaridade ($p < 0,001$) quando comparado com o grupo das soronegativas. Ambos os grupos apresentaram médias de consumo semelhantes, com 4.082,99 Kcal/dia entre as puérperas soropositivas e 4.369,24 kcal/dia entre as soronegativas ($p = 0,258$). Observou-se que as puérperas soropositivas consumiam menos proteínas ($p = 0,048$), carboidratos ($p = 0,028$) e cálcio ($p = 0,001$), e mais gorduras totais ($p = 0,003$). Os ultraprocessados corresponderam a 39,80% das calorias entre as soropositivas, e a 40,10% entre as soronegativas ($p = 0,893$). O consumo destes alimentos esteve associado a um maior consumo de carboidratos ($p < 0,001$), gordura trans ($p = 0,013$) e sódio ($p < 0,001$), e a um menor consumo de proteínas ($p < 0,001$) e fibras ($p = 0,022$).

Conclusão Esses achados demonstram que o consumo de energia e de alimentos ultraprocessados foram semelhantes nos dois grupos, o que reforça a tendência ao consumo elevado de alimentos ultraprocessados na população geral. O consumo de alimentos ultraprocessados foi positivamente associado ao consumo de carboidratos, gorduras trans e sódio, e negativamente associado ao consumo de proteínas e fibras.

Palavras-chave
- HIV
- gestação
- micronutrientes

Introduction

Recent data from the World Health Organization (WHO) indicate that there are 36.7 million people living with the human immunodeficiency virus (HIV) in the world. Sub-Saharan Africa is the most severely affected region, with 1 in every 20 adults infected.[1] In Brazil, approximately 734,000 people are living with HIV, and the national prevalence is of 0.39%. The state of Rio Grande do Sul, in Southern Brazil, has the highest HIV infection rates in the country, with a prevalence of 0.8%. Data from the Brazilian Ministry of Health collected between 2000 and 2014 revealed that there were 92.210 HIV-positive pregnant women nationwide, 30.8% of whom lived in the Southern region of the country, and the city of Porto Alegre, the capital of Rio Grande do Sul, ranked first among Brazilian cities in terms of infection rate.[2]

According to McCoy et al,[3] in Africa, poor diet during pregnancy among HIV-positive women is associated with an increased risk of vertical transmission. HIV-positive pregnant women have increased energy and nutritional needs, due to their illness and to the demands of gestation.[3] An inadequate dietary intake, deficient in micronutrients and macronutrients, could increase the risk of vertical transmission and progression of the disease, increase the chance of opportunistic infections, and affect the effectiveness of antiretroviral drugs.[4]

Since the 1980s, changes in the food system on the national and global levels have led to the increased production, availability, accessibility and commercialization of foods and beverages that have undergone some type of processing. However, such processing is largely ignored in dietary assessments and recommendations, as well as in epidemiological studies.[5] Ultra-processed foods generally contain added sugars, fats and substances derived from food constituents or that have been synthesized in the laboratory. They are poor in micronutrients and high in caloric density.[6] This type of processing confers to the food properties that lead to excessive consumption. Considered

hyper-palatable foods, they activate the nucleus accumbens, which is responsible for the sensation of pleasure and well-being. In addition, they come in many different sizes, have a long shelf-life, are easy to transport, and are ready for consumption, unlike many fresh foods.[7]

Studies have shown that the energy contribution of this type of food has increased significantly over the recent years, while the consumption of fresh or minimally-processed foods has decreased. This increase occurs in every economic stratum, although it tends to be higher among those with lower income, and is associated with increased obesity, chronic diseases and nutritional deficiencies.[8]

In light of the lack of studies on HIV-positive pregnant women, the importance of adequate food intake during gestation and the recent increase in ultra-processed food consumption, the relevance of increasing knowledge about HIV, gestation and nutrition is justified. A better understanding of the subject will enable more relevant diet counseling for HIV-positive women during gestation, which will result in adequate fetal development.[9] Thus, the objective of the present study was to evaluate the daily dietary intake and energy contribution of ultra-processed foods in HIV-positive and HIV-negative pregnant women.

Methods

This cross-sectional, case–control study was conducted with 77 HIV-positive and 79 HIV-negative postpartum women from July 2015 to August 2016. The study is part of a larger project on the repercussions of social and anthropometric factors during the gestation of HIV-positive puerperal women on newborn birth weight. The inclusion criteria were: postpartum women aged $>$ 18 years, diagnosed or not with HIV, who gave birth at a university hospital in Porto Alegre, could answer the questionnaires, and who voluntarily consented to participate. Women with chronic diseases, such as diabetes, systemic arterial hypertension or nephropathies, as well as those who gave birth with twins, were excluded. The data collection was performed in the immediate postpartum period at the obstetric unit of the aforementioned hospital.

The data were collected as part of a larger project based on the study by Bassichetto et al (2013)[9] on HIV-positive pregnant women in São Paulo, which investigated the birth weight of neonates exposed to HIV. The sample size calculations were performed using the WinPepi® software (https://www.brixtonhealth.com/pepi4windows.html, Jerusalem, Israel), version 11.43, considering a 90% power and a significance level of 5%. The sample size was determined to be composed of least 160 subjects, 80 in the HIV-positive group, and 80 in the HIV-negative group. Pregnant women whose caloric intake was higher than 8,795.38 calories per day were excluded because they represented extreme and isolated caloric values in the sample. Thus, the final population consisted of 77 HIV-positive and 79 HIV-negative women.

The data collection was performed by a nutritionist or a previously trained intern. The HIV-positive participants were selected using the inclusion and exclusion criteria, while the HIV-negative participants were selected among occupants of the same hospital bed vacated by the HIV-positive participants. Maternal anthropometric data were collected from medical records, the socioeconomic and demographic data were collected using specific questionnaires, and the dietary intake was evaluated using a semi-quantitative food frequency questionnaire (FFQ) validated for use among pregnant women.[10]

The ultra-processed food intake variable was based on frequency and quantity of consumption, and calculated according to the standardized portion for each food. The FFQ validated for Brazilian pregnant women involved 8 consumption frequency options: "more than 3 times/day"; "2 to 3 times/day"; "1 time/day"; "5 to 6 times/week"; "2 to 4 times/week";"1 time/week"; "1 to 3 times/month"; and "never/almost never".[10] The food list consisted of 104 food items, including foods classified as ultra-processed according to the Food Guide for the Brazilian population, for which standardized portions are offered as a means of evaluating the quantity consumed. According to their classification in the Food Guide for the Brazilian population, the following foods were considered ultra-processed: bread, cookies, cake, salted crackers, French fries, potato chips, popcorn, yogurt, light yogurt, sauces, hamburgers, pizza, mayonnaise, savory and sweet snack products, ice cream, candy, chocolate, pudding, dulce de leche, soft drinks, artificial juice, ham, condensed milk, canned soup, sugary breakfast cereals and chicken nuggets.[11] The foods in the FFQ were divided into three groups (fresh, processed and ultra-processed). The daily food consumption and energy contribution of ultra-processed foods was assessed using the Statistical Package for the Social Sciences (SPSS, SPSS Inc., Chicago, IL, US), version 18.0. The contribution of ultra-processed foods was represented by the sum of the means of the foods belonging to this group.

The social characteristics of the population of the study were defined according to the Brazilian Economic Classification Criterion (CCEB, in Portuguese) points system, which was developed by the Brazilian Association of Research Companies (ABEP, in Portuguese) and updated in 2015, in which a correspondence was made between scores for specific criteria and economic strata, which were classified as A-B, C or D-E.[12]

The data were analyzed using the SPSS. The categorical variables are presented as means of absolute numbers (n) and percentages (%), the symmetric continuous variables are presented as mean and standard deviation (SD), and the asymmetric continuous variables are presented as median and interquartile ranges [25-75 percentile]. The Chi-squared test or the Fisher exact test was used to detect differences between proportions and means. The Student *t*-test or the Mann-Whitney test was used to detect differences between means and medians. Linear regression analyses were used to identify the direction and statistically significant associations between tertiles of caloric intake from ultra-processed foods and nutritional indicators, with and without adjustments for confounding variables (race, social class, age, marital status and level of schooling). The first tertile represents the lowest total caloric intake, the macronutrients and the micronutrients, while the third tertile represents the

highest consumption averages. For all analyses, a significance level of 5% ($p < 0.05$) and a 95% confidence interval (95%CI) were used.

The present study was approved by the Ethics in Research Committee (case 15-0249) of Hospital de Clínicas de Porto Alegre. All participants signed a free and informed consent form in duplicate, with one copy going to the participant and the other to the organizers of the project. Participant anonymity was ensured through the use of data coding and identification numbers.

Results

The sample consisted of 156 postpartum women, 77 HIV-positive and 79 HIV-negative. The characterization of the sample, consisting of HIV-positivity or HIV-negativity and the socioeconomic and demographic characteristics, is shown in ►**Table 1**. There was a statistically significant difference regarding ethnicity: 54.5% of the HIV-positive women and 77.2% of the HIV-negative women were white ($p = 0.005$). Compared to the HIV-negative group, the HIV-positive group had more women of the lowest social class ($p = 0.016$) who lived without a partner ($p < 0.001$) and had lower schooling ($p < 0.001$).

No statistically significant difference was found between the groups regarding the total energy consumption, which averaged 4,082.99 ± 1,488 Kcal/day and 4,369.24 ± 1,656.25 kcal/day for the HIV-positive and HIV-negative groups respectively ($p = 0.258$). Statistically significant results were observed regarding the consumption of macro- and micronutrients, with HIV-positive women presenting a lower intake of protein ($p = 0.048$), carbohydrates ($p = 0.028$) and calcium ($p = 0.001$), and a higher total fat intake ($p = 0.003$) than the HIV-negative group (►**Table 2**). The energy contribution of ultra-processed foods in the daily consumption was of 39.80% and 40.10% in the HIV-positive and HIV-negative groups respectively ($p = 0.893$). There was a significant difference in the calcium intake, with lower consumption in the HIV-positive group ($p = 0.012$). There was no statistically significant difference in daily energy consumption or macronutrient consumption between the groups ($p = 0.893$).

Regarding the HIV-positive participants' total energy intake, 2,241.71 ± 849.61kcal were derived from carbohydrates, 48.20% of which came from ultra-processed foods. A mean of 1,296.82 ± 572.66 kcal came from fats, 33.08% of which were from ultra-processed foods. A mean of 533.38 ± 191.64 kcal were from proteins, 26.17% of which came from ultra-processed foods, which was statistically significant compared with the HIV-negative group ($p = 0.034$).

Since the caloric intake of ultra-processed foods was similar in both groups, the association between the consumption of ultra-processed foods and the consumption of macro- and micronutrients was calculated for the whole sample. ►**Table 3** shows how the sample (n = 156) was divided into tertiles. Each tertile consisted of 52 puerperae: tertile 1 corresponds to the lowest energy consumption from ultra-processed foods, tertile 2, to intermediate consumption, and tertile 3, to the highest consumption. The unadjusted regression analysis showed a positive association between ultra-processed food consumption and the percentage of carbohydrates ($p = 0.002$), trans fats ($p = 0.017$) and sodium ($p < 0.001$), and a negative association between ultra-processed food consumption and the percentage of protein ($p < 0.001$) and fiber ($p = 0.019$). When adjusted for age, schooling, social class, ethnicity and marital status, there were positive associations between ultra-processed food consumption and the following: percentage of carbohydrates, with 3.89% (95%CI: 1.463 to 6.3) in tertile 3; trans fats, with 0.95 g (95%CI: 0.199 to 1.7) more in tertile 3; and sodium, with 1,697.32 mg (95%CI: 991.62 to 2,403.02),] more in tertile 3. The negative association with the protein percentage remained after the adjustment, with 2.96% (95%CI: -3.79 to -2.12), less in tertile 3, and fiber, with 12.05 g (95%CI: -22.36 to - 1.74) less in tertile 3.

Table 1 Demographic and socioeconomic characteristics of HIV-positive and HIV-negative puerperae

Family and maternal characteristics	HIV+ (n = 77)	HIV- (n = 79)	*p*-value
	n (%)	n (%)	
Ethnicity			0.005[a]
White	42 (54.5%)	61 (72.2%)	
Non-white	35 (45.5%)	18 (22.8%)	
Social class			0.016[a]
A-B (upper classes)	5 (6.5%)	18 (22.8%)	
C (middle class)	59 (76.6%)	50 (63.3%)	
D-E (lower classes)	13 (16.9%)	11 (13.9%)	
Lives with partner			< 0.001[a]
Yes	49 (63.6%)	72 (91.1%)	
No	28 (36.4%)	7 (8.9%)	
	Mean ± SD	Mean ± SD	
Maternal age (years)	28.75 ± 5.95	25.53 ± 5.02	< 0.001[b]
Number of Prenatal appointments	8.64 ± 3.71	8.61 ± 3.95	0.963
Schooling (years)	8.55 ± 2.24	10.04 ± 2.31	< 0.001[b]

Abbreviations: HIV, human immunodeficiency virus; HIV-, HIV-negative; HIV +, HIV-positive; SD, standard deviation.
Notes:
[a]Chi-squared test = percentage and absolute frequency.
[b]Student *t*-test = mean ± SD; $p < 0.05$.

Discussion

The objective of the present study was to evaluate the daily dietary intake and the energy contribution of ultra-processed foods in HIV-positive women during gestation, comparing it with that of HIV-negative women. The results show that energy consumption and ultra-processed food consumption were similar in both groups, which reinforces the trend toward high consumption of ultra-processed food in the general population. The multiple regression analysis showed that

Table 2 Contribution of ultra-processed foods to the daily consumption of energy and macro- and micronutrients in HIV-positive and HIV-negative puerperae

	Total (n = 156) mean ± SD	HIV+ (n = 77) mean ± SD	HIV- (n = 79) mean ± SD	*p*-value
Energy				
Total Kcal/day	4,227.95 ± 1,576.92	4,082.99 ± 1,488.00	4,369.24 ± 1,656.25	0.258
Kcal from ultra-processed food/day	1,752.78 ± 1,049.36	1,695.02 ± 1,002.20	1,809.07 ± 1,096.83	0.499
Macronutrients				
% TEV of carbohydrates	56.32 ± 6.44	55.01 ± 6.37	57.28 ± 6.35	0.028
Kcal carbohydrates	2,373.79 ± 924.84	2,241.71 ± 849.61	2,502.52 ± 981.01	0.078
% ultra-processed carbohydrates	46.70 ± 15.73	48.20 ± 14.49	45.23 ± 16.81	0.240
% TEV of protein	13.66 ± 2.57	13.25 ± 2.34	14.06 ± 2.73	0.048
Kcal protein	570.41 ± 216.13	533.38 ± 191.64	606.49 ± 233.17	0.034
% ultra-processed protein	26.50 ± 12.13	26.17 ± 11.96	26.82 ± 12.36	0.738
% TEV of fat	30.10 ± 5.88	31.50 ± 6.11	28.73 ± 5.34	0.003
Kcal fat	1282.09 ± 571.09	1296.82 ± 572.66	1267.73 ± 572.88	0.752
% Ultra-processed fat	35.45 ± 15.37	33.08 ± 16.10	37.76 ± 14.34	0.057
Micronutrients				
Total calcium (mg)	1236.71 ± 633.61	1067.17 ± 562.30	1401.96 ± 658.55	0.001
Ultra-processed calcium (mg)	448.01 ± 304.42	386.24 ± 263.52	508.21 ± 330.23	0.012
Total zinc (mg)	18.83 ± 8.10	17.55 ± 7.54	20.07 ± 8.48	0.051
Ultra-processed zinc (mg)	5.05 ± 3.37	4.73 ± 3.34	5.36 ± 3.38	0.244
Total iron (mg)	23.61 ± 10.20	22.47 ± 9.63	24.72 ± 10.67	0.169
Ultra-processed iron (mg)	10.89 ± 7.57	10.55 ± 7.57	11.23 ± 7.60	0.572
Total sodium (mg)	4769.87 ± 1,986.85	4735.38 ± 1,995.72	4,803.49 ± 1,990.33	0.831
Ultra-processed sodium (mg)	2,532.47 ± 1,577.90	2,485.45 ± 1,619.28	2,578.30 ± 1,545.47	0.715

Abbreviations: HIV, human immunodeficiency virus; HIV-, HIV-negative puerperae; HIV +, HIV-positive puerperae; Kcal, kilocalorie; mg, milligram; SD, standard deviation; TEV, total energy value.
Notes: Statistical test = Student's *t*-test; mean ± SD; $p < 0.05$

ultra-processed food consumption was positively associated with the consumption of carbohydrates, trans fats and sodium, and negatively associated with the consumption of protein and fiber.

Regarding the characterization of the sample, there were more non-white than white HIV-positive women. In line with this, Konopka et al[13] conducted a study whose sample of 139 HIV-positive pregnant women in Southern Brazil consisted of 43.2% of non-whites. In the study by Filgueiras et al,[14] the sample of 237 HIV-positive pregnant women in the state of Paraíba had a non-white prevalence of 77.79%. We observed that a large number of HIV-positive postpartum women (36.4%) reported having no fixed partner. This reflects the social risk to which HIV-positive pregnant women are exposed, since they have less emotional support in this period, which is characterized by several changes in the psychological state. Konopka et al[13] also found that 41.7% of the HIV-positive women in their study had no partner. With respect to age, the mean age of the HIV-positive women in our sample was greater than that of the HIV-negative women (28.75 ± 5.95 versus 25.53 ± 5.02 years respectively). Corroborating this finding, Romanelli et al[15] observed an average age of 29.1 years among HIV-positive postpartum women. The high average age among the HIV-positive group might be explained by their higher parity; Koenig et al[16] associated HIV infection with higher rates of pregnancy.[13–16]

The literature describes HIV-positive pregnant women as having low schooling in general. In the present study, their average schooling was equivalent to elementary school (8.55 ± 2.24 years). Recent data from the Brazilian Ministry of Health reflect our findings, indicating that the majority of Brazilians with HIV have only 5 to 8 years of schooling. A recent study by Yaya et al[17] associated low schooling with less knowledge about HIV and, consequently, greater susceptibility to contracting the infection. Filgueiras et al[14] found that 55.3% of the HIV-positive pregnant women in their study only had elementary education. Konopka et al[13] reported an even larger number in Southern Brazil (which is the region with highest national rates of virus detection): 64.8% of their sample of 139 HIV-positive pregnant women had only up to 8 years of schooling.[2,13,14,17]

Due to the scarcity of studies on food intake among HIV-positive women, the average daily energy consumption of this population during pregnancy has not been described in the

Table 3 Association between tertiles of ultra-processed food consumption (% of total energy) and consumption of macro- and micronutrients among HIV-positive and HIV-negative puerperae

	Unadjusted β* (95%CI)		
Independent variable	**Tertile 1**	**Tertile 2**	**Tertile 3**
% TEV of carbohydrate	1	1.58 (-0.86 to 4.01)	3.82 (1.38 to 6.26)
p-value	–	0.203	0.002
%TEV of protein	1	-1.58 (-2.45 to -0.71)	-3.10 (-3.97 to -2.22)
p-value	–	< 0.001	< 0.001
% TEV of fat	1	0.41 (-1.88 to 2.70)	-0.65 (-2.93 to 1.66)
p-value	–	0.725	0.579
Polyunsaturated fat (g)	1	3.32 (-1.64 to 8.28)	3.44 (-1.52 to 8.40)
p-value	–	0.188	0.173
Monounsaturated fat (g)	1	6.52 (-4.89 to 17.93)	10.16 (-1.25 to 21.56)
p-value	–	0.260	0.080
Saturated fat (g)	1	167.33 (-421.14 to 755.80)	452.49 (-135.98 to 1,040.96)
p-value	–	0.575	0.131
Trans fat (g)	1	0.87 (0.11 to 1.63)	0.93 (0.17 to 1.69)
p-value	–	0.025	0.017
Calcium (mg)	1	54.78 (-190.56 to 300.12)	179.54 (-65.80 to 424.88)
p-value	–	0.660	0.150
Zinc (mg)	1	0.51 (-2.66 to 3.67)	0.29 (-2.87 to 3.45)
p-value	–	0.752	0.858
Iron (mg)	1	1.10 (-2.80 to 4.99)	4.93 (1.03 to 8.82)
p-value	–	0.577	0.013
Sodium (mg)	1	649.71 (-74.33 to 1373.75)	1710.78 (986.74 to 2434.82)
p-value	–	0.078	< 0.001
Fibers (g)	1	-9.95 (-20.32 to 0.417)	-12.40 (-22.77 to -2.03)
p-value	–	0.060	0.019
	Adjusted β* (95%CI)		
Independent variable	**Tertile 1**	**Tertile 2**	**Tertile 3**
% TEV of carbohydrate	1	1.58 (-0.807 to 3.97)	3.89 (1.46 to 6.30)
p-value	–	0.194	0.002
%TEV of protein	1	-1.43 (-2.26 to -0.614)	-2.96 (-3.79 to -2.12)
p-value	–	0.001	< 0.001
Trans fat (g)	1	0.89 (0.145 to 1.63)	0.95 (0.199 to 1.70)
p-value	–	0.019	0.013
Sodium (mg)	1	599.35 (-96.73 to 1,295.44)	1,697.32 (991.62 to 2,403.02)
p-value	–	0.091	< 0.001
Fibers (g)	1	-9.89 (-20.07 to 0.27)	-12.05 (-22.36 to -1.74)
p-value	–	0.056	0.022

Abbreviations: 95%CI, 95% confidence interval; g, gram; HIV, human immunodeficiency virus; mg, milligram; TEV, total energy value.
Notes: Statistical test = linear regression. *Adjusted for age, schooling, social class, ethnicity and marital status.

literature. However, Buss et al[18] applied an FFQ to 578 pregnant women in Southern Brazil, finding an average energy consumption of 2,776 kcal/day. However, these authors excluded individuals whose consumption was lower than 800 kcal or higher than 4,800 kcal, since these values were outside the Institute of Medicine's recommendations for gestation, which require a 300 kcal increase in total energy beginning in the second trimester. The mean energy

consumption in their study was lower than in ours (4,082.99kcal), which might be explained by the exclusion of higher values or by the fact that most pregnant women in their study were not in the third trimester, in which the energy requirements are greater than in the first trimester.[18,19]

Corroborating our findings regarding the consumption of ultra-processed foods (that is, approximately 40% of the total calories), Bielemann et al[20] applied an FFQ to 4,202 young adults in the city of Pelotas, in the state of Rio Grande do Sul, Southern Brazil, and found that 51.2% of their intake came from ultra-processed foods. Canella et al[5] investigated the foods and beverages purchased for domestic consumption by 190,159 Brazilians from 55,970 families who participated in the 2008-2009 Family Budget Survey, and found that 25.5% of the daily energy consumption came from ultra-processed foods. This number, which was much lower than our findings, might be explained by the fact that their data did not include food eaten out of the house.[5,20]

Another recent Brazilian cross-sectional study that verified the food quality of adolescents and adults found that 20.4% of the calories came from ultra-processed foods.[21] Costa et al,[22] in their review of 26 articles on ultra-processed food consumption, reported that the main source of energy was derived from these foods.

Considering the consumption of ultra-processed food during gestation, a Brazilian study (Alves-Santos et al.) with 189 pregnant women found that 43.1% of the daily calories came from this type of food. Corroborating these data, Rohatgi et al[23] found that that 63.2% of the energy consumption of pregnant women in the United States was based on processed and ultra-processed foods. This work reinforces our findings: most pregnant women are getting their calories from ultra-processed foods, which can worsen the health outcomes for them and their children.[23,24]

Regarding the association between the consumption of macro- and micronutrients and HIV positivity, the HIV-positive group had a lower intake of protein, carbohydrates and total fat, as well as a lower calcium intake. There were no statistically significant differences between macro- and micronutrients, except for calcium, which was lower in the HIV-positive group. When we divided ultra-processed food consumption into tertiles, we found a higher consumption of carbohydrates, total fat, trans fat and sodium, and a lower consumption of protein and fiber in women who consumed more ultra-processed foods. Corroborating these findings, Costa Louzada et al,[25] who analyzed the diet of the Brazilian population based on data from the 2008-2009 Family Budget Survey and using two 24-hour intervals to analyze the energy consumption from ultra-processed foods, found excessive consumption of calories, trans fat and sodium, as well as a low consumption of protein and fiber. Bielemann et al[20] also observed that the higher consumption of ultra-processed food products was associated with lower consumption of protein and fiber and higher consumption of trans fat and sodium.[20,25] Rohatgi et al[23] showed that most of the carbohydrates, fats, sugars and sodium consumed by the pregnant women in their study came from ultra-processed foods.[23]

Adequate nutrition during gestation is known to be related to fetal outcomes, and it may influence the health of the baby throughout life. Carbohydrates are important in determining fetal growth, as are lipids, which act in the formation of utero-placental structures and in the development of the central nervous system and retina. However, high consumption of trans fat is associated with obesity and chronic diseases, and has no nutritional benefits. Protein consumption should increase according to trimester, since it is responsible for tissue formation.[5,26]

The balanced intake of macro- and micronutrients during pregnancy is among the most important aspects of adequate fetal development. Micronutrients play an important role during pregnancy. Calcium, which is responsible for bone growth and formation, is not produced endogenously, and is derived from dietary sources. It is known that some factors can alter its absorption, such as fiber and fat intake, for example, and fats are present in high amounts in ultra-processed food. Calcium consumption was lower in the HIV-positive group than in the HIV-negative group (386.24 mg versus 508.21 mg respectively), and was below the recommended levels for pregnant women, which can lead to nutritional deficiencies and negative outcomes, such as impaired bone formation.[19,27,28]

Sodium, which is an essential mineral to regulate the intra- and extracellular fluids, also regulates blood pressure. The main source of this mineral is food. Excessive sodium intake during pregnancy can cause edema and lead to high blood pressure, a factor that increases risk during pregnancy. The sodium consumption among our participants was well above the recommended 1,500 mg/day, averaging 4,735.38 mg/day and 4,803.49 mg/day in the HIV-positive and HIV-negative groups respectively.[13,20]

The present work demonstrates the need for nutritional education during gestation, especially among seropositive individuals, who already have different energy needs due to their illness, as well as a greater risk of negative neonatal outcomes. The effectiveness of an educational intervention in pregnant women and primary prevention have already been elucidated in the literature, such as in a recent study (Rohatgi et al.) conducted in São Paulo, which showed an improvement in eating practices and, consequently, a reduction in the consumption of ultra-processed foods. Recent cohort studies (Gomes et al.) that accompanied women during the gestational period also demonstrated that the consumption of ultra-processed foods was reduced with the advancement of gestation, and was replaced by fresh or minimally-processed foods. This outcome reinforces that feeding is a key factor for the maternal and neonatal outcomes.[23,29,30]

As limitations of the present study, we point out the sample size calculation, which was performed for a larger study. Since this was a cross-sectional study, we were not able to establish cause and effect relationships; thus, longitudinal investigations are necessary to confirm its results. The sample consisted of HIV-positive puerperae, a population that has not yet been studied using validated instruments and techniques. Although the frequencies and distributions may not represent the

population in general, it is believed that the associations observed in the present study are easily generalizable.

Conclusion

In the present study, food consumption among HIV-positive and HIV-negative puerperae was similar. Ultra-processed foods contributed greatly to the total energy consumption of both groups, and this high consumption was directly associated with higher consumption of carbohydrates, trans fat and sodium, as well as lower consumption of protein and fiber. This demonstrates the need for a broader view of pregnant women, especially those who are HIV-positive, since adequate feeding during pregnancy is closely associated with maternal and fetal outcomes. Health care professionals must improve the care for pregnant women with HIV and have a differentiated perspective on their care and follow-up.

Contributors

Agostini CO, Zoche E, Corrêa RS, Chaves EBM, Corleta HvE and Bosa VL contributed to the conception and design of the present study, to the data collection, or to the analysis and interpretation of data, as well as to the writing of the article or to the critical review of the intellectual content and to the final approval of the version to be published.

Conflicts of Interest

The authors have none to declare.

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Trends Associated with Stillbirth in a Maternity Hospital School in the North Zone of São Paulo: A Cross-Sectional Study

Tendências associadas à natimortalidade em uma maternidade-escola na zona norte de São Paulo: um estudo transversal

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Abstract

Objective To evaluate conditions associated with stillbirth (SB), and possible trends related with it, in a maternity hospital school in the North zone of São Paulo.

Methods An observational, cross-sectional study conducted at the Hospital Maternidade-escola de Vila Nova Cachoeirinha with 1,139 SBs in the period of 2003 to 2017. Cases of intermediate SB (ISB) (weight between 500 and 999 g) and late SB (LSB) (weight $\geq$ 1,000 g) were compared. We evaluated clinical data, laboratory tests, and fetal and placental studies. Data were stored in Windows Excel (Microsoft Corp., Redmond, WA, USA) worksheets, according to which graphs and tables were constructed. We used the statistical software SPSS for Windows version 18.0 (SPSS In., Chicago, IL, USA), estimating the prevalence ratio (PR) and odds ratio (OR), considering the 95% confidence interval (95% CI).

Results The general SB rate was 11.9%, and the in-hospital SB rate was 2.8%. Pregnant women younger than 16 years of age were more likely to have ISB (OR 0.32, 0.15–0.76), while patients older than 40 years old had a higher chance of LSB (PR 0.85, 0.72–0.99). A total of 25.7% of the general population did not have prenatal care, and 77.1% of the cases presented fetal death at admission. The cases of ISB had a statistically significant association with home birth (OR 0.61, 0.46–0.80). Cesarean section was performed in 16.1% of the subjects, and misoprostol was the most used method for induction. Necropsy and placental study of the fetuses were performed, respectively, in 94.2% and 97.3% of the cases. Associated causes were not identified in 22.1% of the cases, and the main causes identified were amniotic sac infections (27.9%), fetal malformations (12.5%), placental abruption (11.2%), hypertensive syndromes (8.5%), and maternal syphilis (3.9%), the latter with an increasing trend.

Keywords
- stillbirth
- epidemiology
- primary health care
- prenatal care
- pregnancy high-risk

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Conclusion Among the factors associated to SB were: hypertensive syndromes, amniotic sac infections, fetal malformations, placental abruption and syphilis. There was a growing trend in the number of cases of syphilis, which translates an alert. Diagnostic limitations justify indeterminate causes.

Resumo

Objetivo Avaliar aspectos relacionados à ocorrência da condição de natimortalidade em uma maternidade-escola na zona norte de São Paulo e possíveis tendências associadas aos fatores causais.

Métodos Estudo observacional, transversal, realizado no Hospital Maternidade-escola Vila Nova Cachoeirinha com 1.139 óbitos fetais (OF) no período de 2003 a 2017. Foram comparados os casos de OF intermediários (OFI) (peso entre 500 e 999 g) e OF tardios (OFT) ($\geq$ 1,000 g). Avaliamos dados clínicos, exames laboratoriais, e estudos do feto e da placenta; estes foram armazenados em planilhas de Windows Excel (Microsoft Corp., Redmond, WA USA0, utilizando-se para avaliação estatística o programa SPSS v.18 (SPSS Inc., Chicago, IL, EUA). Foram ainda estimadas a razão de prevalência (RP) e a razão de chances (RC), com intervalo de confiança de 95% (IC 95%).

Resultados O coeficiente de natimortalidade geral foi de 11,9% e o intra-hospitalar foi de 2,8%. Gestantes com menos de 16 anos de idade apresentaram maior chance de ter OFI (RC 0.32, 0.15–0.76) enquanto que pacientes com mais de 40 anos de idade apresentaram maior chance de OFT (RP 0,85; 0,72–0,99). Não fizeram prenatal 25,7% da população geral, sendo que em 77,1% dos casos, a morte fetal já tinha sido apresentada na internação. Os casos de OFI apresentaram associação estatisticamente significante com parto domiciliar (RC 0,42; 0,23–0,75). A cesárea foi realizada em 16,1% das pacientes, sendo o misoprostol o método mais utilizado para indução. Necropsia foi feita em 94,2% dos fetos, e 97,3% das placentas foram para estudo. As causas associadas não foram identificadas em 22,1% dos casos, sendo que as principais causas identificadas foram infecções do saco amniótico e membranas (27,9%), malformações (12,5%), descolamento prematuro de placenta (11,2%), síndromes hipertensivas (8,5%), e sífilis (3,9%), sendo esta última com uma tendência crescente.

Conclusão Destacaram-se como fatores associados à natimortalidade: síndromes hipertensivas, corioamnionites, malformações fetais, descolamento placentário e sífilis. Houve tendência de aumento no número de casos de sífilis, o que traduz uma alerta. Limitações diagnósticas justificam as causas indeterminadas.

Palavras-chave
- natimorto
- epidemiologia
- atenção primária à saúde
- cuidado pré-natal
- gravidez de alto risco

Introduction

Stillbirth (SB) is a reproductive tragedy not only related to immediate maternal risks inherent to clinical management but also to psychosocial problems, such as depression, posttraumatic stress, social stigmatization, and difference in the quality of live of families.[1]

Each year, at least 2.6 million SBs occur worldwide, especially in poor or developing countries.[2] According to the Ministry of Health of Brazil, a total of 351,912 SBs was registered during the period from 2006 to 2016. From this total, 129,173 occurred in the Southeast region, with a monthly average of 11,000 occurrences.[3] Additionally, many epidemiological studies have registered that most SBs would be susceptible to prevention.[4]

Despite the negative impacts they produce, SBs are unattractive from the point of view of clinical research, and most of the time, investigations are very superficial and have a very limited extent, affecting their understanding and implications. Promoting the educational audit of SB cases, performed by a technically qualified team and with availability of resources, such as laboratory evaluations, placenta study, and necropsies, can produce consistent information to understand the factorswith SB and to support prevention strategies.[5]

The assessment of the causes associated with SB remains a major challenge for understanding the problem at a population scale. The recurrent diagnosis of intrauterine hypoxia as a cause of death hardly contributes to understanding the phenomenon. In addition, many studies do not specify whether hypoxia occurred before or during birth.[6]

Thus, SB rates are valuable indicators related to the quality of obstetric care globally, and they contribute to the support of public health planning processes. The more precise the

identification of the associated causes, the better strategies can be planned to improve the quality of prenatal care.[7]

Considering that, in Brazil, more than 98.0% of deliveries are performed in hospitals, the amount of information produced by the local mortality investigation committees allows the identification of factors associated with SB and provides guidelines for more effective prevention in the coverage area.[8]

Therefore, in view of its relevance, our objective is to describe the conditions associated with SB in a maternity hospital school located in the North zone of the city of São Paulo and the epidemiological trends in the last 15 years.

Methods

This is a cross-sectional observational study conducted at Hospital e Maternidade-escola Vila Nova Cachoeirinha (HMEC), located in the North zone of the city of São Paulo. The design of the study followed the Strenghtening the Reporting of Observational Studies in Epidemiology (STROBE)[9] statement, and it included 1,139 cases of SB attended in the period from 2003 to 2017. In view of some registry failures during the data collection, the total number of cases will be different in some variables.

The evaluation of all SBs was based on data from the perinatal mortality committee of the HMEC, using clinical information, notes available in the prenatal folder, maternal laboratory tests and necropsy in SB fetuses, and studies of placenta. The SB definition is according Brazil Ministry of Health based on weight, which defines SB as a death that occurs in any fetus weighing 500 g or more. To allow for international comparisons, we divided the general population according to the birth weight in two groups: intermediate stillbirths (ISBs), those with birth weight between 500 and 999 g, and late stillbirths (LSBs), which consider fetus with 1,000 g or more.[7]

The following variables were selected: age group; number of pregnancies, prenatal care; number of prenatal visits, presence of fetal vitality at admission in hospital; characteristics of birth (site and type of birth), onset of labor, placenta study and necropsy of fetus. The associated causes related to SB were evaluated in addition to the historical evolution of the most frequent reasons, and SB coefficients.

All data was stored in Windows Excel (Microsoft Corp., Redmond, WA, USA) worksheets, and graphs and tables were then constructed based on them. We used the statistical software SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA) to estimate the prevalence ratio (PR) and odds ratio (Odds), considering the 95% confidence interval (95% CI).

The project was approved by the Ethics and Research Committee of HMEC (Reference No. 787.747), according to Resolution No. 466/2012 of the National Health Council (CONEP, in the Portuguese acronym).

Results

During the study period, the total number of live births in the HMEC was 95,650, and the number of SBs was 1,139, resulting in a stillbirth rate (SBR) of 11.9 per 1,000. Taking into account only the cases of fetal deaths that occurred after hospitalization, the coefficient of in-hospital stillbirth (IHSR) was 2.8 per 1,000. (►**Table 1**).

Table 1 Annual distribution of live births, total number of stillbirths, general stillbirth rate and in-hospital stillbirth rate (Maternity School of Vila Nova Cachoeirinha 2003-2017)

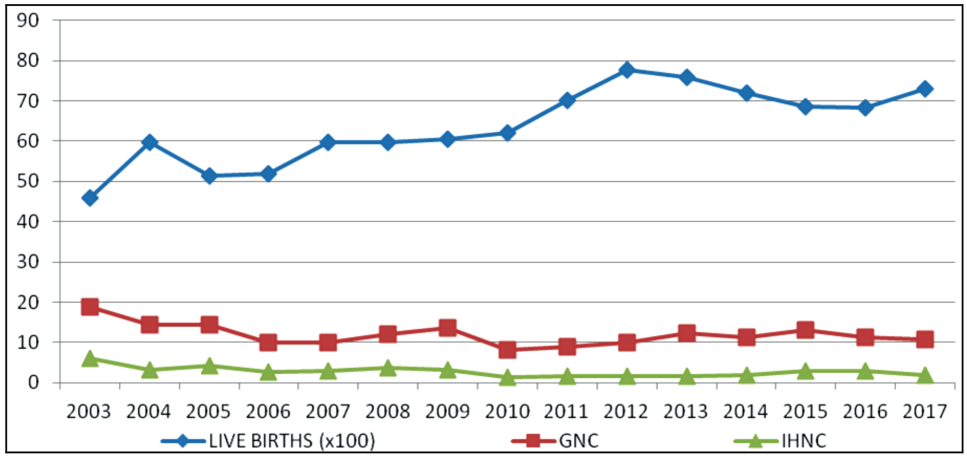
YEAR	LIVE BIRTHS (n)	STILLBIRTHS (n)	SBR*	IHSR*
2003	4,596	88	18.8	6.0
2004	5,973	87	14.3	3.1
2005	5,129	75	14.4	4.2
2006	5,180	52	9.9	2.8
2007	5,980	61	10.1	3.0
2008	5,973	73	12.1	3.8
2009	6,053	83	13.5	3.2
2010	6,205	51	8.1	1.4
2011	7,022	63	8.9	1.7
2012	7,763	79	10.1	1.6
2013	7,592	95	12.3	1.7
2014	7,189	82	11.2	1.8
2015	6,867	92	13.2	2.9
2016	6,820	78	11.3	2.9
2017	7,308	80	10.8	1.9
TOTAL	95,650	1,139	11.93	2.8

Abbreviations: SBR, general stillbirth rate; IHSR, in-hospital stillbirth rate.
*per 1,000

in this table, it is also possible to observe that, over the years, the demand for HMEC care has been increasing. When comparing numbers from 2003 to those of 2017, there was a 59.9% increase in the number of live births. Over the years, despite of the expansion in the number of live births, we can see stable institutional trends in both SBR and IHSR (►**Graphic 1**).

When analyzing maternal and perinatal variables (►**Table 2**), we observed that patients younger than 16 years and over 40 years represented 2.2% and 4.4% of the general population, respectively. However, pregnant women younger than 16 years old were more likely to have ISB (OR of 0.32, 0.15–0.75), while patients over 40 years of age presented a higher chance of LSB (PR 0.85, 0.72–0.99). Women at first pregnancy comprised 37.5% of the population, and this group showed greater chances of ISB (PR 0.79; 0.67- 0.93), while women with more than 5 pregnancies represented 13.4% of the total population with a higher probability of presenting LSB (PR 0.87, 0.78–0.97). Regarding prenatal care, we found that 25.7% of the population had no prenatal visits, a similar distribution for both groups. However, when evaluating the number of visits performed between the patients who had prenatal care, 31.2% presented at least 6 visits, and this possibility was more frequent among the patients who had LSB (OR 4.56, 3.23- 6.44).

As for the presence of fetal vitality at hospital admission, 77.1% of the cases already presented fetal death in the initial care, and this possibility was more likely to occur among the



Graphic 1 Annual distribution of live births, general stillbirth coefficient (GSBC) and intrahospitalar stillbirth coefficient (IHSBC). (Maternity School of Vila Nova Cachoeirinha 2003-2017)

LSB group (OR 0.45, 0.34–0.59). In 96.0% of the cases, the births have occurred at the hospital, but ISB cases were more likely to occur at home (OR 0.42, 0.23–0.75). The labor was already installed in 66.3% of the general population, and this distribution was similar in both groups. Among the patients who underwent induction of labor, vaginal misoprostol was the most commonly used method. Regarding the type of delivery, cesarean section was performed in 16.1% of the cases, and the LSB group had a higher chance of this type of delivery (OR 2.53, 1.68–3.79).

Regarding the possibility of research support being complemented by necropsy and/or placenta study, both the ISB and LSB groups had a similar distribution, with 94.2% and 97.3%, respectively. When we observe the factors associated with fetal deaths, ►**Table 3** shows the main causes according to frequencies. Despite the research methods used, in 22.1% of the study population, the possible cause of fetal death was not identified. This distribution was similar for both ISB and LSB groups. In the same table we can identify the main causes associated with fetal deaths:: infections of the amniotic sac and membranes (27.9%), fetal malformations (12.5%), placental abruption (11.2%), hypertensive syndromes (8.5%), and syphilis (3.9%).

The comparison between the groups showed that the ISB group had higher chances for infection (OR 0.74, 0.56–0.97) and hypertensive syndromes (OR 0.49, 0.27–0.83). On the other hand, the LSB group had higher chances for placental abruption (1.72, 1.12–2.65) and diabetes mellitus (9.38; 1.25–70.55). Regarding syphilis, we found a similar distribution in the groups; however, with a higher prevalence ratio among the LSB patients (0.83; 0.71–0.96).

Trends concerning the five main causes associated with SB, related to the period of the present study, show some stability, despite of alternations over time (Fig. 2), except for amniotic sac and membranes infections, which shows a decresing trend when comparing the initial evaluation from the first years of the study to the evaluation of the last years. The most important aspect to highlight is the increase in maternal syphilis from the year 2013 on, remaining at an outstanding level compared with the previous years (Fig. 2).

Discussion

According to the Ministry of Health of Brazil, SB remains an important public health problem, with stagnant numbers. From 1996 to 2006, the GSBC remained above 10.0%, with regional disparities and worse results in the North and Northeast regions.[7]

Data available in the Tabnet system of the Municipal Health Department of the city of São Paulo shows that, between 2010 and 2016, the total number of fetal deaths in the Northern region of São Paulo is still stable, with around 250 SBs every year. It is important to mention that HMEC attends 25.8% of all cases in the region.[9,10] The set of information provided in this study may be useful for understanding the key factors associated with fetal deaths occurring in this region and supporting strategic measures to reduce their impact on public health.

Maternal age is a single factor associated with adverse pregnancy outcomes, including intrauterine growth restriction (IUGR), preeclampsia, and placental abruption.[11,12] A study performed in the Northeast region of Brazil showed that advanced maternal age persists as an independent factor related to SB.[13]

In the present study, the total number of cases occurred in women of the age group considered adequate for gestation. Although the extremes of age may be a risk factor, the attributable contribution of this population to SB is relatively small. However, the age group under 16 years old presented a higher ISB than LSB rate, suggesting an earlier exposure to risk factors. At the other extreme age group, we observed that pregnant women older than 40 years were more likely to develop LSB, a fact that is possibly associated with a greater range of exposure to factors associated with fetal death, such as maternal diseases and fetal malformations.Therefore, family planning programs could add this message for both age groups.

The number of pregnancies seems to be a risk factor associated with SB, as documented in a multinational study that identified higher risks related to both the first pregnancy and to pregnant women with more than five previous deliveries.[14]

Our population follows the same pattern, but first pregnancy showed a higher ISB rate, while patients with five or more

Table 2 Maternal and perinatal characteristics related to stillbirth. Prevalence rates and odds ratio (Maternity School of Vila Nova Cachoeirinha 2003-2017)

	ISB			LSB			TOTAL		OR
	N	%	PR ISB	N	%	PR ISB	N	%	
Age group									
< 16 years	15	3.9	0.55* (0.39–0.77)	10	1.3	1,67* (1.03–2.70)	25	2.2	0.32* (0.15–0.757)
≥ 16 years	366	96.1		734	98.7		1,100	97.8	
Total	381	100.0		744	100.0		1,125	100.0	
< 40 years	370	97.1	1.53 (0.90–2.59)	706	94.9	0.85* (0.72–0.99)	1,076	95.6	1.81 (0.92–3.58)
≥ 40 years	11	2.9		38	5.1		49	4.4	
Total	381	100.0		744	100.0		1,125	100.0	
Number of gestations									
1	166	43.1	0.79* (0.67–0.93)	257	34.6	1.13* (1.04–1.24)	423	37.5	0.69* (0.54–0.89)
≥ 2	219	56.9		486	65.4		705	62.5	
Total	385	100.0		743	100.0		1,128	100.0	
< 5	346	89.9	1.37* (1.03–1.82)	631	84.9	0.87* (0.78–0.97)	977	86.6	1.57* (1.07–2.32)
≥ 5	39	10.1		112	15.1		151	13.4	
Total	385	100.0		743	100.0		1,128	100.0	
Prenatal care									
No	92	25.8	1.01 (0.83–1.22)	181	25.6	0.99 (0.90–1.10)	789	74.3	1.01 (0.75–1.35)
Yes	264	74.2		525	74.4		273	25.7	
Total	356	100.0		706	100.0		1,062	100.0	
Appointments									
< 6	310	87.1	3.05* (2.30–4.04)	421	59.6	0.67* (0.62–0.72)	731	68.8	4.56* (3.23–6.44)
≥ 6	46	12.9		285	40.4		331	31.2	
Total	356	100.0		706	100.0		1,062	100.0	
Fetal heartrate at admission									
Absent	259	67.3	0.61* (0.52–0.72)	612	82.2	1.37* (1.21–1.55)	871	77.1	0.45* (0.34–0.59)
Present	126	32.7		133	17.8		259	22.9	
Total	385	100.0		745	100.0		1,130	100.0	
Place of birth									
Non-hospital	25	6.5	0.61* (0.46–0.80)	21	2.8	1.46* (1.07–2.01)	46	4.0	0.42* (0.23–0.75)
In hospital	362	93.5		731	97.2		1,093	96.0	
Total	387	100.0		752	100.0		1,139	100.0	
Onset of labor									
Spontaneous	261	67.4	1.05 (0.88–1.25)	494	65.8	0.97 (0.89–1.06)	755	66.3	1.08 (0.83–1.40)
Induction**	126	32.6		257	34.2		383	33.7	
Total	387	100.0		751	100.0		1,138	100.0	
Type of birth#									
Normal	330	91.2	1.98* (1.43–2.74)	587	80.3	0.78*(0.72–0.85)	917	83.9	2.53* (1.68–3.79)
Cesarean	32	8.8		144	19.7		176	16.1	
Total	362	100.0		731	100.0		1,093	100.0	
Necropsy									
Yes	362	95.5	0.77 (0.51–1.17)	690	93.6	1.12 (0.96–1.31)	1,052	94.2	0.69 (0.39–1.22)
No	17	4.5		47	6.4		64	5.8	
Total	379	100.0		737	100.0		1,116	100.0	

(*Continued*)

Table 2 (*Continued*)

	ISB			LSB			TOTAL		OR
	N	%	PR ISB	N	%	PR ISB	N	%	
Study of placenta									
Yes	291	98.0	0.75 (0.38–1.50)	514	97.0	1.14 (0.88–1.48)	805	97.3	0.66 (0.26–1.71)
No	6	2.0		16	3.0		22	2.7	
Total	**297**	**100.0**		**530**	**100.0**		**827**	**100.0**	

Abbreviations: ISB, immediate stillbirth; LSB, late stillbirth; N, number; OR, odds ratio; PR, prevalence ratio.
*Significance (95% confidence interval)
#Only in hospital.
**Misoprostol was the option to ripening cervix in 81.7% of cases.

Table 3 Frequencies and causal factors attributed to intermediate stillbirth and late stillbirth (Maternity School of Vila Nova Cachoeirinha 2003-2017)

ATTRIBUTED FACTORS	ISB			LSB			TOTAL		
	N	%	PR ISB	N	%	PR LSB	N	%	OR
Infections (amniotic sac and membranes)	122	32.0	0.82* (0.69–0.98)	193	25.8	1.11 (1.01–1.23)	315	27.9	0.74* (0.56–0.97)
Indeterminate	89	23.4	0.93 (0.77–1.12)	160	21.4	1.04 (0.94–1,15)	249	22.1	0,89 (0.67–1.20)
Fetal malformation	44	11.5	1.09 (0.84–1,42)	97	13.0	0.96 (0.85–1.08)	141	12.5	1.14 (0.78–1.67)
Placental abruption	30	7.9	1.47* (1.06 - 2.03)	96	12.9	0.85* (0.77–0,95)	126	11.2	1.72* (1.12–2,65)
Hypertensive syndrome	47	12.3	0,66* (0,53 - 0.83)	49	6.6	1,32* (1,08 - 1.62)	96	8.5	0.49* (0.27–0.83)
Syphilis	9	2.4	1.68 (0.93–3.02)	35	4.7	0.83* (0.71–0.96)	44	3.9	2.03 (0.97–4.27)
Umbilical cord changes	12	3.1	1.19 (0.73–1.93)	30	4.,9	0.92 (0.76–1.12)	42	3.7	1.29 (0.65–2.54)
Other placentary disorders	14	3.7	0.96 (0.63–1.48)	26	3.5	1.02 (0.81–1,28)	40	3.5	0.94 (0.49–1.83)
Fetal-fetal transfusion syndrome	6	1.6	1.42 (0.70–2.86)	19	2.5	0,87 (0.69–1.09)	25	2.2	1.63 (0.65–4.12)
Diabetes mellitus	1	0.3	6.51 (0.96–43.94)	18	2.4	0.69* (0.62–0.78)	19	1.7	9.38*(1.25–70.55)
Other causes	5	1.3	1.36 (0.63–2.91)	15	2.0	0.88 (0.68–1.14)	20	1.8	1.54 (0.54–4,27)
TOTAL	**381**	**100.0**		**747**	**100.0**		**1,128**	**100.0**	

Abbreviation: ISB, immediate stillbirth; LSB, late stillbirth; N, number; OR, odds ratio; PR, prevalence ratio.
*Significance (95% confidence interval)

pregnancies are associated to higher LSB risk. Despite these findings, the association of maternal parity and the risk of fetal death should be interpreted with caution, considering that confounding factors may limit this conclusion.[4,14] It should be added that the higher the number of pregnancies, the greater the chance of exposure, following the same logic applied to maternal age.

Regarding prenatal care, the literature is unanimous in considering the qualification of this follow-up of pregnancy as essential for the reduction of maternal and perinatal risks in order to achieve good results. According to the Brazilian Program for Humanization of Prenatal and Childbirth, and to the World Health Organization, the occurrence of SBs is higher among women whose prenatal care was considered inadequate.[15,16]

This statement is confirmed by one study conducted in the Southern region of Brazil, where inadequate prenatal was associated with the occurrence of SB.[17] In the present study, we found that among the total number of cases, 25.7% did not attend any prenatal visits. This expressive rate reveals that many opportunities for intervention probably were lost in order to reduce the risk of fetal death. This concerning situation was similar in both groups.

Regarding the number of prenatal care visits, it seems reasonable that the ISB group would have fewer consultations, since fetal death occurred in the earlier stages of pregnancy. However, even in the LSB group, 68.8% of the cases had less than 6 visits. Perhaps, the same logic applies in this case, and it is reasonable to assume that the number of visits, per se, does

not seem to be associated with the occurrence of SB cases but rather their initial qualification. This aspect deserves special attention because the notes in the prenatal cards are essential for identifying possible factors related to SB. Therefore, strategic actions directed to ensure accessibility to medical care as soon as possible, their initial qualification. In addition, in many cases, the quality of the information available in the prenatal records presented at the time of hospitalization does not help to elucidate the causes of SB.

Although it is possible to understand that the risk of SB is reduced by means of qualified care actions, it should be considered that identifying the moment of the fetal death is a very difficult task. Biological determinisms are complex and, often, not identified in a timely manner. In addition, SB may be the result of different etiologies and not of a single disorder, and it is unlikely that any individual test will be able to predict fetal death and identify all causes.[18] In any case, the SB among hospitalized patients is important to identify possible assistance failures in situations that can be prevented.

We identified that, in the total population, fetal heartbeats were absent at the time of hospital admission in 77.1% of the cases. When comparing the groups, we found out that the ISB group had higher chances of fetal death occurring during hospitalization. We believe that this fact may be associated with institutional characteristics, since HMEC is a reference center to high-risk pregnancies, where several patients remain under institutional care until reaching viable gestational age. Although this phenomenon may occur, it did not significantly affect the evolution of IHSR (in-hospital stillbirth rate) throughout our historical series (►**Graphic 1**).

Regarding delivery care, in 96.0% of all cases, births have occurred in the hospital environment, and, among them, 66.3% of the cases were admitted in spontaneous labor. Cases requiring cervix ripening received intravaginal misoprostol or endocervix Foley catheter, but misoprostol was the more common method used in 81.7% of the cases.

However, a notable fact is that non-hospital births occurred in 4.0% of the population, and the ISB group had greater chances of this type of occurrence. The dramaticity of these situations must be emphasized considering the additional exposure of these women to the risks of severe bleeding and infection. These occurrences were more frequent among the ISB group, but we did not identify a related factor other than the possibility of a smaller fetal volume facilitating their expulsion.

For the care of pregnant women with SB, the indication of cesarean section only makes sense when maternal risks outweigh the benefits, such as instability imposed by placental abruption or risks of uterine rupture.[14]

When evaluating the overall cesarean section rates, it is verified that this occurred in 15.4% of the cases, which allows us to state that they are within the guidelines of care. It is necessary to consider that the main cases of cesarean section were placental abruption, and patients with scars, in whose case the risks of uterine rupture were not negligible. The characteristics of labor assistance verified in our series can provide two topics for obstetric practice: the first is a strong recommendation that vaginal birth is the preferential option for these situations, considering maternal risks. The second refers to the use of misoprostol in adequate doses, and the respect to the time necessary for the onset of labor.[19]

The task of investigating and identifying factors associated with SB remains as an important point to understand this dramatic outcome and to provide alternatives for prevention and counseling.[20] Even with several alternatives available for research, many causes remain unknown.[21] In this scenario, the anatomopathological evaluation of the fetus and placenta may be valuable in elucidating the case. This practice is still not widely adopted and is identified by some authors in only 30.0 to 35.0% of occurrences.[17,20]

In our study, both placenta and fetal studies were performed in expressive percentage (►**Table 2**) and assisted in the definition of the associated cause. Nevertheless, 22.1% of the cases remained as unidentified etiology, with this aspect being similar between the groups. Not having the answer that clarifies a SB is a frustrating experience for the family and the medical staff. Thus, the entire diagnostic arsenal (clinical, imaging, laboratory and pathological anatomy) should be used to elucidate the cause of fetal death.[22] However, in many cases, severe fetal maceration limits a more detailed study of the corpse.

During the study period, there were many factors associated with SB, with some alternations occurring during the years of study (Fig. 2). Amniotic sac and membranes infections had an expressive participation in our sample and was often identified only by the placenta study, in which we can identify chorioamnionitis, frequently associated with funisitis.

Infections can cause SB through several mechanisms, including direct fetal infection, placental injury, and severe maternal illness. Many bacteria, viruses and protozoa have been associated with SBs. In developed countries, up to 24.0% of the cases of SB were attributed to some infection. Thus, screening of maternal infectious processes at sites such as the urinary tract, teeth, and vagina would possibly reduce their impact on the causes of SB. However, to implement these actions is not an easy task in our health system. Regarding fetal anomalies, all conditions were grouped. This group of reasons was associated in 12.5% of the general population, with a similar distribution between ISB and LSB (►**Table 3**). Differently from our results, a study in Southern Brazil that reviewed autopsy records of all SBs ($n = 111$) in one hospital reported that 26.0% of SBs were caused by congenital anomalies. Although studies that evaluate risks indicate that fetal anormalities have strong association with SB, frequencies are very diverse in the literature, ranging from 2.1 to 33.3%. Such differences are most likely related to the various clinical profiles of the institutions where the cases are studied. Centers with a high concentration of this type of problem may have relevant rates in their indicators, but this cannot be transferred to the general population.[4,23–28]

Placental abruption is recognized as one of the main causes of fetal death, with a percentage attribution between 7.5 and 42.0%.[4] Moreover, it is worth mentioning that this condition imposes a higher maternal risk, given its emergency character, with a quick hemodynamic failure of the woman. Besides, there is a very frequent need for cesarean delivery due to the uncertainty of fetal vitality, adding more risks to the care of these patients. The higher chances of this serious obstetric

condition were associated with LSB cases. In view of the dramatic condition of placental abruption and uterine hypertonia, evaluation of fetal conditions is a very difficult task. Therefore, it is understandable that in this singular situation, the rate of cesarean section is higher in view of the uncertainty of fetal death. This is why cesarean birth is the best option when facing such dramatic situations.

The risk of fetal death increases in hypertensive patients, with chronic hypertension and preeclampsia being included in this category, due to varying degrees of placental insufficiency and IUGR in addition to acute events, such as placental abruption.[23]

On a global scale, it is estimated that 2.6 million SBs occur annually around the world and ~ 16.0% of them occur in pregnancies complicated by gestational hypertension.[24] In the present study, 8.5% of the SB cases had hypertensive syndrome as their main cause. It is added that placental abruption, often associated with patients with hypertensive disorders, was also an important cause during the study period (►**Table 3**).

The highest chances of this association were identified among cases of ISB. Possibly, this fact could be explained by the presence of patients in the high-risk unit in the very early stages of gestation, when the expectant management is adopted to improve the prognosis of the newborn in view of extreme prematurity.

Considering that when it comes to hypertension, maternal and perinatal outcomes are directly related to the quality of prenatal care, it would be important to adopt prevention and early detection actions. This would have a positive impact on the reduction of severe cases and on early identification of placental insufficiency, thus allowing more timely actions.

A very concerning condition was the identification of syphilis as responsible for 3.9% of SBs in our population, with a more significant prevalence among the LSB group. In addition, we noticed an increasing trend in its prevalence since 2013 (Fig. 2).

It is estimated that, each year, between 1 and 2 million pregnancies are affected by syphilis in the world. Among the adverse perinatal outcomes in infected pregnant women, we highlight fetal death, which may occur in 30.0 to 40.0% of the cases. A study related to syphilis, conducted in the Americas, has shown that positive sorology has a 6.8-fold higher chance of SB compared with healthy women.[29]

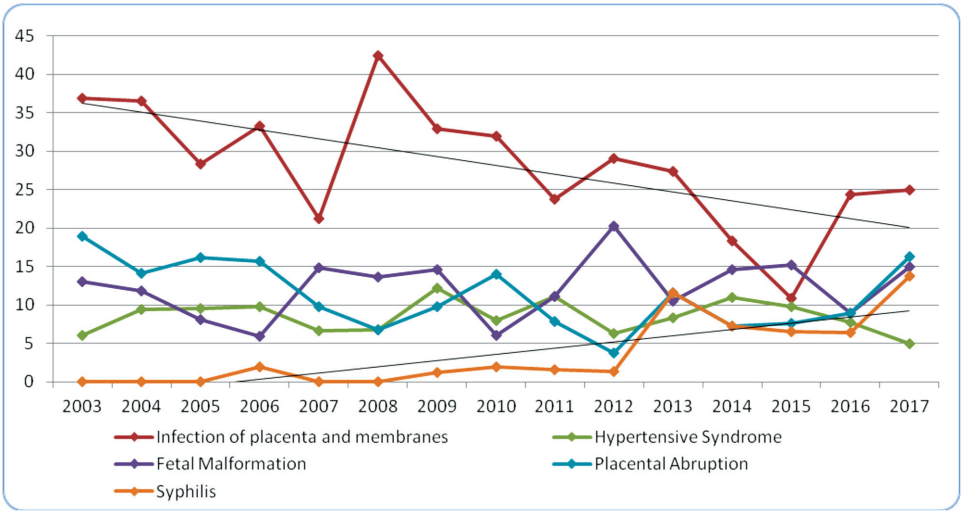
From 2005 to June 2017, 200,253 cases of syphilis were reported in pregnant women in Brazil, 44.2% of whom were residents of the Southeast region.[30] The increase in the number of cases recorded in our study probably runs parallel with the syphilis epidemic detected by the national health authorities.

This constant increase in cases of syphilis in pregnant women may be related to several factors, such as greater coverage of testing, reduction of condom use, resistance of health professionals to the administration of penicillin in primary care, and shortages of penicillin.[30]

Preventing SB attributable to syphilis should be easier in contexts of high prevalence, considering that the diagnosis and treatment of the disease during pregnancy occurred effectively.[29] Unfortunately, this does not seem to be happening.

Regarding the set of factors associated with SB, when evaluating the behavior of the frequencies over the period studied, we found that five factors concentrated the majority of the cases. ►**Graphic 2** illustrates that, over the years, amniotic sac and membranes infections defined as chorioamnionitis have tended to decline: in 2003, they accounted for 36.9% of the cases, and, in 2017, this portion reached 25.0%. We considered it a complex task to identify the reasons for this behavior, considering that we did not detect global assistance actions that could reduce the risks of maternal infection and its consequences.

Despite the persistence of the investigation criteria, indeterminate causes accounted for 22.1% of the cases, revealing difficulties in refining the research. Even with the resources currently available, we are far from a more advanced level of



Graphic 2 Frequency of the main factors related to fetal deaths and trends. Maternity School of Vila Nova Cachoeirinha 2003-2017. (Maternity School of Vila Nova Cachoeirinha 2003-2017)

research that may include cytogenetic studies, fetal tissue cultures, including viral research, screening for hereditary deficiencies, evaluation of fetal and/or placental hemorrhage, dosage of heavy metals and environmental pollutants, among others.

A standardized universal definition of SBs and their causes is a key issue, so that the methodological quality of SB research is improved. In addition, adopting international standardization for the classification of fetal deaths could facilitate comparisons between different regions and guide actions to reduce this phenomenon.[22] More studies about SBs should be further explored by official statistics in view of their undoubted importance in terms of public health and valuable sentinel event of prenatal care quality. Limitations related to more diagnostic methodologies justify the maintenance of expressive rates of undiagnosed fetal deaths.

Conclusion

The present study evaluated a historical series of SB cases, and its methodology allowed identifying how these events occurred at the HMEC. Relevant aspects were identified, such as lack of prenatal care, home birth, and the use of misoprostol for labor induction. The factors associated to the SB presented a certain concentration, during the 15 years of study, particularly the role of infections of amniotic sac and membranes, fetal malformations, placental abruption, hypertensive syndromes, and maternal syphilis. In relation to syphilis, the tendency of growth in its frequency translates an alert in terms of sanitary problem.

Contributions

Each author participated actively in the planning, execution, and conduction of this study. The authors proposed the manuscript, edited, and approved the final version to be published.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Empowering Adolescent Mothers in the Choice of Contraceptive Methods at the Postpartum Period: Avoiding a Subsequent Pregnancy

Empoderando mães adolescentes na escolha do método contraceptivo no pós-parto: Evitando-se a gravidez subsequente

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Abstract

Objective Almost 80% of adolescent pregnancies are unplanned, and between 28 and 63% of adolescent mothers had a repeated pregnancy within 18 months. Among girls with repeated pregnancies, two-thirds reported that the pregnancy was unplanned. We aim to assess contraceptive use by adolescent mothers with increasing choice for long-acting reversible contraception (LARC) methods in postpartum consultation after a semistructured group intervention involving adolescent mothers.

Methods Retrospective observational study conducted at the Universidade Estadual de Campinas, Campinas, state of São Paulo, Brazil, involving new antenatal and postpartum education groups for adolescents. At postpartum consultations, the adolescents chose their contraceptive. The data was compared with previous series followed in a period before the implementation of the education group – a historical control group.

Results We included 129 adolescent after childbirth from January 1st, 2015 through July 31st, 2017. Out of this total, 63% had ever used contraceptive methods before pregnancy, and the most frequent method was combined oral contraceptives (33%) followed by condoms (21%). At the first postpartum consultation, the most common contraceptive chosen was intrauterine contraception (IUC) (37.2%) and depot-medroxyprogesterone acetate (DMPA) (34.1%). When comparing the rates before and after the education interventions, there was a 3-fold increase in the use of IUCs.

Conclusion Antenatal and postpartum education have shown a significant increase in the choice for LARC methods among adolescent mothers, with very high acceptability after a period using the method. The educational groups performed during the antenatal care and beyond the gestational period are easy to be applied worldwide with low dependence on funding.

Keywords

- contraception
- long-acting reversible contraception
- adolescent
- postpartum period
- antenatal education

Resumo

Objetivo Cerca de 80% das gestações na adolescência não são planejadas, e entre 28 e 63% das mães adolescentes apresentam repetição da gravidez em 18 meses. Entre as meninas com gravidez repetida, dois terços relataram que a gravidez não foi planejada.

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Nosso objetivo é avaliar o uso de anticoncepcionais por mães adolescentes com crescente escolha para métodos de contracepção reversível de longa ação (LARCs, na sigla em inglês) na consulta pós-parto após uma intervenção em grupo semiestruturada envolvendo mães adolescentes.

Métodos Estudo observacional retrospectivo realizado na Universidade Estadual de Campinas, São Paulo, SP, Brasil, envolvendo novos grupos de educação pré-natal e pós-parto para adolescentes. Nas consultas pós-parto, os adolescentes optaram pela contracepção. Os dados foram comparados com uma série de casos seguida em um período anterior à implementação do grupo de educação pré-natal - um grupo de controle histórico.

Resultados Foram incluídas 129 adolescentes no período pós-parto de 1° de janeiro de 2015 a 31 de julho de 2017. Destas, 63% já tinham usado métodos contraceptivos antes da gravidez, e o método prévio mais frequente foi contraceptivo oral combinado (33%) seguido por preservativo (21%). Na primeira consulta pós-parto, o anticoncepcional mais comumente escolhido foi o dispositivo intrauterino (DIU) (37,2%) e o acetato de medroxiprogesterona de depósito (DMPA) (34,1%). Ao comparar as taxas antes e depois das intervenções de educação pré-natal, houve um aumento de três vezes no uso de DIUs.

Conclusão Educação pré-natal e pós-parto mostraram um aumento significativo na escolha de métodos contraceptivos reversíveis de longa duração entre mães adolescentes. Grupos educativos realizados durante o pré-natal e além do período gestacional são ferramentas para promoção da saúde e são de fácil aplicação mundial, com baixa dependência de financiamento.

Palavras-chave
- contracepção
- anticoncepcional reversível de longa duração
- adolescente
- pós-parto
- educação pré-natal

Introduction

The United Nations Sustained Development Goals aims to promote good health and well-being, quality education, gender equality, and to reduce inequalities—among other actions—to ensure prosperity for all.[1] Adolescent pregnancy has been associated with social, economic, and health problems and, therefore, has been considered a public health issue, which can influence the level of human development.[2,3] The global adolescent birth rate is 43.9 births/1,000 women aged 15–19 years. In Brazil, this rate is 60.8/1,000, while in developed countries the rate is < 25/1,000.[4] In 2016 in Brazil, one in five babies was born from adolescent girls and, similarly to other Latin American countries, Brazil has the highest number of pregnancies in adolescent girls under 14 years old.[5]

Almost 80% of adolescent pregnancies are unplanned, and between 28 and 63% of adolescent mothers had a repeated pregnancy within 18 months.[6,7] Among girls with repeat pregnancies, two-thirds reported that the pregnancy was unplanned.

Long-acting reversible contraceptive (LARC) methods are intrauterine contraceptives (IUCs) and subdermal implants. These are the contraceptives with the highest efficacy and, consequently, an excellent tool to avoid repeated unplanned pregnancies.[6,8,9]

As the LARCS appear to be the best choice to avoid unplanned pregnancy among adolescents, we have searched our previous data and data from other countries to evaluate the choice of LARCs by adolescents. A previous study conducted by our group among postpartum adolescents in the same setting showed that only 11% chose IUCs as a contraceptive method (we do not have implants to offer at no cost) and depot-medroxyprogesterone acetate (DPMA) injection was chosen by 71%.[10] Furthermore, a large US-based study with more than 21,000 adolescents showed that, at the postpartum period, 15% chose IUCs and 7% chose implants as a contraceptive method.[9]

With the aim to increase the use of LARC methods among adolescents that do not want to get pregnant, since 2014 we have been performing educational semistructured group interventions with counseling during the prenatal care of the adolescent and immediately before the postpartum consultation. During these interventions, we promote antenatal education with the intent to empower the adolescent girls involved to choose the best contraceptive method according to their needs. The objective of our study was to evaluate whether our semistructured group interventions with counseling and an educative purpose increased the use of LARC methods at the postpartum consultation in young mothers.

Methods

A retrospective observational study was performed at the Department of Obstetrics and Gynecology, School of Medical Sciences of the Universidade Estadual de Campinas (UNICAMP, in the Portuguese acronym), Campinas, state of São Paulo, Brazil. The Ethical Committee of the UNICAMP approved this

research (CAAE: 11909413.6.0000.5404). All of the items of the Strengthening the Reporting of Observational Studies in Epidemiology were followed.

Pregnant adolescents < 19 years old attended prenatal care through our specialized service in taking care of adolescent pregnant/mothers. Currently, before medical consultation for antenatal and/or postpartum care, all of the adolescents < 20 years old are invited to participate in an open group discussion during one hour with a multidisciplinary team to learn about human rights and, among these rights, options for contraception. Contraceptive methods; efficacy; and demystifying fears, misconceptions and preconceptions about the methods are openly discussed in these groups. All of the adolescents are also educated about the use of condoms as double protection. The adolescents participated in the group discussion in every antenatal care consultation. All of the adolescents spoke Portuguese, so there were no languages barriers.

A multiprofessional team conducted these groups in routine assistance. All of the information was provided to reduce the vulnerability of the adolescent mothers after delivery. Social and gender vulnerability was indicated in the population who attended at our hospital, which treats an underprivileged portion of the society.

The proposal to conduct a group with antenatal educational was intended to empower girls about human rights, which include sexual and reproductive rights, contraception and health knowledge, as well as to provide guidance on newborn care, breastfeeding, and on the rights of postpartum women. These antenatal groups also aimed to encourage education and healthy nutrition and physical activity counseling and to provide information on gender issues and violence.

We obtained data from medical records of all of the adolescents who underwent postpartum consultation. All data were routinely transcribed into a specific form and inserted into an Excel (Microsoft Corporation, Redmond, WA, USA) spreadsheet. Contraception methods were evaluated at three moments:

1) "Desired method" – the contraceptive method that the adolescent informed as desired at the 1st postpartum consultation.
2) "1st Prescribed method" – the 1st contraceptive method prescribed by the doctor and agreed by the adolescent after analyses of the desired method and after exposing characteristics of all methods available.
3) "Final method" – the final contraceptive method chosen after subsequent postpartum consultations that evaluated the adaptation and desire to change the contraceptive method. In our service, adolescents are routinely followed-up until 1 year after delivery. At this period, the acceptability of the contraceptive method with the desire to maintain the method chosen is evaluated.

In our service, IUC (both copper and the 52mg levonorgestrel-releasing intrauterine system), DMPA, combined oral contraceptives (COCs), progestin-only pills, once-a-month injectable contraceptives, and condoms are available at no costs. Implants are not available.

Statistical analyses were performed using the SAS Statistical Analysis System for Windows, version 9.2 (SAS Institute Inc., Cary, NC, USA) and included the use of the Fisher exact test, of the Kruskal-Wallis test, and of the Bowker test for symmetry. The level of significance was established at 5%. Furthermore, as the intervention was applied for all of the adolescents that were in antenatal care in our service, the control group had to be historical (2011–2013). Therefore, we compared our actual rates of use of IUCs and DMPA with previous results in the same setting prior to the semistructured group interventions.[10]

Results

From January 1st 2015 through July 31st 2017, a total of 129 adolescents were included in the research data. Sociodemographic and obstetrics characteristics are shown in ►**Table 1**. The mean (±standard deviation [SD]) age of the teens and of their partners was 16.1 (±1.6) and 22.1 (±5.7) years old, respectively. Half of them (51%) had a stable partner; nevertheless, 71% of the girls < 15 years old were single.

Table 1 Sociodemographic and gynecologic characteristics, mode of delivery, and habits of postpartum adolescents

Characteristics	*n*	%
Age (years old) (*n* = 129)		
≤ *14*	24	18.6
≥ *15*	105	81.3
Menarche (age) (*n* = 109)		
≤ *12*	78	60.5
≥ *13*	31	24.5
First sexual intercourse (age) (*n* = 99)		
≤ *12*	9	9.0
13–14	54	54.5
≥ *15*	36	36.5
Parity (*n* = 129)		
1	115	89.15
≥ *2*	14	10.85
Marital Status (*n* = 127)		
Single	61	47.2
Stable partner	66	51.1
Previous Contraceptive Method - Yes	81	62.7
Currently Studying - Yes (*n* = 129)	52	40.3
Schooling (*n* = 97)		
≤ *Elementary School*	38	29.4
≥ *High School*	59	45.7
Smoking Status - Yes (*n* = 119)	5	3.8
Alcohol Consumption – Yes (*n* = 119)	1	0.8
Mode of Delivery (*n* = 129)		
Vaginal	92	71.3
Cesarean	37	28.6

Table 2 Correlation between desired, 1st prescribed, and final contraceptive method used in adolescents after childbirth

Desired method		1st Prescribed method			Final method		
n (%)		*n* (%)*			*n* (%) **		
		IUC	DPMA	Others	IUC	DPMA	Others
IUC	41 (32%)	31 (33%)	9 (9.6%)	0	28 (38%)	4 (5.4%)	1 (0.7%)
DPMA	42 (32.5%)	4 (4.3%)	37 (39%)	0	7 (9.5%)	25 (34%)	3 (2.3%)
Others	46 (35.6%)	0	7 (5.4%)	6 (4.6%)	7 (9.5%)	3 (4%)	3 (2.3%)

Abbreviations: DMPA, depot-medroxyprogesterone acetate; IUC, intrauterine contraceptive.
Bowker's test for symmetry: *0.62; ** Kappa= 0.57; Missing = 35 (for prescribed) / 48 (for final method).

Table 3 Adolescent satisfaction with current contraceptive methods

Satisfaction	IUC	DMPA	Others
Good (67)	34 (77.3%)	30 (76.2%)	3 (37%)
Regular (16)	8 (18.2%)	6 (15.4%)	2 (25%)
Bad (7)	2 (4.5%)	3 (7.7%)	2 (25%)
Total	44 (100%)	39 (100%)	7 (100%)
Fisher exact test: $p = 0.161$ Missing = 39			

Abbreviations: DMPA, depot-medroxyprogesterone acetate; IUC, intrauterine contraceptive.

More than half (60.4%) of the teens presented menarche at < 12 years old, and the mean age for the 1st sexual intercourse was 14.1 (±1.4) years old. A total of 63% percent of all the adolescents had ever used contraception before pregnancy, and the most frequently used method was COCs (33%) followed by condoms (21%). The main reasons for abandoning contraception were a desire of pregnancy (23.4%) and irregular use of COCs (22.2%).

Most of the girls involved had vaginal delivery (71.3%), and cesarean delivery was performed due to pelvic cephalic disproportion in 6 cases, to acute fetal distress in 5 cases, and to maternal disease in 6 cases.

The 1st postpartum consultation occurred at 47.7 (±17.1) days after the delivery, and 32% of all the adolescents had already reinitiated sexual activity without protection. At this time, the contraceptive methods most frequently chosen by the adolescents were IUCs in 48 cases (37.2%) and DMPA in 44 cases (34.1%) (►**Table 2**).

The comparison among desired, 1st prescribed, and final contraceptive methods chosen is shown in ►**Table 2**. One-third of the adolescents wished to use IUCs, DPMA or others. The satisfaction with the contraceptive method in 6 months to 1 year is in ►**Table 3**.

In the bivariate analysis, there were no differences among the contraceptive method chosen and the age of the adolescent, the age of the partner, years of schooling, age at menarche, and age at the 1st sexual intercourse (data not shown). However, when we compared the historical rates of contraceptive methods used in our service during two different periods – before and after the antenatal educational and counseling groups – there was a threefold increase in the use of IUCs (►**Fig. 1**).

Discussion

Our data showed an increase in the choice/insertion of IUCs at the 1st postpartum consultation among adolescents after the implementation of counseling and educative groups.

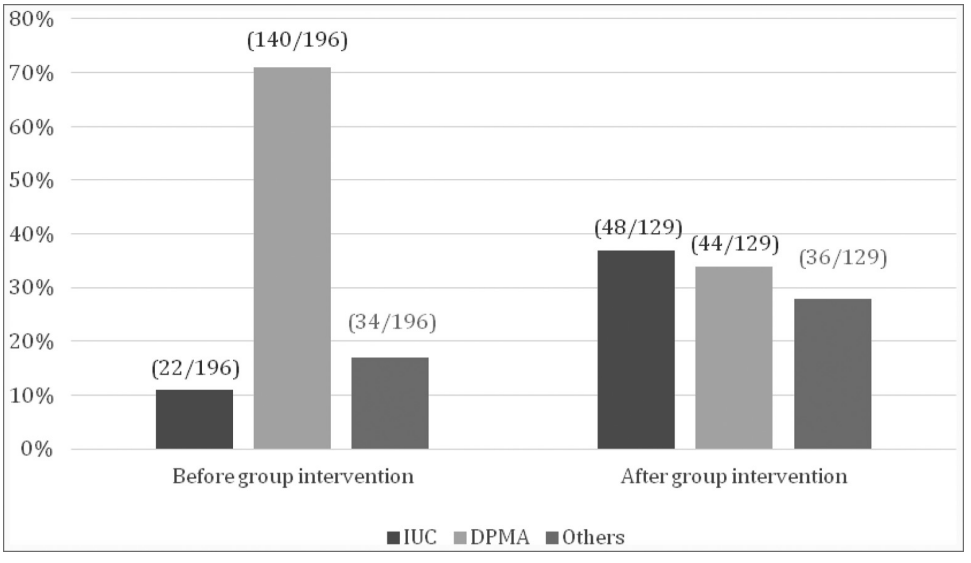

Fig. 1 Comparison among contraception choice before and after the education group.

Previous data from our hospital showed an IUC rate use of only 11%[10]; however, in the present study, IUCs were chosen by 37%. These data supported our hypothesis that after information about contraceptive methods during group interventions, adolescents would choose more LARCs (represented in our service by IUCs).

The United Nations Sustained Development Goals include, among other topics, ensuring access to education, reducing inequality, promoting gender equity and empowering women and girls.[1] For all these goals to be achieved, major transformations on a political level will need to be implemented, but daily actions can make a difference in starting these changes.

Only with effective educational intervention can adolescent girls choose the better contraceptive method according to their needs. In our sample, 77.5% of the girls chose to use a contraceptive method, and 37% of them chose IUCs. These findings are similar to one study that compared the rate of LARCs use by adolescent mothers before and after an intervention that included contraceptive counseling.[11] The authors found that the LARCs rate used to be 40% among adolescents who were part of the intervention compared with 26% in the control group, representing a 13% increase in the use of LARCs in the intervention group.[11]

Contraceptive use among adolescents is still a complicated issue in many settings;[12,13] nevertheless, it is well-established that LARC methods are the best contraceptive choice to avoid unplanned pregnancy.[12–14] LARCs promote similar efficacy between typical and perfect use with only one intervention.[8,13,15]

The postpartum period is an excellent opportunity to initiate contraception because, at this moment, women are motivated to avoid a new pregnancy.[16] Nevertheless, many adolescents sometimes choose less-effective contraceptives or no contraceptive method at all at the postpartum period due to lack of adequate knowledge or access.[17]

Another thing that can make a difference is the time when contraceptive counseling is offered to adolescents during the postpartum period. A Thailand-based study compared the rate of choosing LARCs when contraceptive counseling was offered immediately after birth or within a conventional period (4–6 weeks after delivery). The authors found an odds ratio (OR) of 3.67 (rate of LARCs: 73.7% vs 42.6%) among adolescents who received counseling immediately after birth.[18]

However, both in the immediate postpartum period and in the routine puerperal consultation, adolescent mothers should have a follow-up shortly after consultation because they present high discontinuation rates for the contraceptive methods.[17] The use of LARCs could minimize this risk because it is a new opportunity that healthcare professionals have to reinforce contraceptive usage through counseling. After being clarified about the different contraceptive methods, about the characteristics of each of them and about the need to follow-up compose the reasons the adolescent mothers chose more LARCs in our study.

Although LARCs are apparently the best option for adolescents to avoid unintended pregnancy, the cost is the major reason to not use them.[19] In our service, IUC (copper and hormonal) is the only LARC offered at no cost. The US Contraceptive CHOICE Project offered any type of contraceptive methods at no cost and provided further information about contraceptive methods, including the high efficacy rates of LARCs.[17] In that study, 72% of adolescents choose LARC methods.[17] Among adolescents between 14 and17 years old, 63% chose LARC methods, whereas 29% of the women between 18 and 20 year old chose an implant.[20] The researchers of the project also found that pregnancy, birth, and abortion were lower among adolescents participating in the study when compared with the general adolescent population of the St. Louis, MO, area.[17]

A recent large study in Latin America and the Caribbean shows that LARCs are seldom used.[21] In Brazil, a big country with high rates of teenage pregnancy, LARCs were used in only 2% of all women. The study concluded that LARCs should be expanded and their use promoted, including among young and nulliparous women, and that family planning services, information and counseling should be provided.[21]

Our study presented some limitations. It was conducted in a single center and without the possibility to offer subdermal implants, which obviously affected the ability of the adolescents to choose LARCs. Nevertheless, the strength of the study was that with committed staff and without extra costs, we were able to implement contraception education through antenatal and postpartum consultations. This action promoted knowledge and broke barriers about IUCs in adolescent mothers.

The educational groups performed during antenatal care and extrapolating to educational groups for health promotion besides the gestational period is easy to be applied worldwide with low dependence on funding. Not only LARCs should be offered with no costs, but also education and specialty sexual education should be widespread. It is a start to promote health, gender equality, and empower women as the 2030 United Nations Sustained Development Goals Agenda aims to do.

In conclusion, contraception use to avoid a second pregnancy among young mothers involves political, social, economic, medical, and cultural issues, but can be achieved with low costs using a committed team. We need full-scale educational interventions for all adolescents – girls and boys – to explain the importance of using an effective contraceptive method to avoid unplanned pregnancies, and LARCs are a great alternative to reach this goal.

Contributions

Borovac-Pinheiro A. and Surita F. G. conceived and designed the study. Borovac-Pinheiro A. and Jesus E. A. R. collected the data. All of the authors were involved in the data analysis and interpretation. Borovac-Pinheiro A. and Surita F. G. were involved in writing. All of the authors approved the final version of the manuscript.

Conflicts of Interests

The authors have no conflict of interests to declare.

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Attitudes and Personal Attributes Regarding Patient Receptivity towards the Participation of Medical Students in Gynecological Consultations: A Cross-Sectional Study

Atitudes e atributos pessoais relativos à receptividade das pacientes à participação de estudantes de medicina em consultas ginecológicas: Um estudo de corte transversal

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Abstract

Objective To evaluate the association between the acceptance on the part of the patients and their reasons to consent to or refuse medical student attendance during gynecological outpatient care, considering the participants' demographic characteristics, consultation experience, and gender bias or lack thereof.

Methods Face-to-face interviews with patients waiting for gynecological consultations that had been scheduled in advance at Hospital Universitário de Brasília. Contingency analyses were used to determine the levels of association among the patient variables. The accepted significance level was values of $p < 0.05$.

Results We interviewed 469 patients. The comfort level with the presence of a student was strongly related to the number of students present during the consultation (Cramér V = 0.671). The inclination to grant consent (a series of reasons to consent to or refuse student attendance) was significantly related ($p < 0.001$) to the overall receptivity to student participation ($\rho = 0.482$), the positive appraisal of student-doctor demeanor in previous consultations ($\rho = 0.253$, $N = 408$), and to greater levels of schooling ($\rho = 0.158$). The patients' receptivity was significantly related ($p < 0.001$) to the lack of bias regarding the gender of the physician (Cramér V = 0.388), previous experience with students (Cramér V = 0.235) and awareness of the fact that they would be present (Cramér V = 0.217), older age ($\rho = 0.136$, $p = 0.003$), and multiparity ($\rho = 0.102$, $p = 0.027$).

Conclusion Greater receptivity to student participation related significantly to five conditions in decreasing order of strength of association: lack of bias regarding the gender of the Ob-Gyn, previous experience with student involvement, awareness of the

Keywords
- healthcare
- medical student
- gender
- outpatient care
- gynecology

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presence of students, older age, and multiparity. We also found that a more positive inclination to consent to student attendance correlated positively with a greater receptivity to student participation and to a suitable student-doctor demeanor.

Resumo

Objetivo Avaliar a associação entre as razões das pacientes para consentir ou recusar a presença de estudantes de medicina no ambulatório de Ginecologia, considerando seus fatores demográficos, experiência prévia com alunos, e sensibilidade com relação ao gênero.

Métodos Entrevistas com as pacientes que aguardavam consultas ginecológicas previamente agendadas no Hospital Universitário de Brasília. Análises de contingência foram utilizadas para determinar os níveis de associação entre as variáveis das pacientes. Valores de $p < 0.05$ foram considerados estatisticamente significativos.

Resultados Foram entrevistadas 469 pacientes. Observou-se forte associação entre o conforto com a presença do estudante e o número destes presentes à consulta (V de Cramér = 0.671). A tendência ao consentimento (relação de motivos para consentir ou discordar da presença do estudante) relacionou-se significativamente ($p < 0.001$) à maior receptividade à participação dos alunos ($\rho = 0.482$), a uma avaliação positiva do comportamento aluno-médico em consultas anteriores ($\rho = 0.253$, $N = 408$), e a maior escolaridade das pacientes ($\rho = 0.158$). Observou-se associação significativa entre receptividade das pacientes ($p < 0.001$) e ausência de discriminação quanto ao gênero do médico (V de Cramér = 0.388), experiência prévia com estudantes (V de Cramér = 0.235), ciência de que estariam presentes à consulta (V Cramér = 0.217), idade mais avançada ($\rho = 0.136$; $p = 0.003$), e multiparidade ($\rho = 0.102$; $p = 0.027$).

Conclusão Maior receptividade à participação dos estudantes relacionou-se a cinco condições em ordem decrescente de força de associação: ausência de discriminação quanto ao gênero do médico ginecologista-obstetra, experiência prévia com estudantes, conhecimento antecipado sobre a presença deles, idade mais avançada, e multiparidade. Também foi observada correlação positiva entre maior tendência ao consentimento e maior receptividade à participação dos alunos e comportamento adequado médico-estudante.

Palavras-chave
- atenção à saúde
- estudante de medicina
- gênero
- atendimento ambulatorial
- ginecologia

Introduction

The participation of medical students in gynecologic consultations appears to be critical for an effective educational experience in women's medicine. Crucially, such experiences enable the enhancement of the clinical skills of the students through patient interaction and by partaking in gynecological care under the careful guidance of the medical team. As a result, the students will hopefully be able to meet women's health needs as future primary care physicians.

Therefore, the willingness of the women to consent to student engagement during consultations is critical. However, student participation in gynecological care creates a difficult interpersonal situation given the intimate nature of the clinical procedures. Not all patients are willing to have medical students present during their appointments, and this mostly depends on the age, expectations, and willingness of the women.[1–4] Moreover, gender bias commonly occurs, and restrictions regarding the assistance of male students in gynecological care lead to adverse outcomes, as several authors have reported.[5–7]

Additionally, most patients in these reports voice a preference for a female obstetrics-gynecology (Ob-Gyn) physician.[8,9] Underlying their gender preference (among other reasons), many women may hold a negative stereotype of male Ob-Gyn physicians, which is related to their expectations regarding their desired gynecological care.[10]

Barriers to student participation and gender bias could thwart not only the adequate clinical training but also the student's choice to specialize in Ob-Gyn. Any such tendency could be detrimental in times of increased demand for women's health services. A recent report[11] from our institution revealed a significant decrease in the number of male, but not female, graduates that chose an Ob-Gyn medical residency over a two-decade period.[11] One could ask whether a generational trend among patient attitudes was related to the decline in the specialty's popularity.

The purpose of the present study was to analyze the relationship between patient acceptance (receptivity) and their reasons to consent to or refuse student attendance during gynecological outpatient care, while considering the

participants' demographic characteristics, consultation experience, and gender bias.

Methods

A cross-sectional study was undertaken at the gynecological outpatient unit of Hospital Universitário de Brasília (HUB). We interviewed 471 women who had a medical appointment for any condition over 24 nonconsecutive weeks during 2016and 2017. No exclusion criteria were employed based on demographic characteristics or diagnoses, but two cases were excluded because of failure to answer critical questions. All of the patients that were contacted agreed to participate in the survey. Patients aged $\geq$ 18 years signed an informed consent form, and those under 18 years of age signed an assent form, as did their parents.

Based on a literature review,[1,4,12–14] we developed and pretested 29 outpatient volunteers with a 32-item questionnaire in face-to-face interviews while they waited in the appointment room. The instrument included questions about demographic features, the number of their consultations attended by medical students, their previous experiences with medical students attending a consultation, whether they had received previous information about the presence of medical students, how comfortable they were with the prospect of student attendance, permission for a gynecological examination, if they felt comfortable refusing, and their gender preference regarding their Ob-Gyn physician. The demographic features included age, marital status, parity, schooling, and family monthly income based on the Brazilian monthly minimum wage. In 2016, the monthly minimum wage was R$880.00 ($\sim$ US$271.60), and in 2017, it was R$937.00 ($\sim$ US$289.00).

The questionnaire also included 16 Likert-type questions (with results that range from 5 [strongly agree] to 1 [strongly disagree]) from which we tallied three composite variables. There were six questions about the patients' reasons to refuse student attendance, four on the reasons to consent to it, and six on their appraisal of the students' professional (student-doctor behavior) demeanor in a previous consultation. The student deportment questions included whether the student had asked for permission and showed respect, care, responsibility, communication, and social skills.

Frequency distributions were used to summarize the categorical data. After an analysis of the main components (in which we found a unique component that explained over 40% of the variance in each case), we tallied 3 composite variables using the sum of the participants' responses to the respective questions. The composite variables (and their respective standardized Cronbach α values) included a 6-item index of student-doctor demeanor ($\alpha = 0.81$), a 6-item index of the motivations for refusal ($\alpha = 0.71$) and a 4-item index of the motivations for consent ($\alpha = 0.62$).

We also defined two emergent variables: the first was an index of the patients' receptivity to student participation in their gynecological care, which was tallied by adding the dichotomous responses to the following three ways of acceptance: the comfort with student presence (1 = at ease with either male or female students); the number of students allowed in the consultation (1 = 3 or more students); and a pelvic examination performed by a student of any gender (1 = acceptance). The other emergent variable was the consent inclination index, which was tallied as the difference between the indexes of the reasons for consent and refusal (adjusted to the respective number of questions).

The International Business Machines Statistical Package for the Social Sciences (IBM SPSS Statistics, IBM Corp., Armonk, NY, US) software was used to process the data. The analyses included correlation and crosstabs statistics to measure the relationships and compare the proportions among the identified variables. We reported the measures of association as effect sizes, namely, the values for Cramér V or Spearman ρ. Values of $p < 0.05$ were considered statistically significant.

The Committee of Ethics in Research in Human Beings of Faculdade de Medicina da Universidade de Brasília approved the study (1.126.648).

Results

The patients had a mean age of 43.06 $\pm$ 14.1 years (range: 12–78). Among them, 53.4% were married, 27.4% were unmarried, and the remaining 19.1% were divorced or widowed. A total of 21.7% were nulliparous, 61.4% had given birth 1 to 3 times, and 16.8% had given birth 4 or more times. As for schooling, 23.9% had higher education, 38.6% had finished high school, and the level of schooling of the remaining 37.5% was only up to junior high school. Regarding family income, 63.9% earned less than 3 times the monthly minimum wage, 26.3% earned 3 or 4 times the monthly minimum wage, and 9.8% earned 5 or more times the monthly minimum wage. A majority 290 (61.7%) of the participants had attended 4 or more previous appointments in the outpatient unit, and only 73 (15.7%) were attending an appointment for the first time.

A total of 384 (81.9%) participants reported having previous consultation experiences with a medical student. Among them, more than 396 (96%) agreed (formally and/or strongly) that they had observed 5 of the 6 aspects that compose the student-doctor demeanor during an earlier appointment. However, 74 (18.1%) of those women did not agree with the statement: 'The student (she or he) requested the patient's permission to participate in the consultation.' Additionally, only 227 (48.4%) of the 469 patients asserted that they could refuse student participation in their gynecological care if they wanted to.

Most patients ($n = 331$, 70.6%) felt at ease with the prospect of students, male or female, attending their gynecological consultation. A lower proportion ($n = 86$, 18.3%) only felt at ease with females, while a minority ($n = 51$, 10.9%) felt uneasy with students of any gender, and the single remaining patient was only comfortable with the presence of male students. We reclassified this case into the first group during further analyses. This grouping regarding the level of comfort (three groups: no student, female only, and any gender) was significantly related to the patients' previous consultation experience (no = 0; yes= 1) with a student in attendance (Cramér V = 0.155; $p = 0.003$; $N = 469$). The third group (any

Table 1 Association of the patients' comfort level with the prospect of student presence in the consultation and the number of students that they allowed to attend ($n = 469$)

Comfort level	Acceptable number of students			Total
	None (%)	One or two (%)	Three or more (%)	
At ease with a male or female student	0 (0.0)	155 (46.7)	177 (53.3)	332
At ease only with female students	0 (0.0)	59 (68.6)	27 (31.4)	86
Uneasy either with male or female students	45 (88.2)	4 (7.8)	2 (3.9)	51
Total	45	218	206	469

Note: Measure of association: Cramér V = 0.671; $p < 0.001$.

gender) had six times more experience than the novice participants.

The grouping according to the level of comfort showed a strong association (Cramér V = 0.671; $p < 0.001$; $N = 469$) with the number of students that the patients allowed to attend the consultation, as reported in ►**Table 1**. Greater acceptance of student involvement was linked to lack of gender bias, as 37.7% (177/469) of the participants were at ease with either male or female students, and were tolerant of 3 (or more) students being in the consultation room.

Moreover, the relationship between the grouping by level of comfort and the patients' acceptance or refusal to undergo a pelvic examination performed by a student was significantly linked to gender (Cramér V = 0.276; $p < 0.001$; $N = 468$). Although most participants (275, 58.8%) said they would be at ease with students and would consent to be examined by either male or female students, 40 patients (8.5%) only allowed female attendance and examination. The patients' stance on pelvic examination performed by a student was also significantly related to the number of students that they allowed in the consultation room (Cramér V = 0.191; $p < 0.001$). The significant interrelationships among the three facets of student acceptance supported the creation of a composite variable index of receptivity, as described in the Methods section of the present paper.

The grouping by level of comfort also showed a significant association with the patients' gender preference (male, female, or either one) for Ob-Gyn physician (Cramér V = 0.262; $p < 0.001$; $N = 469$). Notably, 294 patients (62.7%) had no gender preference regarding the Ob-Gyn physician or the student involved in the appointment. In contrast, 38 patients (8.1%) had a preference for a female Ob-Gyn physician and only felt at ease with female students during their consultations.

Most participants agreed with the four reasons to consent to student attendance during their consultation. ►**Table 2** shows their responses (dichotomized between agreement or disagreement). The first reason (students helping in the consultation) was the most discriminant in the relationships between the consenting responses and the patients' stance on the acceptance of a pelvic examination performed by a student.

Furthermore, the participants mostly disagreed with the six reasons to refuse student attendance. The reasons for refusal (dichotomized between disagreement or not) and their percentages of agreement are shown in ►**Table 3**. Shame or fear of the pelvic examination was the most discriminant in the relationships between the reasons for refusal and the patients' stance regarding acceptance of a pelvic examination performed by a student.

Based on the patients' dichotomized opinions on three ways of acceptance (as reported in the Methods section), we generated the following four-level index of receptivity to student engagement among the 469 participants. The levels of receptivity were either 0 (no-way; $n = 63$; 13.4%), 1 (one-way; $n = 89$; 19.0%), 2 (two-way; $n = 162$; 34.5%), or 3 (three-way; $n = 155$; 33.0%). The receptivity index correlated positively with the index of reasons for consent ($\rho = 0.314$; $p < 0.001$;

Table 2 Relationships between the patients' agreement with the reasons to consent to student attendance at a consultation and their ordered stance on the acceptance of a pelvic examination performed by a student ($n = 468$)

Reasons for consent (percentage of agreement)	Acceptance of pelvic examination			Cramér V	*p*-value
	Neither by male or female students, n (%)	Only by female students, n (%)	Either by male or female students, n (%)		
Students' help in the consultation, 412 (88.0%)	23 (67.6)	75 (79.8)	314 (92.4)	0.233	< 0.001
Expecting students attendance, 432 (92.3%)	28 (82.4)	81 (86.2)	323 (95.0)	0.168	0.001
Learning about her own health, 421 (90.0%)	26 (76.5)	81 (86.2)	314 (97.9)	0.150	0.005
Wishing to help in student education, 452 (96.6%)	33 (97.1)	86 (91.5)	333 (97.9)	0.141	0.010

Note: Within each stance group on the examination by a student, the rows show the number and percentage of participants who did agree (formally and/or strongly) with the given reason on each stance regarding the pelvic examination.

Table 3 Relationships between the patients' agreement with a reason to refuse student attendance at a consultation and their ordered stance on the acceptance of a pelvic examination performed by a student ($n = 468$)

Reasons for refusal (percentage of agreement)	Acceptance of pelvic examination			Cramér V	*p*-value
	Neither by male or female students, n (%)	Only by female students, n (%)	Either by male or female students, n (%)		
Feeling shame in examination by a male student, 182 (38.9%)	22 (64.7)	79 (84.0)	81 (23.8)	0.512	< 0.001
Privacy during pelvic examination by an Ob-Gyn physician, 212 (45.3%)	25 (73.5)	71 (75.5)	116 (34.1)	0.366	< 0.001
Feeling shame in examination by a female, student 71 (15.2%)	14 (41.2)	26 (27.7)	31 (9.1)	0.288	< 0.001
Students' lack of expertise, 160 (34.2%)	22 (64.7)	45 (47.9)	93 (27.4)	0.249	< 0.001
Privacy during dialogue with an Ob-Gyn physician, 190 (40.6%)	23 (67.6)	50 (52.2)	117 (34.4)	0.216	< 0.001
Lingering of consultation because of student attendance, 139 (29.7%)	16 (47.1)	34 (36.2)	89 (26.2)	0.137	0.012

Note: Within each stance group on the examination by a student, the rows show the number and percentage of participants who did agree with the given reason to refuse students attendance at the consultation.

$N = 469$), negatively with the index of motives for refusal (ρ= -0.453; $p < 0.001$; $N = 469$), and again positively with the measure of inclination to consent to student attendance (ρ= 0.482; $p < 0.001$; $N = 469$). Additionally, receptivity had a significant relationship with previous experience with (Cramér V = 0.235; $p < 0.001$) and previous knowledge of (Cramér V = 0.217; $p < 0.001$) student attendance.

Consistently, the participants' index of receptivity to student involvement related to their stance regarding the gender of the Ob-Gyn physician 10 (2.1%) of male preference, 81 (17.3%) of female preference and 378 (80.6%) of no gender preference; $N = 469$). The relationship between three ways of acceptance and gender bias regarding the Ob-Gyn physician (dichotomized as bias or no bias) was quite strong (Cramer's $V = 0.388$; $p < 0.001$; $N = 469$). These data are presented in ►**Table 4**.

Notably, the measure of inclination to consent correlated positively with the score for student-doctor demeanor (ρ= 0.253; $p < 0.001$; $N = 408$); namely, a stronger difference in motivation for consent was significantly related to a better appraisal of the students' demeanor during the consultation in previous outpatient appointments. Finally, the indexes of inclination to consent and receptivity displayed distinct relationships with the demographic features. Inclination to consent correlated positively with schooling (ρ= 0.158; $p = 0.001$; $N = 469$) and with family income (ρ= 0.175; $p < .001$; $N = 460$). Receptivity showed weak associations with age (ρ= 0.135; $p = 0.003$; $N = 469$) and parity (ρ= 0.114; $p = 0.027$; $N = 469$).

Table 4 Relationship of the patients' gender bias regarding the Ob-Gyn physician with the index of receptivity to student participation in the gynecological consultation

Three ways of acceptance index (ways of acceptance)	Ob-Gyn gender bias		Total
	Bias, n (%)	No bias, n (%)	
0. No-way	33 (52.4)	30 (47.6)	63
1. One-way	27 (30.3)	62 (69.7)	89
2. Two-way	20 (12.3)	142 (87.7)	162
3. Three-way	11 (7.1)	144 (92.9)	155
Total	91	378	469

Note: Measure of association: Cramér V= 0.388; $p < 0.001$.

Discussion

A crucial part of the education of medical students is learning through interaction and direct contact with the patients. Over the years, this involvement has been viewed positively[5] both by students and patients. However, as the intimacy level increases, the patients' willingness decreases,[5] which is particularly true for a gynecological clinical history and physical examination and may lead women to refuse student attendance.

From this point of view, our finding of a greater acceptance of student participation in gynecological consultations (as shown by the relationship between the stances regarding the possible level of comfort and the number of students that are allowed to attend) is noteworthy and seems consistent with the findings of other studies.[1,4,12–14]

The level of acceptance could derive from situational and sociocultural factors. We suggest that in the context of outpatient gynecological care, the patients' combined affective and cognitive reasons for refusal or consent to student attendance drive the components of receptivity to student

participation. The patients' levels of informed experience, gender bias, and socioeconomic background moderate these relationships.

Our results indicate the positive influence of background familiarity: ill-advised and inexperienced women were less receptive to the students than informed and seasoned women, which is in agreement with other studies.[1,3,5,15,16] We observed a higher rate of acceptance of student presence among patients who knew in advance that students may attend, as described in other reports.[3,17] Other authors noticed that, in addition to a greater level of acceptance, the patients also allowed a higher level of student participation in subsequent visits.[5]

Additionally, the amount of previous experience with students, regardless of gender, seemed to matter. Reciprocal altruism could be at work in the patient-student relationship. We found that most women valued the students' help with the consultation and wished to contribute to the learning of futures doctors, which is in agreement with other studies.[1–3,13,14]

The specific context of outpatient care as a public service in a teaching hospital also seems to be influential. The patients may feel obligated to give their consent and show willingness, and even expect student involvement, in return for the free-of-charge care provided by the staff and students. However, in a study by Berry et al,[13] fewer than half of the patients anticipated that students would be involved in the medical consultations or were aware that their physician could be a professor, despite being in a teaching hospital. Moreover, Ching et al[4] demonstrated a high acceptance rate of student involvement in private schools.

In addition, the health staff could probably help set up a favorable environment for student participation in a healthcare unit by providing patients with information and by introducing the student. Mavis et al[5] observed that the likelihood of a patient agreeing with student involvement was higher when the request came from the doctors themselves, a finding that further emphasizes the importance of the doctor-patient relationship on the student's education, which includes more than the acquisition of specific skills. Despite this, other authors have suggested that a non-physician should request permission so that the patient did not feel pressured to accept.[13]

In the context of the present study, we viewed receptivity as a combination of affective states that resulted from the patients' different opinions regarding student attendance. A patients' inexperience with trainees attending a consultation could lower their receptivity to student involvement, especially male students in gynecological care. Nonetheless, findings from the literature show that most women agree (even those that refuse student involvement) that the best way for the students to develop clinical skills is the effective participation in consultations with real patients, that is, the "hands-on" approach.[2,14,16]

The subjective feeling of many patients that males (students or physicians) have a lower understanding of the needs of women could also be at work. In the literature, the women's preference for female Ob-Gyn physicians has been associated with a negative stereotype about male Ob-Gyn physicians, hinging on the patients' expectations of their desired gynecologic care.[10] The negative gender-role stereotype could be related to the supposed differences in empathy regarding men and women.[18]

However, regardless of the reason, studies have shown that male students have greater difficulty in acquiring experience in gynecological clinical practice.[19,20] The higher proportion of refusals and the greater difficulty in obtaining consent compared with female students could lead to greater anxiety among male students, which could negatively affect their interactions with patients.[20] Additionally, the quality of the clerkship experience could influence the students' choice of Ob-Gyn as a career.[7]

We surmise that some patients' uneasiness at the prospect of student attendance and the consequent refusal of an examination were associated with a fluid sense of being unprotected; this feeling was linked to personal beliefs (such as a need for privacy) and emotions (such as shame or fear), especially concerning male student involvement. However, we argue that physicians of any gender, if they have the proper training, can address such conditions to encourage the interaction between patients and students without gender bias.

Additionally, attention should be given to the differences in the level of comfort regarding gender of students and Ob-Gyn among the patients; in our sample, the distribution was as follows: no gender preference (62.7%), and preference for females (8.1%). The frequency of gender bias regarding the the student and Ob-Gyn physician (preference for females) was higher among younger patients (12–26 years old) than among older patients, but it is not clear whether such opinions are subject to change. In a study by Fortier et al,[21] the patients who changed their minds about accepting students were on average 10.2 years younger than those who didn't change their minds.

The results have been inconsistent regarding the association between demographic characteristics and acceptance of student attendance. Like other studies,[14,19,22] we found a positive association with older age, while two studies[1,3] found that the association was not significant[3] or that it was with younger patients.[1] We also found a significant relationship between acceptance and parity, which is in agreement with other authors,[14,19] but not between acceptance and the patients' marital status, which is in disagreement with other studies.[3,22]

However, we cannot forget that 48.4% of the patients in our study felt that they could refuse the student if they wanted to, which was a better result than those reported by other authors,[12,23] and 18.1% of the patients did not hear a request for permission from the student in attendance. These issues are of critical importance due to the clear need to demonstrate ethical values, to humanize medical education, and for the empowerment of women concerning their rights and choices.

It seems that there still is a misguided belief among physicians that they should not ask patients for permission out of a fear that they could refuse it,[1,5] which appears to be based more on prejudice than on empirical evidence.[17] It is vital for everyone involved in the educational process that this belief does not spread further.

The present study had some limitations. The cross-sectional design and the use of a closed-question survey, which prevented the causal interpretation of the data, restricted its scope. Additionally, the use of a single-site report with patients using a public medical care service hinders the generalization of the findings. Moreover, as suggested by a recent report,[24] there are many aspects to the interactions between patients and students, and we recognize that student engagement in outpatient care involves consent, care, and safety for the women involved, which are issues that were not framed in the survey.

We suggest that it is essential that medical staff and professors explain to patients the importance of their cooperation to the education of future physicians and request their cooperation in this process, without assuming that they are obliged to consent to it without asking for their permission, because in the end, amid so many variables, it seems that the decision to accept student participation involves a balance between altruistic intentions to contribute to the training of future physicians and the private nature of gynecological issues (clinical history and physical examination), as some authors have noted.[4,21] The performance of the medical staff and the absence of biased attitudes are crucial for the teaching of skills and abilities and for the transmission of ethical values, such as observing the autonomy of the patients and showing respect for them.

Conclusion

Greater receptivity to student participation related significantly to five conditions, in decreasing order of strength of association: lack of gender bias regarding the Ob-Gyn physician, previous experience with student involvement, previous information about student presence, older age, and multiparity. We also found that a more positive inclination to consent (that is, a higher motivation to consent and lower motivation do refuse) to student attendance correlated positively with a greater receptivity to student participation and suitable student-doctor demeanor.

Contributions

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

Conflicts to Interest

The authors have none to declare.

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Antiphospholipid Antibody Syndrome and Infertility

Síndrome Anticorpo Antifosfolípide e Infertilidade

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Abstract

Antiphospholipid antibody syndrome (APS) is a systemic, autoimmune, prothrombotic disease characterized by persistent antiphospholipid antibodies (aPLs), thrombosis, recurrent abortion, complications during pregnancy, and occasionally thrombocytopenia. The objective of the present study was to review the pathophysiology of APS and its association with female infertility. A bibliographic review of articles of the past 20 years was performed at the PubMed, Scielo, and Bireme databases. Antiphospholipid antibody syndrome may be associated with primary infertility, interfering with endometrial decidualization and with decreased ovarian reserve. Antiphospholipid antibodies also have direct negative effects on placentation, when they bind to the trophoblast, reducing their capacity for invasion, and proinflammatory effects, such as complement activation and neutrophil recruitment, contributing to placental insufficiency, restricted intrauterine growth, and fetal loss. In relation to thrombosis, APS results in a diffuse thrombotic diathesis, with global and diffuse dysregulation of the homeostatic balance. Knowing the pathophysiology of APS, which is closely linked to female infertility, is essential for new therapeutic approaches, specialized in immunomodulation and inflammatory signaling pathways, to provide important advances in its treatment.

Keywords

- antiphospholipid antibody syndrome
- infertility
- recurrent abortion
- antiphospholipid antibody

Resumo

A Síndrome do anticorpo antifosfolípide (SAF) é uma doença sistêmica, autoimune e pró-trombótica caracterizada por anticorpos antifosfolípides, trombose, aborto recorrente, complicações durante a gestação, e, ocasionalmente, trombocitopenia. O objetivo do presente estudo foi revisar a fisiopatologia da SAF e sua associação com a infertilidade feminina. Foi feita uma revisão bibliográfica dos últimos 20 anos nas bases de dados PubMed, Scielo e Bireme. A SAF pode estar associada à infertilidade primária, interferindo na decidualização endometrial e com baixas reservas ovarianas. Os anticorpos antifosfolípides também apresentam efeito negativo direto na placentação, se ligando ao trofoblasto e diminuindo sua capacidade de invasão, além de efeitos pró-inflamatórios, tais como ativação do sistema de complemento e recrutamento de neutrófilos, contribuindo para a insuficiência placentária, crescimento intrauterino restrito e perda fetal. Quanto a trombose, a SAF resulta em distúrbios trombóticos difusos, com uma desregulação do balanço homeostático. Conhecer a fisiopatologia da SAF, que apresenta associação importante com a infertilidade feminina, é essencial para novas abordagens terapêuticas, principalmente no que tange imunomodulação e os caminhos de ativação inflamatórios.

Palavras-chave

- síndrome do anticorpo antifosfolípide
- infertilidade
- aborto de repetição
- anticorpo antifosfolípide

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Introduction

Antiphospholipid antibody syndrome (APS) was first described in 1983. It is defined as a prothrombotic autoimmune disease, characterized by the presence of persistent antiphospholipid antibodies (aPLs), thrombosis, recurrent abortion, and, occasionally, thrombocytopenia. It can manifest itself in isolation (primary APS) or associated with another autoimmune disease (secondary APS). The most common association is with systemic lupus erythematosus (SLE).[1,2]

Antiphospholipid antibody syndrome, an acquired thrombophilia, is associated with arterial and venous thrombosis, which can occur in unusual sites, such as hepatic veins, visceral veins, and in the cerebral venous circulation. Any signs of thrombosis in these sites require investigation of APS.[3]

The prevalence of the disease is unknown; however, it is estimated to affect $\sim$ 0.5% of the population. The average age at the time of diagnosis is $\sim$ 35 years old, since it is rare in children.[1]

The aPLs are a heterogeneous group of antibodies directed against phospholipids, situated in the endothelial cell membrane, platelets, and other cells involved in the coagulation cascade. Its discovery began with the discovery of cardiolipin in 1906, when Wassermann described it as a marker for syphilis. In 1941, Pangborn isolated and identified the antigen component in heart fragments of cattle, such as cardiolipin (diphosphatidylglycerol). Cardiolipin is a unique phospholipid of biomembranes which have coupled phosphorylation and electron transport, such as mitochondria. There are currently $>$ 10,000 publications on these antibodies, and the most researched in reproductive immunology are lupus anticoagulant, anti-β-2-glycoprotein, and anticardiolipin.[4–6]

According to the revised Sapporo criteria, 2006, the diagnosis of APS occurs when patients present at least one clinical criterion associated with a laboratorial one, **which should be performed with a minimum interval of 12 weeks of the clinical event**.[7,8] Clinical criteria include (►**Table 1**Q4): $\geq$ 1previous thrombosis cases confirmed by histological or imaging tests, or cases of obstetric morbidity,

Table 1 Clinical Criteria of Antiphospholipid Antibody Syndrome

1 Vascular thrombosis
One or more episodes of arterial or venous thrombosis in any tissue or organ, confirmed by validated objective criteria (imaging exams or histopathology).
2 Obstetrics morbidity
(a) One or more unexplained of morphologically normal fetuses with gestational age $\geq$ 10 weeks (normal morphology documented by ultrasonography or direct fetus examination).
(b) One or more premature births of morphologically normal neonates with $<$ 34 weeks of gestational age due to severe pre-eclampsia or pre-eclampsia, or signs of placental insufficiency.
(c) Three or more unexplained spontaneous abortions with $<$ 10 weeks of gestational age, excluding anatomic maternal, hormonal, and chromosomal causes.

Source: Adapted from Kovács et al.[9]

Table 2 Laboratory Criteria of Antiphospholipid Antibody Syndrome

1 Lupus anticoagulant present on plasma, $\geq$ 2 occasions, with 12 weeks of difference, detected according to the guidelines of the International Society of Thrombosis and Hemostasis.
2 Anticardiolipin (IgG or IgM) detected on serum or plasma, and medium or higher titles ($>$ 40 GPL or MPL, or $>$ p 99), in $\geq$ 2 occasions, with 12 weeks of difference, through ELISA standardized exam.
3 Anti-β-2-glycoprotein I (IgG or IgM), detected on serum or plasma (titles $>$ 99 percentile), in $\geq$ 2 occasions, with 12 weeks of difference, through ELISA standardized exam.

Abbreviation: ELISA, Enzyme-Linked Immunonosorbent Assay.
Source: Adapted from Kovács et al.[9]

which include: unexplained death of $\geq$ 1 morphologically normal fetuses with $\geq$ 10 weeks of gestation; $\geq$ 1 normal fetuses born before 34 weeks of gestation (due to pre-eclampsia [PE], eclampsia, or placental insufficiency); or $\geq$ 3 spontaneous miscarriages before 10 weeks of gestation.

The laboratory criteria (►**Table 2**) includes the positivity (on 2 occasions in a range of at least 12 weeks) of $\geq$ 1 of the following aPLs: lupus anticoagulant; anti-β-2-glycoprotein (immunoglobulin M [IgM] and/or immunoglobulin G [IgG]); and anticardiolipin (IgM and/or IgG). Although the Sapporo criteria are widely used in medical practice, it should be noted that they were initially developed to define a uniform cohort of patients with APS for clinical trials, rather than providing a practical system for clinical diagnosis.[3,7]

Antiphospholipid antibodies can also be present even if the patient does not fulfill the clinical criteria for the syndrome (nonspecific autoimmunity).[8]

It is known that the presence of these antibodies is associated with primary infertility. They are more frequent in infertile patients and interfere with the endometrial decidualization and, consequently, with the embryo implantation rates. Others suggest that it can also be associated with decreased ovarian reserve. The ovarian reserve can be evaluated by the dosages of the antimullerian hormone or by the count of antral follicles on the ultrasonography. The antimullerian hormone is produced by growing follicles from granulosa cells that harbor the oocytes until their maturation, and its levels remain stable throughout the whole menstrual cycle.[9,10]

The pathogenesis of obstetric morbidity on APS is not yet fully understood; however, it may happen due to the negative effect that the antiphospholipid antibodies exert on the placental function, decreasing the trophoblastic viability and its invasiveness. Furthermore, recent evidence suggest that the inflammatory factor can also justify the poor obstetrics prognosis. There are experimental studies on animals that confirm the ability of large quantities of antiphospholipid antibodies to induce fetal reabsorption and growth retardation through the placental deposition of IgG and complement, neutrophilic infiltration, and local secretion of tumor necrosis factor alpha (TNF-alfa).[1,11]

The primary treatment of the syndrome, whose main objective is to prevent thrombosis, presents only partial success rates. Nowadays, ~ 80% of the gestations with APS result in live births. However, these gestations have a higher risk of developing PE, ranging from 18 to 40%, a higher risk of restricted intrauterine growth in 5 to 15%, besides a higher risk of premature birth.[12]

Therefore, APS is a syndrome with high prevalence rates, since 15 to 20% of the women with recurrent miscarriage are APS carries.[13] It is necessary to expand the investigations about APS in order to understand its pathogenic mechanisms and its association with female infertility.

Methods

The present study consists of a bibliographic review of articles found in databases, such as PubMed, Scielo, and Bireme, from 1998 to 2018. Two articles, one from 1990 and another from 1995, were also included because of their relevance to the theme of the study. The scientific articles related to the keywords were selected, as well as the others related to the pathophysiology of APS. The used keywords were: *síndrome do anticorpo antifosfolipídeo*, *infertilidade*, *aborto recorrente*, *anticorpo antifosfolipídeo*, *antiphospholipid syndrome*, *infertility*, *recurrent pregnancy loss*, *antiphospholipid antibody*.

Results

Antiphospholipid antibody syndrome and primary infertility

Primary infertility is defined as the absence of gestation after 12 months of intercourse without the use of contraceptives. The global prevalence of infertility is 9%, while the 60-month prevalence of infertility in Europe is estimated to be 1.5%.[10]

A recent literary evaluation analyzed 31 studies, all of which showed a high and important association between aPLs and female infertility. A total of 45% of these studies confirmed the association between anticardiolipin antibody and infertility; however, this rate dropped to 31% when the association with lupus anticoagulant was analyzed. Only 4 studies evaluated anti-β-2-glycoprotein, and yet, 75% of them revealed a positive association with infertility. There was a significant difference of the positivity of anticardiolipin antibody in infertile women, but the frequencies of anti-β-2-glycoprotein and lupus anticoagulant antibodies were similar both in infertile and fertile women. It must be highlighted that < 25% of the studies utilized a medium-high limit to define the positivity of anticardiolipin and/or of anti-β-2-glicoprotein, as recommended by international guidelines. ►**Table 3** reveals the estimated positivity rates of aPLs.[10,14]

Antiphospholipid antibody syndrome and obstetrics morbidity

The abortion rate, when aPL levels are > 90% of the normal population values, is estimated to be 52%. In addition, positive aPLs patients who already had an abortion have a higher risk of obstetric morbidity in future pregnancies.[15]

Table 3 Positivity rates of Antiphospholipid antibodies in infertile women and in the control group

aPL	Number of studies	Infertile women Positivity 0% (0–2-5) 7% (3-7–13-3)	Control group Positivity 0% (0–0) 1-6% (0–3) 2-8%
Lupus anticoagulant	13		
Anticardiolipin	29		
Anti-β-2 glicoprotein	4	7-6%	

Source: Adapted from Chighizola et al.[10]

Although all three antibodies (lupus anticoagulant, anticardiolipin, and anti-β-2 glycoprotein) are associated with recurrent miscarriage, the risk varies according to the positivity of different types of antibodies. For example, the presence of anticardiolipin antibody is associated with an odds ratio (OR) of 22.6% (95%CI [confidence interval]) for recurrent miscarriage. The presence of anti-β-2 glycoprotein antibodies increases the chance of recurrent miscarriage from 6.8% to 22.2% when compared with women positive for lupus anticoagulant or anticardiolipin.[16]

Fetal complications in APS include prematurity, intrauterine growth restriction (IUGR) (due to placental insufficiency) and stillbirth. The "Euro-Phospholipid Project" cohort study analyzed the clinical characteristics of 1,000 patients with APS during a 5-year period, and concluded that these events complicate 28%, 11% and 7% of APS pregnancies, respectively.[17]

A meta-analysis of 2006 revealed a positive association between the presence of anticardiolipin IgG (between high and low titles) and recurrent abortion at < 13 weeks of gestational age (OR 3.56; 95%CI: 1.48–8.59). Other studies suggest that circulating aPLs are the main risk factor for 7 to 25% 1st-trimester gestational losses, whereas prevalence studies showed that 1 in 5% of these patients are lupus anticoagulant-positive. A cohort of 500 women with a history of recurrent abortion revealed that 9.6% were lupus anticoagulant-positive, whereas anticardiolipin IgG and IgM were found on 3.3% and 2.2% of them, respectively.[18,19]

Other obstetrics morbidities, such as PE and/or placental insufficiency and IUGR are also associated with APS. Preeclampsia can occur in between 2 to 8% of 1st gestations, whereas severe preeclampsia can be seen in 0.5% of the gestations in developed countries. Most of these prospective observational studies corroborate the association between aPL with PE and placental insufficiency. A meta-analysis of 2010 exposed that moderate to high titles of anticardiolipin are associated with preeclampsia. Prospective and retrospective studies have shown that the persistence of high titles of aPLs are associated with IUGR and premature birth. Data from case-control studies indicate that aPLs were found in 50% of the patients with a history of PE or IUGR, and in 7% of women without these morbidities.[20–22]

Antiphospholipid antibody syndrome and thrombosis

The association between aPLs and thrombosis is significant. Antiphospholipid antibodies are found in ~ 13% of the

patients with history of stroke, 11% of the patients with acute myocardial infarction, and 9.5% of the patients with a history of deep vein thrombosis.[2] The annual rate of a first thromboembolic event on patients between 35 and 55 years old who are not APS carriers is of ~ 0.4%. On APS carriers, the rates are around 3.8%. The incidence of thrombosis in patients positive for a single antiphospholipid antibody is 1.36%, and increases to 5.3% in patients positive for all 3 antibodies. Therefore, triple positivity presents a higher risk of occurrence and recurrence of thromboembolic events.[23]

Discussion

Antiphospholipid antibody syndrome and primary infertility

The pathogenic mechanism that explains how aPLs induce infertility is not yet fully understood. Some authors believe that aPLs may alter the development of the oocyte after its secretion into the follicular fluid, since gametes or preimplantation embryos do not come into contact with maternal blood.[10]

An alternative theory relies on the fact that the antibodies interfere on uterine decidualization, compromising implantation. Decidualization is the transformation of the endometrial stromal fibroblasts into specialized deciduous secretory cells, which provide a nutritional and immunoprivileged matrix that is essential to embryonic implantation and placental development. In vitro studies also observed the connection between aPLs and endometrial endothelial cells, impairing angiogenesis.[10,24,25]

Evidence on the interaction between aPLs and decidua has been obtained by in vivo studies. A 1990 study showed that mice treated with IgG aPLs showed, on histological examination, decidual necrosis associated with intravascular deposits of IgG and fibrin. In other studies, through the immunohistochemical analysis of the decidua of pregnant mice, it was observed that the decidua is a preferential target for complement deposition after treatment with IgG aPLs.[26–28]

Otherwise, in addition to inflammatory changes in the decidua and its interference with embryo implantation, there is another mechanism by which APS is associated with infertility. It also can decrease ovarian reserve.[29]

The term ovarian reserve, traditionally, has been used to describe the reproductive potential of a woman; in other words, the quantity and quality of the oocytes she possesses. However, ovarian reserve markers serve as a substitute for oocyte quantity, but are poor indicators of oocyte quality. Therefore, the modern use of the term applies to the quantity of remaining oocytes, not to oocyte quality.[30]

Thus, the ovarian reserve can be evaluated by the dosages of the antimullerian hormone or the count of antral follicles on the ultrasonography. Both present the same sensitivity and specificity as predictors of follicular reserve.[10]

A 2014 study assessed the ovarian reserve of patients with APS and observed that these women had a lower count of antral follicles than those in the control group. Vega et al, in 2016,[29] demonstrated a strong association between aPL positivity and decreasing levels of antimullerian hormone. Thus, antiphospholipid antibodies may represent the 1st laboratory markers for early ovarian failure associated with autoimmunity. This suggests that the presence of aPLs in women of reproductive age should be considered a risk factor for the development of premature ovarian failure. The confirmation of this association in future studies, therefore, could lead to the early diagnosis of this condition in many women.[29,31]

Antiphospholipid antibody syndrome and obstetrics morbidity

The pathogenesis of obstetric morbidity in APS is still not completely understood. Initially, intraplacental thrombosis was considered to be the main mechanism of poor obstetric prognosis. However, most subsequent studies have not been able to find blood clots in most placentas from carriers. Other hypotheses, therefore, have been suggested, such as that aPLs induce a direct negative effect on placentation, interfering in both trophoblastic invasion and endometrial angiogenesis.[32]

Immediately after placental implantation, the mononuclear trophoblast (cytotrophoblast) invades the decidua of the uterus, differentiating itself into an extravilous trophoblast. A part of this trophoblast invades the uterine spiral arteries, which supply blood to the decidua, digesting the musculature and replacing the endothelial cells lining these vessels. This invasion is capable of remodeling the spiral arteries and transforming them into nonvasoactive conduits of greater caliber. Up to half of the gestational period, the spiral arteries are remodeled throughout the decidua depth, up to one-third of the depth of the myometrial segments. This remodeling allows a large and uninterrupted blood supply to the fetus during the second half of the gestation, when the demand is greater.[33–35]

The majority of obstetric manifestations of APS, such as preeclampsia and restricted intrauterine growth, present failure of the extravilous trophoblast to adequately remodel the spiral arteries. As a consequence, there is a significant decrease in maternal blood flow to the placenta, causing ischemic injury, lack of nutrients to the fetus, and increased blood flow velocity, which can damage the placenta.[34,35]

A recent meta-analysis of the histopathological findings of placentas affected by aPLs showed five changes associated with aPLs: placental infarction, inadequate remodeling of spiral arteries, decidual inflammation, increased number of syncytial nodes, and decreased synovial vascular membranes. It is important to note that placentas with aPLs rarely present evidence of intravascular or intravilous clots.[35,36]

The negative effect that aPLs exert on human placentation begins with the binding of the antibodies to the trophoblast. It is known that polyclonal IgG antibodies from APS patients and monoclonal antibodies with anti-β-2-glycoprotein activity are able to adhere to the trophoblast and endometrial endothelial cells in vitro. The pathogenic mechanisms by which antiphospholipid antibodies alter placentation will be described in detail below[37]:

1–Antiphospholipid antibodies are able to stimulate the trophoblast to secret inflammatory interleukins, such as IL-1 and IL-8, through the activation of the toll-like receptor (TRL4)[35];

2–Antiphospholipid antibodies limit the migration of trophoblast via mediation of apolipoprotein E receptor 2 (ApoER2), which is expressed in human trophoblast and targets the anti-β-2-glycoprotein complexes. In addition, ApoER2 has been associated with restricted intrauterine growth and fetal loss[35,38];
3–Antiphospholipid antibodies increase the production of extracellular vesicles of the syncytiotrophoblast. In placentas affected by aPLs, there is an increase in syncytial nodes, which are aggregates of syncytiotrophoblast nucleoli and aging markers of them. They are expelled from the placenta in large vesicles as syncytial nuclear aggregates and are responsible for activating the maternal vasculature[36,39];
4–Syncytiotrophoblast produces human chorionic gonadotropin (hCG). Antiphospholipid antibodies reduce the growth of the syncytiotrophoblast in vitro, reducing the production of hCG. As they prevent the formation of new syncytiotrophoblast and induce cell death, they also cause a reduction in transplacental transport, evidenced by decreased levels of the cholesterol transporter ABCA1 in placentas affected by APS[40,41];
5–These antibodies are also capable of blocking endometrial angiogenesis both in vitro and in vivo. One mechanism is the inhibition of the production of factors regulated during angiogenesis, such as vascular endothelial growth factor (VEGF). A study of β-2-glycoprotein involvement has shown that, in contrast to its previously reported anti-angiogenic properties, the cleaved form of β-2-glycoprotein is able to block the activity of angiostatin, a known angiogenesis inhibitor. The inhibitory effect of angiogenesis is demonstrated, but it is not yet known whether it is caused by the imbalance between the cleaved and intact forms of β-2-glycoprotein.[32]

In addition to the changes described above, the inflammatory effects that the antiphospholipid antibodies induce on the trophoblast are significant. According to Holers et al,[11] passive IgG transfer from patients with high aPL titles to pregnant mice resulted in fetal resorption and restricted growth.

Mice models have confirmed a critical role of neutrophils in fetal developmental abnormalities. Pregnant mice treated with aPLs had placental neutrophil infiltration, and the deleterious effects of aPLs on fetal survival and growth were abolished by neutrophil depletion. Neutrophil recruitment is triggered by complement activation at the maternal-fetal interface and leads to elevated TNF-alfa levels, VEGF reduction and, finally, to abnormal placentation and fetal death.[35,42]

Studies in women support the role of complement in the complications of APS pregnancies. The C4d complement fragment, a classic pathway activation marker, is present in placentas of women with APS and PE. Hypofunctional variants inherited from complement regulators provide a higher risk of PE in women with APS. It is possible to suggest that complement-mediated injury is a common pathogenic mechanism that causes abnormal placentation, fetal loss, and restricted intrauterine growth.[35,43]

Table 4 Coagulation process modified by antiphospholipid antibodies

Inhibition of protein C activity
Inhibition of protein S activity
Inhibition of antithrombin activity
Induction of tissue factor in endothelial cells and monocytes
Inhibition of Tissue Factor Pathway Inhibitor (TPFI)
Increased prothrombin deposition, leading to increased thrombin formation
Inhibition of fibrinolysis
Activation of factor XI
Induction of platelet aggregation
Induction of endothelial cell adhesion receptors

Source: Adapted from Salmon et al.[46]

Antiphospholipid antibody syndrome and thrombosis

Alterations in the complement system may contribute to aPL-induced thrombosis, and coagulation factors may activate the complement cascade.[44] The pathophysiology of thrombosis associated with APS is different from other hypercoagulability known conditions. In APS, thrombosis can occur in virtually all vessels, in arteries and veins, as well as in large vessels and in microcirculation. The presence of aPLs is able to interfere with virtually all known homeostatic reactions, as shown in ►**Table 4**. Their presence results in diffuse thrombotic diathesis, suggesting global and general deregulation of the hemostatic equilibrium.[45,46]

It is true that there are many paths by which aPLs induce thrombosis. The other main path, besides the alteration of the homeostatic equilibrium, is the activation of the complement system. Studies have shown that aPL-treated mice showed increased leukocyte adhesion to endothelial cells and were able to conclude that mice deficient in C3, C5 or C5a complement components were resistant to aPL-induced thrombophilia and endothelial cell activation.[47]

Conclusion

Antiphospholipid antibody syndrome is an autoimmune and inflammatory disease associated with a substantial incidence of thrombosis, obstetric morbidity, and infertility. In recent times, aPLs have been recognized as triggers of innate immune inflammatory pathways within the trophoblast and at the maternal-fetal interface. No longer considered simple prothrombotic antibodies that activate the endothelial cells and platelets, aPLs are directly responsible for the connection to the trophoblast and the alteration of its function. The study of the pathophysiology of APS should be encouraged, since innovative therapeutic approaches, focused on immunomodulation and inflammatory signaling pathways, may provide important therapeutic advances for this disease, which has such a significant impact on female fertility.

Conflicts of Interests
No loan, equipment or drugs support were given for the present work, nor was it presented at any congress.

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Rare Case of Sarcomatoid Squamous Cell Carcinoma Arising in an Ovarian Mature Teratoma

Caso raro de carcinoma espinocelular sarcomatoide que surge em um teratoma ovariano maduro

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Abstract

Although mature cystic teratoma (MCT) is benign, malignant transformation (MT) occurs in ~ 1% to 2% of all cases, and usually consists of squamous cell carcinoma (SCC), which accounts for ~ 80% of the cases. Spindle-cell (sarcomatoid) carcinoma (SCSC) is an uncommon type of SCC, comprising up to 3% of all cases. The lack of characteristic symptoms and specific imaging findings may lead to preoperative misdiagnosis. Moreover, the clinicopathologic characteristics, the treatment, the prognostic factors and the mechanism of MT have not yet been well understood due to the rarity of such tumors, especially in women of reproductive age. The authors present a case of a 34-year-old patient with 14 weeks of gestation who was diagnosed with an adnexal mass suggestive of ovarian teratoma. A laparoscopy salpingo-oophorectomy was performed after 6 months of delivery, and the histological exam revealed a sarcomatoid SCC in the MCT.

Keywords
- squamous cell carcinoma
- ovarian mature teratoma
- pregnant women

Resumo

Embora o teratoma cístico maduro (MCT) seja benigno, a transformação maligna (MT) ocorre em cerca de 1% a 2% dos casos, e geralmente apresenta-se sob a forma de carcinoma espinocelular (CEC), responsável por cerca de 80% dos casos. O carcinoma (sarcomatoide) de células fusiformes (CSCF) é um tipo incomum de CEC, compreendendo até 3% de todos os casos. A falta de sintomas característicos e achados imagiológicos específicos pode levar a erros diagnósticos pré-operatórios. Além disso, as características clinico-patológicas, o tratamento, os fatores prognósticos e o mecanismo da MT ainda não são bem compreendidos devido à raridade de tais tumores, principalmente em mulheres em idade reprodutiva. Os autores apresentam um caso de uma paciente de 34 anos com 14 semanas de gestação que foi diagnosticada com uma massa anexial sugestiva de teratoma do ovário. A anexectomia laparoscópica foi realizada após 6 meses do parto, e o exame histológico revelou um CEC sarcomatoide tendo como origem um MCT.

Palavras-chave
- carcinoma de células escamosas
- teratoma maduro ovariano
- gestantes

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Introduction

Ovarian germ-cell tumors account for ~ 20% of all ovarian neoplasms, and for 2% of all ovarian malignancies.[1–3] Mature cystic teratomas (MCTs) are the most common ovarian germ-cell tumors, accounting for ~ 70% of benign ovarian tumors in women under 30 years of age,[4–6] and they are composed of totipotent cells developing into well-differentiated ectodermal, endodermal, and mesodermal tissue.[7] Ectodermal derivatives, which include keratinizing epidermis, sebaceous and sweat glands, hair follicles and neuroectodermal tissues, are often the most prominent.[8] Mesodermal derivatives consist of muscle, bone, cartilage, fat, and occasionally teeth, whereas endodermal derivatives are represented by the thyroid, the salivary gland, the respiratory and gastrointestinal tissues.[8]

Although MCT is benign, malignant transformation (MT) occurs in ~ 1% to 2%[9] of all cases, and usually consists of squamous cell carcinoma (SCC), which accounts for approximately 80% of the cases.[9,10] Squamous cell carcinomas can be ulcerative, flat, polypoid, verrucous or exophytic.[11] Occasionally, SCC variants will be encountered.[11] Together, these variants make up ~ 10% to 15% of all cases of SCC, including verrucous, exophytic or papillary, spindle-cell (sarcomatoid), basaloid and adenosquamous carcinomas.[11] Over the years, many terms have been applied to spindle-cell (sarcomatoid) carcinoma (SCSC), such as carcinosarcoma, pseudosarcoma and squamous cell carcinoma with pseudosarcoma, but SCSC is defined as a spindle-cell neoplasm that simulates a sarcoma and presents epithelial differentiation in both immunohistochemistry and electron microscopy.[12] Spindle-cell (sarcomatoid) carcinoma is an uncommon type of squamous cell carcinoma, comprising up to 3% of all cases of SCC.[11]

Mature cystic teratomas with MT are usually observed in postmenopausal women with a mean age of 45 to 60 years.[9–13] Other less frequent malignancies include mucinous carcinoma, adenocarcinoma arising from the respiratory ciliated epithelium, melanoma, carcinoid, thyroid carcinoma, sebaceous carcinoma, oligodendroglioma and sarcoma.[13] The lack of characteristic symptoms and specific imaging findings may lead to preoperative misdiagnosis.[14] Although the preoperative diagnosis of MCT of the ovary is usually achieved with the use of sonography, computed tomography (CT) and magnetic resonance imaging (MRI), MT it is usually detected incidentally postoperatively, based on detailed pathological examination.[14] The optimal treatment for MT in cases of MCT is uncertain due to the rarity of the disease.[15] The authors present a case of a 34-year-old patient with 14 weeks of gestation who was diagnosed with an adnexal mass suggestive of ovarian teratoma. A laparoscopy salpingo-oophorectomy was performed after 6 months of delivery, and the histological exam revealed a sarcomatoid SCC in the MCT.

Case Description

A 34-year-old patient with 14 weeks of gestation (gravida 1, para 0) was referred to a gynecological consultation for an adnexal right mass. A gynecological ultrasound revealed a unilocular cystic tumor on the right ovary, with 100 mm in size, with mixed echogenicity and acoustic shadows (►**Fig. 1**).[16] According to the simple rules[16] of the International Ovarian Tumor Analysis (IOTA) group, the cyst was classified as benign, because it had one benign feature (unilocular lesion) and no malignant features. We could also identify the so-called IOTA easy descriptors[16] for dermoid cysts, such as unilocular cyst, mixed echogenicity and premenopausal woman.

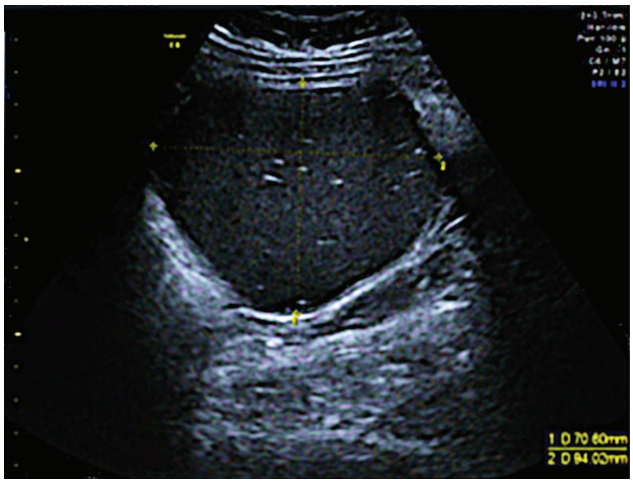

Fig. 1 Ultrasound image of the unilocular cystic tumor on the right ovary with mixed echogenicity and acoustic shadows. According to the International Ovarian Tumor Analysis (IOTA) simple rules, this adnexal mass was classified as benign.[16] Source: Timmerman et al.[16]

Based on the imaging findings, the suspected diagnosis was right ovarian teratoma. The results of the laboratory tests revealed normal serum levels of squamous cell carcinoma antigen (SCCA), carbohydrate antigen (CA) 125, carcinoembryonic antigen (CEA), β-human chorionic gonadotropin (hCG), α-fetoprotein (AFP), lactic dehydrogenase, and CA19-9.

The pregnancy occurred uneventfully, and the patient delivered a healthy new-born. Surgery was delayed for 6 months after delivery. The patient underwent a laparoscopic right-sided salpingo-oophorectomy. During the procedure, we identified a smooth-surfaced, spherical, cystic tumor measuring 100 mm in the right ovary. The uterus and left ovary were macroscopically normal. There was no capsule rupture, and the cyst was extracted with an endo-bag. The anatomopathological exam revealed the presence of a sarcomatoid SCC in an MCT (►**Figs. 2** and **3**).

To exclude distant metastasis, positron emission tomography (PET) was performed, which did not show evidence of locoregional or distant metastasis. The surgical options were fully discussed with the patient, who chose to preserve fertility. A laparotomy of staging was performed with peritoneal fluid cytology, multiple peritoneal biopsies, omentectomy, diaphragmatic dome cytology and pelvic and paraaortic lymphadenectomy. The uterus and left ovary had normal sizes, and did not present macroscopic changes. No tumor alterations were revealed in the staging, and the tumor was classified as stage I. No further treatments were administered. The patient remained asymptomatic and showed no evidence of local recurrence or systemic disease after 3 years of clinical surveillance.

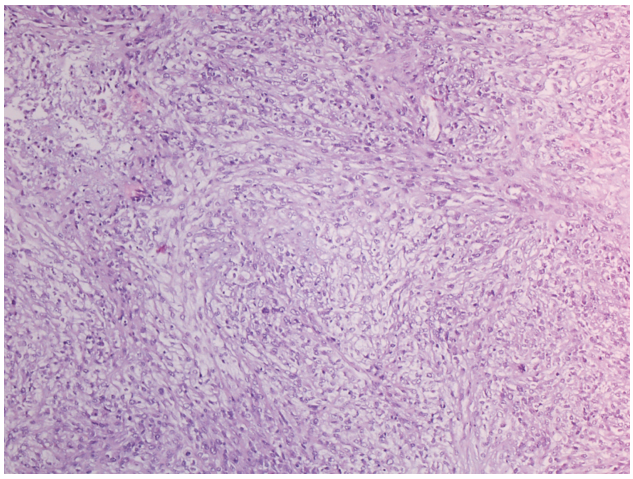

Fig. 2 Histological finding with hematoxylin and eosin staining at original magnification × 10. Malignant proliferation of epithelioid and spindle cells, with a diffuse or fascicular growth pattern. The tumor was a sarcomatoid squamous cell carcinoma.

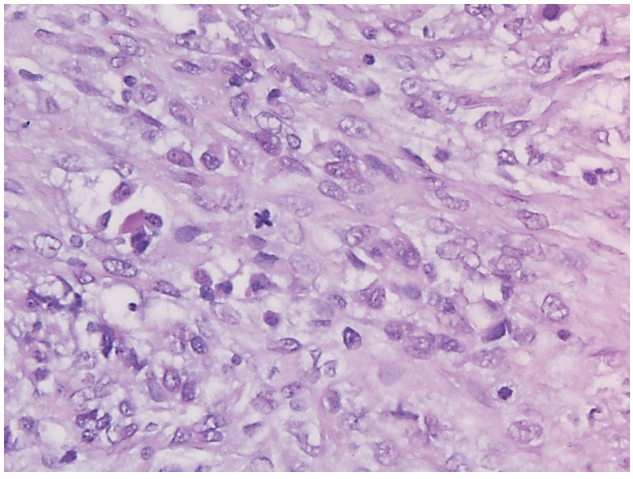

Fig. 3 Histological finding with hematoxylin and eosin staining at original magnification × 40. The cells show oval nuclei with evident pleomorphism and eosinophilic cytoplasms without sharp borders. The mitotic activity was very high (22 mitoses/10 high-power fields). A large immunohistochemical panel (not shown) favored the diagnosis of poorly-differentiated (sarcomatoid) squamous cell carcinoma.

Discussion

In women under 30 years of age, MCTs are the most common ovarian germ-cell tumors.[17] Malignant transformation in MCTs usually occurs later in life, and is reported around the fifth decade.[3] Cases of SCCs arising in an MCT are uncommon, with an incidence lower than 2%,[10] but they are the most common malignancy to arise in MCTs, comprising ~ 80% of malignancies.[17] Moreover, the clinicopathological characteristics, the treatment, the prognostic factors, and the mechanism of MT have not yet been well understood due to the rarity of such tumors, especially in women of reproductive age.[13] Malignant transformation may develop due to the long-term presence of a non-removed MCT.[18] Though the reason for this is not clear, it is postulated by some authors that the long-term presence of an MCT and squamous metaplasia of the columnar epithelium may be followed by such a malignant change.[17] The involvement of the human papillomavirus (HPV) has been suggested, but it must be further investigated.[13]

Clinically, the tumor is usually asymptomatic, and is discovered accidentally during gynecologic investigations.[13] If symptoms are present, they most commonly include increased lower abdominal distension and pain, as well as abdominal or pelvic mass.[6] The symptoms most commonly develop in patients who are postmenopausal or whose tumor has ruptured or underwent a MT.[6] Increased tumor size has been associated with a higher progression to MT in MCTs, and a worse prognosis due to the more aggressive disease.[17] Rupture is an unusual complication of malignant MCTs, occurring in ~ 1% to 2% of patients with SCCs in MCTs.[19] Moreover, in these patients, the preoperative radiological findings may not differ much from those observed in cases of uncomplicated MCT.[18]

Serum tumor marker levels may be high in patients with MT in MCTs. The preoperative serum levels of SCCA are more frequently raised (> 2 ng/mL) in patients with SCC (~ 41.9% of the patients); as far as other markers are concerned, serum CA125, CEA, CA19-9 and macrophage-colony stimulating factor have been found to be elevated in 59.1%, 65.0%, 64.7%, and 71.0% of patients with SCC in MCT respectively.[20] β-human chorionic gonadotropin and AFP are frequently secreted, and may suggest individual tumor subtypes.[21] In the case of an immature teratoma, the levels of AFP may be elevated. while those of hCG and lactic dehydrogenase are normal.[21] An elevated AFP with or without hCG in a young female with an ovarian mass suggests malignant ovarian germ-cell tumors.[21] Although these markers are nonspecific, they can provide prognostic information, so quantitative hCG, AFP, lactic dehydrogenase, and CA125 should be measured preoperatively.[21] However, MT is usually diagnosed by definitive histopathologic examination of the surgical sample.[10]

The authors report a case of a sarcomatoid SCC arising in an ovarian cystic teratoma in a young woman, asymptomatic, with a mass on the right ovary, with sonographic aspects that raised the suspicion of ovarian teratoma. In most series, the median age at the diagnosis of MT of an MCT is 54–61.5 years,[3] and the most common symptoms are abdominal pain, palpable mass and abdominal distension; but some people may be asymptomatic at diagnosis.[22] In some studies,[23] an MCT with a diameter > 100 mm is associated with increased risk of malignancy. In our case, the tumor size was 100 mm, with a benign classification according to the IOTA simple rules.[16] The preoperative serum levels of tumoral markers are more frequently raised.[20] In the case herein reported, all tumoral markers were at normal levels.

To the best of our knowledge, in the ovary, sarcomatoid carcinoma has only been reported as mural nodules in epithelial malignant tumors,[24,25] borderline tumors,[26,27] solid tumors,[12] cystic neoplasms, and in teratomas.[28] Spindle-cell (sarcomatoid) carcinoma is the one SCC variant in which the application of immunohistochemistry may be of value.[11] If the surface epithelium is present, it serves as a good internal control, but it is frequently lost.[11] The individual spindle

neoplastic cells react variably, although most sensitively and reliably with keratin, epithelial membrane antigen, and cytokeratin-18 (CK18).[11] Unfortunately, only ~ 70% of cases will yield any epithelial immunoreactivity.[11] Several other mesenchymal markers can be identified focally, including smooth muscle actin, muscle-specific actin, and rarely, S100 protein.[11] This phenotypic plasticity is expressed by a loss of intercellular cohesion, elongation of the cells, loss of basement membrane, production of connective tissue (collagen), and invasion into the stroma.[11] This type of lineage is to be expected in a tumor that has demonstrated sarcomatoid transformation to the degree observed in SCSCs.[11] In this case, the immunohistochemical panel favored the diagnosis of SCSC. The differential diagnosis for any spindle-cell tumor is most challenging,[11] and it includes several benign and malignant processes, such as fibromatosis, leiomyoma, fibrosarcoma, malignant fibrous histiocytoma, leiomyosarcoma, rhabdomyosarcoma, and angiosarcoma.[11] The sarcomas are characterized by the presence of malignant mesenchymal elements.[11] Carcinosarcoma is a mixed Müllerian tumor (MMT), and it is characterized by the presence of both carcinomatous and sarcomatous components.[11] Moreover, the case herein reported shows that findings of malignant spindle-cell proliferation do not imply that this entity is a sarcoma or a malignant MMT. Additionally, careful tissue sampling and immunohistochemical analysis to distinguish these different entities is mandatory.

In the literature recommendations, the standard primary treatment should consist of bilateral salpingo-oophorectomy, total hysterectomy and comprehensive surgical staging (peritoneal washing, omentectomy, appendectomy, peritoneal biopsies, and pelvic and para-aortic lymphadenectomy) in early stages of the disease, and optimal cytoreductive surgery in advanced stages of the disease.[10] Unilateral salpingo-oophorectomy associated with comprehensive surgical staging can be taken into consideration in young women with early-stage disease wishing to preserve fertility, but few data are currently available in the literature about this conservative approach.[9] The spillage of cyst content should be always avoided, and the surgical removal must be performed with an endoscopic retrieval bag.[10] If spillage does occur, the surgeon must carry out an accurate peritoneal washing with large amounts of warm fluid.[8] After comprehensive surgical staging, patients with stage-Ia tumors can undergo only clinical surveillance, whereas chemotherapy is warranted for those with more advanced diseases.[8,19] Platinum-based chemotherapy has been frequently used in the first-line treatment.[8] Chemotherapy seems to be less effective in SCC in MCTs than in the common epithelial ovarian cancers.[8,19] The role of radiotherapy remains unclear. Due to the limited number of cases for analysis, it was difficult to make definite conclusions with regards to the appropriate adjuvant radiotherapy and chemotherapy for this disease.[13]

In the literature review, the survival outcome of patients with MT in MCTs depends on the stage at diagnosis.[13] Although the application of the International Federation of Gynecology and Obstetrics (Fédération Internationale de Gynécologie et d'Obstétrique, FIGO) staging to SCCs in MCTs does not clearly relate to the graduated outcome of the disease, there are reports of patients with FIGO stages II to IV having a lower probability of long-term survival than patients with stage-I diseases.[3,13] Age, tumor size, clinical stage, histologic differentiation, capsular invasion, and the presence of vascular invasion can provide valuable information for the prediction of the survival of patients with SCCs in MCTs.[3,13] The early diagnosis of the MT before invasion or metastasis is important for the treatment. A large ovarian mass suspected to be a mature teratoma should be more carefully managed in older patients.[13] Recent studies showed that a tumor size ≥150 mm appeared to be strongly associated with aggressive diseases, and generally spreads by direct invasion and peritoneal implantation rather than by metastasis to the regional lymph nodes.[3,20] Squamous cell carcinomas of the ovary spread transmurally with extensive local invasion, which is different from common ovarian tumors, and the overall 5-year survival rate is ~ 50%.[3,20]

In many organs such as the kidney, the breast, and the urinary bladder, sarcomatoid carcinomas are neoplasms, with poor prognosis.[12] As a consequence of the relative rarity and diagnostic heterogeneity of these tumors, it has proven difficult to properly predict their behavior and to determine the optimal management.[11] Although it was first thought to carry an invariably unfavorable prognosis, recent data indicate that this does not apply to stage-Ia tumors.[11] Our findings are consistent with the aforementioned data. In the case herein reported, at diagnosis, the neoplasm was located within the ovary, without invasion of surrounding tissue and lymph node metastases. The patient chose to preserve fertility, and surgical staging did not reveal tumor alterations, and the tumor was classified as stage I. No further treatments were administered. The patient remained asymptomatic, and showed no evidence of local recurrence or systemic disease after 3 years of clinical surveillance.

Conclusion

In conclusion, the MT of MCTs in young women is very rare, and its preoperative diagnosis is difficult. It should be suspected when the patient has a large ovarian mass (≥ 150 mm) and direct invasion or metastasis should be investigated. Moreover, the case herein reported shows that findings of spindle-cell proliferation do not imply that this entity is a sarcoma or a malignant MMT. Additionally, careful tissue sampling and immunohistochemical analysis to distinguish these different entities is mandatory. There is an ongoing debate on the best management practices for this disease entity, and the benefits of early diagnosis and intervention cannot be more emphasized for a better prognosis.

Conflict of Interests
The authors have none to disclose.

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Types of study (adapted from Pereira, 2014*):

Case Report (Case study): In-depth investigation of a situation in which one or a few people are included (usually up to ten);

Case series: A set of patients (for example, more than ten people) with the same diagnosis or undergoing the same intervention. In general, these are consecutive series of patients seen in a hospital or other health institution for a certain period. There is no internal control group formed simultaneously. The comparison is made with external controls. The name of external or historical control is given to the group used to compare the results, but that was not constituted at the same time within the study: for example, the case series is compared with patients from previous years.

Transversal (or Cross-sectional) study: Investigation to determine prevalence; examine the relationship between events (exposure, disease, and other variables of interest) at any given time. Cause and effect data are collected simultaneously: for example, the case series is compared with patients from previous years.

Case-control study: Particular form of etiological investigation of retrospective approach in which the search of causes starts from the effects. Groups of individuals, respectively with and without a particular health problem are compared in relation to past exposures in order to test the hypothesis that exposure to certain risk factors is the contributing cause of the disease. For example, individuals afflicted with low back pain are compared with an equal number of individuals (control group) of the same sex and age, but without low back pain.

Cohort study: Particular form of investigation of etiological factors in which the search of effects starts from the cause; therefore, the opposite of case-control studies. A group of people is identified, and pertinent information on the exposure of interest is collected, so the group can be monitored over time, checking those who do not develop the disease in focus, and if the prior exposure is related to occurrence of disease. For example, smokers are compared to nonsmoker controls; the incidence of bladder cancer is determined for each group.

Randomized study: This has the connotation of an experimental study to evaluate an intervention hence the synonym of *intervention study*. Can be performed in a clinical setting; sometimes referred to simply as clinical trial or clinical study. It is also conducted at the community level. In clinical trials, participants are randomly assigned to form groups called study (experimental) and control (or testimony), whether submitted or not to an intervention (for example, a drug or vaccine). Participants are monitored to verify the occurrence of outcome of interest. This way, the relationship between intervention and effect is examined under controlled observation conditions, usually with double-blind evaluation. In the case of a **randomized study**, inform the number of the Brazilian Registry of Clinical Trials (REBEC) and/or the number of the International Clinical Trials Registration Platform (ICTRP/OMS) on the title page.

Ecological study: Research performed with statistics: the unit of observation and analysis is not constituted of individuals, but of groups of individuals hence the synonyms: study of groups, aggregates, clusters, statistics or community. For example, research on the variation of mortality coefficients for diseases of the vascular system and per capita consumption of wine among European countries.

Systematic Review and Meta-analysis: Type of review in which there is a clearly formulated question, explicit methods are used to critically identify, select and evaluate relevant research, and also to collect and analyze data from the studies included in the review. There is use of strategies to

limit bias in the localization, selection, critical evaluation and synthesis of relevant studies on a given topic. Meta-analysis may or may not be part of the systematic review. Meta-analysis is the review of two or more studies to obtain a global, quantitative estimate of the question or hypothesis investigated; and employs statistical methods to combine the results of the studies used in the review.

Source: *Pereira MG. Artigos Científicos – Como redigir, publicar e avaliar. Rio de Janeiro: Guanabara-Koogan; 2014.

Script for statistical review of original scientific papers

Study objective: Is the study objective sufficiently described, including pre-established hypotheses?

Design: Is the design appropriate to achieve the proposed objective?

Characteristics of the sample: Is there a satisfactory report on the selection of people for inclusion in the study? Has a satisfactory rate of responses (valid cases) been achieved? If participants were followed up, was it long and complete enough? If there was a pairing (eg. of cases and controls), is it appropriate? How did you deal with missing data?

Data Collection (measurement of results): Were the measurement methods detailed for each variable of interest? Is there a description of comparability of the measurement methods used in the groups? Was there consideration of the validity and reproducibility of the methods used?

Sample size: Has adequate information on sample size calculation been provided? Is the logic used to determine the study size described, including practical and statistical considerations?

Statistical Methods: Was the statistical test used for each comparison informed? Indicate if the assumptions for use of the test were followed. Was there information about the methods used for any other analysis? For example, subgroup analysis and sensitivity analysis. Are the main results accompanied by accuracy of the estimate? Inform the p value and confidence interval. Was the alpha level informed? Indicate the alpha level below which the results are statistically significant. Was the beta error informed? Or indicate the statistical power of the sample. Has the adjustment been made to the main confounding factors? Were the reasons that explained the inclusion of some and the exclusion of others described? Is the difference found statistically significant? Make sure there are sufficient analyzes to show the statistically significant difference is not due to any bias (eg. lack of comparability between groups or distortion in data collection). If the difference found is significant, is it also relevant? Specify the clinically important minimal difference. Make clear the distinction between statistically relevant difference and relevant clinical difference. Is it a one- or two-tailed test? Provide this information if appropriate. What statistical program is used? Inform the reference where to find it, and the version used.

Abstract: Does the abstract contain the proper article synthesis?

Recommendation on the article: Is the article in acceptable statistical standard for publication? If not, can the article be accepted after proper review?

Source: *Pereira MG. Artigos Científicos – Como redigir, publicar e avaliar. Rio de Janeiro: Guanabara-Koogan; 2014.

IMPORTANT!

RBGO joined the initiative of the International Committee of Medical Journal Editors (ICMJE) and the EQUATOR Network, which are aimed to improve the presentation of research results. Check the following international guides:

Randomized clinical trial:
http://www.consort-statement.org/downloads/consort-statement

Systematic reviews and meta-analysis: http://www.scielo.br/pdf/ress/v24n2/2237-9622-ress-24-02-00335.pdf

Observational studies in epidemiology: strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_combined.pdf

Qualitative studies: http://intqhc.oxfordjournals.org/content/19/6/349.long

Results

The purpose of the Results section is to show the study findings. It is the original data obtained and synthesized by the author with the aim to answer the question that motivated the investigation. For the writing of the section, present the results in logical sequence in the text, tables and illustrations, first mentioning the most important findings. Do not repeat all information of the tables or illustrations in the text. Emphasize or summarize only important observations. Additional or supplementary materials and technical details may be placed in an appendix where they will be accessible without interrupting the flow of the text. Alternatively, this information may be published only in the electronic version of the Journal. When data are summarized in the results section, provide numerical results not only in derived values (eg. percentages), but also in absolute values from which the derivatives were calculated, and specify the statistical methods used for their analysis. Use only the tables and figures necessary to explain the argument of the work and evaluate its foundation. When scientifically appropriate, include data analysis with variables such as age and sex. Do not exceed the maximum limit of five tables, five charts or five figures. Tables, charts and/or figures should be included in the body of the manuscript and do not count the requested limit of 4000 words.

ATTENTION!

In Case Studies, the Methods and Results sections should be replaced by the term Case Description.

Discussion

In the **Discussion** section, emphasize the new and important aspects of the study and the conclusions derived therefrom. Do not repeat details of data or other information presented in the introduction or results sections. For experimental studies, it is useful to begin the discussion by briefly summarizing the main findings, comparing and contrasting the results with other relevant studies, stating the limitations of the study, and exploring the implications of the findings for future research and clinical practice. Avoid claiming precedence and referring to incomplete studies. Do not discuss data not directly related to the results of the presented study. Propose new hypotheses when justifiable, but qualify them clearly as such. In the last paragraph of the Discussion section, cite which information of your work contributes relatively to advancement of knowledge.

Conclusion

The **Conclusion** section has the function of relating the conclusions to the objectives of the study, but authors should avoid unfounded statements and conclusions not adequately supported by data. In particular, authors should avoid making statements about economic benefits and costs unless their original includes economic analysis and appropriate data.

References

A study is based on the results of other research that preceded it. Once published, it becomes support for future work on the subject. In the report of their research, authors state the references of prior works consulted that they deem pertinent to inform readers, hence the importance of choosing good References. Properly chosen references lend credibility to the report. They are a source for convincing readers of the validity of facts and arguments presented.

Attention! For manuscripts submitted to RBGO, authors should number the references in order of entry into the manuscript and use those numbers for text citations. Avoid excessive references by selecting the most relevant for each statement and giving preference to the most recent work. Do not use hard-to-reach quotations, such as abstracts of papers presented at congresses, theses or restricted publications (non-indexed). Seek to cite the primary and conventional references (articles in scientific journals and textbooks). Do not use references such as 'unpublished observations' and 'personal communication'. Authors' publications (self-citation) should be used only if there is a clear need and relationship with the topic. In this case, include in bibliographical references only original works published in regular journals (do not cite chapters or revisions). The number of references should be 35, in exception review articles. Authors are responsible for the accuracy of data contained in the references.

Please check the American Medical Association (AMA) Citation Style to format your references.

*The Instructions to Authors of this journal were elaborated based in the literary work ***Artigos Científicos: Como redigir, publicar e avaliar de Maurício Gomes Pereira, Editora Guanabara Koogan, 2014.***

Submission of papers

The articles must, necessarily, be submitted electronically, according to the instructions posted on the site: http://mc04.manuscriptcentral.com/rbgo-scielo

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