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Editorial

Maternal Mortality: An Eco-Social Phenomenon that Calls for Systemic Action

Mortalidade Materna: Um Fenômeno Eco-Social que Demanda Ação Sistêmica

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Pregnancy, childbirth, and the postpartum period are phases commonly associated with joy and hope. Even though it may be an unplanned event for many women, pregnancy usually develops without complications most of the times: mother and newborn child start together—and well—a new phase of their lives. This does not mean that the good outcome was achieved without a significant number of women experiencing discomfort, stress, anxiety, fear, or even some sadness. These are conditions that, although not desirable, tend to be present during pregnancy, childbirth, and the postpartum period. However, for some women, this is a period of great anguish, suffering, and risk. Risk of intimate partner violence, of mistreatment in health facilities, of developing physical or psychological sequelae, and risk of dying.[1–4]

A maternal death is an individual, family, and social tragedy. Because it is preventable in the absolute majority of times it occurs, there is no male equivalent, and it disproportionately affects certain groups of women, maternal mortality exceeds the boundaries of clinical obstetrics and reflects broader societal issues.[5–7] While hypertensive complications, bleeding, infection, unsafe abortion, and worsening of preexisting diseases are the main biomedical causes of maternal mortality, tackling it requires broader actions.[8,9]

Considered as causes of complications of pregnancy, intrinsic or extrinsic etiological agents (such as uterine atony or bacterial infection) do not act in isolation on women to produce complications. The etiological agents act under the influence of several other factors, in a complex and multifactorial process known as the health-disease process (►**Fig. 1**). Over thousands of years, the characteristics of the environment favored the evolution of current human beings. Among the innate characteristics and potential of *Homo sapiens*, lies the biological basis of pregnancy and childbirth. This includes, for instance, the shape of the pelvis and the complex endocrinology of parturition. The innate characteristics and potential of the species favored the development, over time, of the current human culture and society. Culture and society are the origin of the guiding principles of social organization, the legal and political structure, and the mode of production of the economy. In this context, human interaction with the planet has produced environmental degradation, with consequences that include the increasing concentration of particulate matter in the atmosphere and the acceleration of global warming. The latter, besides being responsible for the melting of ice glaciers and the rise of the sea level, is associated with a greater frequency and intensity of extreme climate events, including heat waves or drought or severe storms and heavy rain. These events affect maternal health and have been associated with an increased maternal and perinatal morbidity and mortality.[7,10]

Together, the innate characteristics of *H. sapiens*, their culture and society, and the environment are super determinants of the whole health-disease process, thus originating the so-called primary determinants of health. Education, income, ethnicity and gender issues affect the risk of a woman dying during pregnancy, childbirth, and postpartum/postabortion period. Women of color, those living on the outskirts of large cities or in rural areas, those with little access to education or income, are the women experiencing the highest maternal mortality.[6] Women deprived of their liberty, migrant women, women victims of trafficking and women in prostitution are frequently invisibilized and subject of additional marginalization and risk. The factors arising from or associated with the global climate emergency (e.g., extreme weather, heat stress, poor air quality, or changing distribution of infectious disease vectors) must also be highlighted.[10–12] Under the influence of these determinants, the individual, family and community characteristics give rise to lifestyle patterns, which may accentuate or reduce risks. Likewise, the family and community organization can act as a protection and support network for women, reducing the risk of mortality, or, on the contrary, favoring harmful lifestyles. Also coming from the principles and structures of society, social facilities (such as schools and the health system itself) undertake processes and practices capable of functioning

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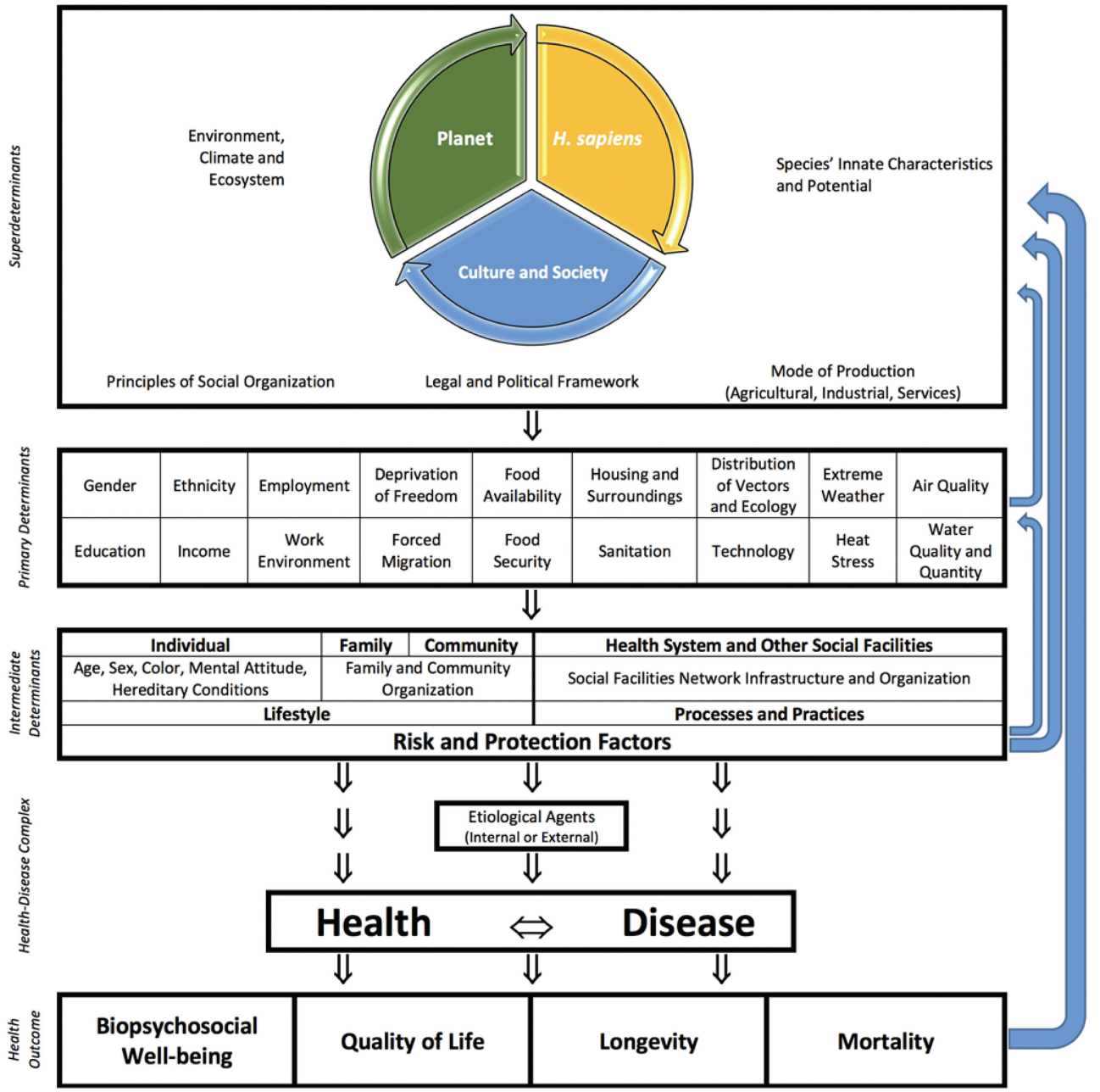

Fig. 1 The health-disease process (eco-social model).

as protective factors, mitigating the negative effects of the primary determinants and enhancing their positive effects. On the other hand, by becoming permeable to structural bias, health and social facilities risk reproducing violence, including abuse, disrespect and mistreatment of women during pregnancy, childbirth, and in the postpartum/postabortion period.

Given the broad determinants of maternal mortality and the complex health-disease process, maternal mortality has long ceased to be "just" a health indicator and became a social development indicator. Hence its inclusion as a progress indicator of two successive global initiatives, the Millennium Development Goals (2000–2015) and the Sustainable Development Goals (2016–2030). Both initiatives, promoted by the United Nations (UN), seek to encourage the governments of the signatory countries to implement programs to promote social development and eliminate extreme poverty.[13]

The World Health Organization (WHO) estimates that in the early 1990s there were ~ 500,000 maternal deaths per year worldwide. According to the UN health agency, the annual number of maternal deaths around the world would be just over 450,000 deaths in 2000 and 295,000 in 2017. The global maternal mortality ratio in 2000 and 2017 was estimated at 342 and 211 maternal deaths per 100,000 live births, respectively. In Brazil, the maternal mortality ratio in 2000 was estimated by the WHO at 69 deaths per 100,000 live births, and, in 2017, 60 deaths per 100,000 live births. The WHO estimated for 2017 a total of 1,700 maternal deaths in Brazil, with the lifetime risk of 1 maternal death for 940 women.[14] There is some methodological difficulty in generating reliable global estimates over time, and

all these estimates have a relatively wide range of unreliability. The Brazilian Ministry of Health generates its own estimates of maternal mortality. Although the estimates are compatible, considering their degree of uncertainty, the maternal mortality ratio estimated by the Brazilian Ministry of Health is slightly higher than that estimated internationally (64 maternal deaths per 100,000 live births in 2017). Within the scope of the Sustainable Development Goals, the target is to achieve a global maternal mortality ratio of 70 maternal deaths per 100,000 live births in 2030. For the global target to be achieved, each country needs to contribute to a certain reduction in mortality. For Brazil, the target maternal mortality ratio for 2030 is 30 maternal deaths per 100,000 live births.[15]

Considering the evolution of the maternal mortality ratio in Brazil since 1990, the most substantial reduction took place in the last decade of the 20th century. This reduction of maternal mortality has been partially and ecologically attributed to a greater access to primary health care during pregnancy (i.e., antenatal care), greater coordination between the different levels of the health system, and improvements in emergency services. These advances occurred in the context of greater economic stability and the implementation of the Unified Health System (SUS) in Brazil, which occurred in the beginning of the 1990s. In the 2000s, the rate of reduction in the maternal mortality ratio decreased and started to tend to stability, suggesting the need for more intense social transformations as well as greater gains in efficiency and quality in the health system.[15,16]

Although there is no shortcut to reduce maternal mortality —social development is necessary for substantial and sustainable gains—the health sector cannot be exempted from its central role in tackling maternal mortality. The reduction in maternal mortality occurs over a long journey, which can be divided into stages. According to the theory of obstetric transition (►**Box 1**), Brazil is between stages III and IV of this transition.[17] At this point, although issues of access to health care may persist, the quality of care becomes a major determinant of pregnancy outcomes. Eliminating delays within the system itself becomes a priority. It is important to note an apparent contradiction: while maternal mortality is largely preventable, a sizable number of women will experience complications almost inevitably. The preventability of some of the main complications (for example, preeclampsia and postpartum hemorrhage) has limitations, and their prompt recognition and proper management are essential. Thus, delays in recognizing complications by women themselves or health professionals, in the decision to seek help, in obtaining access to the health system, as well as in receiving adequate, respectful and quality care in health facilities become significant determinants of maternal mortality. In this context, health and social facilities—particularly the health system—function as safeguards and protection networks: the ability to neutralize the negative effects of primary determinants can be a measure of their efficiency, whereas the system's permeability to the primary determinants can indicate the opposite. Thus, it is essential that structuring actions are implemented and developed with a goal to strengthen the health system and reduce the system response time (►**Box 2**).[9,17–19]

Box 1 The obstetric transition

The obstetric transition is a theory about the pathway for maternal mortality reduction. It considers the levels of maternal mortality and fertility, the pattern of biomedical causes and care. The obstetric transition is divided in stages, and at country level; it is highly related to the degree of social development.

- **Stage I** (maternal mortality ratio $>$ 1,000 maternal deaths/100,000 live births): Most women experience a situation that is close to the natural history of pregnancy and childbirth. Stage I is characterized by a very high maternal mortality rate, with high fertility and a predominance of direct causes of maternal mortality, in addition to a large proportion of deaths attributable to communicable diseases, such as malaria. Most women do not receive professional obstetric care or have access to health facilities. The priority at this stage is the promotion of social development and primary prevention measures including: reproductive planning, iron supplementation, insecticide-treated mosquito nets and the removal of barriers to access the health system.
- **Stage II** (maternal mortality rate: 999–300 maternal deaths/100,000 live births): mortality and fertility remain very high, with a pattern of causes similar to that of stage I. However, a greater proportion of women begin to seek and receive care in health units. The priorities at this stage are similar to those at stage I.
- **Stage III** (maternal mortality ratio: 299–50 maternal deaths/100,000 live births): fertility is variable, and the direct causes of mortality still predominate. This is a complex stage, because access remains a problem for a large part of the population. However, as a growing proportion of pregnant women reach health services, the quality of care is a major determinant of health outcomes, particularly related to overwhelmed health services. The priorities at this stage include reducing social inequalities and improving quality of care. Primary prevention, as well as secondary and tertiary prevention, is critical to improving maternal health outcomes at this stage. In other words, the quality of care and the proper management of complications are essential to reduce maternal mortality.
- **Stage IV** (maternity mortality ratio $<$ 50 maternal deaths/100,000 live births): maternal mortality is low. There is a low fertility rate. Indirect causes of maternal mortality, especially non-communicable diseases, are increasingly important. One aspect that emerges at this stage is the growing role of medicalization as a threat to quality and improvement in health outcomes. The priority at this stage is to consolidate social gains and intensify the improvement of quality and quaternary prevention (prevention of iatrogenic diseases).
- **Stage V** (all preventable maternal deaths are avoided). Maternal mortality is very low, the fertility rate is low or very low and indirect obstetric causes associated with chronic-degenerative disorders are the main causes of maternal mortality. The main challenges at this stage are the consolidation of advances against structural violence, effective management of vulnerable populations (for example, immigrants, refugees and displaced persons in their own country), and sustainability of excellence in quality of care.

Conclusion

Maternal mortality is a difficult puzzle to solve. However, progress made in the last few decades is encouraging. In

Box 2 Interventions to improve quality of care in maternity and women's health services

- Implementation of social control and community participation in maternity and women's health services, with representatives of female users of the service, health professionals, and managers (i.e., a Health Facility Council);
- Implementation of a Quality Control Commission, responsible for:
  - Analyzing the infrastructure, process, and health outcomes indicators, including users' satisfaction;
  - Identifying obstacles to the provision of **women-centered, timely, appropriate and respectful quality care guided by the best scientific evidence**
  - Proposing solutions to overcome the identified obstacles
- Generate actionable information through:
  - Electronic information systems
  - Audit and feedback of selected near-miss cases and all maternal and perinatal deaths. Feedback to professionals and teams is essential.
- Redesign local maternal mortality committees into instances of audit and feedback or quality control commissions. The committees need to strive for local impact through feedback to local teams.
- Systematize assistance through guidelines, protocols and standard operating procedures based on scientific evidence, including communication protocols and teamwork. Consider adopting structured emergency response packages (for example, ALSO, ALARM, FAST-M, surviving sepsis campaign care bundles);
- Implementation of standard operating procedures, protocols, and guidelines into clinical practice through:
  - Local handbooks
  - Physical and electronic reminders
  - Local opinion leaders
  - Drills and simulations

Brazil, the major obstacle is to advance the quest for social justice, particularly from an ethnic and gender perspective, expanding women's access to education and income, with special emphasis on women of color. In addition, it is essential to make a leap in the quality and effectiveness in public health services. The provision of women-centered, timely, appropriate and respectful quality care guided by the best scientific evidence should be the major goal of all maternity and women's health services. For this, the state needs to strengthen the public sector health system, and the society needs to exercise its primary role of defense and social control of the public health system.

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

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Local References for Ultrasound-Estimated Fetal Weight Based on 2,211 Singleton Pregnancies in the City of Curitiba, South of Brazil

Referências locais para o peso fetal estimado por ultrassom baseado em 2.211 gestações únicas na cidade de Curitiba, Sul do Brasil

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Abstract

Objective To develop reference curves of estimated fetal weight for a local population in Curitiba, South of Brazil, and compare them with the curves established for other populations.

Methods An observational, cross-sectional, retrospective study was conducted. A reference model for estimated fetal weight was developed using a local sample of 2,211 singleton pregnancies with low risk of growth disorders and well-defined gestational age. This model was compared graphically with the Hadlock and Intergrowth 21st curves.

Results Reference curves for estimated fetal weight were developed for a local population. The coefficient of determination was $R^2 = 99.11\%$, indicating that 99.11% of the fetal weight variations were explained by the model. Compared with Hadlock curves, the 50th, 90th, and 97th percentiles in this model were lower, whereas the 10th percentile nearly overlapped, and the 3rd percentile was slightly higher in the proposed model. The percentiles were higher in the proposed model compared with the Intergrowth 21st curves, particularly for the 3rd, 10th, and 50th percentiles.

Conclusion We provide a local reference curve for estimated fetal weight. The proposed model was different from other models, and these differences might be due to the use of different populations for model construction.

Keywords
- fetal weight
- prenatal ultrasonography
- growth charts
- percentiles
- reference curves

Resumo

Objetivo Desenvolver curvas de referência para o peso fetal estimado em uma população de Curitiba, Sul do Brasil, e compará-las com curvas estabelecidas para outras populações.

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Métodos Foi realizado um estudo observacional, transversal e retrospectivo. Um modelo de referência para o peso fetal estimado foi desenvolvido usando uma amostra local de 2.211 gestações únicas de baixo risco de distúrbios do crescimento e idade gestacional bem definida. Este modelo foi comparado graficamente com as curvas de Hadlock e *Intergrowth 21st*.

Resultados As curvas de referência para o peso fetal estimado foram desenvolvidas para uma população local. O coeficiente de determinação foi de $R^2 = 99{,}11\%$, indicando que 99,11% das variações do peso fetal foram explicadas pelo modelo. Em comparação com as curvas de Hadlock, os percentis 50, 90, e 97 neste modelo foram inferiores, enquanto o percentil 10 quase se sobrepôs, e o percentil 3 foi ligeiramente superior no modelo proposto. Os percentis foram maiores no modelo proposto em comparação com as curvas do *Intergrowth 21st*, particularmente para os percentis 3, 10, e 50.

Conclusão Fornecemos uma curva de referência local para o peso fetal estimado. O modelo proposto foi diferente de outros modelos, e essas diferenças podem ser devido ao uso de diferentes populações para a construção do modelo.

Palavras-chave
- peso fetal
- ultrassonografia pré-natal
- curvas de crescimento
- percentis
- curvas de referência

Introduction

Changes in intrauterine growth and prematurity are the major determinants of neonatal morbidity and mortality.[1] Intrauterine growth restriction (IUGR), a condition in which a fetus cannot reach its biological growth potential,[2] is strongly associated with perinatal morbidity and mortality and acute fetal distress. It is estimated that 1 to 2% of neonatal deaths worldwide are a direct result of IUGR in term newborns.[3] In addition, there is a correlation between IUGR and delayed neurodevelopment[4] and chronic diseases in adulthood, including chronic arterial hypertension, type II diabetes mellitus, and cardiovascular diseases.[5] Macrosomic or large-for-gestational-age fetuses present higher risk of intrauterine death and adverse perinatal outcomes, such as shoulder dystocia, humeral and clavicular fracture, brachial plexus and facial palsy, asphyxia, meconium aspiration, hypoglycemia, neonatal hyperbilirubinemia, hypertrophic cardiomyopathy, and prolonged stay in intensive care units.[6] Therefore, the adequate identification of these fetuses is crucial for prenatal management and for determining the optimal time for delivery.

Some studies have provided reference charts for fetal biometric parameters, although there are discrepancies in median values and percentile curves.[7,8] These differences may be due to racial, maternal, biological, and demographic factors[9] as well as to methodological failure in published studies.[10]

The data published by the Brazilian Institute of Geography and Statistics in the 2010 census[11] indicated that 47.7% of Brazilians are classified as white, 43.1% as mixed race, 7.6% as black, 1.05% as Asian, and 0.43% as indigenous people. Therefore, almost 50% of the Brazilian population can be considered of mixed race. In the city of Curitiba, 78% of the population are white, 2.8% are black, 1.3% are Asian, and 16% are of mixed race,[12] evidencing ethnic variations even within a single country. In Brazil, the most used reference is that published by Hadlock et al,[13] which is based on a predominantly Caucasian and middle-class population comprising 392 pregnant women.

Based on this information, we developed a reference curve for the city of Curitiba, South of Brazil, using data obtained from 2,211 tests conducted in a population classified as having a low risk of fetal growth disorders.

Methods

The present observational, cross-sectional and retrospective study was approved by the research ethics committee of the Hospital of Universidade Federal do Paraná (UFPR) on March 30, 2016 under Opinion No. 1.470.703.

For developing the estimated fetal weight reference curve, pregnant women at gestational weeks 14 to 41 were subjected to routine ultrasound examination at a private clinic in Curitiba from March 2011 to March 2015. The examinations were conducted by 10 medical specialists in fetal medicine using GE ultrasound devices models Voluson 730 Expert and Voluson S6 (GE Medical System, Zipf, Austria).

The inclusion criteria were low-risk pregnant women with a singleton gestation and well-defined gestational age, confirmed by the date of the last menstrual period, when the difference between this date and first trimester ultrasound was less than 5 days, or by the measurement of the crown-to-rump length (CRL) in an examination conducted before the gestational age of 13 weeks and 6 days. Multiple pregnancies, fetuses with congenital malformations or chromosomal abnormalities, congenital infections, fetal deaths, and pregnant women with diseases associated with fetal growth disorders (chronic arterial hypertension, gestational hypertension, preeclampsia, previous or gestational diabetes mellitus, chronic renal disease, chronic pulmonary disease, cyanotic heart disease, alcohol abuse, smoking, systemic lupus erythematosus, antiphospholipid

syndrome, and thrombophilia)as well as those who were living in high altitudes were excluded.

A total of 8,447 examinations were conducted in 2,211 patients. Gestational age in weeks and days and fetal weight in grams (estimated by Hadlock's formula: Log 10 [weight] = 1.3596–[0.
00386 × AC × FL] + [0.0064 × HC] + [0.00061 × BPD × AC] -
+ [0.0424 × AC] + [0.174 × FL], in which AC is abdominal circumference, FL is femoral length, HC is head circumference, and BPD is biparietal diameter) were recorded in a Microsoft Excel 2007 worksheet (Microsoft Corporation, Redmond, WA, USA).

For the inclusion of only one examination per pregnant woman and for obtaining homogeneity in the examinations, the Linear Integer Programming technique and LINGO 13 software (LINDO Systems Inc., Chicago, IL, USA) together with Microsoft Excel 2007 were used. The technique was executed a second time for the remaining examinations. The first sample was used to create the curve (training sample), and the second one was used to validate the model (test sample).

The protocol developed by Altman and Chitty[14] was used to calculate the estimated fetal weight curves and correlate fetal weight (in grams) with gestational age (in weeks and days). One of the protocol's recommendations is that reference percentiles be calculated using cross-sectional studies, that is, with one observation per fetus. The standard deviation of the weight was modeled as a function of the gestational period. The quality of the model was evaluated by considering the coefficient of determination and analyzing the residues of the adjusted model. The model was estimated using the training dataset and validated in the second dataset. The generated model was compared graphically with the Hadlock model[13] because the latter is the most commonly used. The generated model was also compared with the curve of the Intergrowth 21st project,[15] a prescriptive curve of how growth should occur under optimal conditions, which was designed for international use.

Results

A sample of 2,211 ultrasound examinations was generated, one for each pregnant woman, of which 1,836 (83%) were white, 310 (14%) were mixed race, 44 (2%) were black, and 21 (1%) were Asian. There was adequate distribution across the 28 weeks of gestation analyzed (14 to 41 weeks of gestation) and a standard deviation of 0.173. We believe that the majority of the pregnant women had moderate/high socioeconomic status, because the ultrasound examinations were performed in a private clinic and all ultrasound examinations were private or covered by health insurance. The distribution of the examinations is presented in ►**Table 1**.

The model was executed a 2nd time using the remaining 6,236 examinations. This 2nd execution used the same extraction method to generate a second sample with 1,957 examinations. The first sample was used to create the curve (training sample), whereas the second sample was used to validate the curve (test sample).

Table 1 Frequencies of cases at each gestational age

Gestational age (weeks)	Total ultrasound examinations	Examinations used to adjust the proposed model
14–14 + 6	128	46
15–15 + 6	226	58
16–16 + 6	295	76
17–17 + 6	323	82
1818 + 6	260	67
19–19 + 6	153	40
20–20 + 6	215	56
21–21 + 6	417	106
22–22 + 6	659	166
23–23 + 6	396	102
24–24 + 6	149	38
25–25 + 6	125	49
26–26 + 6	190	49
27–27 + 6	291	74
28–28 + 6	385	97
29–29 + 6	310	80
30–30 + 6	300	78
31–31 + 6	373	96
32–32 + 6	388	97
33–33 + 6	357	91
34–34 + 6	432	111
35–35 + 6	476	120
36–36 + 6	584	148
37–37 + 6	565	141
38–38 + 6	334	86
39–39 + 6	91	35
40–40 + 6	20	17
41–41 + 6	5	5
Total	8,447	2,211

The gestational periods and fetal weights determined for the 2,211 examinations were considered for assessing the correlation between the gestational week and estimated fetal weight on ultrasound. The estimation of the model considered the gestational period in weeks as the explanatory variable and the natural logarithm of fetal weight on ultrasound as the response variable. The best fit was obtained using a quadratic model given by the following equation: $(\widehat{\ln}\ \text{weight}) = 0.6034575 + 0.3320483.\text{week} - 0.003589055.\text{week}^2$. The estimated weight of each fetus according to the gestation period is given by: estimated weight = $e^{(0.6034575+0.3320483.\text{week}-0.003589055.\text{week}^2)}$.

The standard deviation of fetal weight was modeled according to the gestational period, as proposed by Altman and Chitty.[14] For this estimation, the absolute values of the residues obtained with the model presented above were considered. The best ratio obtained for estimating the standard deviation was

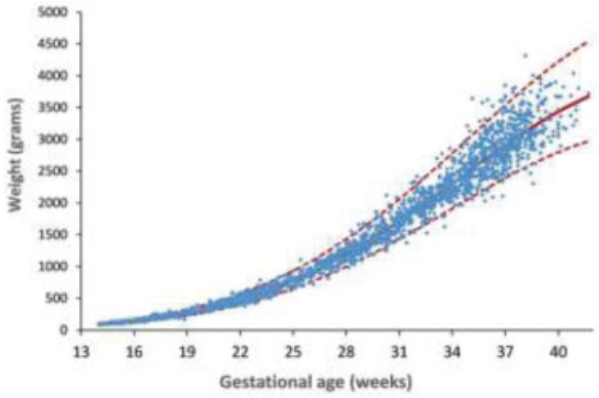

Fig. 1 Fetal estimated weight and gestational ages of the evaluated cases. The adjusted curve correlating fetal weight and gestational period with a 95% confidence interval for the individual observations is also shown.

quadratic. Below is the model used for estimating the standard deviation of fetal weight as a function of the gestational week.

$$\widehat{SD} = \frac{\sqrt{\pi}}{2}(0.099235 - 0.002235.\,week + 0.000046.\,week^2)$$

Therefore, the scores for each case were calculated using the following equation:

$$score = \frac{(\ln weight - \widehat{\ln}\ weight)}{\widehat{SD}}$$

The model's coefficient of determination was $R^2 = 99.11\%$, indicating that 99.11% of fetal weight variations were explained by the model. ►**Fig. 1** shows the results of fetal weights and gestational periods of the evaluated cases. The adjusted curve correlating fetal weight and gestational period with a 95% confidence interval for the individual observations is also shown. The fetal weights in each gestational week for each percentile (3rd, 5th, 10th, 50th, 90th, 95th, and 97th) are shown in ►**Table 2**.

►**Fig. 2** shows the calculated scores based on the above equation, together with the values of the standardized normal distribution (–1.64; 1.64), which indicates the range corresponding to 90% of the area under the curve of this distribution. For the model data, 89.5% of the scores were within this range, indicating a good adherence to the model. This percentage was 89% in the tested dataset, indicating a very good reproducibility of the model for estimating weights using data that were not used in the adjustment.

►**Fig. 3** shows the calculated values based on the above equation together with the values of the standardized normal distribution (–1.96; 1.96), which indicate the range

Table 2 Percentiles of estimated fetal weight (grams) at each gestational age

Gestational age (week)	3rd	5th	10th	25th	50th	75th	90th	95th	97th
14	78.8	80.6	83.5	88.5	94.5	100.9	107.0	110.8	113.4
15	99.2	101.4	105.0	111.3	118.7	126.6	134.2	138.9	142.1
16	123.9	126.7	131.2	138.9	148.0	157.8	167.1	172.9	176.8
17	153.7	157.2	162.6	172.1	183.3	195.2	206.6	213.8	218.5
18	189.3	193.4	200.1	211.7	225.3	239.8	253.7	262.4	268.2
19	231.3	236.4	244.4	258.4	275.0	292.6	309.4	319.9	326.9
20	280.6	286.7	296.4	313.3	333.2	354.4	374.7	387.3	395.8
21	337.8	345.2	356.8	377.0	400.9	426.3	450.5	465.6	475.7
22	403.8	412.5	426.3	450.4	478.9	509.1	537.9	555.9	567.9
23	479.0	489.4	505.7	534.3	567.9	603.6	637.7	659.0	673.3
24	564.1	576.3	595.5	629.1	668.7	710.7	750.8	775.9	792.6
25	659.5	673.7	696.2	735.5	781.7	830.9	877.8	907.1	926.6
26	765.2	781.8	807.9	853.6	907.3	964.5	1,019.0	1,053.1	1,075.8
27	881.4	900.5	930.7	983.5	1,045.6	1,111.6	1,174.7	1,214.1	1,240.4
28	1,007.8	1,029.7	1,064.4	1,124.9	1,196.3	1,272.2	1,344.6	1,389.9	1,420.1
29	1,143.7	1,168.7	1,208.3	1,277.5	1,358.9	1,445.6	1,528.4	1,580.1	1,614.7
30	1,288.5	1,316.8	1,361.7	1,440.2	1,532.7	1,631.1	1,725.0	1,783.8	1,823.1
31	1,440.9	1,472.8	1,523.4	1,611.9	1,716.2	1,827.3	1,933.4	1,999.8	2,044.2
32	1,599.4	1,635.2	1,691.9	1,791.0	1,908.0	2,032.6	2,151.7	2,226.3	2,276.2
33	1,762.3	1,802.1	1,865.2	1,975.7	2,106.1	2,245.0	2,378.0	2,461.3	2,516.9
34	1,927.4	1,971.5	2,041.3	2,163.6	2,308.0	2,462.1	2,609.6	2,702.0	2,763.8
35	2,092.5	2,141.0	2,217.8	2,352.3	2,511.3	2,681.1	2,843.7	2,945.7	3,013.9
36	2,255.0	2,307.9	2,391.8	2,538.9	2,712.9	2,898.9	3,077.1	3189.0	3,263.8
37	2,412.1	2,469.6	2,560.7	2,720.5	2,909.8	3,112.2	3,306.5	3,428.4	3,510.1
38	2,561.2	2,623.1	2,721.4	2,894.0	3,098.6	3,317.6	3,528.0	3,660.2	3,748.8
39	2,699.3	2,765.7	2,871.1	3,056.3	3,276.0	3,511.6	3,738.1	3,880.6	3,976.0
40	2,823.8	2,894.5	3,006.8	3,204.3	3,438.9	3,690.7	3,933.1	4,085.7	4,187.9

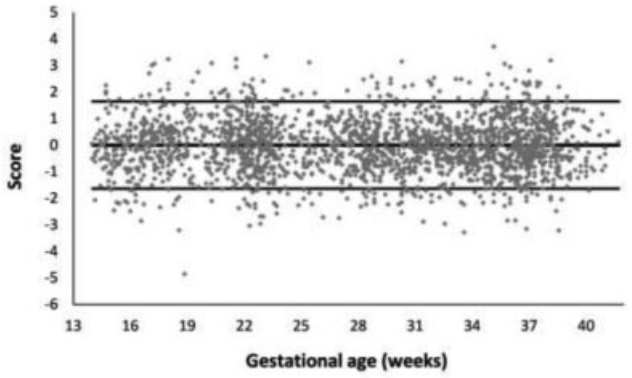

Fig. 2 Calculated scores at a confidence interval of 90%.

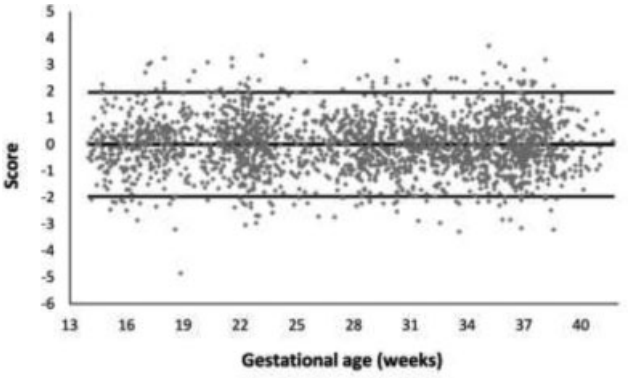

Fig. 3 Calculated scores at a confidence interval of 95%.

corresponding to 95% of the area under the curve of this distribution. For the model data, 94.1% of the scores were within this range, indicating good adherence to the model. This percentage was 94% in the tested dataset, indicating very good reproducibility of the model for estimating weights using data that were not used in the adjustment.

The proposed model was compared graphically with the Hadlock references and the curves developed in the Intergrowth 21st project (►**Fig. 4**).

Additionally, the proposed model was compared graphically with the Fetal Medicine Foundation (FMF),[16] and the World Health Organization (WHO),[17] models (►**Fig. 5**).

Discussion

We have developed reference curves for estimated fetal weight for a local population based on the hypothesis that these curves were different from those established for other populations. The distribution of racial population was in agreement with the data from the last local census,[12] despite being a population with moderate/high socioeconomic status from a private service. The proposed model was constructed after excluding gestations at risk of growth disorders and by including normal fetuses, thus defining a reference curve.

Following the recommendation of Altman and Chitty,[14] each fetus was included only once because the inclusion of multiple observations of the same fetus would characterize a growth curve, and, in this case, the effective sample size tends to be the number of fetuses and not the number of observations. Although our data were collected retrospectively, the use of Linear Integer Programming allowed us to select only one

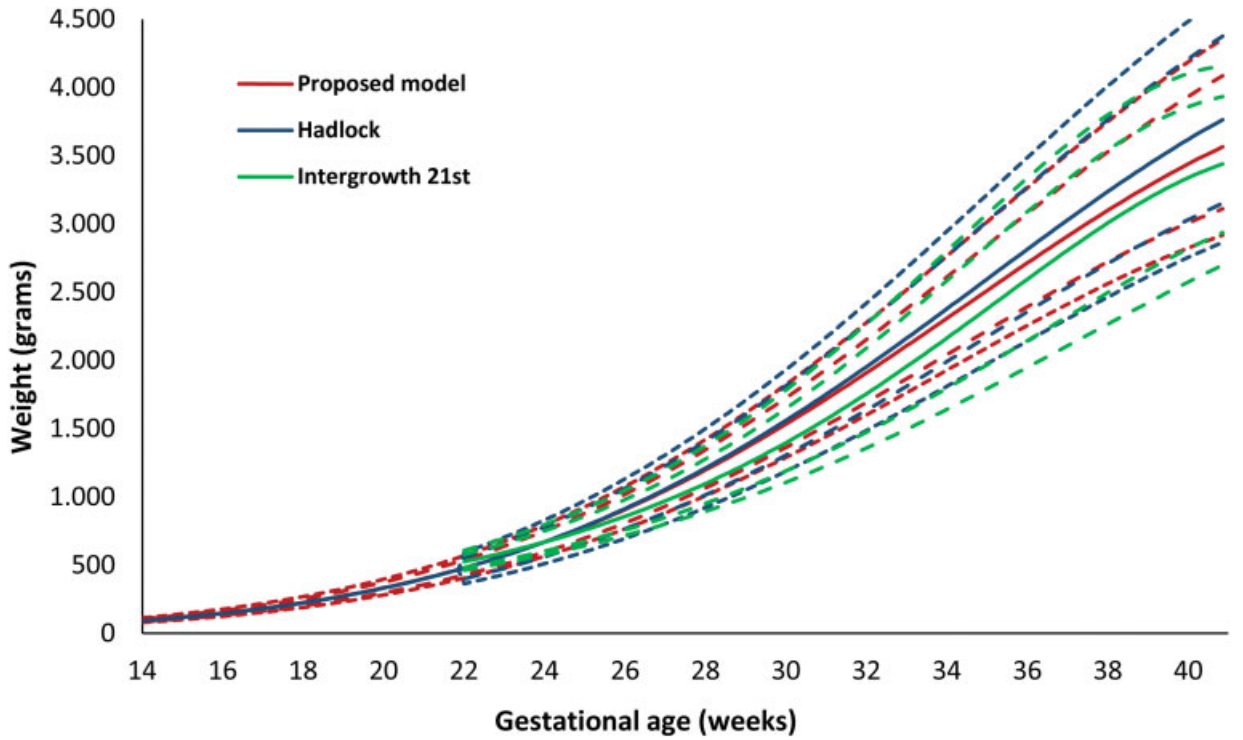

Fig. 4 Proposed, Hadlock, and Intergrowth 21st models according to fetal estimated weight—Curves for the 3rd, 10th, 50th, 90th and 97th percentiles.

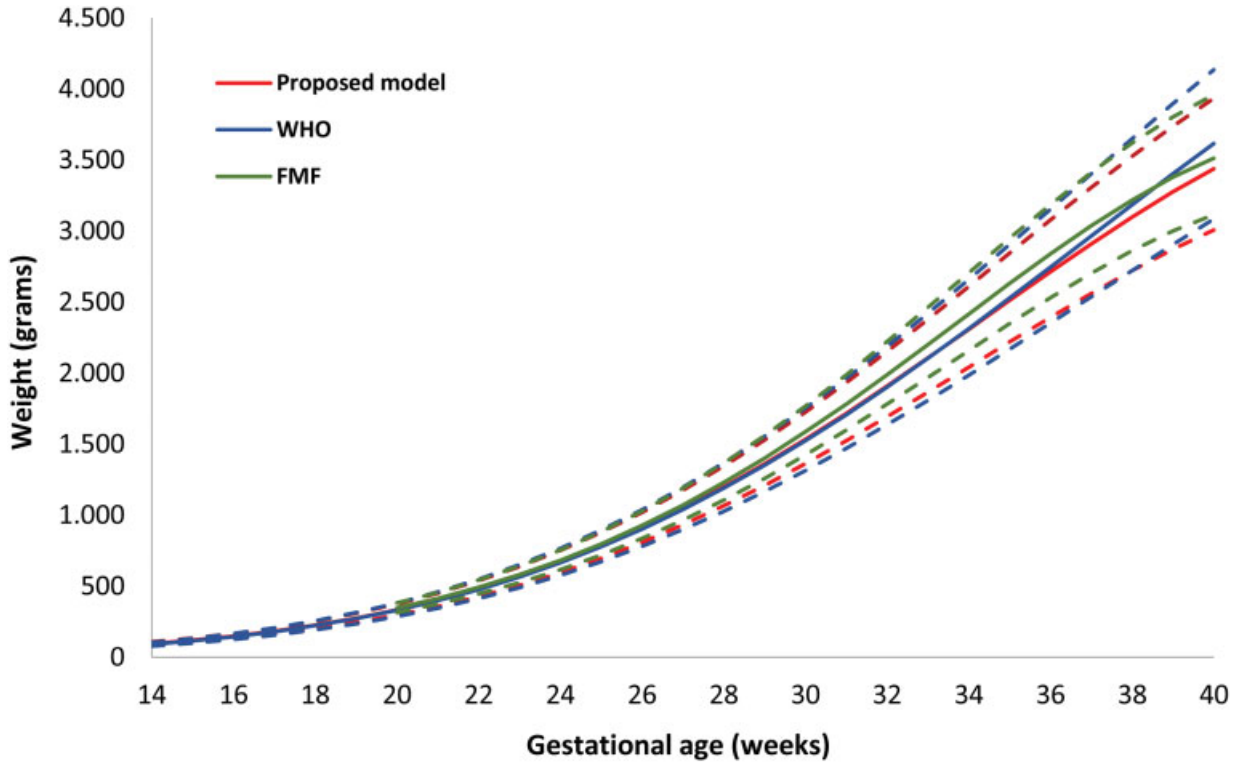

Fig. 5 Proposed, Fetal Medicine Foundation, and World Health Organization models according to fetal estimated weight—Curves for the 10th, 50th, 90th percentiles.

observation for each fetus, with homogeneous distribution across the evaluated gestational weeks. The use of this technique also allowed evaluating the reproducibility of the model in a population that was not included in the study, and the results indicated that reproducibility was very good in this population. Another advantage of the selected sample is that all patients had first trimester ultrasonography data for adequate determination of gestational age.

A disadvantage of the retrospective nature of the study is that it did not allow confirming whether a factor that could affect fetal growth was truly absent. Another limitation was that there was no standardization of data collection or blinding of the measurements on the screen of the ultrasound devices for the examiner, and this limitation might interfere with the obtained values. Moreover, the obtained curves might be affected by the fact that some examinations might have been requested by clinical indication because of suspected pathological growth. However, we believe that the influence of this factor, if present, is minimal because an overrepresentation of fetuses that were small for gestational age (SGA) and/or with IUGR or large for gestational age (LGA) in this sample would result in lower percentile values at the lower limit and an increase in curve percentiles, respectively, in contrast with what we observed by comparing our curves with other reference curves.

Compared with the Hadlock curves,[13] the 50th, 90th, and 97th percentiles in the proposed model were lower than those found by Hadlock, whereas the 10th percentile almost overlapped, and the 3rd percentile was slightly higher in our model. With regard to the curves of Intergrowth 21st [15] the 3rd, 10th, and 50th percentiles were higher in our model. Additionally, the proposed model was also compared with the Fetal medicine Foundation (FMF)[16] and World health Organization (WHO)[17] curves showing slight differences. While the 10th percentile was similar for the proposed and the WHO models, the FMF model was higher. With regarding to the 90th percentile, the proposed model was lower. Therefore, the use of all five models in the same population would result in different fetal classifications for estimated fetal weight and could reflect differences in the populations used for constructing the references.

Two Brazilian studies developed estimated fetal weight curves based on local populations[18,19] in the cities of São Paulo and Campinas, which are both located in the southeast of Brazil, and both found that the mean values were slightly lower than those presented by Hadlock et al.[13] A similar result was also observed in the model proposed in the current study for higher percentiles, but it was not observed in the 3rd and 10th percentiles, demonstrating that local variations might occur within a single country. Addressing these small differences may be important for adequately diagnosing growth disorders. Therefore, evaluating the performance of these curves in the populations for which they were developed is essential to assess whether they are in fact more adequate than the curves currently in use.

Conclusion

In summary, we provide reference curves for estimated fetal weight for a local population living in the city of Curitiba,

South of Brazil. The differences relative to the Hadlock and Intergrowth 21st Project curves may reflect differences in the populations on which the models were based. The implications of these differences for prenatal management and perinatal outcome could not be assessed in this study, and further research is needed to assess the application of these models to local populations for determining such implications.

Contributors

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

Conflict of Interests

The authors have no conflict of interests to declare.

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Pubic Arch Angle Measurement by Transperineal Ultrasonography: A Prospective Cross-Sectional Study

Medida do ângulo do arco púbico por ultrassonografia transperineal: um estudo prospectivo transversal

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Abstract

Objective To evaluate the ability of the pubic arch angle (PAA) as measured by transperineal ultrasonography during labor to predict the delivery type and cephalic pole disengagement mode.

Methods The present prospective cross-sectional study included 221 women in singleton-gestational labor $\geq$ 37 weeks with cephalic fetuses who underwent PAA measurement using transperineal ultrasonography. These measurements were correlated with the delivery type, cephalic pole disengagement mode, and fetal and maternal characteristics.

Results Out of the subjects, 153 (69.2%) had spontaneous vaginal delivery, 7 (3.2%) gave birth by forceps, and 61 (27.6%) delivered by cesarean section. For the analysis, deliveries were divided into two groups: vaginal and surgical (forceps and cesarean). The mean PAA was $102 \pm 7.5^{\circ}$ (range, 79.3–117.7°). No statistically significant difference was observed in delivery type ($102.6 \pm 7.2^{\circ}$ versus $100.8 \pm 7.9^{\circ}$, $p = 0.105$). The occipitoanterior position was seen in 94.1% of the fetuses and the occipitoposterior position in 5.8%. A narrower PAA was found in the group of surgical deliveries ($97.9 \pm 9.6^{\circ}$ versus $102.6 \pm 7.3^{\circ}$, $p = 0.049$). Multivariate regression analysis showed that PAA was a predictive variable for the occurrence of head disengagement in occipital varieties after birth (odds ratio, 0.9; 95% confidence interval, 0.82–0.99; $p = 0.026$).

Conclusion Ultrasonographic measurement of the PAA was not a predictor of delivery type, but was associated with the persistence of occipital varieties after birth.

Keywords
- labor
- ultrasonography
- cephalopelvic disproportion
- vaginal delivery
- cesarean section

Resumo

Objetivo Avaliar a medida do ângulo do arco púbico (AAP) por ultrassonografia transperineal durante trabalho de parto em predizer tipo de parto e modo de desprendimento do polo cefálico.

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Métodos Um estudo prospectivo transversal foi conduzido com 221 mulheres em trabalho de parto com gestação única ≥ 37 semanas, com fetos em apresentação cefálica, foram submetidas à avaliação ultrassonográfica por via transperineal para aferição do AAP. Correlações com tipo de parto, modo de desprendimento do polo cefálico e características fetais e maternas foram realizadas.

Resultados Um total de 153 (69,2%) mulheres apresentaram parto vaginal espontâneo, 7 (3,2%) parto a fórceps e 61 (27,6%) parto cesárea. Para fins de análise, dividiu-se os partos em dois grupos: partos vaginais e cirúrgicos (fórceps e cesáreas). A média do AAP foi $102 \pm 7{,}5^{\circ}$ (variação: 79,3–117,7°). Não foi observada significância estatística do AAP em relação ao tipo de parto ($102{,}6 \pm 7{,}2^{\circ}$ versus $100{,}8 \pm 7{,}9^{\circ}$; $p = 0{,}105$). Um total de 94,1% dos fetos desprenderam em variedade de posição occipito anterior e 5,8% em occipito posterior. Encontrou-se AAP mais estreitado no grupo de partos cirúrgicos ($97{,}9 \pm 9{,}6^{\circ}$ *versus* $102{,}6 \pm 7{,}3^{\circ}$; $p = 0{,}049$). A análise de regressão multivariada demonstrou que AAP foi uma variável de proteção para a ocorrência de desprendimento da cabeça em variedades occipito posteriores ao nascimento (odds ratio [OR]= 0,9; índice de confiança (IC) 95%: 0,82–0,99; $p = 0{,}026$).

Conclusão A medida ultrassonográfica do AAP não foi preditora do tipo de parto, porém demonstrou associação com persistência de variedades occipito posteriores ao nascimento.

Palavras-chave
- trabalho de parto
- ultrassonografia
- desproporção cefalo-pélvica
- parto vaginal
- cesárea

Introduction

A good proportion between the fetal head and maternal pelvis is a fundamental condition for the physiological presentation of childbirth. During its descent, the cephalic pole performs flexion, rotation, and extension and develops plastic alterations in its format. The birth canal also adapts—that is, mobility of the sacrococcygeal joint increases and the soft tissues become distended. Such changes are necessary since the head diameters of a term fetus are similar to the main diameters of the pelvis, requiring the latter to adapt to the birth canal to enable the fetus to cross it.[1]

The disparity between pelvic architecture or size and the fetal head constitutes an obstetric entity called cephalopelvic disproportion (CPD), a cause of increased operative emergencies during delivery and adverse perinatal outcomes, accounting for 8% of all maternal deaths worldwide.[2] Cephalopelvic disproportion is diagnosed during labor, and its prediction at the end of gestation or onset of labor improves fetal outcomes and avoids stress and dissatisfaction in pregnant women due to prolonged labor that ultimately results in emergency cesarean section.[3]

Pelvimetry, a method that studies pelvic shape and proportions, can be performed clinically through the measurement of the diagonal conjugate, interischial distance, and bituberous diameter[1] or using imaging methods such as radiography, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography.[4,5] The accuracy of the clinical detection of pelvic narrowing is limited to 50%.[6] The use of X-rays not only causes exposure to ionizing radiation, but also doubles the incidence of abdominal births.[7] Computed tomography and MRI are effective but very costly and often impractical within an obstetric center.

Ultrasonography is highly accessible in delivery rooms, has a smaller learning curve, is painless, is easy to perform, and is relatively innocuous. For these reasons, it has become a widely used method.[8–12] The main parameter studied on ultrasonography in such cases is the pubic arch angle (PAA), which is formed by the confluence of the pubic bone rami at the level of the symphysis.[13] This angle provides indirect information about pelvic shape and obstetric dimensions such as the superior aperture of the pelvis and the interspinous distance.[14] The gynecoid pelvis has a wide PAA and favors rotation of the cephalic pole to the occipitoanterior position. In women with a narrow anterior pelvic compartment in which the PAA is decreased, as in android pelvis, the pubic rami converge at a sharper angle. In these situations, the fetal head tends to position itself in the posterior compartment of the birth canal, being forced against the soft tissues and bony structures in this region. This impairs the rotation of the occiput to the anterior positions, increasing the frequency of transversal and persistent posterior varieties and leading to the occurrence of dystocia and surgical delivery.[15–17]

Several studies have evaluated the efficacy of the PAA measurement, both before and during labor, at predicting the delivery route and cephalic pole detachment mode.[13,17] These studies examined specific population groups from Europe, the Middle East, and Oceania. However, evaluations in other populations with different anthropometric characteristics are required to corroborate the applicability of this method and increase its acceptability; notably in the Brazilian population that presents anthropometric heterogeneity due to its racial mixture.

The objective of the present study was to analyze whether the PAA measure, as a parameter of pelvic proportion, is able

to predict the delivery type and cephalic pole disengagement mode.

Methods

The present prospective cross-sectional study was conducted between February and September 2017 at the Assis Chateaubriand Teaching Maternity of the Universidade Federal do Ceará (UFC), Fortaleza, state of Ceará, Brazil. A convenience sample of 221 parturients was recruited in the first or second phase of labor according to the clinical evolution at admission. Transperineal ultrasonography was used to measure the PAA (exposure variable); these data were compared with delivery type (vaginal and surgical) and cephalic pole disengagement mode (occipitoanterior or occipitoposterior, variables of outcome) in search of associations. The sum of the forceps and cesarean deliveries was considered surgical delivery. Other relevant information possibly capable of predicting delivery type and cephalic pole disengagement mode or of distorting the associations described above was also studied. This included maternal age, maternal height, body mass index (BMI), parity, birthweight, type of labor onset (spontaneous or induced), labor analgesia, and use of uterotonic agents. Gestational age was not compared because all patients in the study were full term ($\geq$ 37 weeks). Informed consent was obtained from all patients, and the present study was approved by the UFC Research Ethics Committee under the opinion number 1.010.040.

The inclusion criterion was a singleton pregnancy with a live fetus without structural anomalies in cephalic presentation with estimated fetal weight by ultrasound considered adequate for gestational age and biparietal diameter $<$ 2 standard deviations (SDs) for gestational age; regardless of whether the amniotic sac was intact or broken or whether the patients received labor analgesia. Patients were excluded if on admission they presented urgent situations requiring immediate pregnancy resolution by cesarean section, such as: uterine rupture, umbilical cord prolapse, placental abruption with changes in fetal auscultation, and cardiotocographic tracings classified in category 3 of the National Institute of Child Health and Human Development 2008.[18] Also, newborns with $\geq$ 4,000 g were excluded.

Pubic arch angle measurement was performed by a single examiner (Carvalho R. H.) using a Logic C5 Premium ultrasound device (General Electric, Milwaukee, WI, USA) equipped with a two-dimensional (3–5 MHz) convex transducer. The PAA measurements were obtained transperineally, outside the period of contraction or pull, with the women in the dorsal decubitus position and the legs ajar and semi-flexed.

The probe was positioned transversally in contact with the perineum at the level of the clitoris. The transducer was tilted at $\sim$ 45° until an image of the symphysis with the 2 branches of the pubic bone in symmetrical position was obtained. The lines for angle measurement were positioned on the lower edges of the right and left pubic branches, forming a triangle based on the ischial tuberosities bilaterally and on the convergence at the center of the symphysis as the apex (►**Fig. 1**), as previously described by Gilboa et al.[13] Three PAA measurements were obtained from each participant, and the average of the three measurements was considered.

Ultrasound findings were not revealed to the members of the obstetrical staff to avoid interference with labor. The follow-up of the delivery was the responsibility of the on-call care team, which followed the routine recommended by institutional protocols.[19]

The descriptive data are presented as mean $\pm$ SD or *n* (%). The Chi-squared and Fisher exact tests were used to analyze the categorical variables, and the Mann-Whitney or Student *t*-test test was used to analyze continuous variables according to the normality of the data. The analyzed variables were PAA; patient age, height, body mass index (BMI), and parity; birth weight; labor onset type (spontaneous or induced); labor analgesia; and the use of uterotonic agents according to

Fig. 1 Schematic drawing of the pubic arch angle (PAA) (left) and PAA image obtained by transperineal ultrasonography during the first phase of delivery (right).

delivery type (vaginal or surgical) and cephalic pole disengagement mode (occipitoanterior or occipitoposterior) as the outcome variables.

All variables presenting a value of $p < 0.20$ for one or both outcomes were subjected to multiple logistic regression analysis for both outcomes (surgical delivery and cephalic pole disengagement in the occipitoposterior position). Values of $p < 0.05$ were considered statistically significant. The gross odds ratio (OR) was calculated and adjusted with its respective 95% confidence interval (CI). The data were analyzed by SPSS for Windows, version 13.0 (SPSS, Inc., Chicago, IL, USA).

Results

The clinical and obstetric characteristics of the 221 participants as well as the birth and outcome details are shown in ►**Table 1**.

Table 1 Characteristics of the study population, deliveries, and outcomes

Variable	Mean ± SD	*n* (%)
Maternal age (years old)	24.2 ± 6.8	–
Parity		
0	–	129 (58.4)
1	–	63 (28.5)
2	–	19 (8.6)
3	–	7 (3.2)
4	–	1 (0.5)
5	–	1 (0.5)
9	–	1 (0.5)
Maternal height (m)	1.57 ± 0.6	–
Maternal weight (kg)	72.4 ± 14	–
BMI (kg/m^2)	29.3 ± 4.7	–
Gestational age (US) (weeks)	39.4 ± 1.1	–
Birth weight (g)	3.312.1 ± 427	–
Labor analgesia	–	32 (14.5)
Use of uterotonic agents	–	78 (36.1)
Previous cesarean section	–	16 (7.2)
Labor induction	–	16 (7.3)
Delivery type		
Spontaneous vaginal	–	153 (69.2)
Forceps	–	7 (3.2)
Cesarean section	–	61 (27.6)
Cephalic pole disengagement		
Occipitoanterior	–	161 (94.2)
Occipitoposterior	–	10 (5.8)

Abbreviations: BMI, body mass index; SD, standard deviation; US, ultrasonography.

There were 153 (69.2%) vaginal deliveries, 7 (3.2%) forceps deliveries, and 61 (27.6%) cesarean deliveries. ►**Table 2** shows the univariate analysis results stratified according to delivery type (vaginal versus surgical). Surgical delivery was associated with shorter maternal height (1.58 ± 0.06 m versus 1.55 ± 0.06 m; $p < 0.001$), higher BMI (28.6 ± 4.6 - kg/m^2 versus 30.8 ± 4.7 kg/m^2; $p < 0.001$), greater use of labor analgesia (15/153 or 9.9% versus 17/68 or 17%; $p < 0.003$), and lower parity (78/153 or 51% versus 51/68 or 75%; $p < 0.001$). No statistically significant difference was observed for PAA among delivery types (102.6 ± 7.20° versus 100.8 ± 7.90°; $p = 0.105$).

►**Table 3** shows the stratification of the data by fetal occiput position on disengagement. In 171/221 study patients, it was possible to retrieve this information from the medical records. An association was noted between the use of labor analgesia and the occurrence of disengagement in the occipital position at birth (20/161 or 12.2% versus 4/10 or 40%; $p = 0.013$). Pubic arch angle regarding fetal occiput position on disengagement differed significantly. Narrower angles were associated with occipitoposterior positions (102.6 ± 7.30° versus 97.9 ± 9.60°; $p = 0.049$).

The results of the multivariate regression model of variables with p values < 0.20 are shown in ►**Tables 4** and **5**. In the analysis of the surgical delivery type outcome (►**Table 4**), 4 variables were relevant, representing a risk for this type of resolution: maternal height < 1.57 m (OR: 3.05; 95%CI: 1.55–6.02; $p = 0.001$); BMI/obesity (OR: 3.89; 95%CI: 1.38–-10.93; $p = 0.010$); nulliparity (OR: 2.89; 95%CI: 1.42–5.87; $p = 0.003$), and use of labor analgesia (OR: 2.68; 95%CI: 1.08–6.68; $p = 0.034$). When analyzing the outcome variable of cephalic pole disengagement in the posterior positions

Table 2 Population characteristics stratified by delivery type

	Vaginal ($n = 153$)	Surgical (forceps and cesarean section) ($n = 68$)	*p-value*
Age (years old)	24.0 ± 6.91	24.57 ± 6.66	0.588[a]
Height (m)	1.58 ± 0.06	1.55 ± 0.06	< 0.001[a]
BMI (kg/m^2)	28.6 ± 4.55	30.82 ± 4.73	0.001[a]
Parity			0.001[b]
Nulliparous	78 (51%)	51 (75%)	
Multiparous	75 (49%)	17 (25%)	
Labor analgesia	15 (9.9%)	17 (25%)	< 0.003[b]
Delivery type			0.622[b]
Spontaneous	141 (92.2%)	63 (94%)	
Induced	12 (7.8%)	4 (6%)	
Use of uterotonic agents	48 (32.2%)	30 (44.8%)	0.075[b]
Birth weight (g)	3287.9 ± 429.83	366.4 ± 418.84	0.208[a]
Pubic arc angle (°)	102.56 ± 7.22	100.8 ± 7.96	0.105[a]

Abbreviation: BMI, body mass index.
[a]Student *t*-test.
[b]Chi-squared test.

Table 3 Population characteristics stratified by fetal occiput position on disengagement

Variable	Occipitoanterior ($n = 161$)	Occipitoposterior ($n = 10$)	*p-value*
Age (years old)	24.17 ± 6.71	22 ± 7.24	0.324[a]
Height (m)	1.58 ± 0.06	1.58 ± 0.05	0.647[a]
BMI (kg/m^2)	28.95 ± 4.61	27.8 ± 3.54	0.444[a]
Parity			0.271[b]
Nulliparous	86 (52.1%)	7 (70%)	
Multiparous	79 (47.9%)	3 (30%)	
Labor analgesia	20 (12.2%)	4 (40%)	0.013[b]
Delivery type			0.670[b]
Spontaneous	153 (92.7%)	8 (88.9%)	
Induced	12 (7.3%)	1 (11.1%)	
Use of uterotonic agents	53 (32.9%)	6 (60%)	0.080[b]
Birthweight (g)	3310.38 ± 430.27	3088 ± 296.41	0.109[a]
Pubic arc angle (°)	102.58 ± 7.27	97.92 ± 9.59	0.049[a]

Abbreviation: BMI, body mass index.
[a]Student *t*-test.
[b]Chi-squared test.

(►**Table 5**), labor analgesia did not differ significantly, unlike the PAA, which showed an association as a protection factor for this occurrence (OR: 0.90; 95%CI: 0.82–0.99; $p = 0.026$). The PAA showed a negative correlation with fetal head disengagement at the occipitoposterior position — that is, each degree of PAA decrease caused an 11% increase in the risk of delivery with the cephalic pole at the posterior occipitoposition.

Discussion

Most groups that use intrapartum ultrasound in centers in Europe, the Middle East, Asia, and North America apply three-dimensional (3D) technology.[13,15,17,20] In the present study, two-dimensional (2D) ultrasonography was used since it is the method available in most maternity hospitals in Brazil and is less costly and easier to perform. Torkildsen et al[21] found good intraobserver agreement and reproducibility between 2D and 3D techniques. Corroborating this finding, the results of the present study were close to those found in studies that used 2D technology, with a mean PAA of 102.0 ± 7.5°. Using 2D ultrasonography, Gilboa et al[13] found a mean PAA of 101.1 ± 13.1° in a cohort of 62 Israeli women in the prolonged second stage of labor. Applying 3D technology, Albrich et al[20] found a mean PAA of 109.3 ± 8.9° in a cohort of 611 Australian women at between 34 and 36 weeks of gestation.

Our study results demonstrate that maternal height, BMI, and epidural analgesia influence delivery type. Surgical delivery occurred more frequently in shorter or obese women as well as in those who used labor analgesia, corroborating findings in the literature, which demonstrated an increase in the incidence of surgical delivery with short maternal height and obesity[22,23] as well as higher occurrences of instrumental deliveries in patients receiving epidural analgesia.[24]

The PAA was not a predictor of delivery type as in other studies, which also failed to demonstrate this association.[20,25] However, contrary results were obtained by Gilboa et al[13] and Ghi et al,[17] who observed that women with surgical delivery outcomes had smaller PAAs than those who had vaginal delivery (97.1 ± 11.5° versus 110.1 ± 14.0° and 111.4 ± 13.5° versus 118.4 ± 11.4°, respectively). It should be considered that, unlike in the current study, the population evaluated in those studies consisted only of pregnant women in the second phase of labor;[13,17] in one, all patients selected presented progression failure at this stage.[13] Some factors should be considered in the evaluation of these conflicting results, such as different study designs, various pelvic conformations, and various delivery modes and different rates of uterotonic agent use and analgesia that affect the local incidence of cesarean section and interfere with the study findings.

Table 4 Logistic regression analysis results of surgical delivery outcome

Variable	Univariate			Multivariate		
	B	OR (95%CI)	*p-value*	B	OR (95%CI)	*p-value*
Height < 1.57 m	0.95	2.58 (1.41–4.73)	0.002	1.12	3.05 (1.55–6.02)	0.001
BMI (kg/m^2)						
Adequate		reference				
Overweight	0.87	2.38 (1.03–7.293)	0.043	0.90	2.47 (0.87–6.97)	0.089
Obese	0.34	3.62 (1.39–9.46)	0.009	1.36	3.89 (1.38–10.93)	0.010
Nulliparous	1.06	2.89 (1.53–5.44)	0.001	1.06	2.89 (1.42–5.87)	0.003
Labor analgesia	1.11	3.04 (1.42–6.54)	0.004	0.99	2.68 (1.08–6.68)	0.034
Use of uterotonic agents	0.53	1.71 (0.94–3.08)	0.007	0.21	1.22 (0.60–2.51)	0.574
Birth weight > 3,325 g	0.27	1.31 (0.74–2.32)	0.358	0.40	1.5 (0.77–2.92)	0.236
Pubic arc angle (°)	-0.03	0.97 (0.93–1.01)	0.106	-0.04	0.97 (0.92–1.01)	0.116

B, variable coefficient in the regression model; BMI, body mass index; CI, confidence interval; OR, odds ratio.
R^2 Nagelkerke = 0.24; Median height, 1.57 m (1.54–1.1 m); Median birthweight, 3,325 g (2,995–3,615 g).

Table 5 Logistic regression analysis results of fetal head disengagement (occipitoposterior) outcome

Variable	Univariate			Multivariate		
	B	OR (95%CI)	*p-value*	B	OR (95%CI)	*p-value*
Height < 1.57 m	0.04	1.04 (0.29–3.72)	0.955	-0.08	0.92 (0.22–3.86)	0.913
BMI (kg/m^2)						
Adequate		reference				
Overweight	0.11	1.11 (0.26–4.72)	0.886	0.23	1.25 (0.25–6.19)	0.782
Obese	−1.75	0.17 (0.02–1.74)	0.136	−2.01	0.13 (0.01–1.56)	0.108
Nulliparous	0.76	2.14 (0.54–8.58)	0.281	0.28	1.32 (0.26–6.80)	0.737
Labor analgesia	1.57	4.8 (1.25–18.49)	0.023	1.08	2.96 (0.56–15.71)	0.203
Use of uterotonic agents	0.53	1.71 (0.94–3.08)	0.094	0.79	2.20 (0.46–10.43)	0.320
Birth weight > 3325 g	−1.37	0.25 (0.05–1.23)	0.088	−1.45	0.24 (0.04–1.50)	0.126
Pubic arc angle (°)	−0.08	0.93 (0.86–1)	0.060	−0.11	0.90 (0.82–0.99)	0.026

B, variable coefficient in the regression model; BMI, body mass index; CI, confidence interval; OR, odds ratio.
R^2 Nagelkerke = 0.274; Median height, 1.57 m (1.54–1.1 m); Median birth weight, 3,325 g (2,995–3,615 m).

Considering the fetal head disengagement outcome variable, the PAA was associated with the occurrence of occipitoposterior varieties. Smaller PAAs were observed in patients who delivered fetuses in the occipitoposterior position than in the anterior positions. Ghi et al[17] also found an association between PAA narrowing and the occipitoposterior variety at delivery (OR: 1.04; 95%CI: 1.01–1.08). These results demonstrated a lower PAA in patients who gave birth to fetuses with heads in posterior varieties than in those whose fetuses were delivered in anterior positions ($104.3 \pm 16.8°$ versus $116.4 \pm 11.9°$).[17] The findings of these two studies reinforce a recent hypothesis in the literature that assumes that the occurrence of persistent occipitoposterior varieties in labor may be an adaptive phenomenon to narrowing of the anterior pelvic compartment.[15] When the care team is aware that the parturient has a reduced PAA, this provides guidance on a likely prolongation of labor in addition to favoring a more attentive attitude regarding the possibility of dystocia as well as the possible need for an instrumental delivery and an episiotomy.

Regarding the limitations of the present study, it is possible that the low socioeconomic level of the studied population impacted the different types of childbirth. The preference for cesarean section influenced by sociocultural factors[26] was associated with the low use of instrumental delivery and the nonuse of manual head rotation in the facility where the present study was performed, resulting in an increased incidence of cesarean section, and may have interfered with the attempt to demonstrate the association of the PAA with delivery type. No other methods, such as CT or MRI, were used to validate the ultrasound measurements. The incomplete medical records caused gaps that made it difficult to analyze some of the data more substantially, such as the duration of the second phase of labor that was cited by Gilboa et al[13] as inversely proportional to the measurement of the PAA. Another limitation to be considered is that the present study did not intend to apply 3D ultrasound or other 2D ultrasound parameters to assess maternal pelvis or fetal head malposition (deflection and asynclitism) that contribute to the occurrence of dystocia.[27]

New studies are required to clarify the discordant results in the literature regarding the influence of PAA on the evolution of labor. However, the importance of this knowledge for better delivery assistance is well understood at our institution; due to the good sampling and technical rigor used, these data can be extrapolated to parturients similar to those included in the present study.

Conclusion

In summary, the ultrasound measurement of the PAA was not a predictor of delivery type but was associated with the persistence of occipitoposterior varieties in fetal head disengagement.

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

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

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Frequency of Congenital Anomalies in the Brazilian Midwest and the Association with Maternal Risk Factors: Case-control Study

Frequência das anomalias congênitas no centro-oeste brasileiro e a associação com fatores de risco materno: estudo caso-controle

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Abstract

Objective To evaluate the frequency of structural congenital anomalies (CAs) in the midwest of Brazil and its association with maternal risk factors.

Methods This was a prospective, observational, case-control study based on a hospital population. Pregnant women attended at a fetal medicine service in Brazil were analyzed in the period from October 2014 to February 2016.A total of 357 pregnant women were included, 223 of whom had fetuses with structural anomalies (group case), and 134 of whom had structurally normal fetuses (control group). The clinical history was made previous to prenatal consultation, and the diagnosis of the structural CA was performed through ultrasound.

Results A frequency of 64.27% ($n = 223$) of pregnant women with fetuses with structural anomalies was observed. The most frequent structural CAs were those of the central nervous system (30.94%), followed by anomalies of the genitourinary system (23.80%), and, finally, by multiple CAs (16.60%). The background of previous children with CAs (odds ratio [OR]: 3.85; $p = 0.022$), family history (OR: 6.03; $p = < 0.001$), and consanguinity between the progenitors (OR: 4.43; $p = 0.034$) influenced the occurrence of structural CA.

Conclusion The most frequent CAs are those of the central nervous system, followed by those of the genitourinary system, and then multiple anomalies. The maternal risk factors that may have influenced the occurrence of structural CA were previous children with CA, family history, and consanguinity among the parents.

Keywords

- congenital anomalies
- ultrasound
- prenatal
- prenatal diagnosis
- risk factors

Resumo

Objetivo Avaliar a frequência de anomalias congênitas (ACs) estruturais no centro-oeste brasileiro e a associação com fatores de risco maternos.

Métodos Estudo prospectivo, observacional, caso-controle, baseado em uma população hospitalar. Foram analisadas gestantes atendidas em um serviço de medicina

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fetal no Brasil, no período de outubro de 2014 a fevereiro de 2016. Foram analisadas 357 gestantes, dentre as quais 223 tiveram fetos com ACs estruturais (grupo controle) e 134 tiveram fetos estruturalmente normais (grupo controle). A história clínica foi feita antes da consulta de pré-natal, e o diagnóstico da AC estrutural foi realizado por ultrassonografia.

Resultados Observou-se uma frequência de 64,27% ($n = 223$) de gestantes com fetos com ACs estruturais. As ACs estruturais mais frequentes foram as do sistema nervoso central (30,94%), seguidas das anomalias do sistema gênito-urinário (23,80%), e, por fim, das ACs múltiplas (16,60%). Antecedentes de crianças com AC (razão de probabiliade [RP]: 3,85; $p = 0,022$), antecedentes familiares (RP: 6,03; $p = < 0,001$), e consanguinidade entre os grupos progenitores (RP: 4,43; $p = 0,034$) influenciaram a ocorrência de AC estrutural.

Conclusão As ACs mais frequentes foram as do sistema nervoso central, as do sistema gênito-urinário, e as ACs múltiplas. Os fatores de risco maternos que podem ter influenciado a ocorrência de AC estrutural foram antecedentes de crianças com AC, história familiar, e a consanguinidade entre os pais.

Palavras-chave
- anomalias congênitas
- ultrassom
- pré-natal
- diagnóstico pré-natal
- fatores de risco

Introduction

Congenital anomalies (CAs) are among the main causes of death in children under 5 years of age.[1] It is estimated that between 3 and 7% of children are born with birth defects worldwide,[2] and that ~ 270,000 newborns die during the first 28 days of life every year.[2,3] In developed countries, CA is the leading cause of death in children, while in developing countries, mortality by CA is still not considered a public health problem.[4] However, with the control of infections and diseases of nutritional deficiency, there is a tendency to reduce infant mortality for these reasons; thus, congenital malformations have become important causes of perinatal mortality in countries such as Brazil.[5,6] Currently, ~ 60% of the etiology of CAs in human beings are not elucidated. However, in around 25% of CAs, the causes seem to be multifactorial, reflecting a complex interaction of known and unknown genetic and environmental factors, including sociocultural, racial, and ethnic variables.[7] In Brazil, there is a shortage of data on the incidence of CA and the associated maternal risk factors. The absence of comprehensive studies on CAs in Brazil justifies a prospective study case control that aims to describe the frequency of structural CAs and the characteristics of pregnant women to determine possible risk factors associated with the structural CA. The results presented herein can help in the development of strategies to improve the management, genetic counseling, and rehabilitation of patients with CA as well as the taking of public health measures to determine risk factors.

Methods

This was a prospective, observational, case-control study based on a hospital population. Pregnant women attended at a fetal medicine service in Brazil were analyzed in the period from October 2014 to February 2016.The research ethics committee of the institution approved the research with the number 808.377. Participants who responded to the questions asked during the interview and performed all the prenatal follow-up at the institution were included in the study. The collection of data was obtained through interview of the pregnant women, using a preform that contained personal and family history (maternal age, maternal ethnicity, previous children with CA, CA family history, and consanguinity) data. Data on previous obstetric history (number of previous pregnancies and prior abortions) were also verified. The presence of structural CA and its classification was confirmed by prenatal ultrasound evaluation by a fetal medicine specialist in. After the monitoring of ultrasounds, the pregnant women were categorized in the case or control groups. The case group was made up of pregnant women of fetuses with structural anomalies, and the control group by pregnant women whose fetuses did not have structural abnormalities. The pregnant women in the case group were accompanied by the main researcher in all the consultations performed after the diagnosis of CA. Thus, it was possible to update the information concerning the development of the fetus. The results of childbirth and newborns with structural anomaly were obtained by telephone contact with the pregnant women, in the computerized reports system, and, in the cases of childbirth performed in the hospital where the study was conducted, by consulting the medical file. The data were analyzed through descriptive statistics (average, standard deviation [SD], absolute frequency, relative frequency, median, confidence interval [CI]), Chi-squared tests, odds ratio, and the IBM SPSS Statistics for Windows version 22.0 software (IBM Corp., Armonk, NY, USA). Values of $p < 0.05$ were considered statistically significant.

Results

In the investigation period, 357 pregnant women were sent for attendance at the institution. Of these, 62.46% (223/357)

were pregnant with fetuses with structural anomalies (case group), and 37.54% (134/357) were pregnant with structurally normal fetuses (control group). The average age of pregnant women in the case group was 25.73 years, and, in the control group, it was 25.39 years. ►**Table 1** describes the study population in detail.

Table 1 Description of sociodemographic and obstetric data of pregnant women

Variables	Population			
	Case		Control	
	n	%	n	%
Maternal age				
≤ 18	32	14.34%	19	14.18%
19–24	70	31.40%	46	34.33%
25–30	69	30.94%	34	25.37%
31–36	41	18.39%	26	19.40%
≥ 37	11	4.93%	9	6.72%
Ethnicity				
White	46	20.62%	45	33.58%
Brown	128	57.40%	62	46.27%
Black	45	20.20%	27	20.15%
Indigenous	4	1.80%	0	–
Nr. of gestations				
Primigravida	92	41.26%	46	34.33%
Multigravida	131	58.74%	88	65.67%
One previous gestation	*68*	*51.91%*	*42*	*47.73%*
Two previous gestations	*38*	*29.00%*	*33*	*37.50%*
≥ Three previous gestations	*25*	*19.09%*	*13*	*14.77%*
History of abortion				
No	180	80.72%	120	89.55%
Yes	43	19.28%	14	10.45%
Previous gestation	*12*	*27.91%*	*5*	*35.72%*
In one of two previous pregnancies	*18*	*41.86%*	*2*	*14.28%*
In one of ≥ three previous pregnancies	*13*	*30.23%*	*7*	*50.00%*
Children with CA				
No	205	91.93%	131	97.76%
Yes	18	8.07%	3	2.24%
Previous gestation	*2*	*11.11%*	2	66.67%
In one of two previous pregnancies	*10*	*55.56%*	0	–
In one of ≥ three previous pregnancies	*6*	*33.33%*	1	33.33%
Family history of CA				
No	148	66.37%	124	91.94%
Yes	75	33.63%	10	8.06%
Parents with CA	*7*	*9.33%*	1	*10.00%*
Brothers or grandmothers with CA	*23*	*30.67%*	4	*40.00%*
Uncles and grandmothers with CA	*10*	*13.33%*	0	-
Uncles, grandmothers, and cousins with CA	*22*	*29.33%*	5	*50.00%*
CA in several relatives	*13*	*17.33%*	0	-
Consanguinity				
No	209	93.72%	132	98.51%
Yes	14	6.28%	2	1.49%
Total	223	100%	134	100%

Abbreviations: %, frequency; CA, congenital anomaly; mean, arithmetic mean; n, sample.

Table 2 Distribution of main structural congenital anomalies according to topography and type of lesion

Congenital anomalies	n	%
Central nervous system		
Hydrocephalus	23	33.33%
Anencephaly	16	23.20%
Meningocele	7	10.14%
Others	23	33.33%
Total	69	100%
Genitourinary system		
Renal dysplasia	20	37.73%
Hydronephrosis	13	24.53%
Pyelectasis	12	22.64%
Others	8	15.10%
Total	53	100%
Multiple anomalies		
Craniofacial and limbs	13	35.14%
Craniofacial and cardiac	9	24.32%
Craniofacial and digestive	6	16.22%
Others	9	24.32%
Total	37	100%

Abbreviations: %, frequency; n, sample.

The most frequently diagnosed CAs were anomalies of the central nervous system (CNS) (30.94%; $n = 69$), followed by anomalies of the genitourinary system (GUSs) (23.80%; $n = 53$), and, finally, by multiple congenital anomalies (MCAs) (16.60%; $n = 37$). ►**Table 2** demonstrates the distribution of major structural CAs, according to topography and type of lesion. In addition, other abnormalities, such as abdominal (8.52%; $n = 19$), cardiovascular (6.30%; $n = 14$), and lymphatic system (5.82%; $n = 13$), among others (8.02%; $n = 18$), were observed.

Table 3 Distribution of cases of fetal evaluation according to the characteristics of pregnant women attended at a fetal medicine service

Variables	Population						
	Case		Control		OR	95%CI	*p*-value
	n	%	n	%			
Maternal age							
< 35	21	90.42%	12	80.96%	–	0.50–2.22	0.884
≥ 35	202	90.58%	122	91.04%			
Nr. of gestations							
Primigravida	92	41.26%	46	34.33%	–	0.86–2.10	0.193
Multigravida	131	58.74%	88	65.67%			
Previous children with CA							
Yes	18	8.07	3	2.24%	3.85	1.11–13.27	0.022
No	205	91.93	131	97.76%			
Family history of CA							
Yes	75	33.63%	10	8.06%	6.03	3.12–12.67	< 0.001
No	148	66.37%	124	91.94%			
Consanguinity							
Yes	14	6.28%	2	1.49%	4.43	0.99–19.76	0.034
No	209	93.72%	132	98.51%			
Total	223	100%	134	100%			

Abbreviations: %, frequency; 95%CI, 95% confidence interval; CA, congenital anomaly; n, sample; OR, odds ratio.

When comparing the case group with the control group, the data analysis revealed a statistically significant difference in relation to the CA family history ($p < 0.001$, CI: 3.12–12.67), indicating that pregnant women with relatives who have structural CAs have 6.03 more chance of develop fetuses with structural CAs. Patients with previous children with CAs ($p = 0.022$) and consanguinity ($p = 0.034$) also showed a statistically significant difference between the groups (►**Table 3**).

Discussion

During the investigation period, a frequency of 62.46% of pregnant women with fetuses carrying structural anomalies was observed. The CNS, GUS, and MC anomalies were the most frequent ones. Indian studies showed similar results.[8–10]

Differently, other studies report higher frequency of CAs of the cardiovascular system.[5,11–13] On the other hand, the higher frequency of CNS has been reported in several studies in Iran,[14] Japan,[15] Pakistan,[16,17] China,[18] Nigeria,[19] Tanzania,[20] and India.[8–10]

The etiology of CNS anomalies is multifactor and involves complex interactions between genetic and environmental factors, constituting one of the most common congenital defects.[9,21,22] Among the anomalies of the CNS observed in this study, hydrocephalus and anencephaly were the most reported changes, which is similar to other studies that also reported hydrocephalus[8,14,17,23] and the anencephaly[8,15,17,24] among the most common malformations.

The data in this study indicated that the occurrence of fetal malformation in one or more family members is associated with the development of CAs in the current gestation. Pregnant women who have a family history of CAs are 6.03 times more likely to develop fetuses with some structural anomaly. the literature data already highlighted this association.[8,23] Correia et al[25] revealed that 16% of families with registered cases of fetal malformations in Portugal had one or more family members with CAs. In addition, studies indicate that some specific CAs, such as those of the kidney and heart, have the potential to aggregate into families.[26,27]

In this study, the pregnant women who have had children with some CA presented 3.85 times more chance of having other children with malformations. These data are similar to the results of Lie et al,[28] which showed that mothers who already had a child with CA would have a 2.4 times greater risk of having a second gestation affected when compared with a pregnant woman without a history of CA occurrence. Marwah et al[8] observed higher frequency of malformations in pregnant women who had already had children with CA. Thus, possibly, there is a strong tendency of recurrence of specific defects in the same family, indicating the persistence of a causal factor.

Regarding consanguinity, it was verified that consanguineous parents presented 4.43 times more chance of having children with anomalies than parents with no degree of kinship. These data are concordant with other studies that show a positive association between CA and consanguineous parents.[8,9,11,23,29] However, Hatibaruah and Hussain[30] found no relation between consanguinity and CA, and Neira et al[31] did not observe cases of consanguinity among the parents of malformed newborns.

Maternal age is considered an important parameter in the birth of a fetus with CA and patients aged <20 or >40 years old may showed increased risk of having children with certain birth defects.[32] However, in our study, the correlation between maternal age and CA was not evident ($p = 0.884$). Similar to our findings, the study by Francine et al.[11] et al also did not report the occurrence of this association. Despide, some studies have reported the association of increased maternal age and the occurrence of CA.[8,15]

There are few studies in the literature that evaluate number of pregnancies as a risk factor for the occurrence of CA. Our study found no differences between the occurrence of AC between and multigravida and primigravida. But, we can verify a higher frequency of CA in multigravida and this result is in agreement with other data in the literature.[8,16,30] While, other studies have reported a higher frequency of CA in primigravida.[9,30–33] Thus, the data still do not conclude how parity can influence the occurrence of CA.

The differences between studies can be reflected in different racial, ethnic, and social factors in various regions of the world. Other justifications for these variations include the different study methodologies used for sampling, accessibility, and use of advanced diagnostic techniques, which improve the early and correct detection of CAs.[14]

The current study presents some limitations. First of all, the collected data were from a fetal medicine service, and the prevalence showed may be greater than that of the general population. Because genetic tests are not offered by the institution, tests such as karyotype, that could prove the influence of parental genetics in the occurrence of structural CA, were not performed. However, we recognize the importance of such tests. Despite the aforementioned limitations, we emphasize the importance of this work, mainly because it is prospective and because it presents the reality from the midwest of Brazil.

Conclusion

In the present study's population, a higher frequency of CNS, GUS, and MC anomalies was observed. The maternal risk factors that may have influenced the occurrence of structural CAs were previous children with CA, family history, and consanguinity. The results related here are important for the development of strategies to improve the management, genetic counseling, and rehabilitation of patients with CA as well as for the taking of public health measures for risk factors.

Contributions

Moraes C. L.: project development, data collection or management, data analysis, and manuscript writing/editing. Melo N. C.: data collection or management, data analysis, and manuscript writing/editing. Amaral W. N.: project development, manuscript writing, and critical review.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Consecutive Use of the 52 mg Levonorgestrel-releasing Intrauterine System: Variations in Bleeding Patterns

Uso consecutivo do sistema intrauterino de levonorgestrel 52 mg: Variações no padrão de sangramento

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Abstract

Objective Changes in bleeding patterns could influence the decisions of healthcare professionals to change the levonorgestrel-releasing intrauterine system (LNG-IUS) before 7 years of use, the recommended period of extended use. We evaluated changes in the bleeding patterns of users of the 52 mg LNG-IUS at the end of use of the first (IUS-1) and during the second device (IUS-2) use.

Methods We performed an audit of the medical records of all women who used two consecutive LNG-IUSs at the Family Planning clinic. We evaluated the sociodemographic/gynecological variables, the length of use, and the bleeding patterns reported in the reference periods of 90 days before removal of the IUS-1 and at the last return in use of IUS-2. We used the McNemar test to compare bleeding patterns. Statistical significance was established at $p < 0.05$.

Results We evaluated 301 women aged (mean $\pm$ SD) 32 ($\pm$6.1) years, with lengths of use of 68.9 ($\pm$16.8) and 20.3 ($\pm$16.7) months for the IUS-1 and IUS-2, respectively. No pregnancies were reported. Bleeding patterns varied significantly among women who used the IUS-2 for $\geq$7 months to 6 years when compared the bleeding patterns reported in IUS-1 use. Eighty-nine out of 221 (40%) women maintained amenorrhea and infrequent bleeding; 66 (30%) evolved to bleeding patterns with light flow, and 66 (30%) maintained or evolved to heavy flow patterns ($p = 0.012$). No differences were observed among the 80 women with $\leq$ 6 months of use.

Conclusion Changes in bleeding patterns occur during the use of LNG-IUS and should not be decisive for the early replacement of the device.

Keywords
- levonorgestrel intrauterine system
- consecutive use
- bleeding patterns

Resumo

Objetivo Variações no padrão de sangramento podem afetar a decisão de troca do sistema intrauterino de levonorgestrel (SIU-LNG) antes do período de uso estendido recomendado de 7 anos. Nós avaliamos mudanças no padrão de sangramento de usuárias ao final do uso do primeiro SIU-LNG 52 mg (SIU-1) e durante o uso do segundo dispositivo (SIU-2).

Métodos Revisamos os prontuários de todas as mulheres que inseriram consecutivamente o SIU-LNG no ambulatório de Planejamento Familiar. Foram avaliadas as variáveis

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sociodemográficas/ginecológicas, o tempo de uso, e os padrões de sangramento relatados nos períodos de referência de 90 dias antes da remoção do SIU-1 e no último retorno em uso do SIU-2. Usamos o teste de McNemar para comparar os padrões de sangramento. A significância estatística foi estabelecida em $p < 0,05$.

Resultados Analisamos os dados de 301 mulheres com idade (média ± desvio padrão [DP]) de 32 (±6,1) anos e tempo de uso de 68,9 (±16,8) e 20,3 (±16,7) meses para o SIU-1 e SIU-2, respectivamente. Nenhuma gravidez foi relatada. Os padrões de sangramento variaram significativamente durante o uso do SIU-2 (≥ 7 meses a 6 anos) em relação ao padrão relatado no SIU-1. Oitenta e nove das 221 (40%) mulheres mantiveram amenorreia e sangramento infrequente; 66 (30%) evoluíram para padrões de sangramento com fluxo leve e 66 (30%) mantiveram ou evoluíram para padrões de fluxo intenso ($p = 0,012$). Não foram observadas diferenças entre as 80 mulheres que utilizavam o SIU-2 há ≤ 6 meses.

Conclusão Mudanças nos padrões de sangramento ocorrem durante o uso do LNG-IUS e não devem ser decisivas para a troca precoce do dispositivo.

Palavras-chave
- Sistema Intrauterino De Levonorgestrel
- uso consecutivo
- padrão de sangramento

Introduction

The 52 mg levonorgestrel-releasing intrauterine system (LNG-IUS) is a long-acting, reversible contraceptive method, also used as treatment for heavy menstrual bleeding.[1,2] It has been widely used with high satisfaction rates, and many women opt for the insertion of a new IUS after the end of the approved lifespan of 5 years.[3,4] In addition, it has been reported that this device could be used beyond the approved 5-year lifetime, and data have been published up to 7 years of use, which improves cost-effectiveness.[5–7] However, some users and healthcare professionals (HCPs) associate changes in bleeding patterns at the end of the approved lifespan with decreasing contraceptive efficacy of the method, which does not seem supported by the medical literature.[5–7]

The high effectiveness of LNG-IUS is attributable to two mechanisms of local action: the antiproliferative effect upon the endometrium, which induces amenorrhea, and the effect on cervical mucus, which impairs sperm penetration.[8–10] The 52 mg LNG-IUS releases 20 µg/day immediately after device placement and declines over time to 10 to 12 µg/day up to 5 years of use; however, LNG has been detected in the 8th year of use.[11,12] The serum mean (±SEM) LNG levels decreased from 253 ± 27 pg/ml (range, 86–760) during the first 2 months after placement to 137 ± 12 (range, 23–393) at 7 years of use and 119 ± 9 pg/ml (range, 110–129) at 8 years after placement.[11] The reduction of LNG levels correlated to increments of endometrial thickness (from 2.8 ± -0.1 mm at 84 months of use to 3.8 ± -0.5 mm at 102 months of use).[11] The authors reported that as LNG decreased over time, the amenorrhea rate decreased from 41.8% at 84 months to 31.5% at 102 months of use, but no correlations were found between serum LNG levels and bleeding patterns.[11]

Despite the lower release of LNG with over time use, the described contraceptive failure is 0.2/100 women-years (WY) and is similar to the rates reported for new LNG-IUSs loaded with 19.5 mg (Kyleena— Bayer PLC, Reading, Berkshire, UK), which release 16 µg/day and 7.4 µg/day of LNG at the 1st and 5th year of use, respectively, and only slightly less (0.4/100 WY) for the LNG-IUS loaded with 13.5 mg (Jaydess/Skyla – Bayer Canada, Toronto, ON, Canada), which releases 12 µg/day and 5 µg/day at the end of the 1st and 3rd year of use, respectively.[13–15]

Despite the large body of evidence concerning efficacy and bleeding patterns among 52 mg LNG-IUS users, information about the use of 2nd or 3rd consecutive LNG-IUSs is scarce.[1,3,4,13,16,17] It is not well established whether users of the LNG-IUS maintain the same bleeding patterns observed at the end of the 5-year approved lifespan after changing the device out for a new one or if the bleeding patterns change to a lighter or heavier flow. It is important to know if changes in the bleeding pattern still occur during the predicted period of high contraceptive efficacy of the method. This information may help to dispel the idea that the changes in menstrual pattern that take place in year 5 of using the method correspond to a decrease in the contraceptive efficacy.

The objective of our study was to assess and compare self-reported bleeding patterns of LNG-IUS users with reference periods of 90 days before the removal of first IUS (IUS-1), after the approved lifespan and same-day replacement with a second IUS (IUS-2), and at the last annual return visit of IUS-2.

Methods

This was a retrospective cohort study conducted at the Family Planning clinic, Department of Obstetrics and Gynecology, The ethical committee of the institution approved the study protocol and authorized the data collection and analysis; the information was unidentifiable following collection. The medical records of all women who received a 52 mg LNG-IUS (Mirena—Bayer Oy, Turku, Finland) for contraception at our service and consecutively received an IUS-2 were included in the study. The data were collected from information contained in the medical records of the service. Women who did not have information

about bleeding patterns in the medical records were not included. We obtained sociodemographic and obstetrics information, total length of use, bleeding patterns and rates and reasons for discontinuation of the IUS-2. The professionals of our service followed an interview script about the women's menstrual history at the time of insertion of the IUS, and the women are questioned about the menstrual bleeding presented in the last 90 days on subsequent return visits. They were categorized into 5 patterns: amenorrhea (no bleeding), infrequent bleeding (1–2 episodes of bleeding and/or spotting), frequent bleeding (> 5 episodes of bleeding and/or spotting), regular bleeding (3–5 episodes of bleeding and/or spotting), and prolonged bleeding (> 14 consecutive days of bleeding and spotting).[18] For this study, we collected information on bleeding patterns self-reported by women in a reference period of the last 90 days before IUS-1 removal and 90 days before the last return visit to the clinic when using IUS-2. The patterns of "frequent" and "prolonged" bleeding were computed together for analysis as "frequent/prolonged" bleeding due to the scarce number of women with these patterns.

Statistical Analysis

We used the χ^2, Fisher exact, Mann-Whitney, and Kruskal-Wallis tests followed by a post-hoc Dunn test to identify the variables with association. For comparisons between bleeding patterns, we used the McNemar test. Statistical significance level was established at $p < 0.05$. The Statistical Analysis System (SAS) software program, version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the analysis.

Results

Between 2007 and 2017, 12,570 LNG-IUSs were inserted at our service. We reviewed the medical charts of 316 women who received a 2nd consecutive LNG-IUS on the same day as the removal of the 1st one at the end of the approved lifespan. From those women, 15 were excluded due to lack of reliable information; consequently, we report information regarding 301 women with information about bleeding patterns. The mean (±standard error of the mean [SEM]) age at IUS-1 and IUS-2 insertion was 32.0 (±0.35) and 37.7 (±0.37), respectively. The length of use of IUS-1 and IUS-2 was 68.9 (±0.97) and 20.3 (±0.96) months, respectively. Most of the women attended ≤ 8 years of schooling and were living with a partner (►**Table 1**).

We also observed that at the end of use of the IUS-1, 43.8%, 23.9%, 24.9%, and 7.3% of women had reported amenorrhea, infrequent, regular, and frequent/prolonged bleeding, respectively (►**Table 2**). The length of use of the IUS-1 was different according to the bleeding pattern and was longer among women with amenorrhea compared with those with regular or frequent/prolonged bleeding; it was also longer among women with infrequent compared with those with frequent/prolonged bleeding (►**Table 2**). Additionally, the length of use (IUS-1 + IUS-2) was significantly higher among women with amenorrhea compared with women with frequent/prolonged bleeding or regular bleeding (►**Table 2**).

Table 1 Characteristics of users of a second consecutive levonogestrel-releasing intrauterine system

Variables	n = 301 (100%) n (%)
Age at IUS-1 placement, mean (SEM)	32.0 (0.35)
Age at IUS-2 placement, mean (SEM)*	37.7 (0.37)
Schooling (years), n (%)**	
≤ 8	243 (82.6)
> 8	51 (17.1)
Marital status, n (%)***	
With a partner	246 (82.8)
Without a partner	51 (17.1)
Number of pregnancies, mean (SD)	1.7 (0.9)
Number of deliveries, mean (SD)	1.5 (0.8)
Length of use of the IUS-1 (months), mean (SEM)	68.9 (0.97)
Length of use of the IUS-2 (months), mean (SEM)	20.3 (0.96)

Abbreviations: IUS, intrauterine system; SD, standard deviation; SEM, standard error of the mean.
*Missing = 2 (299 women evaluated); **Missing = 7 (294 women evaluated); ***Missing = 4 (297 women evaluated).

At the last visit using the IUS-2, we observed an increment of users with amenorrhea (50.8%) and infrequent bleeding (28.5%), and a low proportion of women with regular (15.6%) or frequent/prolonged bleeding (4.9%) (►**Table 3**).

►**Table 4** shows the comparison between the frequencies of bleeding patterns presented at the end of use of the IUS-1 and at the last visit using the IUS-2. Of the 221 women who used the IUS-2 from 7 months to 6 years, only 89/221 women (40%) maintained the same patterns of amenorrhea and infrequent bleeding; 66 (30%) evolved to bleeding patterns with lighter flow, and 66 (30%) maintained or evolved to patterns with heavier flow than presented when in use of IUS-1 ($p = 0.012$). Among the 104 women with amenorrhea at the end of IUS-1 use, only 70 continued to experience amenorrhea (►**Table 4**).

Of the 80 women who used the IUS-2 for only 6 months, there were no differences when comparing the bleeding patterns with those observed at the end of use of the IUS-1 ($p = 0.1163$). At the end of the data collection (September/2017), 277 (92%) women were still using the device and 9 were using a 3rd LNG-IUS after the end of the approved lifespan. Also, 24 women had the device removed: 3 wished to become pregnant, 9 reached menopause, and 12 had expulsions.

Discussion

Our results showed that women using a 52 mg LNG-IUS had significantly varied bleeding patterns over time while using this method. We emphasize that women with amenorrhea at the end of use of the IUS-1 also changed to other bleeding patterns like infrequent (24%), and even regular and

Table 2 Bleeding patterns reported at the end of use of the first intrauterine system and its relationship with some variables

Variables	Amenorrhea n = 132 (43.8%) n (%)	Infrequent n = 72 (23.9%) n (%)	Regular n = 75 (24.9%) n (%)	Frequent/prolonged n = 22 (7.3%) n (%)	*p*-value*
Age at IUS-1, mean (SD)¶	31.8 (6.1)	32.3 (6.0)	32.0 (6.0)	33.1 (7.7)	0.742
Age at IUS-2, mean (SD)¥	37.9 (6.2)	37.8 (6.4)*	37.1 (6.6)**	38.3 (8.4)	0.758
Number of pregnancies, mean (SD)	1.7 (0.9)	1.9 (0.8)	1.8 (0.9)	1.6 (1.4)	0.082
Number of deliveries, mean (SD)	1.5 (0.7)	1.7 (0.7)	1.6 (0.8)	1.4 (0.9)	0.183
Number of abortions, mean (SD)	0.1 (0.5)	0.1 (0.4)	0.3 (0.7)	0.1 (0.6)	0.362
Length of use of IUS-1, months, mean (SD)	73.0 (10.4)	68.7 (17.4)	63.8 (22.4)	63.1 (18.3)	0.0002#
Length of use of IUS-2, months, mean (SD)	21.9 (16.8)	16.6 (15.6)	20.0 (18.2)	23.5 (13.4)	0.055
Total length of use months, mean (SD)	95.4 (21.0)	85.4 (18.2)	84.3 (21.7)	86.5 (23.6)	0.0006&

Abbreviation: IUS-1, first intrauterine system; ISU-2, second intrauterine system; SD, standard deviation.
¶Age at first placement; ¥Age at second placement; *Kruskal Wallis test; #Post-hoc Dunn test – amenorrhea > frequent/prolonged and amenorrhea > regular; spotting > frequent/prolonged; &Post-hoc Dunn test – amenorrhea > frequent/prolonged and amenorrhea > regular; *Missing = 1 (71 women evaluated); **Missing = 1 (74 women evaluated).

Table 3 Distribution of women according to bleeding patterns reported during the last 90 days of use of the 1st intrauterine system and 90 days before the last return visit using the 2nd intrauterine system

Bleeding pattern	Last 90 days of use of the IUS-1 n = 301 n (%)	Length of use of the IUS-2	
		≤ 6 months n = 80 n (%)	> 7 months–6 years n = 221 n (%)
Amenorrhea	132 (43.8)	35 (43.7)	118 (53.4)
Infrequent	72 (23.9)	24 (30.0)	62 (28.0)
Regular	75 (24.9)	17 (21.2)	30 (13.5)
Frequent/prolonged	22 (7.3)	4 (5.0)	11 (4.9)

Abbreviation: IUS, intrauterine system.

frequent/prolonged bleeding (8.6%), during the use of the IUS-2.

Our findings are important to HCPs to determine how to counsel women on when to change the LNG-IUS and to consider the possibility of extended use for 7 years and beyond.[5,7] In our service, some HCPs have expressed concerns of reduced contraceptive effectiveness when women keep the same device beyond the manufacturer-recommended 5 years, mainly among women who reported changes in their bleeding patterns and especially if they experienced amenorrhea at any time during use and changed to other bleeding patterns after 5 years of use. The behavior of the HCPs for early removal and replacement of the IUS was reflected in the results presented in this report showing long periods of use for women with amenorrhea and short periods among women with other bleeding patterns.

Because no correlation was reported between serum LNG concentrations and bleeding patterns, we can speculate that low doses of LNG after the 5th year of use of the 52 mg LNG-IUS maintain the high contraceptive efficacy independently of the observed bleeding patterns, which were observed previously.[6,7,11,12,19]

We found at end use of IUS-1 that amenorrhea was observed in 43.8% of users; this result is in agreement with a recent prospective study that described 41.8% of amenorrhea at 5 years of use of the LNG-IUS.[13]

Our results showed that women with amenorrhea displayed infrequent and regular bleeding patterns in the 2

Table 4 Bleeding pattern variations during the last 90 days before removal of the 1st intrauterine system and 90 days before last visit using the 2nd intrauterine system for > 7 months to 6 years

Bleeding pattern with IUS-1	Bleeding pattern with IUS-2				
	Amenorrhea n = 118 n (%)	Infrequent n = 62 n (%)	Regular n = 30 n (%)	Frequent/prolonged n = 11 n (%)	*p*-value@
Amenorrhea, *n* = 104	70 (59.3)	25 (40.3)	3 (10.0)	6 (54.5)	0.012
Infrequent, *n* = 48	23 (19.5)	19 (30.6)	5 (16.6)	1 (9.0)	
Regular, *n* = 50	16 (13.5)	14 (22.5)	18 (60.0)	2 (18.1)	
Frequent/prolonged, *n* = 19	9 (7.6)	4 (6.4)	4 (13.3)	2 (18.1)	

@McNemar test. Excludes the 80 women with length of use of the IUS-2 ≤ 6 months.

study periods within the range described in previous prospective studies with slight variations, possibly due to the retrospective characteristic of our study.[4,16,17] A Sweden-based study followed 82 women who underwent a 2nd consecutive IUS placement after 7 years of use with the 1st one, and the authors reported that 26% and 60% of participants experienced amenorrhea in the 1st period for the 1st IUS and for the last 5 years of use for the 2nd device, respectively, while showing 70% and 28% with regular/scanty bleeding patterns while using the 1st and 2nd IUSs, respectively.[4]

In addition, a multicenter study of 204 women with a 15-month follow-up evaluated bleeding patterns during the 1st LNG-IUS (between 4.3 and 4.9 years) and showed a mean of 7 and 8 days of bleeding/spotting at 90 days before and after changing the device, respectively, decreasing to 4 days after 1 year of use with the 2nd IUS.[16] Of the 204 women in that study, 170 women remained at follow-up, and the bleeding patterns described in the last 90 days 2 to 5 years after placement of the 2nd IUS showed reductions of bleeding in 70% of the women, while > 49% of women experienced amenorrhea, which was associated with high rates of satisfaction and continuation.[17] The results of our study were similar to those found in these prospective studies.[4,16,17]

The main limitation of the present study was the retrospective design, which could introduce bias. On the other hand, the main strength is that we evaluated the same cohort of women at two different moments, which may have contributed, at least in part, to the quality of the evaluation of the variations between bleeding patterns. Additionally, another strength is that we assessed the bleeding patterns 90 days before the last annual consultation of the IUS-2, which occurred between 7 months and 6 years after placement.

Our study has two major implications for HCPs who provide care in family planning. First, the bleeding patterns observed in LNG-IUS users did not change in the first 6 months after changing the device for a new one. Second, in the period from 7 months up to 6 years after the 2nd device placement, it is expected that the bleeding patterns will vary from the pattern observed when removing the 1st IUS. This information may help users and HCPs to more readily accept the extended use of the method and prevent both from interpreting changes in bleeding patterns as decreasing the efficacy of the method.

Although users of a second LNG-IUS reported high rates of amenorrhea and infrequent bleeding and lower rates of regular, frequent/prolonged bleeding after changing the LNG-IUS, some women also experienced bleeding pattern changes from light flow to frequent/prolonged flow, which has not been found to be linked to contraceptive efficacy.

As we evaluated the time of IUS-2 use for up to 6 years of use, a period in which its efficacy is still high, these changes in bleeding pattern did not appear to indicate a decrease in the contraceptive efficacy of the method. In addition, we did not have any pregnancy in the period of IUS-2 use.

Conclusion

Changes in bleeding patterns occur during the use of LNG-IUS and should not be decisive for the early replacement of the device.

Conflict of Interests

The authors have no conflict of interests to declare.

Contributors

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

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Is there an Increased Risk for Unfavorable Obstetric Outcomes in Women with Endometriosis? An Evaluation of Evidences

Existe um risco maior para desfechos obstétricos desfavoráveis em mulheres com endometriose? Uma avaliação das evidências

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Abstract

Objective The present study is a systematic review of the literature to assess whether the presence of endometriosis determines or contributes to adverse obstetric outcomes.

Data Sources The present work was carried out at the Hospital Israelita Albert Einstein, São Paulo, state of São Paulo, Brazil, in accordance to the PRISMA methodology for systematic reviews. A review of the literature was performed using PubMed, Web of Science and Scopus databases. The keywords used were: *pregnancy outcome*, *pregnancy complications*, *obstetrical complications*, *obstetrics*, *obstetric outcomes* and *endometriosis*. The survey was further completed by a manually executed review of cross-referenced articles, which was last performed on November 30, 2018.

Selection of studies The survey disclosed a total of 2,468 articles, published from May 1946 to October 2017. A total of 18 studies were selected to be further classified according to their quality and relevance.

Data Collection The Newcastle–Ottawa Quality Assessment Scale was used for classification. Five studies of greater impact and superior evidence quality and 13 studies of moderate evidence quality were selected. We analyzed the studies for the characteristics of their patients plus how endometriosis was diagnosed and their respective obstetric outcomes taking into account their statistical relevance.

Data Synthesis Analyses of the higher impact and better quality studies have shown high incidence of preterm birth and placenta previa in patients with endometriosis.

Conclusion Placenta previa and preterm birth are the most statistically significant outcomes related to endometriosis, as indicated by our systematic review. The present information is useful to alert obstetricians and patients about possible unfavorable obstetric outcomes.

Keywords

- endometriosis
- pregnancy complications
- obstetric complications
- pregnancy outcomes
- obstetric outcomes

Resumo

Objetivo Realizar uma revisão sistemática e crítica da literatura de modo a avaliar se a presença de endometriose determina desfechos obstétricos adversos na gestação.

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Fonte dos dados O presente estudo foi realizado no Hospital Israelita Albert Einstein, São Paulo, SP, Brasil, de acordo com a metodologia PRISMA para revisões sistemáticas. As bases de dados usadas para a revisão de literatura foram Pubmed, Web of Science e Scopus. As palavras-chave usadas foram: *pregnancy outcome*, *pregnancy complications*, *obstetrical complications*, *obstetrics*, *obstetric outcomes* e *endometriosis*. Uma revisão manual de artigos com referências cruzadas completou a pesquisa, que foi realizada pela última vez em 30 de novembro de 2018.

Seleção dos estudos A pesquisa contou com o total de 2.468 artigos, publicados de maio de 1946 a outubro de 2017. Foram selecionados 18 estudos com base em sua relevância.

Coleta de dados A metodologia Newcastle–Ottawa Quality Assessment Scale foi usada para selecionar 5 estudos cuja evidência era de melhor qualidade e 13 estudos de moderada qualidade de evidência. As características das populações dos estudos foram analisadas, assim como a doença endometriose foi diagnosticada e os respectivos desfechos obstétricos nas pacientes observando-se a relevância estatística dos estudos.

Síntese dos dados A análise dos estudos de maior impacto e de melhor qualidade de evidência mostram que placenta prévia e ocorrência de nascimentos pré-termo são os desfechos obstétricos desfavoráveis de maior incidência em pacientes com endometriose.

Conclusão Placenta prévia e nascimentos pré-termo são os desfechos obstétricos com maior significância estatística relacionados à endometriose. Esta informação é útil para alertar obstetras e pacientes com endometriose para possíveis desfechos obstétricos desfavoráveis.

Palavras-Chave
- endometriose
- complicações da gravidez
- complicações obstétricas
- desfechos da gravidez
- desfechos obstétricos

Introduction

Endometriosis is defined by the presence of endometrial (glandular and/or stromal) tissue outside the uterus. The most frequent sites of lesion are the pelvic viscera and the peritoneum, and the disease can be classified as superficial, deep or ovarian and/or peritoneal. The most severe forms can lead to deformities of the Fallopian ducts and may affect the urinary tract and intestinal walls.[1] It is estimated that endometriosis affects 10% of women of reproductive age, is associated with pelvic pain in 30% and causes infertility in 30 to 40%.[2–4] In recent years, there has been considerable progress in understanding the pathogenesis, the evolution, the diagnosis and the treatment of the disease.[5]

It is important to emphasize that infertility alone is already associated to a greater risk of obstetric complications such as pre-eclampsia, gestational hypertension, prematurity, hemorrhage before delivery and the need of cesarean section.[6] Some studies postulated the association of endometriosis with unfavorable obstetric outcomes, such as pre-eclampsia or spontaneous hemoperitoneum, and the occurrence of sigmoid perforation or appendicitis.[7,8] While not yet clarified, these associations may occur due to endometrial resistance to progesterone, inadequate uterine contractions, excessive stimulation of the endometrium caused by free radicals, changes in the uterine junctional zone, and inflammatory processes causing endometrial, peritoneal and systemic manifestations.[1,9–12] These mechanisms will be addressed in the discussion of the present study.

Two systematic reviews that related endometriosis to gestational risks have been recently published; however, there is a methodological gap regarding the heterogeneity among the groups studied, the confirmatory diagnosis of endometriosis, the sample size of each published study, and the inclusion of patients who were already classified as having high-risk gestations (symptomatic patients who sought out clinics and hospitals).[13,14]

Therefore, the goal of our study was to perform a systematic review of the literature to assess whether the presence of endometriosis in fact results in adverse obstetric outcomes. We took the data quality of the analyzed articles into consideration to reach the conclusions.

Methods

The present study was carried out at the Hospital Israelita Albert Einstein, São Paulo, state of São Paulo, Brazil, according to the PRISMA methodology for systematic reviews. To identify relevant articles to be included in the study, a review of the literature was done using the PubMed, Web of Science and Scopus databases. The keywords used were: *pregnancy outcome*, *pregnancy complications*, *obstetrical complications*, *obstetrics*, *obstetric outcomes* and *endometriosis*. The search period was from May 1946 to October 2017. A manual review of cross-referenced articles

completed the survey, which was last performed on August 30, 2018.

Studies Selection

Studies were selected using the following predetermined inclusion criteria: [i]women who had a diagnosis of endometriosis during or before pregnancy compared to a control group of women without the diagnosis [ii] any outcomes of interest in the present pregnancy, and [iii] observational, cohort or case-controlled human study design that were reported in English. The primary outcomes of the present study were determined previously and included the following adverse obstetric and perinatal outcomes: abortion, ectopic gestation, fetal loss, pre-eclampsia, bleeding during pregnancy, placental retention, placenta previa, premature placental abruption, premature membranes rupture, preterm labor, cesarean section, postpartum hemorrhage, preterm delivery, small for gestational age (SGA) fetus, stillborn neonate and neonatal death. The secondary outcomes were the presence of any other clinically important adverse pregnancy outcomes reported in the literature. Information extracted from each study included: the country where the research was done; the name of the cohort study; duration and sample size; inclusion criteria; definition of reference or control group; endometriosis diagnostic criteria; obstetric or neonatal outcomes; demographics to which the studies were adjusted.

Selection Criteria

We excluded from the analyses the studies that were not prospective or retrospective cohort or case-control, as well as those not written in English or lacking data. The study selection process, full text screening, and data extraction was conducted independently by two researchers (Annicchino G. and Piccinato C. A.), following the PRISMA guidelines. Disagreements were solved after consulting a third opinion (Podgaec S.).

Data Extraction

One review author (Annicchino G.) independently standardized the data extraction approach from the eligible studies. Information was gathered on the cohort configuration, endometriosis diagnosis and its stage, conceptive method, use of assisted reproductive techniques and detailed obstetric and perinatal outcomes.

Data Analysis

Data for adverse outcomes were collected as dichotomous data, and the results are presented as odds ratios (ORs) with 95% confidence interval (CI).

Assessment of Bias Risk

The quality of the included studies was assessed by the Newcastle-Ottawa Quality Assessment Scale (NOS, scores of 0–9 stars) for the selection of study groups (up to 4 stars/points); comparability of groups (up to 2 stars/points); and, the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively (up to 3 stars/points).[15]

Results

The search identified a total of 2,468 articles, ranging from May 1946 to October 2017, of which 1,630 were from PubMed, 738 from Scopus and 68 from Web of science, 459 duplicates and 585 revisions or published in other languages. By limiting the research to only English-written articles, and excluding duplicate articles and systematic reviews, we found 1,358 articles. The initial selection was done by reading the titles and abstracts of the articles. All case-control, prospective or retrospective cohort studies evaluating obstetric outcomes in women diagnosed with endometriosis were included. Fifty articles were read in full. No date limit was imposed, and two reviewers (Annicchino G. and Podgaec S.) independently nonblindly assessed the eligibility of the articles following the standardized protocol. Disagreement regarding the inclusion of studies were discussed and, by consensus, the articles were included or excluded. The references of these articles were also searched resulting in finding one additional study. A systematic review was performed analyzing the year of publication, number of patients involved in the study, type of study, and the results and conclusions of each study resulting in the selection of 18 studies (►**Fig. 1**).

All of the articles within the described theme were included, regardless of the age of the patients, type of pregnancy (single or multiple), gestational age or form of conception (natural or artificial). The diagnosis method of endometriosis was not taken into consideration for exclusion or inclusion purposes; it could be clinical, surgical or histopathological. These 18 studies were classified according to their relevance using the NOS scale (scores of 0–9 stars). Studies with NOS ≥ 4 were regarded as moderate quality and ≥ 8 were regarded as high-quality. According to this evaluation, 5 studies of greater impact and quality of superior evidence and 13 studies of moderate quality of evidence were selected (►**Supplementary Material Appendix 1**). ►**Table 1** exhibits the data of the control groups, how the disease was diagnosed, and other particularities of the studies. ►**Tables 2a**, **2b** and **2c** display the studies in which the obstetric outcomes were studied in relation to endometriosis and their statistical relevance.

Summary of the Studies with Superior Quality of Evidence

The largest and most detailed publication for the assessment of obstetric and neonatal complications in women with endometriosis was published in 2017 by Berlac et al.[16] In this retrospective cohort study, data from every pregnant woman registered in Denmark at The National Health Register were computed from women with clinically diagnosed endometriosis. They were identified as having been diagnosed through the ICD-10 classification and were compared with women without the disease.[16]

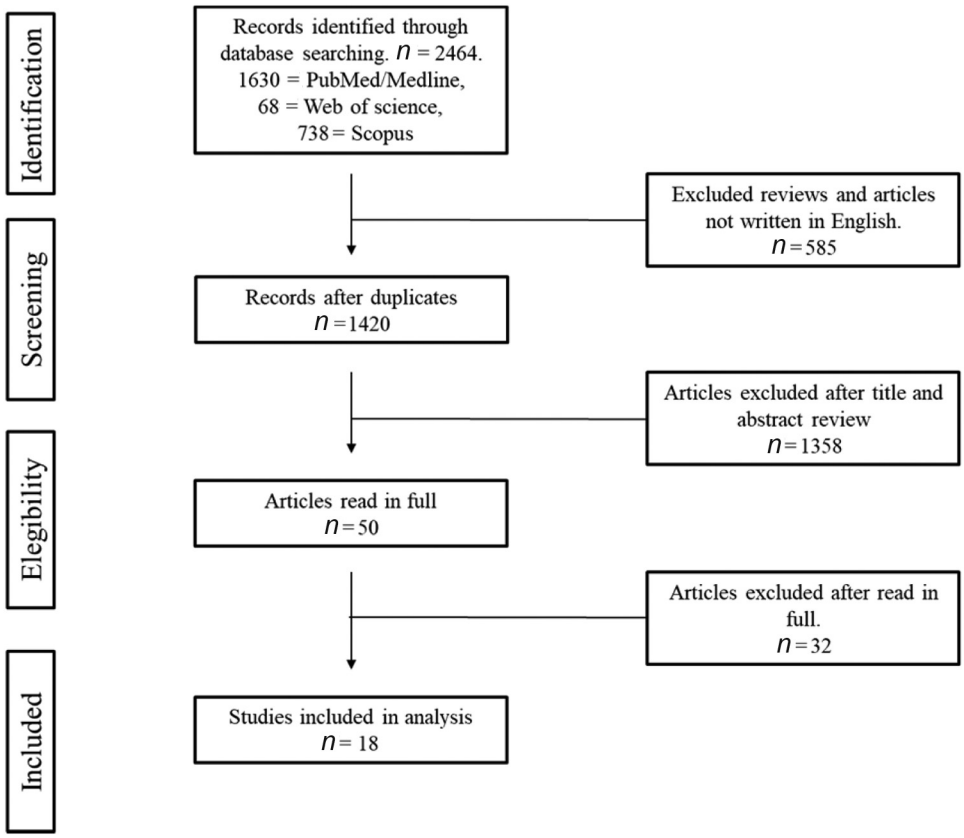

Table 1 Study population and methodology of the evaluated studies according to the diagnosis of endometriosis, conceptive method, and criteria of analyses (FIV and endometriosis stage)

Obstetric outcomes – higher risk in patients with endometriosis					
Higher quality studies	**POPULATION**	**ENDOMETRIOSIS DIAGNOSIS**	**MODE OF CONCEPTION**	**WAS FIV TAKEN AS A BIAS?**	**STAGE OF THE DISEASE TAKEN AS ACCOUNT?**
Berlac et al, 2017[16]	11,739 women with endometriosis diagnosis vs. 615,533 women without endometriosis diagnosis.	Clinical ICD-10	Natural and artificial	Yes	Yes
Glavind et al, 2017[17]	82,793 women, 1,719 cases with endometriosis diagnosis.	ICD 10 and/or laparoscopic	Natural and artificial	Yes	No
Mannini et al, 2016[18]	Cases n= 262. A) 40 with DIE B) 222 without DIE (B.1- 188 singleton pregnancy and/or spontaneous pregnancy / B.2- 74 multiple gestation and/or FIV) vs. Control $n = 524$ without endometriosis.	Surgical and anatomopathological	Natural and artificial	Yes	Yes
Saraswat et al, 2016[19]	Cases $n = 5,375$ women with endometriosis diagnosis vs. Control $n = 8280$ women without endometriosis.	Surgical	Not evaluated	No	No
Stephansson et al, 2009[20]	Cases ($n = 13,090$ endometriosis diagnosis) vs. Control ($n = 1,429,585$)	Clinical ICD-8: 625.3; ICD-9: 617; and ICD-10: n80	Natural and artificial	No	No
Lower quality studies	**POPULATION**	**ENDOMETRIOSIS DIAGNOSIS**	**MODE OF CONCEPTION**	**WAS FIV TAKEN AS A BIAS?**	**DEGREE OF THE DISEASE TAKEN AS ACCOUNT?**
Turocy et al, 2017[21]	Women with transferred embryos ($n = 1,616$), 160 in the n with diagnosis of endometriosis.	Surgical	Artificial	No	Yes

(*Continued*)

Table 1 (*Continued*)

Obstetric outcomes – higher risk in patients with endometriosis					
Santulli et al, 2016[22]	Case $n = 284$, women diagnosed with endometriosis (A. superficial 52 / B. endometrioma / C. Deep infiltration) vs. Control $n = 466$, women without diagnosis of endometriosis.	Surgical and anatomopathological	Natural and artificial	Yes	Yes
Fujii et al, 2016[23]	Case n= 92 women with endometriosis diagnosis vs. Control n= 512 women without endometriosis	Laparoscopic	Artificial	No	Yes
Jaques et al, 2016[6]	2,316 pregnancies by assisted reproduction and 160 with diagnosis of endometriosis	Surgical or clinical by image + clinical exam	Artificial	No	Yes
Lin et al, 2015[24]	249 cases (women with endometriosis) vs. 249 controls (women without endometriosis)	Surgical and anatomopathological	Natural	No	No
Conti et al, 2014[25]	Population 2,239 women. Singleton pregnancy 1,331 control vs. 219 cases diagnosed with endometriosis. Multiparas: 592 control vs. 97 with diagnosis of endometriosis.	Surgical and anatomopathological	Natural and artificial	Yes	Yes
Aris, 2014[26]	Cases $n = 784$ women with endometriosis vs. Control $n = 30,284$ women without endometriosis.	Surgical	Natural and artificial	No	No
Mekaru et al, 2013[27]	108 pregnant women who had previously undergone laparoscopy to investigate infertility. 49 cases diagnosed with endometriosis vs. 59 controls.	Laparoscopic	Natural	No	Yes
Vercellini et al, 2012[28]	419 cases (150 rectovaginal, 69 ovarian and peritoneal, 100 ovarian, 100 peritoneal)	Clinical by image	Natural	No	Yes
Hadfield et al, 2009[29]	Cases (n= 3,239 with endometriosis diagnosis) vs. Control ($n = 205,640$)	Clinical ICD-10	Natural and artificial	Yes	Yes
Brosens et al, 2007[30]	Cases ($n = 245$ with diagnosis of infertility associated with endometriosis) vs. Control ($n = 274$ infertility associated with male factors)	Laparoscopic	Artificial	No	No
Hjordt Hansen et al, 2007[31]	Cases n= 24,667 women with endometriosis diagnosis vs. Control n= 98,668 women without endometriosis.	Clinical - ICD10 80–80.9	Natural or artificial	No	Yes
Matorras et al, 1998[32]	Cases $n = 174$ infertile women diagnosed with endometriosis. Control $n = 174$ infertile women without endometriosis.	Laparoscopic	Natural or artificial	Yes	Yes

Abbreviations: DIE, Deep infiltrative endometriosis; FIV, in vitro fertilization.

The study performed by Berlac et al[16] is listed in ►**Table 2**.

A sub-analysis was also performed for primiparous women and those who underwent gynecological surgery before pregnancy, as listed in ►**Table 1**.

These data is all shown in ►**Tables 2a**, **2b** and **2c** and are described here as follows. Berlac et al[16] found in a cohort of 19,331 deliveries (case group with 11,739 women and control group with 6,533 women) increased risks in the group diagnosed with endometriosis for: pre-eclampsia (OR 1.7; 95% CI 1.5–2.0), bleeding during pregnancy (OR 2.3; 95% CI 2.0–2.5), premature placental abruption (OR 2.0; 95% CI 1.7–2.3), placenta previa (OR 3.9; 95% CI 3.5–4.3), premature rupture of membranes (RPMO) (OR 1.7; 95% CI 1.5–1.8), placental retention (OR 3.1; 95% CI 1.4–6.6), preterm newborn with < 28 weeks (OR 3,1; 95% CI 2.7–3.6), SGA (OR 1.5; 95% CI 1.4–1.6), congenital malformation (OR 1.3; 95% 1.3–1.4), neonatal death (OR 1.8; 95% CI 1.4–2.1).[16]

Glavind et al[17] also conducted a large retrospective cohort study to examine the association between endometriosis and the risk of pre-eclampsia, cesarean delivery, postpartum

Table 2a – Evaluation of the following risks of adverse obstetric outcomes: abortion, ectopic gestation, congenital malformations, fetal loss, stillborn and neonatal death in women with endometriosis according to the quality of the studies analyzed.

Obstetric outcomes – higher risk in patients with endometriosis						
Higher quality Studies	**Abortion**	**Ectopic gestation**	**Congenital malformation**	**Fetal loss**	**Stillborn**	**Neonatal death**
Berlac et al, 2017[16]			OR 1.3; 95% CI 1.3–-1.4			OR 1.8, 95% CI 1.4–2.1
Glavind et al, 2017[17]						
Saraswat et al, 2017[19]	OR 1.76; 95% CI 1.44–-2.15	OR 2,70; 95% CI 1.09–-6.72				NR
Mannini et al, 2016[18]						
Stephansson et al, 2009[20]						
Lower quality Studies	**Abortion**	**Ectopic gestation**	**Congenital malformation**	**Fetal loss**	**Stillborn**	**Neonatal death**
Turocy et al, 2017[21]	OR 0.57; 95% CI 0.28–1.15	OR 1.52, 95% CI 0.19–11.93				
Santulli et al, 2016[22]	OR 1.70, 95% CI 1.34–2.26					
Fujii et al, 2016[23]						
Jaques et al, 2016[6]						
Lin et al, 2015[24]						
Conti et al, 2014[25]						
Aris. 2014[26]	OR 1.89; 95% CI 1,23–2,93			OR 2.03; 95% CI 1,42–2,90	OR 2.29; 95% CI 1.24–5.22	
Mekaru et al, 2013[27]	NR					
Vercellini et al, 2012[28]						
Hadfield et al, 2009[29]						
Bronsens et al, 2007[30]						
Hjordt Hansen et al, 2007[31]	OR 1.2; 95% CI 1.2-1.3	OR 1.9, 95% CI 1.8–-2.1				
Matorras et al, 1998[32]	NR					

Abbreviation: NR, not relevant.

hemorrhage, preterm delivery, and birth to SGA infants. The data were obtained from the Aarhus birth Cohort, a Danish national registry of patients of 82,793 of one-fetus pregnancies. Of these, 1,213 were diagnosed with endometriosis and 1,719 pregnancies were included in the group of women to be studied.[17]

The diagnosis of endometriosis was validated based on the identification of ICD 10–N80 and ICD 8–625.3 taken from the national database of patients. The results corroborated with laparoscopic confirmation in 33% of the cases; however, the severity of the disease was not taken into account. This was the first large study with histopathological confirmation of the diagnosis of endometriosis. The results are presented in ►**Table 2c**. An increased risk of preterm birth (OR 1.91; 95% CI 1.16–3.15), pre-eclampsia (OR 1.37; 95% CI 1.06–1.77) and delivery by cesarean section (OR 1.83; 95% CI 1.60–2.09) was found. There was no association with postpartum hemorrhage or SGA.[17]

In 2017, Mannini et al[18] conducted a retrospective cohort at a tertiary hospital in Berlin between January 2009 and December 2014. The case group contained 262 pregnant women with surgical diagnosis of endometriosis, and 524 women without this disease in the control group. Results are shown in ►**Tables 2b** and **2c**. Increased risk was shown in patients with endometriosis for placenta previa (OR 0.29; 95% CI 0.10–0.81), intrahepatic cholestasis (OR 0.21; 95% CI 0.08–0.54), labor induction (OR 0.05; 95% CI 0.34–0.69) and preterm delivery (OR 0.32, 95% CI 0.20–0.52). There was no association with transient hypertensive gestational disease, gestational diabetes, hemorrhage, cesarean delivery or intrauterine growth restriction.[18]

From 1981 to 2010, a cohort study evaluated data from all Scottish hospitals as reported by Saraswat et al.[19] A total of 42,092 women were diagnosed with endometriosis and 8,719 women were identified as having had postdiagnosis pregnancies. Women without surgical diagnosis ($n = 2,962$) were excluded from the case group, as the author only included patients who had confirmed the disease through laparoscopy (98.7%) or laparotomy (1.3%). Results are summarized in ►**Table 2**. The authors reported increased risk in women with the diagnosis of endometriosis for abortion (OR 1.76; 95% CI 1.44–2.15), ectopic pregnancy (OR 2.70; 95% CI 1.09–6.72), placenta previa (OR 2.24; 95% CI 1.52–3.31), antepartum hemorrhage (OR 1.67; 95%, CI 1.39–2.0),

Table 2b Evaluation of the following risks of adverse obstetric outcomes: pre-eclampsia, gestational diabetes, cholestasis, premature placental abruption, premature rupture of membranes and preterm labor in women with endometriosis according to the quality of the studies analyzed.

Higher quality studies	Pre-eclampsia	Gestational diabetes	Cholestasis	Premature placental abruption	Premature rupture of membranes	Preterm labor
Berlac et al, 2017[16]	OR 1.7; 95% CI 1.5–2.0			OR 2.0; 95% CI 1.7-2.3	OR 1.7; 95% CI 1.5-1.8	
Glavind et al, 2017[17]	OR 1.37; 95% CI 1.06–1.77					
Saraswat et al, 2017[19]	NR			NR		
Mannini et al, 2016[18]	NR	NR	OR 0.21; 95% CI 0.08–0.54			OR 0.32; 95% CI 0.20–0.52
Stephansson et al, 2009[20]						
Lower quality studies	**Pre-eclampsia**	**Gestational diabetes**	**Cholestasis**	**Premature placental abruption**	**Premature rupture of membranes**	**Preterm labor**
Turocy et al, 2017[21]						
Santulli et al, 2016[22]						
Fujii et al, 2016[23]						
Jaques et al, 2016[6]	OR 8.53; 95% CI 1.05–69.40					
Lin et al, 2015[24]	NR			NR		
Conti et al, 2014[25]	NR	OR 2.13; 95% CI 1.32–3.44			OR 2.93; 95% CI 1.24–6.87	
Aris. 2014[26]	NR	NR				
Mekaru et al, 2013[27]	NR					
Vercellini et al, 2012[28]						
Hadfield et al, 2009[29]	NR					
Bronsens et al, 2007[30]	OR 6.6; 95% CI 1.2–37					
Hjordt Hansen et al, 2007[31]						
Matorras et al, 1998[32]						

Abbreviation: NR, not relevant.

postpartum hemorrhage (OR 1.30; 95% CI 1.61–1.46), preterm birth (OR 1.26, 95% CI 1.07–1.49) and cesarean delivery (OR 1.4; 95% CI 1.26–1.55). There was no association with transitory hypertensive disease during pregnancy, pre-eclampsia, placental abruption, SGA and stillbirth.[19]

Stephansson et al[20] published in 2009 a large retrospective study that examined the association between unfavorable obstetric outcomes, assisted reproduction and endometriosis. The data were taken from the medical birth register, a database of the Swedish population, between the years 1992 and 2006. The case group included 13,090 one-fetus pregnancies of women diagnosed with endometriosis. As a result see ►**Tables 2a**, **2b** and **2c**; there was an increased risk for preterm birth (OR 1.33; 95% CI 1.23–1.44), pre-eclampsia (OR 1.13; 95% CI 1.02–1.26), antenatal bleeding and placental complications (OR 1.76; 95% CI 1.56–1.99) and cesarean delivery (OR 1.47; 95% CI 1.54–1.75).[20]

Summary of Studies with Moderate Quality of Evidence

Studies that assessed smaller control groups than those mentioned above also showed a correlation between unfavorable obstetric outcomes and women diagnosed with endometriosis. The oldest of them evaluated 174 women with endometriosis and compared it to the same number of women without diagnosis.[32] The authors examined the possibility of higher rates of abortion in the case group, but did not observe this correlation. Mekaru et al[27] also reached this result after evaluating a group of 108 pregnant women who had previously undergone laparoscopy to investigate infertility. In contrast, Saraswat et al,[19] Turocy et al,[21] Santulli et al,[22] Aris,[26] and Hjordt Hansen et al[31] published results showing increased risk of abortion in women with endometriosis.

Table 2c Evaluation of the following risks of adverse obstetric outcomes: bleeding during pregnancy, placenta previa, preterm newborn, placental retention, cesarean section, fetus small for gestational age and postpartum hemorrhage in women with endometriosis according to the quality of the studies analyzed.

Higher quality studies	Bleeding during pregnancy	Placenta previa	Pre term newborn	Placental retention	Cesarian	Small for gestacional age	Postpartum haemorrhage
Berlac et al, 2017[16]	OR 2.3; 95% CI 2.0–2.5	OR 3,9; 95% CI 3.5–4.3	OR 3.1; ,95% CI 2.7–3.6	OR 3.1, 95% CI 1.4–6.6		OR 1.5; 95% CI 1.4–1.6	
Glavind et al, 2017[17]	NR		OR 1.91; 95% CI 1.16–3.15		OR 1.83; 95% CI 1.60–2.09	NR	
Saraswat et al, 2017[19]	OR 1.67; 95% CI 1.39–2.0	OR 2.24; 95% CI 1,52-3.31	OR 1.26; 95% CI 1.07–1.49		OR 1.4; 95% IC 1.26–1.55	NR	OR 1.30; 95% CI 1.61–1.46
Mannini et al, 2016[18]	NR	OR 0.29; 95% CI 0.10–0.81			NR		
Stephansson et al, 2009[20]			OR 1.33; 95% CI 1.23–1.44				
Lower quality studies	**Bleeding during pregnancy**	**Placenta previa**	**Pre term newborn**	**Placental retention**	**Cesarian**	**Small for gestational age**	
Turocy et al, 2017[21]							
Santulli et al, 2016[22]							
Fujii et al, 2016[23]		OR 15.1,;95% CI 4,40–61.7	OR 2.08, 95% CI 1.07–3.89				
Jaques et al, 2016[6]	OR 2.05; 95% CI 1.02–4.11		OR 2.34; 95% CI 1.01–5.41		OR 2.64; 95% CI 1.37–5.07		
Lin et al, 2015[24]		OR 4.51; 95% CI 1.23–16.50	OR 2.42; 95% CI 1,05–5,57		OR 1.93; 95% CI 1.31–2.84	NR	
Conti et al, 2014[25]			OR 2.24; 95% CI 1.46–3.44			OR 2.72; 95% CI 1.46-5.06	
Aris et al, 2014[26]						NR	
Mekaru et al, 2013[27]					NR	NR	
Vercellini et al, 2012[28]		OR 5.81; 95% CI 1.53–22.03					
Hadfield et al, 2009[29]							
Bronsens et al, 2007[30]							
Hjordt Hansen et al, 2007[31]							
Matorras et al, 1998[32]							

Abbreviation: NR, not relevant.
Obstetric outcomes – higher risk in patients with endometriosis.

When evaluating the correlation between transient hypertensive disease during pregnancy and endometriosis, most studies did not report this association, as shown in the studies by Mannini et al,[18] Saraswat et al,[19] Lin et al,[24] Conti et al,[25] Aris,[26] Mekaru et al,[27] Hadfield et al,[29] and Brosens et al.[30] While specifying the obstetric outcome for pre-eclampsia, some results did show statistical significance when related to the diagnosis of endometriosis, as described by Berlac et al,[16] Glavind et al[17] and Brosens et al.[30] But the results reported by Saraswat et al,[19] Conti et al[25] and Aris[26] disagreed as they show negative association between endometriosis and the outcome in question.[9,16–19,24–27,29,30]

Many authors also evaluated the relationship between pregnant women with endometriosis and placental disorders such as premature rupture of membranes, placenta previa and premature placental abruption. Berlac et al,[16] Conti et al,[25] and Harada et al,[33] who included premature rupture of membranes in the studied outcomes, concluded that women with endometriosis are a risk group to present these pathologies. The investigated placental outcomes were linked to the diagnosis of endometriosis in the studies by Berlac et al,[16] Mannini et al,[18] Saraswat et al,[19] Fujii et al,[23] Lin et al[24] and Vercellini et al[28] and Harada et al,[33] showing a strong correlation among them. Premature placental abruption was identified to be associated with endometriosis in the studies by Berlac et al[16] and Harada et al.[33] However, Lin et al[24] did not find the same association.[16,18,19,23–25,28–34]

Many authors place newborn-related outcomes among the unfavorable obstetric results to be evaluated in women with endometriosis. All of the studies that evaluated preterm birth found a positive correlation, as reported by Berlac et al,[16] Glavind et al,[17] Saraswat et al,[19] Stephansson et al,[20] Fujii et al,[23] Jacques et al,[34] Lin et al,[24] and Conti et al.[25] Berlac et al[16] and Conti et al[25] included SGA fetuses, and also obtained a

positive correlation with increased risk in women with endometriosis.

The delivery route was also evaluated in many studies included in the present systematic review. Glavind et al,[17] Saraswat et al,[19] Jacques et al[34] and Lin et al[24] reported higher risk of cesarean delivery in women diagnosed with endometriosis. However, Mannini et al[18] and Mekaru et al[27] did not report this association.[17,19,24,27,34]

Discussion

The present systematic review highlighted observational studies, some more robust with larger control groups and others with more restricted groups (►**Table 1**). The highest agreement between studies of greater quality of evidence is the high incidence of preterm birth and placenta previa in patients with endometriosis.[16,18,19] Moderate quality studies also showed endometriosis-diagnosed patients to have more abortion occurrences and cesarean deliveries.[21,22,24,25,31,34] Generally, most studies highlight the impact of endometriosis on unfavorable obstetric outcomes, although only three less relevant case-control group studies found no evidence of higher risk (►**Table 2**).[27,29,32]

The causes of higher risk for obstetric complications have not yet been defined, and the underlying pathophysiological factors are still unclear.[35] Despite this, endomyometrial changes present in patients with endometriosis seem to be responsible for several obstetric adverse factors such as abortion, fetal growth restriction, placenta previa, and preterm delivery or SGA infants.[35] More specifically, in relation to the increased incidence of complications such as preterm birth and placenta previa, we can emphasize alterations in endometrial hormonal receptivity, decidualization and remodeling of the spiral uterine arteries and inflammatory state that alter the regulation of the endocrine immune system in patients with endometriosis.[18,36]

The reason why some placentas are implanted in the lower segment of the uterus remains under discussion. As gestation progresses, 90% of low-insertion placentas move towards the uterine fundus. The placenta grows preferably towards the best-vascularized area, which is the uterine fundus (trophotropism), and the placenta that remains in the least vascularized area undergoes atrophy. Uterine contractions lead to detachment of this area of the placenta and subsequent bleeding, which further stimulates uterine contraction.[37] Resistance to progesterone and inadequate uterine contractions occurring in women with endometriosis may explain the greater frequency of placenta previa in this subgroup.[18] Endometriosis also leads to a hyperinflammatory state of the endometrium that causes endometrial endocrine immune balance disorder (increase in sex hormones, neurohormones, cytokines and growth factors). This disorder is thought to influence the interaction of decidua/trophoblast and activate the mechanisms of preterm delivery when the imbalance between pro-inflammatory and anti-inflammatory mechanisms of the placenta occurs.[7] These mechanisms found in patients with endometriosis may justify the greater obstetric risks.

In the last 20 years, several studies focused on the evaluation of this diversity of obstetric complications, with premature rupture of membranes and cases of placenta previa being the most commonly associated complications in the representative studies. Reviews on the topic report the same aforementioned complications in women diagnosed with endometriosis as those found in the present systematic review. However, in our review, we perceived that among all analyzed studies, there is great statistical heterogeneity and their quality was not taken into account. Therefore, to be able to derive significant conclusions from our study we chose to assign greater importance to the quality of each of the studies. This approach minimized the possible biases of each study and allowed a better analysis of the results.[13]

At the same time, there is a concern in the literature regarding the results found in a number of different studies (bias, false positives or false negatives).[38,39] In this respect, systematic reviews are able to extract from the studies information on data quality, sample size, possible biases and methodological description. Despite the volume of studies published with endometriosis in pregnancy, there is the need to prepare large studies, with carefully selected control groups (to avoid bias), based on a working hypothesis compatible with existing results from previous reviews, and focusing on the association and risk between endometriosis and unfavorable obstetric outcomes.

Nonetheless, our study also presents limitations in view of those of each of the articles analyzed. Inherent characteristics of many studies, such as methodological flaws, lack of histological confirmation of endometriosis, and small number of patients were a frequent finding.[16,32] Another divergence among the studies was whether infertility and in vitro fertilization were considered as a bias (►**Table 1**). It is important to note that endometriosis and infertility may be independent risk factors, since polymorphisms in genes associated with infertility, regardless of endometriosis, are also related to unfavorable obstetric outcomes.[40] To minimize the mentioned limitations of many studies, we used the NOS scale method to classify and assign higher or lower quality to each study as explained.

Finally, through the present data compilation, it is possible to direct the search for endometriosis-associated obstetric complications looking for the underlying causes and mechanisms. It also informs on possible guidelines for the clinical care of patients with surgical diagnosis of endometriosis, in order to reduce the rates of comorbidities associated with endometriosis in pregnancy.

Conclusion

Endometriosis is a disease that extends beyond the presence of ectopic endometrial implants. The condition of the endometrium can determine the quality of implantation and placental development, influencing obstetric outcomes, especially preterm birth and placenta previa. More studies paying more attention to the quality of the methodology, with adequate experimental designs and without bias such as in vitro fertilization, are necessary. The information gathered is useful to

alert obstetricians and women diagnosed with endometriosis about possible unfavorable obstetric outcomes.

Contributors

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

Conflict to Interests

The authors have no conflict of interests to declare.

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Quality of Life for Women with Human Papillomavirus-induced Lesions

Qualidade de vida de mulheres com lesões induzidas Pelo Papilomavírus Humano

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Abstract

Objective To reveal the changes in the quality of life reported by women with Human papillomavirus (HPV)-induced lesions.

Methods This is a cross-sectional, descriptive-exploratory study of a qualitative approach performed from June to August 2016. Semi-structured face-to-face interviews based on five questions on the concept of quality of life were used. The data were submitted to thematic analysis. All ethical aspects have been contemplated.

Results A total of 20 women aged between 25 and 59 years old were interviewed. From the analysis of the data, the following thematic units emerged: physical and emotional changes, especially complaints of pruritus, discharge and pain, worry, fear, shame and sadness; changes in sexual and affective relationships with decreased libido, dyspareunia and interruption of sexual activity; changes in social relationships resulting in absenteeism at work.

Conclusion Human papillomavirus infection impairs the quality of life of women as it significantly affects sexual, affective, physical, emotional, and everyday habits. Therefore, HPV infection can lead to exponential changes in the quality of life of women, which can be mitigated by the availability of sources of support such as family, friends and the multi-professional team, helping to improve knowledge and cope with HPV.

Keywords
- papillomavirus infections
- quality of life
- women's health
- gynecology
- qualitative research

Resumo

Objetivo Desvelar as alterações na qualidade de vida referidas por mulheres com lesões induzidas pelo papilomavírus humano (HPV).

Métodos Trata-se de um estudo transversal, descritivo-exploratório, de abordagem qualitativa, realizada no período de junho a agosto de 2016. Foram utilizadas entrevistas semiestruturadas face a face, a partir de cinco questões fundamentadas

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no conceito de qualidade de vida. Os dados obtidos foram submetidos a análise temática. Todos os aspectos éticos foram contemplados.

Resultados Foram entrevistadas 20 mulheres com idades entre 25 e 59 anos. A partir da análise dos dados, emergiram as seguintes unidades temáticas: alterações físicas e emocionais com destaque para as queixas de prurido, corrimento e dor, preocupação, medo, vergonha e tristeza; alterações nas relações sexuais e afetivas com diminuição da libido, dispareunia e interrupção da atividade sexual; alterações nas relações sociais com ausências consecutivas no trabalho.

Conclusão A infecção pelo HPV prejudica a qualidade de vida das mulheres, uma vez que afeta de maneira considerável os aspectos sexuais, afetivos, físicos, emocionais e hábitos cotidianos. Portanto, a infecção pelo HPV pode acarretar mudanças exponenciais na qualidade de vida de mulheres, as quais podem ser amenizadas pela disponibilidade de fontes de apoio, como família, amigos e equipe multiprofissional, que auxiliam no nível de conhecimento e enfrentamento do HPV.

Palavras-chave
- infecções por papillomavirus
- qualidade de vida
- saúde da mulher
- ginecologia
- pesquisa qualitativa

Introduction

Humanpapillomavirus (HPV) is a group of 226 viruses cataloged by the International Human Papillomavirus (HPV) Reference Center, in which each type of this large group receives a number. Only 13 types are evaluated as oncogenic because they present a greater probability or risk of generating persistent infections and precursor lesions. They usually do not have symptoms and are spontaneously eliminated by the organism.[1–3]

The Information Center on HPV and Cervical Cancer (ICO) estimated that there were $\sim$ 5,880,000 HPV-infected people in the world in 2017 and 2,784,000 women $>$ 15 years old.[4] In Brazil, an epidemiological study on the prevalence of HPV infection indicated the overall rate of 54.6% of infected people between 16 and 25 years old.[5]

Although HPV has the ability to infect the epithelium of both genders, the damage done to women is greater and more frequent. According to the Centers for Disease Control and Prevention (CDC), HPV-related cancers are not commonly found in men, with HPV infection being the most common sexually transmitted infection (STI).[3] In addition, women have different biological characteristics to men, with less thinner genital mucosa with a larger contact surface, favoring a higher risk of contagion.[6]

The social and economic inequalities experienced by women with HPV infection have several consequences related to stigma and prejudice, impacting their family, social, affective and sexual relationships.[7] In today's society, women play a variety of roles like mother, wife, daughter, and housewife, and sometimes they neglect to look after themselves, with a negative effect on their quality of life.

The World Health Organization (WHO) Quality of Life Group defines quality of life as *"the individual's perception of their position in life in the culture and value system context in which they live and in relation to their goals, expectations, standards, and concerns."*[8]

Therefore, evaluating the quality of life of women with HPV infection is an important tool for the development of interventions regarding their physical, psychosocial and economic impact.[9,10]

In addition, the broad concept of quality of life proposed by Fayers et al[11] includes important aspects that include physical, emotional, cognitive and sexual functioning, physical symptoms and toxicity, social well-being, existential issues, and also the general state of health. Therefore, the aim of the present study was to reveal the changes in quality of life reported by women with human papillomavirus-induced lesions.

Methods

This is a cross-sectional, descriptive-exploratory, qualitative study performed from June to August 2016 in an outpatient clinic of a public hospital in the interior of the state of São Paulo, Brazil, specializing in infectious diseases in gynecology.

To obtain a heterogeneous sample, the participants in the study were women aged $\geq$ 18 years old with a proven diagnosis of HPV infection with clinical lesions (condylomatosis) and subclinical lesions. The diagnosis was made through clinical examination and biopsies with histopathological examination. In the cases of subclinical lesions of cervical intraepithelial neoplasia II and III, the diagnosis was made through pap smears (cytopathology), colposcopy and biopsies. For subclinical lesions, vulvar intraepithelial neoplasia and vaginal intraepithelial neoplasia, the diagnosis was made through clinical examination and biopsies with a histopathological examination.

The determination of the presence of the viral DNA HPV in the samples of biopsies collected was performed through the molecular diagnostic technique with the polymerase chain reaction (PCR) method. Polymerase chain reaction is one of the most sensitive and commonly used techniques for detecting HPV.[12–14] It is a molecular biology method based on the selective amplification of a specific DNA sequence.

Polymerase chain reaction-amplified products can be analyzed in several ways, including gel electrophoresis (agarose or polyacrylamide), dot blotting, reverse-blot hybridization, and direct sequencing of DNA.[15]

Those with coinfection by the human immunodeficiency virus, considered a confounding factor, were excluded. The selection of the women was a matter of convenience, selecting those who came to the clinic on the day of the scheduled medical appointment.

To evaluate the quality of life, the data were collected through a semistructured face-to-face interview, based on five questions proposed by Fayers et al[11] on the concept of quality of life.

The questions were: 1: Do you know why HPV infection happens? 2: Has there been any change in your sex life after the diagnosis of HPV?; 3: Has there been any change in your daily life (work, daily activities) after the diagnosis of HPV?; 4: How do you feel about the diagnosis of HPV?; 5: Do you feel any physical discomfort related to HPV?

The interviews lasted from 30 to 40 minutes. Nobody refused to participate, and none of the participants dropped out during data collection or after. The interviews were conducted in a private setting in the outpatient clinic, where only the researcher and the interviewee were present, to preserve the privacy of the participants.

The number of participants was based on the precepts of theoretical data saturation, as the interviews revealed the recurrence of ideas and practices related to the object of study.[16]

For the analysis of the data, the fully transcribed interviews generated a textual corpus that was submitted to thematic analysis after an exhaustive reading of the reports.[16]

An alphanumeric code made up of the letter "E" and the arabic numeral corresponding to the sequence of the interviews was used for the identification of the participants interviewed, thereby ensuring their anonymity.

All of the recommendations of Resolution 466/12 of the National Health Council were respected; therefore, the interviews were only conducted after approval of the study by the Research Ethics Committee (CAAE: 38995114.0.0000.5393, opinion n°1,080/473), and all of the participants read and signed the Informed Consent Term.

Results

A total of women aged between 25 and 59 years old were interviewed. Their cultural, social and educational characteristics are described in ►**Table 1**.

Their diagnosis was varied, 4 women with condylomatosis (20.0%), 5 women with grade II cervical intraepithelial neoplasia (CIN) (25.0%), 7 with grade III CIN (35.0%), 2 with vulvar intraepithelial neoplasia (10.0%), and 2 with intraepithelial vaginal neoplasia (10.0%). From the data analysis, three thematic units emerged: physical and emotional changes; changes in sexual and affective relationships; changes in social relationships.

Physical and Emotional Changes

The women, as participants in the study, reported physical and emotional changes in their lives related to HPV infection.

Table 1 Distribution of women ($n = 20$) according to cultural, social and educational characteristics

Variables	*n* (%)
Ethnicity / skin color (self-declared)	
White	7(35.0)
Brown	11(55.0)
Black	2(10.0)
Occupation	
Housekeeper	10(50.0)
Saleswoman	4(20.0)
Unemployed	2(10.0)
Merchant	2(10.0)
Retired	2(10.0)
Schooling (years studied)	
9–12	17(85.0)
> 12	3(15.0)
Economic situation (minimum wages*)	
1 to 3	18(90.0)
4 to 6	2(10.0)
Marital status	
Married	13(65.0)
Common-law marriage	5(25.0)
Single	2(10.0)

*Value of minimum wage in 2016: R$ 880,00.

In the physical changes, abdominal pain (cramps) and genitalia pain were evidenced.

> […] I feel pain when I clean the house. Sometimes, when I make some effort at home I feel cramps (E2).

> I have pain in my "lower stomach"and when I pee (E3).

> […] I feel pain in my belly […] (E15).

> I feel pain when I wash it (genitalia) in the shower (E19).

Pain is perceived while carrying out everyday activities such as housekeeping and showering. Also, the presence of pruritus (itching) was also found in the speeches of the participants.

> I feel itchy a lot […] (E8)

> […] sometimes I feel itchy (E15).

> I feel itchy a lot […] it bothers me when I sit down […] (E19).

Regarding the emotional changes, the testimonies of the women showed the feelings of worry, sadness, and despair regarding the diagnosis of HPV, especially when it has been discovered.

[…] it seems that just thinking about "this thing" makes me worried, sad […] (E7).

The day I found out, I only cried, I became very sad and worried […] (E8).

I was very sad when I found out, but nowadays, I don't keep thinking about it in order not to suffer […] (E9).

[…] when I discovered it, I was desperate […] (E13).

[…] I was very worried and a little desperate, I feel very ashamed […] (E15).

There is also a feeling of shame in relation to other people in their social life, such as their children, as they have an STI.

[…] I am very ashamed […] (E3).

[…] I got really bad when I found out. I kept thinking about what people would think of me (E16).

After I discovered it, I didn't even leave the house anymore because I thought people knew what I had […] (E19).

When I found out, I was "stuck." I thought of my children. I was ashamed […] (E20).

With emotional changes, fear became present in the life of these women with HPV, through the knowledge of the association of the virus with the risk of cancer and, consequently, the fear of death.

When I discovered it, I was very scared of cancer and I was thinking that my hair would fall out and I would get thin […] (E2).

[…] I thought it was very serious, I thought it was cancer and I was afraid of dying (E10).

[…] I'm very scared of dying because of this… I can't die because I have two daughters to raise (E1).

Changes in Sexual and Affective Relationships

Changes in the sexual and affective relationships of the women related to HPV were reported. The speeches show the loss of desire of the women and feeling of embarrassment of having sex after the HPV diagnosis.

[…] I have less desire to have sex […] (E1).

[…] I have almost no intercourse with my husband because I no longer have any desire (E8).

[…] now I have less desire […] (E15).

At the beginning of the treatment, I had no desire to have intercourse […] (E16).

At first, I felt very ashamed and didn't feel like doing anything, and it continued and we finished […] (E19).

The sensation and fear of pain, discomfort, and bleeding during sexual intercourse was reported several times, also negatively influencing having sex.

[…] I'm afraid of it hurting. Because sometimes, depending on the position, it hurts. I feel a lot of pain during sex […] (E2).

[…] In the beginning, it hurt a lot to have intercourse. […] I feel pain during intercourse, and it bothers me (E3).

[…] I only feel pain when I have sex […] (E7).

[…] I was afraid of it hurting […] (E10).

[…] sometimes, it bleeds during sex […] (E11).

[…] sometimes, when I have intercourse, it bleeds […] (E15).

Interruption of sexual activities correlating with HPV infection was also evidenced.

[…] Since I discovered that I had this, 4 years ago, I have not had sex again (E6).

[…] After the doctor discovered it here, I did not have sex until the day I had the laser (E12).

Also, as a consequence of the changes in sexual life, conjugal problems emerged. Dyspareunia and decreased libido are corroborating conditions for this situation.

[…] My husband always complains because I feel a lot of pain […] (E1).

I almost have no intercourse with my husband anymore because I don't want to, and he always gets angry about it […] (E8).

The risk of infidelity and the mistrust of the partner were also highlighted by several women as a conflictive situation, causing wear and tear in the affective relationship.

[…] I get angry, you know? Because my husband always had other women, and he never caught anything! "It" never appeared in him […] (E1).

[…] I don't trust my partner, and I have already quarreled a lot with him […] (E5).

[…] I was very suspicious of my boyfriend, but he said it was not him because he had nothing […] (E11).

[…] at first, I mistrusted him […] (E17).

It is also possible to verify that condom use encouraged by the partner and the fear of infertility also affected the affective relationships.

[…] I never used condoms because my husband never let me (E2).

[…] When I told my husband, he didn't like it because he was afraid that I couldn't have any more children (E3).

On the other hand, there were three partners (15%) who faced the situation in a positive way, offering support and strengthening the affective relationship.

[…] in the beginning, my husband thought that I didn't want to have intercourse, but now he understands the situation […] (E10).

[…] I told my husband and he faced it very well […] (E13).

The relationship between me and my husband remains the same […] (E15).

Changes in the Social Relationships of Women with HPV Infection

The changes in social relationships included two antagonistic situations. Most of the interviewees affirmed that they maintained normal social activities, even with HPV infection.

[…] I don't stop going out because of this disease […] (E2).

[…] no, nothing has changed in my daily life […] (E4).

However, some women reported lack of motivation to enjoy social activities after the diagnosis of HPV.

[…] after I found out (HPV), I didn't even leave the house because I thought people knew what I had […] (E19).

Also, HPV infection and its treatment had an impact on women's professional lives, mainly in terms of work-related absenteeism, leading in some cases to them losing their job.

[…] I always miss work so I came here […] (E3).

[…] I have had to miss my work on many occasions to come here (E6).

[…] I lost my job because I always needed to be absent so I came here (E20).

To face this difficulty, participant E10 reported the strategy used to not have a change in professional life.

[…] There was no change in what I do because I work (I'm a cleaner), but I come here the day I can be absent from my work […] (E10).

Discussion

When women face the fact that they have HPV infection, they go through different situations that change their daily life by having to face the peculiarities of the diagnosis and to adapt to this new reality.[17,18] Such a condition leads to physical, emotional, affective, sexual, and social changes.

In the present study, it was possible to verify physical changes such as pain and pruritus caused by HPV infection. However, most HPV infections are asymptomatic or not apparent and are transient, and may spontaneously disappear. It is estimated that in only 5% of infected people will there be some form of manifestation. However, as the disease progresses, precursor lesions or early-stage cancer may result in vaginal bleeding, discharge, and pain.[19]

The emotional aspect was also affected as a result of the infection caused by HPV. The positive diagnosis of an STI brings about feelings such as sadness, confusion, fear, fear of being judged, malaise, family contempt, partner anger, and bargaining behavior.[20]

Corroborating the results found in the present study, an investigation performed to assess the psychosocial burden and impact on the quality of life of HPV-related diseases observed a significant psychosocial impact in women.[21] Regarding the feelings of shame described by some women, Yang et al[22] reported that the impact of shame and stigma on the diagnosis of HPV disclosure may influence the initial decision to use the vaccine.

In a study designed to assess the prevalence of shame in women diagnosed with HPV/CIN, these women had a substantially higher state of shame than women diagnosed with another STI.[23]

Concerning feelings of fear of cancer and death, similar findings have been reported in studies involving women with HPV.[24]

In terms of sexual and affective aspects, the study by Dominiak-Felden et al[21] determined that infections caused by HPV have a negative impact on sexual functioning, especially in those diagnosed with CIN II and/or CIN III when compared with women in the general population.

Corroborating with the findings, a study conducted in Fortaleza, state of Ceará, Brazil, with 100 women diagnosed with HPV infection showed that 55.5% of the women stated there was a decrease in libido; also, 60.0% reported a decrease in the frequency of intercourse, and 37.8% reported sexual abstinence.[25]

Regarding the complaints of dyspareunia and leucorrhea, an investigation performed in Ecuador found an association between exposure to HPV infection and the presence of whitish vaginal secretion and dyspareunia.[26]

Thus, one of the most significant characteristics found in women diagnosed with HPV is the genital change, which may not only cause pain and bleeding in sexual intercourse but

also shame and embarrassment, which could lead to marital problems.[17,27,28]

Thus, legitimating the findings of the present study, the distrust and the risk of infidelity were also pointed out by Jeng et al[29] as possible causes of conflict with the partner because they believed that alleged extramarital affairs could be the source of the infection.

In terms of the non-use of condoms, a similar result was found in a Brazilian study involving 977 women diagnosed with HPV infection in which it was possible to verify that the non-use of protection methods in stable relationships suggests an excessive confidence in the affective partner.[7]

However, the risk of cervical cancer and the fear of infertility are real concerns, especially in the lives of women with HPV infection, as described in a multicenter study in China.[28]

Despite the strengthening of affective-sexual relationships being a threat to the use of protection methods, these relationships are an important source of emotional support when there are fears of infection, and they also give practical support, helping in domestic activities or accompanying the patient to medical consultations.[27]

Regarding the social relationships changes, although most of the participants in the present study have normal social activities, and the lack of motivation to enjoy social activities and absenteeism at work with risk of layoffs are reported, corroborating with other studies.[28,30,31]

The HPV-related stigma added to misinformation leads to isolation through fear of disclosure of the diagnosis and negative self-image compared with other people.[31]

Regarding the social changes, similar aspects were revealed in a study developed in Ethiopia, in which the number of days of being absent from work for outpatient follow-up or hospitalization were quantified, with frequent absenteeism threatening the maintenance of employment.[30]

In this sense, considering the changes related to living with HPV infection, the importance of support networks can be seen. A study performed in Mexico pointed out that informal networks such as family and friends, and formal networks such as churches, support groups, and medical professionals and their guidelines help people to cope with HPV infection.[27] Thus, the emotional burden is inversely proportional to the knowledge of the infection.[28,31]

The present study allows changes in the quality of life of women with HPV infection to be seen and, therefore, enables the management of and intervention in situations that can significantly affect treatment.

Conclusion

The results show that, in general, women with HPV infection face a variety of physical, emotional, affective-sexual, and social changes, modifying their quality of life. Complaints of pain, pruritus and the presence of warts, discharge and bleeding can decrease libido and negatively impact self-image, influencing affective-sexual relationships. Human papillomavirus-related stigma and shame at the diagnosis lead to the loss of motivation of social activities, and absences from work for outpatient follow-up increase the fear of disclosure, as well as being a risk for future dismissals. Therefore, HPV infection can lead to exponential changes in the quality of life of women and can be mitigated by the availability of sources of support such as family, friends and the multi-professional team, helping to improve knowledge and cope with HPV.

Contributors
All of the authors participated in the concept and design of the study; analysis and interpretation of data; drafting or revising of the manuscript, and they have approved the manuscript as submitted. All of the authors are responsible for the reported research.

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

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Thromboprophylaxis during the Pregnancy-Puerperal Cycle - Literature Review

Tromboprofilaxia no ciclo gravídico-puerperal – Revisão da literatura

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Abstract

Objective To identify current strategies and recommendations for venous thromboembolism prophylaxis associated with the pregnancy-puerperal cycle, a condition of high morbidity and mortality among women.

Methods The literature search was performed between May and October 2019, using the PubMed database, including papers published in Portuguese, English and Spanish. The terms *thromboembolism* (Mesh) AND *pregnancy* (Mesh) OR *postpartum* (Mesh) were used as descriptors, including randomized controlled trials, meta-analyses, systematic reviews and guidelines published from 2009 to 2019, presenting strategies for prevention of thromboembolism during pregnancy and the postpartum.

Results Eight articles met the inclusion criteria. Many studies evaluated were excluded because they did not address prevention strategies. We compiled the recommendations from the American Society of Hematologists, the American College of Obstetricians and Gynecologists, the Royal College of Obstetricians and Gynecologists, the Society of Obstetricians and Gynaecologists of Canada, the American College of Chest Physicians and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists.

Conclusion: There are some gaps in the research, and clinical studies with appropriate methodology are needed to support decisions made regarding the risk of thromboembolism in the perigestational period. Thus, the attention of the professionals involved in the care of pregnant and postpartum women is crucial, as it is a condition associated with high morbidity and mortality.

Keywords
- thromboembolism
- thrombosis
- pregnancy
- postpartum
- disease prevention

Resumo

Objetivo Identificar as estratégias e recomendações atuais para profilaxia de tromboembolismo venoso associado ao ciclo gravídico-puerperal, condição de alta morbimortalidade entre mulheres.

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Métodos A busca na literatura ocorreu entre maio e outubro de 2019, com pesquisa na base de dados do PubMed, contemplando trabalhos publicados nos idiomas português, inglês e espanhol. Os termos *thromboembolism* (Mesh) AND *pregnancy* (Mesh) OR *postpartum* (Mesh) foram utilizados como descritores, incluindo ensaios clínicos randomizados, metanálises, revisões sistemáticas e diretrizes publicadas entre 2009 a 20019, apresentando estratégias de prevenção de tromboembolismo venoso durante a gravidez e o pós-parto.

Resultados Oito artigos abordando estratégias de tromboprofilaxia primária e secundária durante a gestação, parto e puerpério foram selecionados para a presente revisão sistemática. Muitos estudos avaliados foram excluídos por não abordarem estratégias de prevenção. Foram compiladas as recomendações das seguintes sociedades: American Society of Hematologists, American College of Obstetricians and Gynecologists, Royal College of Obstetricians and Gynecologists, Society of Obstetricians and Gynaecologists of Canada, American College of Chest Physicians e Royal Australian and New Zealand College of Obstetricians and Gynaecologists.

Conclusão Até o presente momento, há algumas lacunas e estudos clínicos com metodologia adequada se fazem necessários para respaldar a tomada de decisão frente ao risco de tromboembolismo venoso no período perigestacional. Torna-se fundamental a atenção dos profissionais envolvidos no atendimento às gestantes e puérperas, pois trata-se de uma condição associada a alta morbimortalidade.

Palavras-chave
- Tromboembolismo
- trombose
- gestação
- pós-parto
- prevenção de doenças

Introduction

Venous thromboembolism (VTE), manifested as pulmonary embolism (PE) or deep-vein thrombosis (DVT), affects ~ 1 to 2 per 1,000 pregnancies. Despite its low-incidence rates, it stands out as a relevant etiology of maternal morbimortality as it is the cause of 10 to 15% of deaths occurring during the pregnancy-puerperal cycle.[1,2] However, it is a preventable condition if adequate measures for thromboprophylaxis are provided.

Pregnant women present a four times greater risk of presenting with VTE when compared to nonpregnant women in the same age group, and the occurrence of DVT is more common, especially in the left lower limb, throughout pregnancy.[3] During the postpartum period, the increase in risk is approximately 10 times greater,[4] with PE being the most frequent manifestation when compared to isolated DVT.

The risk of VTE exists beginning in the first 3 months of pregnancy, before anatomical alterations become visible.[5] It persists during the whole pregnancy, increases in the 3rd trimester, and markedly rises during the postpartum.[6,7] Statistically, the number of incidences during pregnancy is similar to the puerperium, but considering the shorter duration of the postpartum, the daily risk is higher during the first weeks after giving birth, especially the first 7 days, when 50% of such events occur.[8]

Callaghan et al[9] reported a 72% increase in the incidence of VTE in women admitted for childbirth between the years of 1998 and 2009, attributed to an increase in the prevalence of prothrombotic conditions such as obesity, maternal age, cesareans and other comorbidities.

Recently, epidemiological data has also evidenced a substantial growth in the incidence of VTE during recent decades. When assessing hospitalizations due to VTE during the pregnancy-puerperal cycle, it is possible to verify an estimated increase during pregnancy and the puerperium of 17% and 47%, respectively,[10] reinforcing the need for adoption of specific measures for thromboprophylaxis.

Morbidity due to VTE during pregnancy can be acute or delayed, with significant impact on the quality of life of the patient.[11] Pulmonary hypertension occurs in ~ 4% of patients within 2 years of a PE diagnosis. The occurrence of post-thrombotic syndrome (PTS) was observed in 42% of women with DVT and in 24% of women who presented PE related to pregnancy.[12]

Thromboembolic disease imposes risks both to the mother and the fetus, and the peculiarities intrinsic to the pregnancy-postpartum period make thromboprophylaxis challenging in this context.

The available guidelines for thromboprophylaxis during pregnancy and the postpartum present a certain degree of uncertainty due to the lack of studies performed on this specific population, sometimes resulting in extrapolation based on data from studies that examined nonpregnant patients.

The Royal College of Obstetricians and Gynaecologists (RCOG),[13] the American Society of Hematologists (ASH),[14] and the American College of Obstetricians and Gynaecologists (ACOG)[8,15] published new guidelines with recommendations that were both accordant and incongruent with previous publications. Before that, recommendations were published by the Society of Obstetricians and Gynaecologists of Canada (SOGC)[16] in 2014, the American College of Chest Physicians (ACCP)[17] in 2012, and by The Royal Australian and

New Zealand College of Obstetricians and Gynaecologists (RANZCOG)[18] in 2012.

The aim of the present study is to identify strategies and recommendations for primary and secondary prophylaxis during pregnancy, childbirth and the puerperium, according to current knowledge, describing the complexity and relevance of the subject, which often makes valuable the conjoint approach of obstetricians, vascular surgeons and hematologists. For this purpose, a review will be made about the pathophysiological aspects of VTE in the pregnancy-puerperal cycle and the recommendations of the main guidelines identified will be compiled. It should be emphasized that guidance specifically concerning thrombophilia is outside the scope of the present article, and a consultation to the guidelines recommended by the ASH[14] and the ACOG,[8] both published in 2018, is advised.

Methods

The literature review for the proposed research was conducted between May and October of 2019 using an online search in the PubMed – U.S. National Library of Medicine Databases. The terms *thromboembolism* (Mesh) AND *pregnancy* (Mesh) OR *postpartum* (Mesh) were used as descriptors. The search included randomized controlled trials, meta-analyses, systematic reviews and guidelines published from 2009 to 2019, presenting strategies for prevention of VTE during pregnancy and the postpartum. Abstracts that met the inclusion criteria and were published in Portuguese, English and Spanish were considered. Studies performed in populations outside the pregnancy-puerperal cycle, with specific thrombophilia or with thrombosis in atypical sites were excluded. "Grey literature" (unpublished) has been identified by searching the websites of databases as well as national and international medical societies. The studies were selected by title and then by summary by the same authors who conducted the research. The papers that met the eligibility criteria were fully evaluated. One relevant full text – The RCOG guideline[13]–from a bibliography hand search was included for its relevance. The study inclusion process is shown in ►**Figure 1**.

Results

Of the articles selected from the database and those manually included, eight met the inclusion criteria. Many studies evaluated were excluded because they did not address prevention strategies. One randomized controlled trial evaluated two doses of enoxaparin specifically in obese women. The other studies included were guidelines from medical societies. Information was analyzed regarding authorship, year of publication, study design and main findings (►**Box 1**).

Physiopathology of Venous Thromboembolism during Pregnancy, Labor and the Postpartum

Pregnancy is a prothrombotic state due to physiological and anatomical alterations that comprise the three key elements of the Virchow triad: venous stasis, hypercoagulability and endothelial lesion. Stasis is due to the compression of the pelvic vessels and the inferior vena cava by the pregnant uterus.[3,20] The physiological increase of coagulating molecules such as fibrinogen, VII, VIII, X and von Willebrand factors, PAI 1 and 2 and the concomitant reduced synthesis of the natural anticoagulant S protein lead to a hypercoagulable state.[21] These alterations presumably represent an evolutional gain, with the purpose of reducing hemorrhagic complications, mainly during the peripartum and the puerperium. Endothelial injury is a consequence of vascular damage during labor and childbirth (vaginal or cesarean section).

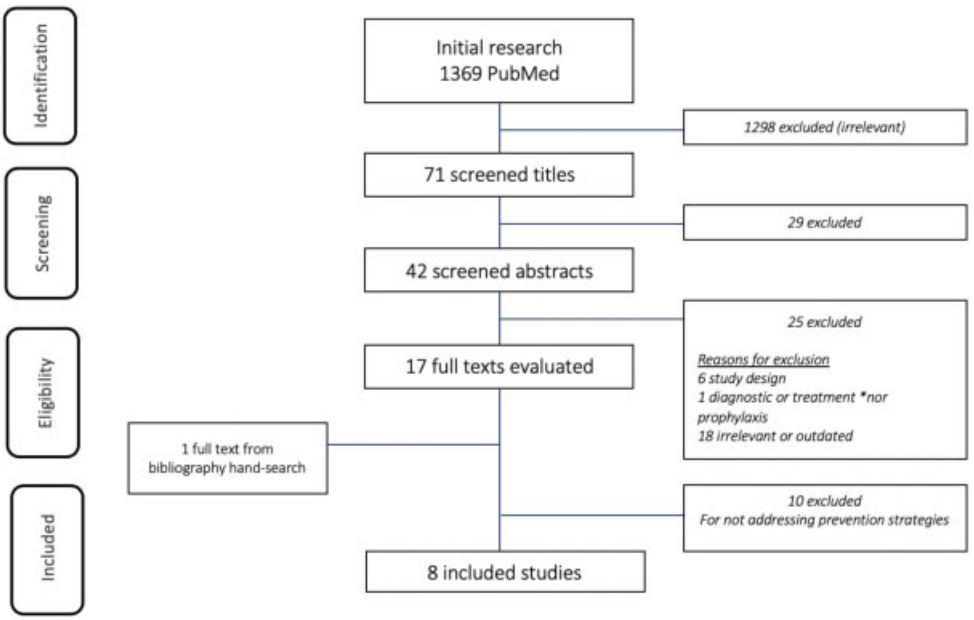

Fig. 1 Flowchart of article eligibility and final inclusion in the present systematic review. **Source:** Reducing the risk of venous thrombosis and embolism during pregnancy and the puerperium.[13]

Box 1 Selected studies and characteristics

Authors/year	Country	Study design	Main findings
Bates et al (2018)[14]–American Society of Hematology	USA	Guideline	The panel agreed on 31 recommendations related to the treatment of VTE and superficial vein thrombosis, diagnosis of VTE, and thrombosis prophylaxis
American College of Obstetricians and Gynecologists (2018)[15]	USA	Guideline	Summarizes the available data to provide practical approaches
Stephenson et al (2016)[19]	USA	Randomized controlled trial	Comparing two enoxaparin dosing strategies at achieving prophylactic anti-Xa levels in women with a body mass index (BMI) ¶ 35 (kg/m2) postcesarean delivery, the authors found that weight-based dosing twice daily more effectively achieved prophylactic anti-Xa levels than fixed dosing daily
RCOG (2015)[13]	UK	Guideline	Summarizes the available data and the quality of the evidence to provide practical approaches
Chan et al (2014)[16]–SOGC	Canada	Guideline	Summarizes the available data and the quality of the evidence to provide practical approaches
Bates et al (2012)[17]–ACCP	USA	Guideline	Summarizes the available data to provide practical approaches
McLintock et al (2012)[18] - RANZCOG	Australia/ New Zealand	Guideline	Compilation of recommendations from the Specialty Society Guidelines

Abbreviations: ACCP, American College of Chest Physicians; RANZCOG, Royal Australian and New Zealand College of Obstetricians and Gynaecologists; SOGC, Society of Obstetricians and Gynaecologists of Canada; VTE, venous thromboembolism;

Risk Factors for Thromboembolism in the Pregnancy-Puerperal Cycle

It is possible to divide the risk factors for VTE as preexisting, obstetric and transitory.[13] Among preexisting factors, there is prior occurrence of VTE; maternal age > 35 years old; body mass index (BMI) > 30 before pregnancy or during early pregnancy; multiple births (> 3 children); hereditary thrombophilia (antithrombin deficiency, protein C deficiency and protein S deficiency, mutation in the prothrombin gene and presence of the factor V Leiden); antiphospholipid syndrome; presence of comorbidities (cancer, heart failure, autoimmune diseases, intestinal inflammatory diseases, nephrotic syndrome, diabetic nephropathy); smoking; large varicose veins (symptomatic or above the knee or associated to phlebitis, edema or trophic alterations) and reduced mobility (i.e.: paraplegia).[13]

From the obstetric viewpoint, the risk conditions are multiple pregnancies; present pre-eclampsia; cesarean section, with four times greater risk than vaginal delivery; prolonged labor, with a duration of > 24 hours; use of rotation forceps; premature delivery or fetal death and postpartum hemorrhage, considered when there is a loss of > 1 liter of blood or when a blood transfusion is required.[13]

Other factors to be considered are surgical procedures during pregnancy or the puerperium (with the exception of perineal raphe); dehydration due to hyperemesis; ovarian hyperstimulation syndrome (only in the 1st trimester); assisted reproduction and in vitro fertilization (IVF); hospitalization or immobility (> 3 days in bed); presence of systemic infection and long-distance travel (duration of > 4 hours).[13]

Thromboprophylaxis Methods during Pregnancy

Considering the risks of the mother-baby binomial and possible morbidities that may occur after a thromboembolic event, the implementation of thromboprophylaxis measures are mandatory in all health institutions rendering obstetric care. The prevention of thrombus formation can be achieved by mechanical or pharmaceutical methods.[22]

Mechanical Methods

Mechanical methods, which include deambulation, elastic compression and pneumatic compression, regulate the stasis risk factor by increasing the venous flow without elevating the risk of bleeding. These methods have been efficient in reducing the risk of VTE in two thirds of the general surgical population. Considering that data is scarce for the use of mechanical methods during pregnancy, the benefits are based on the results found in the surgical population outside the pregnancy-puerperal cycle.[22] The medical team must assure to maintain the pregnant patient as active as possible and assess the risks and benefits of pharmaceutical thromboprophylaxis in situations of reduced mobility (such as hospitalization or prolonged bed rest). Elastic stockings, indicated as adjuvants in the prophylaxis of obstetric VTE, have been efficient in promoting an increase in venous flow and a significant reduction in the caliber of the femoral vein, reducing venous stasis. Although they are commonly prescribed for women who have recently given birth, their use is possible throughout all phases of pregnancy.[23,24] There are various models of sequential compression devices and there

is no evidence of superiority among them in the prevention of VTE prophylaxis.[25]

Pharmacological Methods

The benefits of anticoagulants in the prevention of VTE need to be confronted with the increase of hemorrhagic risk during pregnancy, the peripartum and the puerperium. There is heterogeneity amongst guideline recommendations related to indications, dosages and duration of thromboprophylaxis.[26] There is low level of evidence and most guidance derive from retrospective studies, prospective cohorts and the opinion of experts.

No evidence supports the use of routine prophylaxis,[27] therefore the use of risk stratification systems may guide decision-making.[28] Despite the lack of randomized and controlled studies to guide prevention strategies, there is no doubt that there are benefits to thromboprophylaxis in the reduction of the recurrence of the VTE, and some authors encourage institutions to adopt their own protocols. The clinical choice should be made through shared decision-making and incorporating patient preferences and values.

Heparins

Heparins enhance the action of antithrombin – an endogenous anticoagulant. Unfractionated heparin (UFH) and low molecular-weight heparins (LMWHs) do not cross the placental barrier and are not secreted in the maternal milk – thus, are considered safe during pregnancy and the puerperium.[29] It is important to remember the physiological changes that occur during pregnancy, such as increase of 1) maternal plasmatic volume (40-50%), 2) proteins that reduce the bioavailability of heparin and 3) glomerular filtration rate, increasing renal clearance.[8] Low molecular-weight heparins (dalteparin and enoxaparin) are the pre- and postnatal drugs of choice for thromboprophylaxis[8,12,14,17] Studies of the general population demonstrate that LMWHs are as efficient as UFH for thromboprophylaxis as well as safer – osteoporosis, fractures, and the risks of thrombocytopenia induced by heparin are significantly lower with LMWHs.[8,13] Neither UFH or LMWHs are associated with significant bone demineralization when used in prophylactic dosages during the period of pregnancy.[30] Both drugs show a clinically significant incidence of bone loss ($\geq$ 10%) in only between 2 and 2.5% of patients.[31] The potential advantages of LMWHs for short- and long-term use include predictable treatment response, longer half-lives, less allergic reactions, and lower risk of thrombocytopenia induced by heparin.[8]

Women receiving prophylactic dosages of LMWHs during pregnancy must be counseled to discontinue its use 24 hours before scheduled childbirth or as soon as they begin labor (contractions, vaginal bleeding, rupture of membranes or loss of mucus plug).[22] Hematoma in the vertebral canal is a rare complication of the neuraxial blockade. It is recommended to wait at least 12 hours between the last prophylactic dose of LMWHs (low dosage) and the blockade.[32] Protocols for LMWHs dosages are detailed in ►**Tables 1** and **2**.

Table 1 Thromboprophylaxis regimen with low molecular-weight heparin doses calculated by weight (adapted from the Royal College of Obstetricians and Gynaecologists)[13]

Weight	Enoxaparin	Dalteparin
< 50Kg	20mg/day	2500 U/day
50–90 Kg	40 mg/day	5000 U/day
91–130 Kg	60mg/day	7500 U/day
131–170 Kg	80 mg/day	10,000 U/day
> 170 Kg	0,6mg/Kg/day	75 U/Kg/day
High prophylactic dosage for women between 50–90Kg	40mg 12/12h	5,000 U 12/12h

Source: Reducing the risk of venous thrombosis and embolism during pregnancy and the puerperium.[13]

Table 2 Thromboprophylaxis during pregnancy with low molecular-weight heparin according to the American College of Obstetricians and Gynecologists (extracted from ACOG)[8]

Regimen	Dosage
Prophylactic dosage	Enoxaparin 40 mg SC once a day Dalteparin 5,000 U SC once a day
Intermediate dosage	Enoxaparin 40 mg SC 12/12h Dalteparin 5,000 U SC 12/12h
Adjusted dosage (therapeutic)	Enoxaparin 1mg/Kg 12/12h Dalteparin 200 U/Kg once a day

Abbreviation: SC, subcutaneous.
Source: ACOG Practice Bulletin No. 196.[8]

The ideal dosage of LMWHs for thromboprophylaxis during pregnancy is unknown and will possibly be clarified after the publication of the results of the Highlow Trial (NCT 01828697; www.highlowstudy.org), a randomized and multicenter study being done that intends to comparatively assess the safety and effectiveness of prophylactic versus intermediate dosages of LMWHs.[33]

It should be observed that robust data is not available to support the use of a specific regimen by pregnant or puerperal obese women, therefore, in practice, the recommendations of the RCOG[13] are followed. A single randomized clinical trial was published with data on thromboprophylaxis in the population of obese pregnant women undergoing cesarean delivery, showing that when compared to the fixed daily dose (40mg/day), the weight-based enoxaparin dose administered twice daily (0.5mg/ kg 12/12h) more effectively achieved prophylactic levels of anti-Xa activity without reaching therapeutic levels.[19] Routine platelet monitoring of patients using LMWHs is not necessary, unless there is a history of exposure to UFH.

Regarding anti-Xa activity, no routine dosage indication is established in the main guidelines. Those advocating against routine monitoring emphasize that the correlation of anti-Xa activity with gestational outcome and recurrence of VTE is scantly understood.[13,34] However, a retrospective study has reported that 79% of the patients receiving prophylactic LMWHs were outside the target anti-Xa activity range (0.2-0.6 UI/mL), with a recommended dosage adjustment

Table 3 Unfractionated heparin dosages according to the American College of Obstetricians and Gynecologists (extracted from ACOG)[8]

Regimen	Dosage
Prophylactic UFH	5,000-7,500 U SC 12/12h in the 1st trimester 7,500-10,000 U SC 12/12h in the 2nd trimester 10,000 U 12/12h in the 3rd trimester
Adjusted dosage (through aPTT) of UFH	10,000 U or more, SC 12/12h – adjusted for aPTT between 1.5-2.5x control 6 hours after injection

Abbreviations: UFH, unfractioned heparin; SC, subcutaneous; aPTT, activated partial thromboplastin time.
Source: ACOG Practice Bulletin No. 196.[8]

when < 0.3 UI/mL.[34] During the peripartum of high-risk patients, LMWHs could be replaced with UFH, considering its shorter half-life, quick monitoring of its effect (aPTT) and easy reversibility.[8,13] The UFH dosage regimen recommended by The American College of Obstetricians and Gynecologists is described in ►**Table 3**.

Fondaparinux

Fondaparinux is a pentasaccharide that crosses the placental barrier, yet as of today it is not possible to exclude the possibility of damage to the fetus. There are reports of isolated cases of its use in more advanced stages of pregnancy. Its use during this period should be restricted to patients with contraindication to heparin (thrombocytopenia induced by heparin or allergies). In the breastfeeding phase, it is considered safe.[17]

Vitamin K Antagonists

Warfarin has always been used for secondary prophylaxis in the nongestational population.[26] However, findings that vitamin K antagonists (VKAs) cross the placental barrier and cause fetal abnormalities (nasal and member hypoplasia, chondral calcification, scoliosis, fetus intracranial hemorrhage and schizencephaly – clefts in the cerebral hemisphere) from the 6th week of pregnancy, led to a restriction of its use. Besides that, the exposure to VKAs in the 3rd trimester was associated with peripartum fetal hemorrhage, and its use in the 2nd trimester is associated with neurological impairment (cognitive and behavioral).[35] Despite the risks of VKA use throughout pregnancy, its use is safe during breastfeeding.[8,13,17,30]

Direct Oral Anticoagulants

Due to lack of data regarding the effectiveness and safety of direct oral anticoagulants (DOACs) during pregnancy and breastfeeding, its use is not recommended during this period.[31]

Thromboprophylaxis Strategies during Pregnancy

There are no large-scale randomized studies, and the main recommendations come from medical guidelines. Following are compiled recommendations from the RANZCOG, the ACCP, the SOGC, the RCOG, the ACOG and the ASH.[8,13–18] The strategy recommended by the RCOG[13] is considered an achievement in thromboprophylaxis during the pregnancy-puerperal cycle as its implementation at the beginning of this century decreased the maternal mortality rate by $> 50\%$ (1.94 maternal deaths for every 100,000 births in 2003–2005 to **0.79** in 2006–2008).[36,37] The British guideline recommends pharmacological prophylaxis with greater frequency than the North American guidelines. Due to its impact in maternal morbimortality, its recommendations were adopted by other countries as well as by the Safe Motherhood Initiative. A summary of the RCOG[13] recommendations to prevent thrombosis during pregnancy and the puerperium is demonstrated in ►**Figures 2** and **3**.

The ACCP[17] recommendations include more frequent pharmacological prophylaxis, also due to indications after cesarean sections, based on risk factors. Blondon et al[38] published a meta-analysis that showed cesarean section as an independent risk factor for VTE postpartum, with greater risks related to emergency procedures. The ASH[14] recommendation addresses more specific situations concerning thrombophilia, which may be useful for those interested in this subject matter. It is important to emphasize that the lack of thorough studies justifies the variance of conduct between medical societies. For further details, see ►**Box 2**.

Peripartum Management

To date, there are no randomized controlled trials or systematic reviews that have simultaneously evaluated VTE recurrence outcomes versus hemorrhagic complications, in the context of the management of peripartum anticoagulation, but there are some options for anticoagulation in this context. One strategy is to stop heparinization before induction of scheduled vaginal or cesarean delivery. The suspension time will depend on the type and dose of heparin in use, respecting the deadlines recommended and described in different anesthesiology guidelines.[1,36]

It is recommended that therapeutic LMWHs should be discontinued 24 hours before neuraxial blockade and, in the case of prophylactic dose, 10 to 12 hours before,[32,39] considering the 24-hour interval increase in some situations.[39]

There is insufficient scientific evidence to recommend a specific 12 to 24 hour interval for patients on intermediate doses. Unfractionated heparin, when administered intravenously, may be suspended 4 to 6 hours before anesthetic blockade.[32,39] For cases in which UFH is administered subcutaneously, the Society for Obstetric Anesthesia and Perinatology (SOAP)[32] recommends 12 hours of interval between the use of UFH and neuraxial blockade, if the dose is from 7,500 IU to 10,000 IU.

It is also recommended that regimens with doses above the prophylactic dose (UFH, 5000UI, 8/8h, subcutaneous route) have their coagulation status assessed by activated partial thromboplastin time (aPTT) dosage and/or anti-Xa activity. Additionally, the Brazilian Society of Anesthesiology (SBA, in the Portuguese acronym) additionally recommends

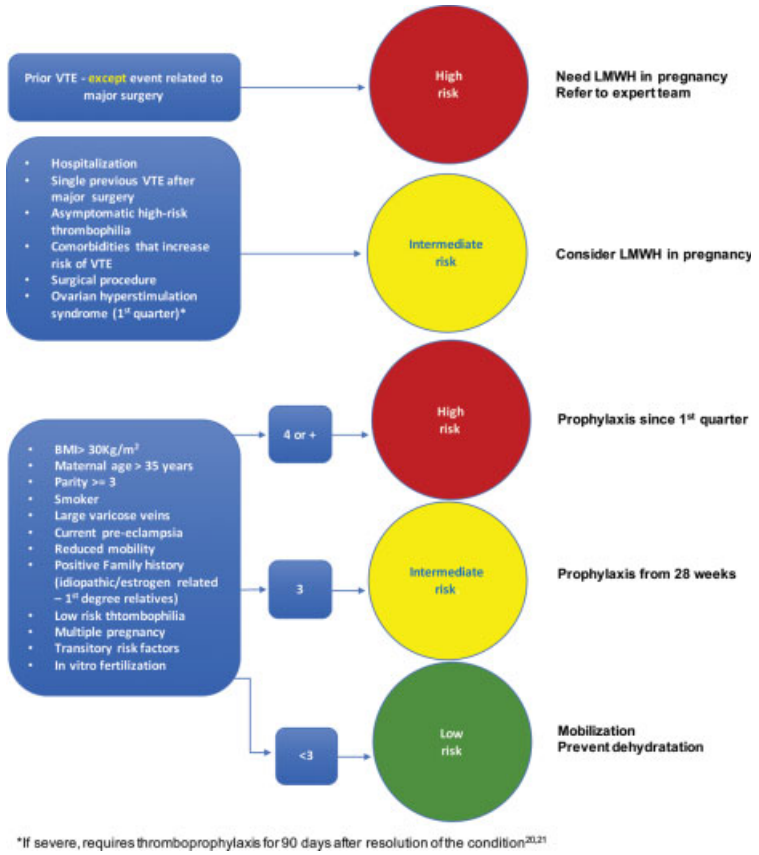

Fig. 2 Stratification of the risks during pregnancy (adapted from the Royal College of Obstetricians and Gynaecologists).[13] **Source:** Reducing the risk of venous thrombosis and embolism during pregnancy and the puerperium.[13]

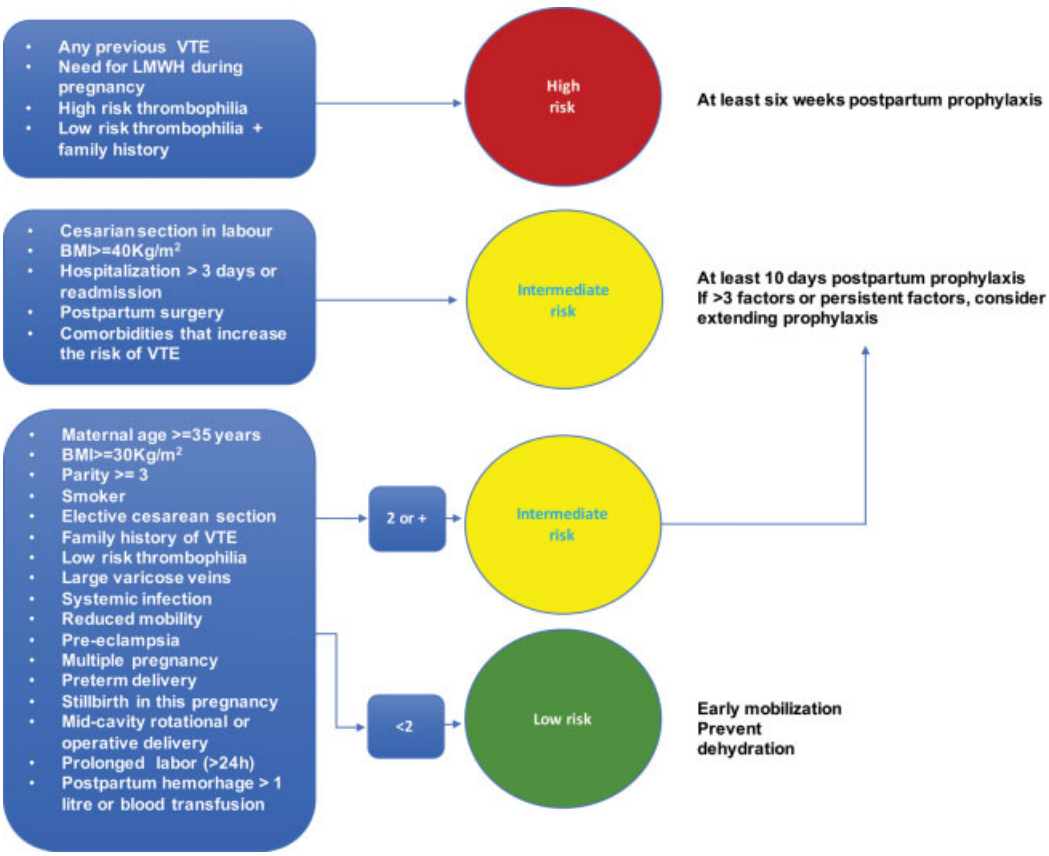

Fig. 3 Stratification of the risks during the puerperium (adapted from the Royal College of Obstetricians and Gynaecologists).[13]

Box 2 Compilation of the ACOG, ACCP, ASH, RANZCOG and SOGC guidelines[8,14–18]

	ACOG	ACCP	ASH	RANZCOG	SOGC
Previous idiopathic VTE **or** associated to hormonal risk factor (estrogen)	Pharmacological prophylaxis during pregnancy and puerperium	Pharmacological prophylaxis during pregnancy and puerperium	Pharmacological prophylaxis during pregnancy and puerperium	Pharmacological prophylaxis during pregnancy and puerperium	Pharmacological prophylaxis during pregnancy and puerperium
Sole prior occurrence of VTE associated to a greater reversible risk factor (non-hormonal)/ without thrombophilia	Pregnancy: Monitoring Puerperium: Pharmacological prophylaxis in the case of additional risk factors (i.e. family history, caesarian section, etc.)	Pregnancy: Monitoring Puerperium: Pharmacological prophylaxis	Pregnancy: Monitoring Puerperium: Pharmacological prophylaxis	Pregnancy: Monitoring Puerperium: Pharmacological prophylaxis	
Background of multiple thrombotic events	Pharmacological prophylaxis during pregnancy and puerperium	Pharmacological prophylaxis during pregnancy and puerperium		Pharmacological prophylaxis during pregnancy and puerperium	Pharmacological prophylaxis during pregnancy and puerperium
Low risk asymptomatic thrombophilia[*1] **and** negative family history for VTE	Monitoring during pregnancy and puerperium. Prophylaxis in puerperium if additional risk factors.	Monitoring during pregnancy and puerperium	Monitoring during pregnancy and puerperium		
Low risk asymptomatic thrombophilia **and** positive family history for VTE	Monitoring or prophylaxis during pregnancy and pharmacological prophylaxis during puerperium	Monitoring during pregnancy and pharmacological prophylaxis during puerperium	If C and S deficiency does not indicate primary prophylaxis during pregnancy, only in the puerperium. If heterozygosis for FVL or mutant prothrombin does not indicate it.	Pregnancy: observation unless other risk factors Puerperium: consider prophylaxis especially if other risk factors	
Low risk thrombophilia **and** sole prior occurrence of VTE (anticoagulation already concluded)	Prophylaxis during pregnancy and puerperium	Prophylaxis during pregnancy and puerperium			Prophylaxis during pregnancy and puerperium
High risk asymptomatic thrombophilia[*2] **and** negative family history for VTE[*3]	Prophylaxis during pregnancy and puerperium	Pregnancy: Monitoring Puerperium: LMWH prophylactic or therapeutic dosage or VKA (RNI:2-3) for 6 weeks	AT deficiency: monitoring during pregnancy and puerperium. Mutant prothrombin or homozygous V Leiden factor: monitoring in pregnancy and prophylaxis during puerperium		Pregnancy and puerperium: prophylaxis if any high-risk thrombophilia
Patient receiving anticoagulants and becomes pregnant	Pregnancy: adjusted dosage of LMWH or UFH Puerperium: therapeutic anticoagulation (VKA and LMWH may be used during breastfeeding)	Pregnancy: LMWH in therapeutic dosage or 75% of the dosage Puerperium: therapeutic anticoagulation (VKA and LMWH may be used during breastfeeding)	Pregnancy: LMWH in one dosage or twice a day Puerperium: UFH, LMWH, fondaparinux[*4], warfarin or acenocoumarol are considered options by ASH (strong recommendation with very low level of evidence)	Pregnancy: therapeutic anticoagulation Puerperium: return to pre-pregnancy anticoagulation	
Dosages of LMWH	Prophylactic, intermediate or adjusted dosage during pregnancy and puerperium	Prophylactic or intermediate dosage during pregnancy and puerperium	Pregnancy: ASH is in favor of the standard dosage and against the use of intermediate dosage Puerperium: standard or intermediate dosage	Prophylactic, intermediate or adjusted dosage during pregnancy and puerperium	Prophylactic, intermediate or adjusted dosage during pregnancy and puerperium

Abbreviations: ACCP, American College of Chest Physicians; ACOG, American College of Obstetricians and Gynaecologists; ASH, American Society of Hematologists; LMWH, low molecular-weight heparin; RANZCOG, Royal Australian and New Zealand College of Obstetricians and Gynaecologists; SOGC, Society of Obstetricians and Gynaecologists of Canada; UFH, unfractionated heparin; VKA, vitamin K antagonists; VTE, venous tromboembolia; INR, International Normalized Ratio; FVL, Factor V Leiden; AT, Antithrombin.

[*1] Low risk thrombophilia: deficiency in protein S or C, heterozygosis for Factor V Leiden (FVL) or mutant prothrombin G20210A; [*2] High risk thrombophilia: homozygosis for Factor V Leiden or for mutant prothrombin G20210A, heterozygosis for Factor V Leiden and mutantrothrombin (combined thrombophilia) or deficiency in antithrombin; [*3] Family history: immediate family members with prior history of thromboembolism; [*4] The ACCP does not recommend the use of fondaparinux during breastfeeding (degree of recommendation 2C).

the assessment of platelet counts in patients using UFH if it has not been done within 5 days before delivery.[39]

Another strategy is to transition the anticoagulation of LMWHs to UFH, with discontinuation immediately after the onset of labor.

The ASH[14] has as an additional option to wait for the spontaneous start of labor if the pregnant woman is using prophylactic UFH or LMWHs, reserving the scheduled delivery only for situations in which the pregnant woman is using therapeutic doses.

In face of these possibilities, a multidisciplinary management is recommended, as well as discussing options with the patient so that she may participate in the decision-making process and become aware of the potential impact upon labor analgesia access. This should be done in such a manner that the choices may be individualized, aiming to respect not only maternal preferences but also the safety of the mother-baby binomial.

It is also recommended to evaluate the potential risk factors for postpartum hemorrhage (PPH) in order to identify the most vulnerable patients. The RCOG, in its PPH guideline, mentions the 4Ts associated with increased risk of bleeding: tone (multiple pregnancy, previous PPH, fetal macrosomia, and general anesthesia are associated with uterine hypotonia); thrombin (pre-eclampsia); trauma (episiotomy, perineal laceration) and tissue (accretism or placental retention).[40]

As the primary mechanism of postpartum hemostasis is compression of the uterine vessels by sustained contraction of myometrial fibers, it is assumed that heparinization does not increase bleeding by uterine hypotonia. However, bleeding due to vaginal or cesarean section trauma may be magnified by the use of heparin in the hours before delivery. Thus, the active participation of the obstetric team in the third stage of labor is necessary to minimize trauma and stimulate uterine contractility (through the use of uterotonics such as oxytocin, for example) in women with reported use of heparin in the moments before delivery.[17]

The presence of hereditary thrombophilia does not change the usual obstetric indications that define the mode of delivery. However, induction of full-term vaginal delivery may be considered to better adjust the last dose of anticoagulant, considering the possibility of neuraxial blockade.[8,15] Scheduling delivery of the patient at high thrombotic risk may exclude an element of uncertainty for the pregnant women as well as for the medical team, thus reducing the likelihood of maternal and fetal exposure to general anesthesia if the patient progresses to emergency cesarean section.

The use of an intrapartum pneumatic compression device should be considered in patients with known thrombophilia until they resume ambulation,[8,15] and it is important to emphasize that they should not be used in patients with acute thrombotic events due to the risk of embolization of these thrombi. The ACOG recommends that all women with thrombophilia undergoing cesarean section receive at least an intermittent pneumatic compression device.[8] It is suggested to consider the criteria in ►**Box 2** to determine the appropriate prophylaxis strategy.

Conclusion

Despite expansive knowledge concerning the risk factors for treatment and prevention of VTE during pregnancy and the puerperal period, management of these patients is extremely difficult due to the potential for complications, along with the need to balance the well-being of mother and fetus during decision-making. Accordingly, there is a general understanding that all women should have the opportunity to take part in choosing their prophylactic and/or therapeutic strategy. Despite the recommendations of guidelines becoming increasingly consistent about the safe and effective use of anticoagulants in order to prevent and treat VTE in this population, as of today there are still significant voids, therefore high-quality research in this area should be a priority. Further information should be collected on issues such as the ideal LMWHs prophylaxis dosage for prevention of recurrent VTE during the pre- and postpartum periods; the absolute risk of VTE during pregnancy, delivery and puerperium in combination with clinical risk factors; and the impact of the application of risk scores to prevent VTE and bleeding risks.

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

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Congenital Complete Atrioventricular Heart Block in a Pregnant Woman with Sjögren Syndrome: Prenatal Care Follow-Up and the Challenge of Intrauterine Treatment

Bloqueio atrioventricular completo congênito em uma mulher grávida com síndrome de Sjögren: seguimento pré-natal e desafio do tratamento intrauterino

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Abstract

The present report describes a case of complete atrioventricular block (CAVB) diagnosed at 25 weeks of gestation in a pregnant woman with Sjögren's syndrome and positive anti-Ro/SSA antibodies. Fluorinated steroids (dexamethasone and betamethasone) and terbuline were used to increase the fetal heart rate, but the fetal heart block was not reversible, and the administration of drugs was discontinued due to maternal collateral effects. Follow-up fetal echocardiograms were performed, and the fetus evolved with pericardial effusion, presence of fibroelastosis in the right ventricle, and ventricular dysfunction. Interruption of pregnancy by cesarean section was indicated at 34 weeks of gestation, and a cardiac pacemaker was implanted in the male newborn immediately after birth. Therapy for fetuses with CAVB is controversial mainly regarding the use or not of corticosteroids; however, monitoring of the atrioventricular interval by fetal echocardiography should be performed in fetuses from pregnant women with positive autoantibodies anti-Ro/SSA and/or anti-La/SSB to prevent the progression to CAVB.

Keywords

- complete congenital heart block
- maternal autoantibodies
- prenatal diagnosis
- prevention
- intrauterine treatment

Resumo

Este relato descreve um caso de bloqueio atrioventricular completo (BAVC) diagnosticado com 25 semanas de gestação em uma mulher com síndrome de Sjögren e anticorpos anti-Ro/SSA positivos. Esteroides fluoretados (dexametasona e betametasona) e terbulina foram utilizados para aumentar a frequência cardíaca fetal, mas o bloqueio cardíaco fetal não foi reversível, e a administração dos medicamentos foi interrompida devido a efeitos colaterais maternos. Ecocardiogramas fetais de acompanhamento foram realizados, e o feto evoluiu com derrame pericárdico, presença de fibroelastose no ventrículo direito, e disfunção ventricular. A interrupção da gravidez por cesariana foi indicada com 34 semanas, e um marca-passo cardíaco foi implantado no recém-nascido do sexo masculino imediatamente após o nascimento. A terapia para fetos com BAVC é controversa, principalmente no que diz respeito ao uso ou não de corticosteroides; no entanto, o monitoramento do intervalo atrioventricular pela ecocardiografia fetal deve ser feito em fetos de mulheres grávidas com autoanticorpos positivos anti-Ro/SSA e/ou anti-La/SSB para impedir a progressão para o BAVC.

Palavras-chave

- bloqueio cardíaco congênito completo
- autoanticorpos maternos
- diagnóstico pré-natal
- prevenção
- tratamento intrauterino

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Introduction

The incidence of atrioventricular block (AVB) is of 1 per 15,000–20,000 live births, and 50% to 55% of these cases are caused by the presence of structural congenital heart disease.[1] In total, 40% of AVBs are mainly related to SSA/Ro- or SSB/La-positive maternal antibodies. These antibodies may cross the placental circulation and lead to immune-mediated inflammation or fibrosis of fetal conduction cardiac tissue.[2,3]

There are three types of AVB: first, second (incomplete), and third degrees (complete). In first-degree AVB, all electrical impulses are conducted from the atria to the ventricles, with a prolonged atrioventricular (AV) conduction time. In second-degree AVB, not all impulses are conducted from the atria to the ventricles. In complete or third-degree AVB, there is no conduction of electrical impulses from the atria to the ventricles. Thus, complete AVB (CAVB) is characterized by AV dissociation and low ventricular heart rate (HR < 60 bpm) (►**Fig. 1**).[2,3]

In fetuses, the time between atrial and ventricular contractions (AV interval) can be measured using either the ultrasound M-mode (D) or Doppler mode. The AV interval is equivalent to the mechanical PR interval, and it is considered to be extended when its value is above 150 ms. However, the treatment of intrauterine AVB is controversial and involves close monitoring of signs of fetal heart failure.[2,3] In the present article, we describe a case of AVB associated with maternal autoimmune disease, as well as the guidelines for follow-up and intrauterine treatment.

Case Report

A 35-year-old primigravida from the city of Sorocaba, Brazil, with Sjögren syndrome and anti-Ro/SSA-positive

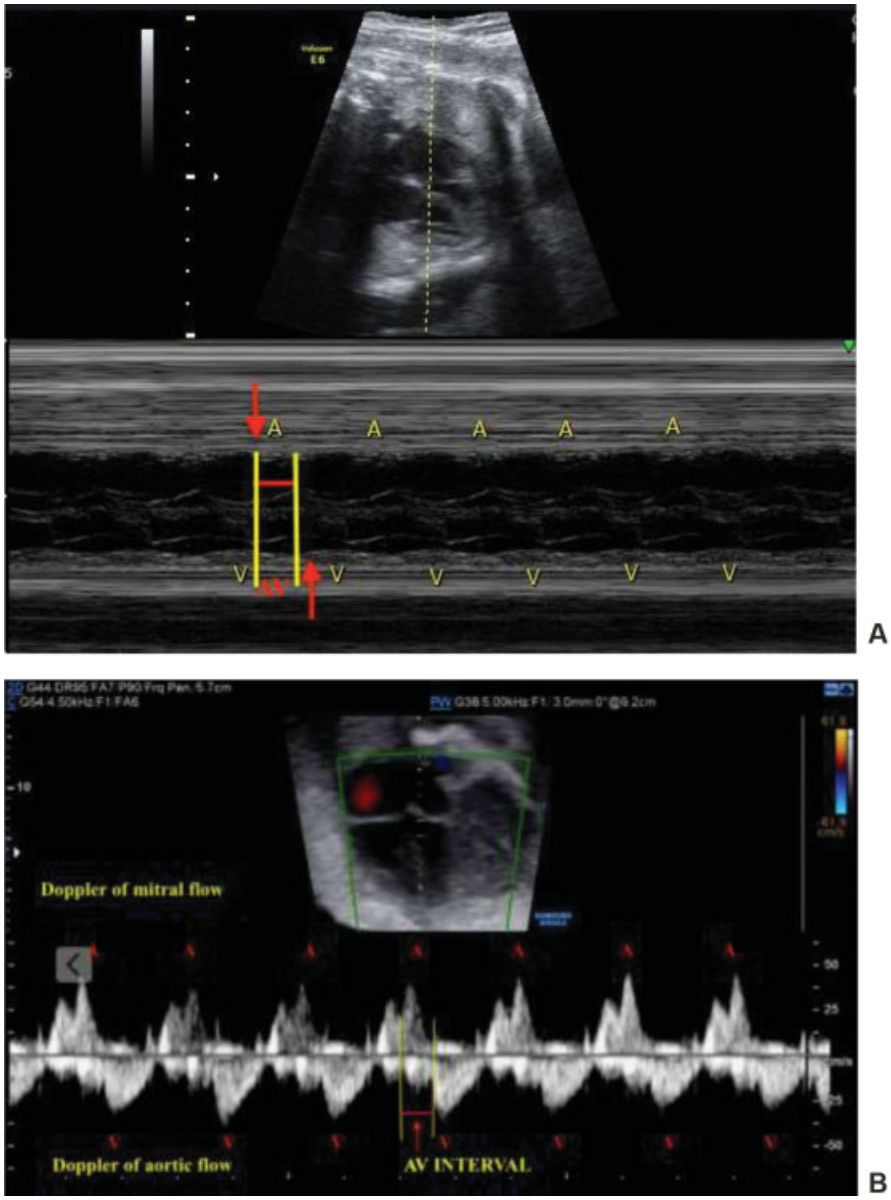

Fig. 1 Assessment of the atrioventricular interval time (AV interval, which is analogous to the electrical PR interval) by fetal echocardiogram: M-mode ultrasound (**A**) and Doppler of the mitral and aortic flow (**B**). Abbreviations: A: atrial contraction; V: ventricular contraction.

and anti-La/SSB-negative antibodies was examined at our department with a singleton gestation of 25 weeks; the patient was referred for fetal bradycardia with a heart rate (HR) of 45 bpm for 21 weeks. She had an initial diagnosis of left atrial isomerism associated with interventricular communication. After parental counseling, intrauterine pacemaker placement was indicated; however, the patient refused it. Clinical and echocardiographic follow-ups were conducted, and the mother was treated with corticosteroids and β-adrenergic agents.

The patient was diagnosed with gestational diabetes mellitus due to corticosteroid use (8 mg/day), and had a HR of 200 bpm associated with symptoms after terbutaline use (400 mg/day). The first fetal echocardiogram, after a protocol to screen for congenital heart disease, showed an anatomically normal heart with bradycardic rhythm, ventricular HR of 40 bpm, and atrial HR of 147 bpm, and a diagnosis of CAVB was made (►**Fig. 2**). The administration of terbutaline was suspended and corticosteroid weaning was started due to the side effects, with improvement in

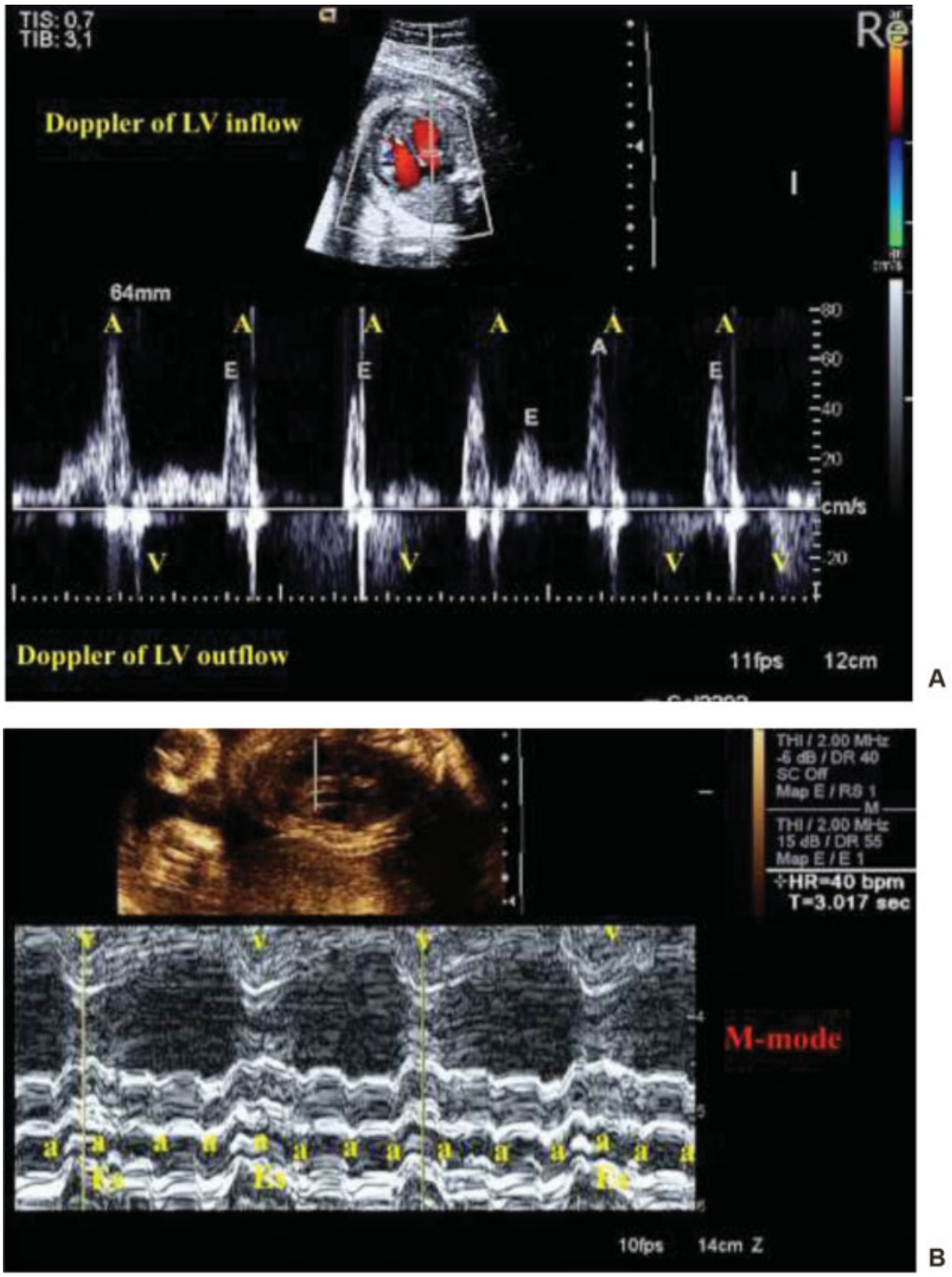

Fig. 2 (**A**) Left inflow and outflow tract view showing complete atrioventricular (AV) block by analysis of the inflow and outflow tract Doppler waves. (**B**) M-mode ultrasound showing complete AV block by atrial and ventricular wall movement recordings. Note presence of atrial extrasystoles. Abbreviations: A: atrial contraction; V: ventricular contraction; aEs: atrial extrasystoles; HR: heart rate.

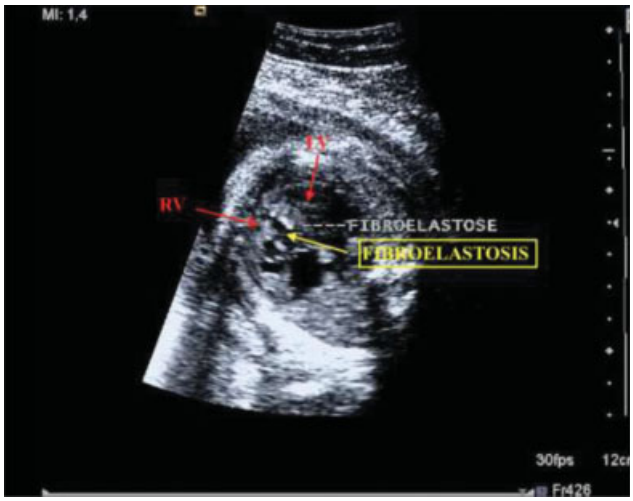

Fig. 3 Fetal echocardiogram performed at 32 weeks of gestation showing signs of RV fibroelastosis. Abbreviations: RV: right ventricle, LV: left ventricle; HR: heart rate.

fasting glucose and glycated hemoglobin (HbA1c) levels. At 32 weeks of gestation, the fetus showed effusions on echocardiographic follow-up with discrete pericardial effusion in the lateral wall of the right atrium and suspected right ventricular fibroelastosis (►**Fig. 3**). Another echocardiogram at 34 weeks showed worsening of the fetal pericardial effusion and ventricular dysfunction, and an emergency delivery was indicated. A cesarean section was performed, and a male infant was delivered, weighing 2,240 g, with Apgar scores of 4, 7, and 9 at the 1st, 5th, and 10th minutes respectively. The newborn was intubated in the delivery room. Transthoracic echocardiography immediately after birth confirmed normal cardiac anatomy, presence of moderate pericardial effusion without signs of restriction (►**Fig. 2**), and an HR of 40 bpm. Epinephrine was started at a dose of 0.1 µg/kg/min for hemodynamic support, and a 2-hour pacemaker was implanted. The infant's condition was stable, and he was successfully extubated at 5 days of age, after extubation failure due to pulmonary hypertension in the first 24 hours. The infant was discharged in 10 days with an HR of 130 bpm and good clinical condition.

Discussion

Sjögren syndrome is one of the three most common autoimmune diseases, with a prevalence of 0.1 to 5% of the population,[4] occurring most often in women, in a 9:1 ratio, with a higher prevalence in the fifth decade of life.[2] This disease is related to the presence of autoantibodies in 60% of the cases.[3] These antibodies cause damage to the fetal heart conduction system, leading to CAVB, which, in turn, is associated with a 30% mortality rate.[5]

Complete atrioventricular block is characterized by a complete dissociation between atrial and ventricular activity, with ventricular frequency usually below 60 bpm, in which fetuses with ventricular HR $<$ 55 bpm have a poorer prognosis[6] due to the presence of endocardial fibroelastosis and signs of fetal hydrops.[7,8]

The follow-up and treatment of these cases is not well-established, and the use of fluorinated corticosteroids (dexamethasone or betamethasone at a dose of 4 to 8 mg/day) is indicated in cases of incomplete AVB (first or second degrees) to prevent progression to CAVB or to achieve incomplete AVB reversal and decrease myocardial fibroelastosis. There is evidence against the use of corticosteroids in cases of CAVB due to the deleterious effects on pregnant women and the presence of irreversible fibrosis in the cardiac conduction tissue of the fetus.[9–11]

In the present case, the woman had been using dexamethasone since the diagnosis of CAVB at 23 weeks, without significant change in HR, which was maintained at $\sim$ 47 bpm. However, the patient developed gestational diabetes mellitus; thus, the administration of the medication was discontinued after a gradual dose reduction. Some studies point to the occurrence of side effects of corticosteroids and recommend that the medication be discontinued in their presence.[2,3,9] Eliasson et al[9] performed a multicenter study with 175 patients and demonstrated that, apart from the adverse side effects, the use of corticosteroids showed no beneficial effect in fetuses with HR $<$ 50 bpm or on the presence of hydrops and/or cardiomyopathy.

Some authors recommend the use of intravenous immunoglobulin in cases in which the fetus has systolic cardiac dysfunction and/or signs of endocardial fibroelastosis and/or myocarditis; however, its efficacy has not been proven.[2,3] Regarding the use of β-sympathomimetics, the patient used terbutaline and developed tachycardia and an estimated HR of 200 bpm, which was associated with symptoms such as malaise and tremors. Yoshida et al[12] reported the case of a pregnant woman at 22 weeks of gestation with CAVB in which terbutaline was chosen as a β-sympathomimetic drug due to good transplacental passage, to increase the fetal HR and prevent myocardial failure. Another study reported a 10% to 15% increase in fetal HR.[6] However, despite the increase in fetal HR, there are no studies demonstrating a benefit in terms of survival of these fetuses with this treatment approach.[12]

As there are no studies demonstrating that the use of these medications can modify the survival of these fetuses, pregnancy monitoring was performed every two days after the discontinuation of the corticosteroids and terbutaline, at which time the signs of heart failure were evaluated with the Huhta cardiovascular score[13] along with HR monitoring.

Percutaneous fetal implantation of a cardiac pacemaker has been shown to be effective in experimental studies, suggesting that it could be used in hydropic human fetuses with CAVB. However, there are no studies that prove its effectiveness in human fetuses.[3,14]

Some authors recommend continuous fetal echocardiographic surveillance from 16 weeks of gestation in pregnant women with Sjögren syndrome or other autoimmune diseases with positive anti-Ro/SSA and/or anti-La/SSB antibodies for the early diagnosis and early treatment of first- and second-degree AVB.[2,3,15] Patients with anti-Ro/SSA and/or anti-La/SSB antibodies should be advised of the high risk of fetal AVB or neonatal systemic lupus erythematosus, so that the pregnancy can be planned during periods of disease stability, that is, when

the patient has low levels of anti-Ro/SSAor anti-La/SSB antibodies. Since 2017, the European League Against Rheumatism (EULAR) has been recommending that hydroxychloroquine should be used during pregnancy, even when the pregnant woman is asymptomatic.[16]

The follow-up and treatment of fetuses with CAVB is still controversial in terms of the use of corticosteroids. However, attention should be paid to the fetuses of pregnant women with positive autoantibodies, with monitoring by fetal echocardiography, to prevent progression to CAVB.

Conflict of Interests

The authors have none conflict of interests to declare.

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The abstract should provide the context or basis for the study, establish the objectives, basic procedures, main outcomes and key findings. It should emphasize new and important aspects of the study or observations. Since the abstract is the only substantive part of the article indexed in many electronic databases, authors should ensure it reflects the article content in an accurate and highlighted manner. Do not use abbreviations, symbols and references in the abstract. In case of original articles from clinical trials, authors must inform the registration number at the end of the text.

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Conclusions: Indicate the main conclusions and their clinical usefulness.

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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.

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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.

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*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.***

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