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Editorial

Thinking about COVID-19 Scenario in Brazil: The Alternation between the Useful, the Uncertain and the Futile

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The only pandemic comparable to the current event caused by the new coronavirus (SARS-CoV-2), the disease called COVID-19, was that of the Spanish Flu in 1918.[1] At that time, with slow and scarce intercontinental transport, diseases spreading infectious diseases were unlikely. Nowadays, on the contrary, the ability to move a highly infectious virus is enormous. Likewise, information, whether scientific or opinionated, moves easily around the world today. Not casually, the term "viralization" is used when any information quickly reverberates through the internet.

In this context, the useful, the uncertain and the futile alternate in published news about COVID-19. And the scientific literature is not shielded from this. It can be said that the disease caused by SARS-CoV-2 is for health research today as nothing seems to have been. It is a completely uncontrolled worldwide phenomenon. The scientific community inhales and exhales COVID-19 in 2020. The disease is a fever, not just literally, and we are still looking for a good way to fight it.

In addition to what we mentioned above, is the fact that, in some way, any researcher in the field, anywhere, wants to discover how to free the world from COVID-19 and raise the glories of a new discovery for themselves or their work group. To that end, the number of published studies and texts grows so quickly that it becomes almost impossible to follow a reliable line of reasoning or to envision a truth. For the reader to understand what it is about, querying the term COVID-19 to the PubMed database (https://pubmed.ncbi.nlm.nih.gov) on August 14, 2020 resulted in an impressive 40,850 references. A little more than 8 months ago, when the disease appeared, predicting a scientific production with such a volume in such a short time would sound absurd. Limiting ourselves to a comparison with a relatively recent example, the search for the term Zika in that database, on the same date, resulted in about 8 thousand and two hundred references, and 5 years have passed since the identification of its correlation with the epidemic of microcephaly among exposed fetuses. It is through this path that the uncertainties are broadly presented.

Indeed, the rapid dissemination of data on COVID-19 or any other disease with a similar impact would be highly welcome by the medical community, but not without the scrutiny of the scientific method and the minimum time required for research. In the absence of that time and effective scrutiny tools, distorted versions of the facts easily intertwine with the relevant data and appropriate their reliable appearances. This ultimately generates countless interpretations for each relevant aspect of the disease. Yes, it is the effect of the post-truth that also echoes in science, when reason and emotion are mixed, taking people to the extreme of faithfully believing in the data that meet their fears and desires.

As we have suggested, science needs time to be a real science, usually a long time. And it is exactly in a scenario of anguish and collective uncertainties that the scientific method should be followed strictly, with well-defined research steps, leading to clear and reproducible results. In the COVID-19 pandemic, it would be important for the information to be made public only after the rigorous follow-up of cases, minimizing the impact of fragile and contradictory information, which highlights the general insecurity scenario. It would be a movement contrary to what we are experiencing, in which the accelerated consumption of pseudo-scientific or pre-scientific information occurs both through traditional documentation vehicles and through social networks.

Not without reason, the whole world is watching closely the curves of COVID-19 in Brazil. Currently, the Brazilian epidemic is one of the fastest growing in the world[2]; our numbers of new cases and deaths, since the beginning of the pandemic until now, are only below the numbers observed for the United States. The national epidemiological curve, which describes daily case reports, and which is influenced by the curves of large cities, suggests that we may be on a

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plateau without knowing whether it will precede the epidemic's shrinkage or end in a second wave of growth. This is because countless mathematical models have been made available, without any of them having stood out for their reliability until now, especially when applied to a country of continental dimensions such as Brazil, in which the process of internalization of the disease may be just beginning.

It is important that health authorities and managers are aligned with scientific evidence so that their leadership on the epidemic reinforces measures with a positive impact on the health of the population and minimizes potential deviations caused by the dissemination of misleading and potentially harmful information. It is not what has happened, apparently. On the contrary, we are supporting the recommendation for the use of certain drugs in the treatment of COVID-19, when scientific evidence with the greatest possible impact indicates their ineffectiveness.[3–5] The result? Mistakenly, many Brazilian citizens have been inspired by the intransigence coming from health authorities and managers, and by the aggressiveness of positions pro- or counter- any intervention, making them echo, in spite of what happens in academic circles.

In truth, the problems are not limited to those described above. In Brazil, there are those who claim that the seriousness of COVID-19 is not true, based on the comparison between the accumulated numbers of deaths in 2020 and 2019, in the same period. According to this analysis, the disease should not kill so much, since the number of deaths appears to be lower in 2020. But we consider this conclusion to be wrong since the data from the Ministry of Health's Hospitalization System are not yet consolidated and, even if were, the independence (fluctuation) of numbers from one year to another is an essential precept to interpret them. Think outside the box: even if the number of deaths in 2020 is, so far, lower than the number of deaths in the same period last year, that argument would not be valid. Otherwise, we would have to conclude that the COVID-19 epidemic brought gains to Brazil and to thank SARS-CoV-2 for having reduced the number of hospital admissions and deaths. That would be a huge folly.

The issue of numbers is much more complex than it appears to be. The quality of the counting of cases of a specific disease depends on an efficient epidemiological surveillance in all stages, namely: making the diagnosis; filling in the notification itself; systematization and computerization of data by local epidemiological surveillance services, at municipal and state levels; integration and, finally, accounting at the national level. Thus, one cannot fail to glimpse the negative impact of an epidemic at each point in the information generation process, leading to the possibility of error in the final count of cases of the disease in question. We will be close to the real numbers only in the medium to long term, when the worst scenario is expected to have passed.

It is also possible that, with the burden caused by the COVID-19 epidemic in Brazil, other diagnoses are being underreported. If we see, for example, the decrease in the diagnosis of flu syndrome by other respiratory viruses (which, in fact, is happening), we could assume that there is less circulation of seasonal respiratory viruses, while we have greater circulation of SARS-CoV-2. But we can also think that, as a direct consequence of the epidemic, less diagnostic tests are being carried out to identify other etiologic agents, with less notification and surveillance regarding other respiratory viruses.

It is important to comment, at this point, on the strategy of social distancing. It is well known that this intervention is far from being an isolated solution to the epidemic in a country with the size and intellectual and cultural diversity of Brazil. But which other strategy of similar scope would we have to overcome social distancing in efficiency at this time? Mathematical calculations indicate the effectiveness of the combination of early lockdown, measures of social distancing and personal protection,[6] and their effectiveness seems to have been demonstrated elsewhere in the world, of which New Zealand is perhaps the prime example.[7] Furthermore, relaxation experiences without clear and well-understood rules for reopening economic activities can be catastrophic, with an important increase in the number of cases. The same calculations that point to the efficiency of social distancing estimate that, in scenarios of high incidence of the disease and confinement lasting less than 45 days, any relaxation should lead to new waves of growth of the epidemic.[6]

Undeniably, the available knowledge suggests that we will only have a reassuring perspective when there is at least one of the following situations: (i) an effective drug, which can appear at any time, but without strong candidates so far; (ii) vaccination immunization, which is perhaps the most feasible and close to occurring, although we still do not have final information on the efficacy of the vaccines under study and it is not possible to predict the ability to distribute the vaccine to the population in sufficient quantities and in a short time; or (iii) herd immunity.

In principle, the herd immunity required to contain COVID-19 has been estimated to be close to 70%.[8] However, recently published studies suggest that it may be between 20[9] and 43%,[10] taking into account variations in transmissibility between different groups of people within the same population. To see such an abbreviation for collective immunity would mean bringing the horizons of resumption of social life and the economy closer together, which undoubtedly suffered intensely from the global health emergency that we are experiencing in 2020. On the other hand, it is frightening to think about the number of deaths we owe arrive before collective immunity is reached, even at 20%, considering the prevalence of infection among Brazilians, which is still supposedly small. By the way, it is true that the prevalence of SARS-CoV-2 may be underestimated, since few asymptomatic people are tested. Thus, it is very difficult to fit the pieces of this puzzle called COVID-19.

We dare to end the reflection by touching on philosophical questions. Issues related to COVID-19 have long since seemed to move away from science: today, the COVID-19 pandemic seems to be more of an object of passion and passionate people who usually only see what is desirable to see. In other words, in passion, facts are subject to the imagination of those who see them through the lens of their own expectations. There is no logical reasoning that stands out and, therefore, it threatens

scientific thinking so much. Health professionals need to be aware of such deviations, because although there is always the possibility to rectify them, there is not always enough time to reverse their consequences. If the best way to deal with all of this is still not defined by science, it will certainly not be defined on its absence.

Conflict of Interests

The authors have no conflict of interests to declare.

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Cesarean-section Rates in Brazil from 2014 to 2016: Cross-sectional Analysis Using the Robson Classification

Taxas de cesariana no Brasil de 2014 a 2016: Análise transversal utilizando a classificação de Robson

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Abstract

Objective To obtain cesarean-section (CS) rates according to the Robson Group Classification in five different regions of Brazil.

Methods A descriptive epidemiological study using data from secondary birth records from the Computer Science Department of the Brazilian Unified Health System (Datasus, in Portuguese) between January 1st, 2014, and December 31st, 2016, including all live births in Brazil.

Results The overall rate of CS was of 56%. The sample was divided into 11 groups, and vaginal births were more frequent in groups 1 (53.6%), 3 (80.0%) and 4 (55.1%). The highest CS rates were found in groups 5 (85.7%), 6 (89.5%), 7 (85.2%) and 9 (97.0%). The overall CS rate per region varied from 46.2% in the North to 62.1% in the Midwest. Group 5 was the largest obstetric population in the South, Southeast and Midwest, and group 3 was the largest in the North and Northeast. Group 5 contributed the most to the overall CS rate, accounting for 30.8% of CSs.

Conclusion Over half of the births in Brazil were cesarean sections. The Midwest had the highest CS rates, while the North had the lowest. The largest obstetric population in the North and in the Northeast was composed of women in group 3, while in the South, Southeast and Midwest it was group 5. Among all regions, the largest contribution to the overall CS rate was from group 5.

Keywords

- cesarean section
- vaginal birth after cesarean section
- obstetric delivery
- repeat cesarean section
- induced labor

Resumo

Objetivo Identificar as taxas de cesárea de acordo com a Classificação de Robson nas cinco regiões do Brasil.

Métodos Estudo epidemiológico descritivo utilizando dados secundários obtidos do Departamento de Informática do Sistema Único de Saúde (Datasus) entre 1° de janeiro de 2014 e 31 de dezembro de 2016, incluindo todos os nascidos vivos no Brasil.

Resultados Cesáreas representaram 56% de todos os nascimentos. A amostra foi dividida em 11 grupos, e partos vaginais foram mais frequentes nos grupos 1 (53,6%), 3

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- cesárea
- nascimento vaginal após cesárea
- parto obstétrico
- cesárea repetida
- trabalho de parto induzido

(80,0%) e 4 (55,1%). As maiores taxas de cesárea foram encontradas nos grupos 5 (85,7%), 6 (89,5%), 7 (85,2%) e 9 (97,0%). A taxa geral de cesárea variou de 46,2% no Norte a 62,1% no Centro-Oeste. O grupo 5 representou a maior população obstétrica no Sul, Sudeste e Centro-Oeste, e o grupo 3, no Norte e Nordeste. O grupo 5 contribuiu mais para a taxa geral de cesárea, totalizando 30,8%.

Conclusão Mais da metade dos nascimentos no Brasil ocorreu por cesárea. O Centro-Oeste apresentou a maior taxa, e o Norte, a mais baixa. A maior população obstétrica no Norte e no Nordeste foi o grupo 3, enquanto no Sul, Sudeste e Centro-Oeste foi o grupo 5. Entre todas as regiões, a maior contribuição para a taxa geral de cesárea foi do grupo 5.

Introduction

Cesarean section (CS) is a surgical procedure that reduces maternal and neonatal morbidity and mortality when performed for clinical reasons. However, there is evidence that CS rates higher than 10% to 15% are associated with higher morbidity and mortality risks for the mother and the newborn.[1,2] Based on a global study of maternal and fetal complications in 24 countries, the World Health Organization (WHO) stated that CS is associated with higher risks than vaginal delivery, and should therefore be offered when a clear benefit is expected, offsetting the higher costs and additional risks.[3] Other concerns and controversies around mode of delivery include inequalities in the performance of CS not only among different countries, but also between the public and private systems within the same country,[4] and the costs imposed upon the already financially overburdened healthcare systems.[5]

Recently, CS percentages regarding the total amount of births have increased worldwide, especially in middle and high-income countries, the latter especially affected by the obstetric transition phenomenon.[2] Brazil stands out with world's second highest CS rate, surmounted only by the Dominican Republic,[6] and over half of the births in the country are through CS.[4] The reasons CS rates are increasing are not simple to understand once they might combine financial, social, healthcare system, medical and cultural factors.[1]

One way to tackle the issue of optimizing cesarean section practices is to identify whether there are specific groups of pregnant women contributing to the rise in the overall surgery rate, and subsequently to direct tailored interventions targeting their specificities. A 2011 WHO systematic review suggested that the Robson classification is the most appropriate system available to monitor and compare CS rates within a women-based classification.[7] The Robson classification is a prospective instrument based on six obstetric parameters (parity, previous CS, gestational age, onset of labor, fetal presentation, and the number of fetuses) that divides pregnant women into 10 groups.[8,9] Those groups are fully inclusive and mutually exclusive, meaning that every pregnant woman will fit into one of them and no more than one. Its simplicity, reproducibility and clinical relevance have led to its universal adoption in recent years, with endorsement from the WHO.[9,10]

In 2014, the Brazilian Ministry of Health chose to apply the Robson classification to its annual live birth statistics, since then enabling the national assessment of the association of selected obstetric parameters with mode of delivery. In this context, the present study aims to address CS rates according to the Robson classification in the five geographic regions of Brazil, to provide evidence to better understand and outline strategies to help reduce the high CS rate in the country.

Methods

The present is a descriptive epidemiological cross-sectional study using secondary database data of the Computer Science Department of the Brazilian Unified Health System (Datasus, in Portuguese) from 2014 to 2016. The study population includes all live births in Brazilian territory within the selected period. Geographically, the Brazilian territory is divided into five regions: North, Northeast, Midwest, Southeast and South, and the stratification was included in the analyses. When information on mode of delivery was not available, the subjects were excluded ($n = 10{,}503$; $< 0.01\%$ of total births).

Data was obtained from the Ministry of Health's Live Birth Information System (Sinasc, in Portuguese), through the Datasus online platform, using the Tabnet application, which was developed by Datasus.[10] All live births that occur in the country receive a unique record in the Sinasc database, which comprises mandatory birth notification data as defined by the Brazilian federal government and includes all births: vaginal, instrumental and CS births both from public and private institutions, as well as out-of-hospital births (including planned and unplanned homebirths). This database also includes information about birth dates, time and location, as well as maternal and newborn characteristics. The Sinasc is an effective tool to assess information on births in Brazil, covering more than 90% of all births nationwide.[11] In the present study, data were extracted filtered by region, using the dependent variable "Robson's groups" and the independent variable "mode of delivery."

The Robson Classification comprises a categorization of pregnant women into ten groups at the time of their admission for birth.[8] The classification is based on six obstetric characteristics shown in ►**Table 1**.

Table 1 Overall cesarean section (CS) rate and in each Robson group in Brazil

Robson classification	Cesarean section rates (%)
1. Nulliparous, single cephalic, ≥ 37 weeks, in spontaneous labor	46.4
2. Nulliparous, single cephalic, ≥ 37 weeks, induced or CS before labor	69.0
3. Multiparous (excluding previous CS), single cephalic, ≥ 37 weeks, in spontaneous labor	20.0
4. Multiparous (excluding previous CS), single cephalic, ≥ 37 weeks, induced or CS before labor	44.9
5. Previous CS, single cephalic, ≥ 37 weeks	85.7
6. All nulliparous breeches	89.5
7. All multiparous breeches (including previous CS)	85.2
8. All multiple pregnancies (including previous CS)	82.8
9. All women with a single pregnancy in transverse or oblique lie (including those with previous CS)	97.0
10. All single cephalic, < 37 weeks (including previous CS)	50.3
11. Births not classified in any groups due to lack of information	59.1
Total	56.0

Births not classified in any groups due to lack of information were included in the present study under the unofficial terminology "group 11."

The outcomes in the present study included national and regional data on: a) CS rates according to each Robson group; b) obstetric population size in each Robson group; and c) the relative contribution of each Robson group to the overall CS rate in Brazil.

Results

Cesarean section was the most common mode of delivery in the country in the 2014–2016 period, comprehending 56% of all births (►**Table 1**). Only three Robson groups had a higher proportion of vaginal deliveries when compared with the proportion of CSs: groups 1, 3, and 4. The highest CS rates were found in the multiparous group with a history of previous CS and single cephalic fetus at term (group 5), in non-cephalic presentations in general (groups 6, 7 and 9) and in multiple pregnancies (group 8), as shown in ►**Table 1**.

The overall CS rate ranged from 46.2% in the North to 62.1% in the Midwest (►**Table 2**). The Midwest showed the highest CS rates in the 5 largest groups of pregnant women (groups 1 to 5), while the lowest CS rates had a heterogeneous distribution between the regions.

►**Fig. 1** presents a boxplot showing the variability in CS rates across the regions of Brazil for each Robson group. The "x" marker inside each box denotes the mean rate of CSs among the five regions, while the middle horizontal line represents the median rate. There are also whiskers above and below the boxes representing the maximum and minimum CS rates found for each group when comparing the 5 regions. Women with a single pregnancy in transverse or oblique lie – including those with previous CS (group 9) – had the smallest variability: only 1.6% among the 5 regions. The largest differences in CS rates among regions were identified in preterm cephalic births (group 10): from 38.5% in the North to 57.3% in the South (18.8% of absolute difference), and in multiple pregnancies (group 8): from 75.4% in the Northeast to 86.3% in the South (10.9% of absolute difference; ►**Table 2**).

Table 2 Cesarean section rate (%) in each Robson group by region

Robson group	North	Northeast	Midwest	Southeast	South
1	42.5†	45.8	53.8*	46.9	45.2
2	68.3	63.6†	73.4*	69.1	72.5
3	17.4	21.9	24.0*	18.9	16.9†
4	46.9	45.3	50.4*	43.0†	46.7
5	80.5†	85.6	87.5*	86.4	85.7
6	89.6	83.9†	90.5	91.1	93.2*
7	86.0	79.2†	87.6	86.9	89.3*
8	78.3	75.4†	87.2	85.8	86.3*
9	98.0*	97.1	97.8	96.4†	96.9
10	38.5†	43.3	53.3	56.2	57.3*
11	50.9	50.5†	76.7	66.9	71.8*
Total	46.2	50.2	62.1*	59.7	61.2

Notes: *Highest values for each Robson group; †lowest values for each Robson group.

The size of the Robson groups varied from region to region (►**Table 3**). Group 5 (all multiparous women with at least 1 previous CS with a single fetus, cephalic, ≥ 37 weeks) comprised the largest obstetric population in the South, Southeast, and Midwest, while group 3 (multiparous women without previous CS with a single fetus, cephalic, ≥ 37 weeks, in spontaneous labor) was the largest obstetric population in the North and Northeast.

The size of group 2 (single cephalic nulliparous women, ≥ 37 weeks, whose delivery was induced or who underwent CS before the onset of labor) varied significantly among regions, representing only 6.7% of all pregnant women in the North region, and 21.7% of all pregnant women in the South region. An opposite trend was observed in group 3 (multiparous women without previous CS, single fetus, cephalic, ≥ 37 weeks, in spontaneous labor): the lowest proportion was found in the South region (13.2%), and the largest, in the North region (27.2%).

In all regions, the group that most contributed to the overall CS rate was group 5, which accounted for 30.8% of CSs in the country (►**Table 4**). The second largest contribution to CS rates in the North, Northeast and Midwest was from group

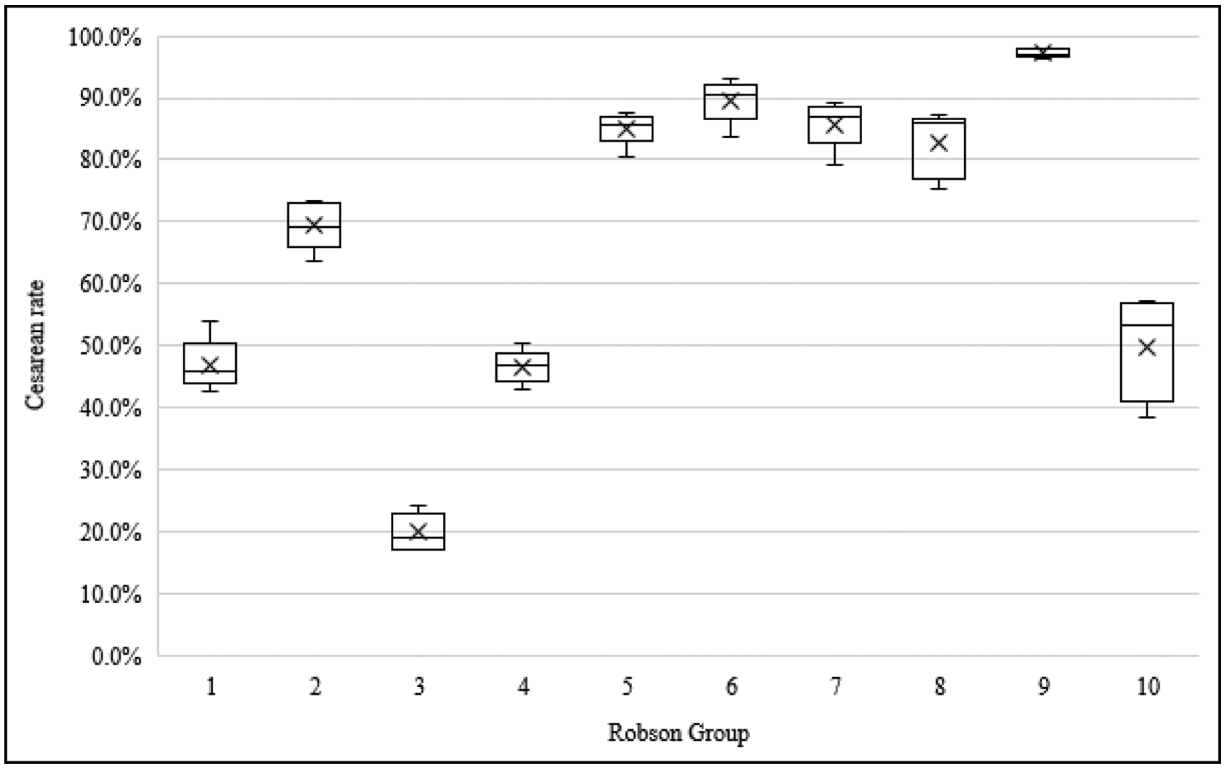

Fig. 1 Interregional variability in the CS rate in each Robson group.

Table 3 Relative distribution of live births (%) per Robson group

Robson group	North	Northeast	Midwest	Southeast	South	Brazil
1	21.3	22.0	18.3	14.3	13.4	17.4
2	6.7	10.4	12.6	20.3	21.7	15.6
3	27.2	23.5	17.5	13.6	13.2	18.1
4	5.4	7.3	7.7	11.9	12.0	9.6
5	16.3	16.2	22.7	22.4	22.8	20.1
6	1.1	1.3	1.6	1.5	1.8	1.4
7	1.8	1.7	2.4	1.7	2.1	1.9
8	1.5	1.8	2.0	2.3	2.2	2.0
9	0.3	0.3	0.2	0.2	0.3	0.2
10	9.9	9.4	8.2	8.8	8.5	9.0
11	8.5	6.2	6.7	3.1	1.9	4.6

Table 4 Relative contribution of each Robson group (%) to the overall cesarean section rate by region

Robson group	North	Northeast	Midwest	Southeast	South	Brazil
1	19.6	20.1	15.9	11.2	9.9	14.4
2	10.0	13.2	14.9	23.4	25.7	19.2
3	10.3	10.2	6.8	4.3	3.7	6.4
4	5.5	6.6	6.2	8.5	9.2	7.7
5	28.5	27.5	32.0	32.5	31.9	30.8
6	2.1	2.1	2.4	2.2	2.8	2.3
7	3.4	2.7	3.4	2.5	3.0	2.8
8	2.5	2.7	2.9	3.3	3.1	3.0
9	0.7	0.5	0.3	0.3	0.5	0.4
10	8.2	8.1	7.0	8.2	8.0	8.1
11	9.4	6.2	8.2	3.4	2.2	4.9

1 (nulliparous, single fetus, cephalic, $\geq$ 37 weeks, in spontaneous labor), while in the South and Southeast, group 2 contributed the most for CS rates.

Discussion

More than 8 million births in Brazil from 2014 to 2016 were analyzed using the Robson classification system. It was possible to observe that CS is the most common mode of delivery both overall in the country and in all geographic regions, except for the North.

Cesarean section rates in Brazil were estimated in 30% in the early 1980s, reached 40% in the early 1990s, and exceeded 50% in 2012.[12] The dramatic increase in CS rates has multifactorial causes – that are not the main scope of the present article – and some possible reasons for the CS rates in the country to stand out are a common cultural belief that vaginal delivery is an uncontrollably painful process, fueled by infrequent adoption of non-pharmacological pain relief methods and low availability of regional anesthesia at Brazilian maternity facilities. At the same time, the media has historically pictured vaginal birth as a dangerous and

unpredictable event, reinforcing the belief that adverse perinatal outcomes are direct consequences of the non-use of CS or delay in performing the surgery.[12–15] Another point that may contribute to CS rates is that in Brazil most births are performed by medical doctors. The role of midwives and nurse-midwives in childbirth assistance is limited and uneven in different locations in the country.[14]

The rates of CS in each Robson group can vary in countries depending on the characteristics of the obstetric population. Therefore, there are no ideal rates established. The WHO Multi-Country study[16] applied data from selected health facilities with low CS and positive maternal and neonatal childbirth outcomes in 29 countries to create a global reference for CS rates. The findings indicated which CS rate could be achieved in each Robson group without worsening the obstetrical outcomes. Thus, groups 5 to 8 had the highest CS rates (74.4%, 78.5%, 73.8%, and 57.7% respectively), and groups 1 and 3 had the lowest (9.8% and 1.3% respectively). Group 2 had almost 40% of CSs, and group 4, a rate of 23.7%. The overall CS rate was 18.5%.[16]

In the present study with Brazilian data, higher CS rates were found in the South, Southeast and Midwest regions. It is worth mentioning that private health system utilization is also higher in these three regions,[13] probably contributing to those rates, since CSs are more commonly performed at private health facilities in Brazil.[12–15,17] Higher education, better socioeconomic status and living in urban areas may also play a part in raising CS rates in the aforementioned regions, when compared with the North and Northeast. All of those aspects have already been historically associated with higher chances of CS.[18] The lower CS rates in the Brazilian Northern region may also be explained by sociocultural aspects or local obstetrical care characteristics, both of which were not addressed in the present study.

Higher overall CS rates were also found in geographic regions with the highest proportion of multiparous women who had previous CS and a single-term cephalic fetus (Robson group 5). The frequency of primary CS in nulliparous women in the recent past resulted in this group's expansion as one of its direct consequences. In this study, the highest CS rates in nulliparous, single-term, cephalic, term fetuses (Robson groups 1 and 2) were found in the Midwest region, which was also the location with the highest overall CS rate (62.1%).

The largest obstetric population in Brazil was classified as Robson group 5, which had the largest participation in the overall CS rate in all 5 geographic regions as well (almost 1/3 of all surgeries). Therefore, a substantial impact over the country's overall CS rate could be achieved in the future by applying specific interventions addressing directly this group of women with previous uterine scars. For instance, the decrease in CS rates in nulliparous women could lead to a decline in the population size of group 5, and to an increase in Groups 3 and 4, in which CS rates are 3 times lower. Additionally, a trial of labor should be offered to multiparous women with previous CS who choose to have vaginal delivery, as stated by the Royal College of Obstetricians and Gynecologists,[19] the American College of Obstetricians and Gynecologists,[20] and the Brazilian guidelines,[4] which could result in a direct decrease in CS rates in Group 5.

Robson groups 1 and 2 (nulliparous single-term cephalic fetuses) accounted for approximately 1/3 of all CSs in every region of the country. While in Brazil groups 1 and 2 combined represent a CS rate of 57.1%, in France they reach 23.2%,[21] and, in Sweden, 14.3%.[22] Brennan et al[23] analyzed nine institutional cohorts from nine countries and found that CS rates in these two groups can largely explain the variations in the overall CS rate in different settings. Therefore, efforts to reduce the overall CS rate should also focus on managing these groups of nulliparous women.

Non-cephalic presentations (groups 6, 7 and 9), multiple pregnancies (group 8) and preterm births (group 10) displayed a very similar proportion within the obstetric population in each region, and had a relatively small contribution to the overall CS rate due to their reduced absolute magnitude. The external cephalic version technique in non-cephalic presentations could decrease the population size of these groups in which CS rates are very high, contributing to reduce the overall CS rate.

The births recorded as Group 11 (not classified in Robson's group due to lack of required parameters) were scarce, especially considering that the Ministry of Health only recently adopted the classification. The highest underreporting rate was found in the North (8.5%), and the lowest, in the South (1.9%).

Considering the current evidence advocated by the WHO that CS rates higher than 10% are not associated with a reduction in maternal and neonatal mortality rates,[24,25] the use of the Robson classification comparing CS rates and obstetrical outcomes is a way to contribute to future discussions on the topic.[10] In the present study, applying the Robson classification enabled us to identify specific obstetric characteristics of women who underwent CS. Compared with having one single national or regional CS rate, to understand the factors associated with having a CS under the perspective of the Robson groups might enable a much broader analysis of the Brazilian context. The findings might therefore be employed to design health policies addressing those specific population groups in the future and tackle the issue of the increasing CS rates in the country.

The present study has several limitations. First, it is a secondary analysis based on the Sinasc database, which prevented us from obtaining further details on clinical features available from hospital charts. Second, the data were extracted from a short period of time (from 2014 to 2016). Finally, Robson groups 2, 4 and 5 comprehend both women under labor induction or who underwent CS before the onset of labor. Since the two categories are not individualized, it is not possible to establish the role of labor induction upon birth outcome, and the weight of elective CS before the onset of labor might play a role on the global CS rates. Among the latter, 50% were scheduled CSs that, therefore, could not have been studied regarding possible associations to the global CS rates.

In the present study, it was possible to profile the CS rate in Brazil applying the Robson classification (ten-group

classification) instead of using an absolute generic percentage to evaluate the heterogeneous obstetric population. The study sample was large, comprising 8,854,727 live newborns and few missing data on mode of delivery ($< 0.01\%$).

Future studies comprising a larger time span might help understand the temporal trend of CS rates in Brazil. As previously published studies have already proposed, in the future, groups 2, 4 and 5 should be divided into subgroups: "a) labor induction; and b) cesarean section before the onset of labor."[22,26] This would enable a proper evaluation of the burden of each of the conditions upon CS rates. The availability of data regarding maternal and perinatal outcomes through the Brazilian Ministry of Health together with information about mode of delivery and Robson Group classification would provide better means to analyze obstetrical practices in the country. The obtained data could contribute to the development of better care strategies and policies for the health of women and newborns.[27]

Conclusion

Most of births in Brazil occurred through CS. The Midwest region had the highest CS rate, while the North region had the lowest CS rate. The largest obstetric populations in the North and in the Northeast regions were included in group 3. In the South, Southeast and Midwest, the more prevalent population was included in group 5. Among all regions, the largest contribution to the overall CS rate was from group 5, accounting for 30.8% of CSs in the country.

Contributors
Roxana Knobel worked on the conceptualization and design of the study, on data collection and analysis, drafted the manuscript, critically reviewed and revised the manuscript, and approved the final version to be submitted. Thiago Jose Pinheiro Lopes worked on the conceptualization and design of the study, on data collection and analysis, drafted the manuscript, critically reviewed and revised the manuscript, and approved the final version to be submitted. Mariane de Oliveira Menezes worked on analysis and interpretation of data, as well as writing of the article, critical review of the intellectual content, and final approval of the version to be published. Carla Betina Andreucci worked on analysis and interpretation of data, as well as writing of the article, critical review of the intellectual content, and final approval of the version to be published. Juliana Toledo Gieburowski worked on analysis and interpretation of data, as well as writing of the article, critical review of the intellectual content, and final approval of the version to be published. Maira Libertad Soligo Takemoto worked on analysis and interpretation of data, as well as writing of the article, critical review of the intellectual content, and final approval of the version to be published. All authors have made substantive contributions to the present manuscript, and all have reviewed the final paper prior to its submission.

Conflicts of Interest
The authors have none to declare.

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Twin Pregnancies, Crown-rump Length and Birthweight Discordancy: The Influence of Chorionicity

Gestações gemelares, comprimento craniocaudal e discordância de peso ao nascimento: a influência da corionicidade

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Abstract

Objective The purpose of the present study was to analyze the influence of chorionicity in the biometric parameters crown-rump length (CRL), birthweight (BW), crown-rump length discordancy (CRLD) and birthweight discordancy (BWD), determine the correlation between these latter two in cases of intertwin discordancy, and to analyze the influence of chronicity in the presence of these discordancies with clinical relevance ($>$ 10% and $>$ 15%, respectively).

Methods The present study was a retrospective study based on the twin pregnancy database of the Centro Hospitalar S. João (2010–2015), including 486 fetuses among 66 monochorionic (MC) and 177 dichorionic gestations (DC). The inclusion criteria were multiple pregnancies with 2 fetuses and healthy twin gestations. The exclusion criteria were trichorionic gestations and pregnancies with inconclusive chorionicity, multiple pregnancy with $\geq$ 3 fetuses and pathological twin gestations.

Results No statistically significant difference was found in BW ($p = 0.09$) and in its discordancy ($p = 0.06$) nor in CRL ($p = 0.48$) and its discordancy ($p = 0.74$) between MCs and DCs. Crown-rump length discordancy and birthweight discordancy were correlated by the regression line "BWD = 0.8864 x CRLD + 0.0743," with $r^2 = 0.1599$. Crown-rump length discordancy $>$ 10% was found in 7.58% of monochorionic and in 13.56% of dichorionic twins. Birthweight discordancy $>$ 15% was detected in 16.67% of monochorionic and in 31.64% of dichorionic twins.

Conclusion No statistically significant influence of chorionicity was identified in both birthweight and birthweight discordancy, as in crown-rump length and crown-rump length discordancy. Birthweight discordancy was correlated to crown-rump length discordancy in 20% of cases.

Keywords
- fetal growth
- growth discordancy
- crown-rump length
- birthweight
- chorionicity
- twins

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Resumo

Objetivo O objetivo do presente estudo foi analisar a influência da corionicidade nos parâmetros biométricos comprimento craniocaudal, peso ao nascimento, discordância de comprimento craniocaudal e discordância de peso ao nascimento, determinar a correlação entre estes dois últimos caso haja discordância intergemelar e analisar a influência da corionicidade na presença destas discordâncias com relevância clínica ($>$ 10% e $>$ 15%, respectivamente).

Métodos O presente estudo foi um estudo retrospectivo baseado na base de dados de gestações gemelares do Centro Hospitalar S. João (2010–2015), incluindo 486 fetos de 66 gestações monocoriônicas e 177 dicoriônicas. Os critérios de inclusão foram gestações múltiplas de 2 fetos e gestações gemelares saudáveis. Os critérios de exclusão foram gestações tricoriônicas ou de corionicidade inconclusiva, gestações múltiplas com $\geq$ 3 fetos e gestações gemelares patológicas.

Resultados Não se encontrou diferença estatisticamente significativa no peso ao nascimento ($p = 0{,}09$) e sua discordância ($p = 0{,}06$) nem no comprimento craniocaudal ($p = 0{,}48$) e sua discordância ($p = 0{,}74$) entre gestações monocoriônicas e dicoriônicas. Considerando todas as gestações, as discordâncias de comprimento craniocaudal e peso ao nascimento foram correlacionadas pela reta de regressão "discordância de peso ao nascimento $= 0.8864$ x discordância de comprimento craniocaudal $+ 0.0743$," com $r^2 = 0{,}1599$. A discordância de comprimento craniocaudal $>$ 10% descobriu-se em 7.58% das gestações monocoriônicas e em 13.56% das dicoriônicas. A discordância de peso ao nascimento $>$ 15% detectou-se em 16.67% das gestações monocoriônicas e em 31.64% das dicoriônicas.

Conclusão Não se identificou influência estatisticamente significativa no peso ao nascimento e sua discordância, bem como no comprimento craniocaudal e sua discordância. A discordância de peso ao nascimento correlacionou-se com a discordância de comprimento craniocaudal em 20% dos casos.

Palavras-chave

- crescimento fetal
- discordância de crescimento
- comprimento craniocaudal
- peso ao nascimento
- corionicidade
- gêmeos

Introduction

Twinning is increasing worldwide with increased maternal age and more common use of assisted reproduction. The higher risk of mortality and morbidity in multiples is widely recognized.[1–3,5–7,10–12,16–19,24,26,30,32,34,35] According to the classification of twin pregnancies, no matter how many fetuses we are dealing with (zygosity), what really counts for defining perinatal outcome of twin pregnancies is the type of placentation (chorionicity).[1,2,4–6,10,23,35] However, in the literature, other authors favor a contrasting opinion.[7] Furthermore, the importance of chorionicity on twin growth patterns is well-established, being monochorionic twin gestations (MC) the ones with a less favorable scenario. In fact, growth restriction, low birthweight (BW) and birthweight discordancy $>$ 25% are common findings in multiple pregnancies, mainly among MC twins.[8,21,23,24,27–31,35,36] Birthweight discordancy affects up to 20% of MC and only 8% of dichorionic twin gestations (DC), being unequal placental sharing the major contributor.[21,28] This condition can be divided into 3 categories: $<$ 15% (concordant growth), 15–25% (mildly discordant growth) and $>$ 25% (severely discordant growth).[20,22,24–26,30,36] These abnormal growth patterns related to chorionicity cause worse outcomes since the obstetric management is not well-established yet.[28,31] The use of first trimester transvaginal ultrasonography is therefore mandatory to obtain an early accurate determination of multiple gestations, to define their chorionicity and zygosity, as well as to calculate some important biometric parameters such as crown-rump length (CRL) and its inter-twin discordancy.[1,9,35] Some authors have analyzed this inter-twin CRL discordancy (CRLD), which is considered to be of major clinical importance when $\geq$ 10%, as a predictor of an increased risk for fetal anomalies and growth restriction, affecting BW in the long run.[32,33] Contrarily, other studies classified the CRLD as a poor predictor of adverse outcome due to its lack of accuracy, proving useless as a screening method in the current clinical practice.[33,34] The purpose of the present study was to analyze the influence of chorionicity in the biometric parameters CRL, BW, CRLD and BWD, determine the correlation between these latter two in cases of inter-twin discordancy, and to analyze the influence of chronicity in the presence of these discordancies with clinical relevance ($>$ 10% and $>$ 15%, respectively).

Methods

The present study was a retrospective study based on the twin pregnancy database of Centro Hospitalar S. João related to a period of 5 years (2010–2015). We considered a total of 706 fetuses. From those, we included 486 fetuses, 132 from 66 MC

(each one with fetus 1 and fetus 2) and 354 from 177 DC (each one with fetus 1 and fetus 2). The inclusion criteria were multiple pregnancies with 2 fetuses and healthy twin gestations. The exclusion criteria were trichorionic gestations and pregnancies with inconclusive chorionicity, multiple pregnancies with $\geq$ 3 fetuses and pathological twin gestations. By healthy and nonpathological twin gestations, the authors considered gestations without malformed fetuses or other fetal pathologies that could interfere in the spontaneous inter-twin discordancy, congenital anomalies, twin-to-twin transfusion syndrome, selective intrauterine growth restriction and presence of maternal pathologies (pre-eclampsia, diabetes, etc). In this database, we considered two biometric parameters: CRL, evaluated in the 1st trimester obstetric ultrasound (performed between the 11th and 14th weeks of gestation), as well as BW, confirmed after birth. Chorionicity was confirmed in the 1st trimester obstetric ultrasound. The defined objectives for the statistical analysis were: 1st – analyze individually the biometric parameters CRL, BW, CRLD and birthweight discordancy, according to chorionicity (among 3 different samples – all fetuses, only fetuses 1 and only fetuses 2–concerning CRL and BW, and among all gestations, concerning CRLD and birthweight discordancy); 2nd- determine the association between CRLD and birthweight discordancy and analyze the regression line of their association graph; 3rd – discordancy of CRL and discordancy of BW were analyzed for both MCs and DCs considering as clinically relevant a CRLD > 10% and a birthweight discordancy > 15%. The discordancy of each parameter was calculated by using the ratio between the difference of the measurements of the two fetuses of the same gestation and the larger measurement between them. The first objective was used to demonstrate that the population of MCs and DCs is comparable since the study included only twin pregnancies that had a normal outcome. In this case, it is possible to evaluate the early ultrasound parameters and their birthweight discordancy in the two populations studied. The statistical analysis was performed using IBM SPSS Statistics for Windows, Version 23 (IBM Corp., Armonk, NY, USA), and the chosen significance value for the applied statistical tests was 0.05. The present investigation was approved by the ethics committee of the hospital and authorized by the Centro Hospitalar S. João Board of Directors.

Table 2 Influence of chorionicity type in crown-rump length discordancy (CRLD) and in birthweight discordancy (BWD) (%)

	Crown-rump length discordancy (CRDL) (%)			
	Total	Monochorionic	Dichorionic	*P*
All gestations	5,00 ± 4,80	4,90 ± 5,00	5,10 ± 4,70	0,74
	Birthweight discordancy (BWD) (%)			
	Total	Monochorionic	Dichorionic	*P*
All gestations	12.00 ± 10,65	9.80 ± 8,80	12,70 ± 11,20	0,06

Results

For the 1st objective, we analyzed the data from 3 different samples (all fetuses, fetuses 1 and fetuses 2) concerning CRL and BW according to their chorionicity. Regarding the influence of chorionicity type among all fetuses, we obtained, with the parametric *t*-test, $p = 0.48$ (> 0.05), for CRL, and $p = 0.09$ (> 0.05), for BW. Concerning the influence of chorionicity for fetuses 1, we obtained, with the parametric *t*-test, $p = 0.68$ (> 0.05), for the CRL, and $p = 0.12$ (> 0.05), for BW. In what concerns the influence of chorionicity for fetuses 2, we obtained, with the parametric *t*-test, $p = 0.56$ (> 0.05), for CRL, and $p = 0.40$ (> 0.05), for BW. All these results are depicted in ►**Table 1**.

Second, we also analyzed, among all gestations, the influence of chorionicity in CRLD and birthweight discordancy, obtaining $p = 0.74$ (> 0.05) and $p = 0.06$ (> 0.05), respectively. These results are displayed in ►**Table 2**.

Concerning the 2nd objective, we determined the association between CRLD and birthweight discordancy and analyzed the regression line of their association graph. Among all gestations, the correlation between CRLD and birthweight discordancy can be seen in ►**Fig. 1**, in which the regression line is defined by birthweight discordancy = 0.8864 x CRLD + 0.0743, with r2 = 0.1599, being r2 (coefficient of determination) the variation of birthweight discordancy explained by CRLD.

The same analysis was performed among MCs and DCs (►**Fig. 2**). In MCs, the association graph had a regression line defined by birthweight discordancy = 0.7312 x CRLD + 0.0623, with r2 = 0.1763; and, in DCs, the association graph had a

Table 1 Influence of chorionicity in crown-rump length (mm) and birthweight (g)

	Crown-rump length (mm)			
	Total	**Monochorionic**	**Dichorionic**	***p-value***
All fetuses	61.32 ± 11.27	62.01 ± 14.12	61.07 ± 10.03	0.48
Fetuses 1	61.35 ± 11.27	62.08 ± 13.76	61.31 ± 9.92	0.68
Fetuses 2	61.34 ± 11.28	61.94 ± 14.59	60.82 ± 10.17	0.56
	Birthweight (g)			
	Total	**Monochorionic**	**Dichorionic**	***p-value***
All fetuses	2219.07 ± 542.21	2150.87 ± 554.75	2244.50 ± 536.81	0.09
Fetuses 1	2220.12 ± 542.27	2168.26 ± 591.43	2290.17 ± 522.44	0.12
Fetuses 2	2218.69 ± 542.70	2133.48 ± 519.44	2198.84 ± 548.47	0.40

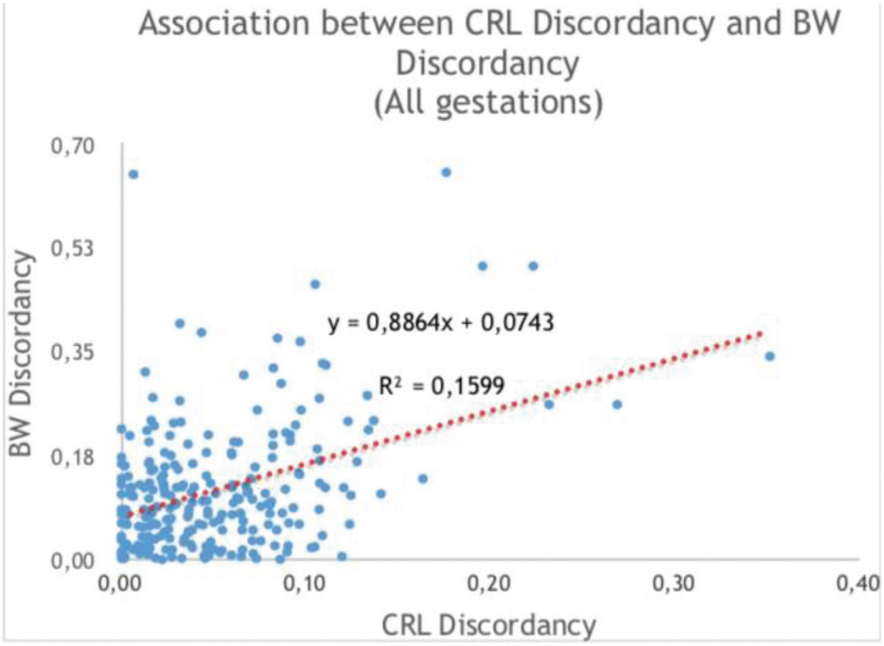

Fig. 1 Correlation between crown-rump length discordancy (CRLD) and birthweight discordancy (BWD), among all gestations.

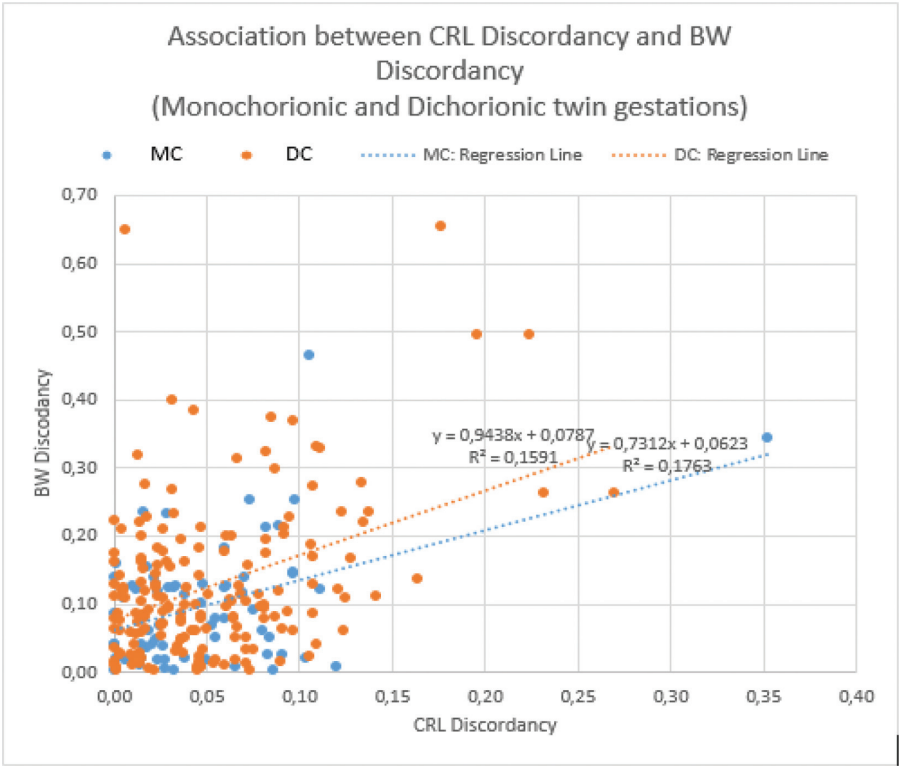

Fig. 2 Correlation between crown-rump length discordancy (CRLD) and birthweight discordancy (BWD), among monochorionic and dichorionic gestations.

regression line defined by birthweight discordancy = 0.9438 x CRLD + 0,0787, with r2 = 0.1591, similar to the results showed among all gestations.

Concerning the 3rd objective, CRL discordancy and BW discordancy for both MC and DC were analyzed. According to the literature, discordancy in CRL ≥ 10% and, in BW, ≥ 15% was considered of major clinical importance. The results achieved showed that 7.58% of MCs showed a CRLD of at least 10%, against 13.56% among DCs. It was also verified that 16.67% of MCs had a birthweight discordancy of at least 15%, against 31.64% among DCs.

Discussion

No statistically significant differences for CRL and BW according to chorionicity were found, but a borderline, although non-statistically significant difference, was observed for BW. A similar situation was identified for the influence of

chorionicity in birthweight discordancy and CRLD. This can be explained by an early developmental phase in which the CRL measurement is performed, and therefore the influence of chorionicity in fetal growth may not be noticeable until later in pregnancy when the BW is estimated. The fetal growth progression and the later phases of development will possibly allow for more biometric differences and diverse growth of the two fetuses when there are two placentas available (DCs). This first conclusion was compatible with the results found in the reviewed literature.[1–6,10,23] Maybe in future studies with a larger sample, this influence of chorionicity in BW and birthweight discordancy will become more apparent.

Among all gestations, nearly 16% of the birthweight discordancy is correlated to CRLD. Among MCs, nearly 18% of the birthweight discordancy is correlated to the CRLD, not very different from what happens in DCs, in which nearly 16% of the BWD is correlated to the CRLD. BWD may be correlated in this present extension to CRLD, but not really explained by it since other variables were not studied. So, it would be interesting in future studies to clarify the other putative determinants that could explain $\sim$ 80% of the birthweight discordancy other than CRLD, which only seems to account for nearly 20%. This second conclusion was matched with the results found by other authors, such as Grande et al.[32]

There is a higher percentage of discordancy in CRL $\geq$ 10% in DCs (13.56%) than in MCs (7.58%). Regarding the BW discordancy, there is also a greater percentage of major and clinically relevant discordancy in DCs (31.54%) than in MCs (16.67%). This third conclusion was contradicted by the reviewed literature, being necessary some other studies to clear up this point.[28] Moreover, pathological cases with selective intrauterine growth restriction were one of the exclusion criteria of the present study, and this is probably one of the reasons why birthweight discordancy is greater in dichorionic pregnancies. Therefore, care should be taken in the generalization of this conclusion by the analysis of the data collected.

The present study had some possible limitations, such as the intraobserver and interobserver variability in the measurements of the biometric parameters, since CRL and BW measurements were performed by different certified health professionals, as well as the limitation related to the sample length, which should be larger in future studies to clarify the influence of chorionicity in later stages of twin pregnancies. Moreover, the statistical analysis would be more interesting if applied in the future in a prospective study, accompanying the twin pregnancies until the birth of the babies or even trying to go forward perceiving the later consequences of the birthweight discordancy.

As strengths, the present study raises the issue of the possible influence of chorionicity in twins' growth and the future consequences of birthweight discordancy and CRLD in the potential of fetal growth according to the type of placentation.

Conclusion

According to the main objectives of the present study, no statistically significant influence of chorionicity could be identified in both BW and birthweight discordancy, as well as in CRL and CRLD. Nevertheless, birthweight discordancy was explained in nearly 20% by the influence of CRLD. This findings should let all the health providers aware of the main importance of strict and precocious twin pregnancies' surveillance to prevent any disturbance of fetal growth and development.

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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The Effect of Small Size Uterine Fibroids on Pregnancy Outcomes in High-risk Pregnancies

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Abstract

Objective To evaluate the obstetric outcomes of singleton high-risk pregnancies with a small size uterine fibroid.

Methods This retrospective cohort study was conducted among 172 high-risk pregnant women who were followed-up by a single surgeon between 2016 and 2019. Pregnant women with preconceptionally diagnosed small size (< 5 cm) single uterine fibroids ($n = 25$) were compared with pregnant women without uterine fibroids ($n = 147$) in terms of obstetric outcomes.

Results There was no statistically significant difference between the groups in terms of adverse pregnancy outcomes. The size of the fibroids was increased in 60% of the cases, and the growth percentage of the fibroids was 25% during pregnancy. Intrapartum and short-term complication was not observed in women who underwent cesarean myomectomy.

Conclusion Small size uterine fibroids seem to have no adverse effect on pregnancy outcomes even in high-risk pregnancies, and cesarean myomectomy may be safely performed in properly selected cases.

Keywords

- uterine fibroid
- myoma
- pregnancy
- CS myomectomy

Introduction

Uterine fibroids (also known as myomas) are benign monoclonal smooth muscle neoplasms and are the most common pelvic tumors in women of reproductive age. The incidence of fibroids in pregnancy is from 3.3 to 10.7%.[1,2] Although most pregnancies in women with fibroids are uneventful, adverse pregnancy outcomes due to fibroids, such as miscarriage, preterm labor, placenta previa, placental abruption, fetal growth restriction, malpresentation, and peripartum hemorrhage, may occur in 10 to 30% of these patients.[3] Moreover, the most common complications of fibroids during pregnancy are pain due to degeneration or torsion of the pedunculated fibroid, as well as pelvic pressure-related problems and vaginal bleeding.[4,5] The frequency of major adverse outcomes correlates with the size of the fibroid and is especially high in women with fibroids > 5 cm in diameter.[6,7]

The majority of prospective studies using ultrasound to follow the size of uterine fibroids during pregnancy have shown that fibroid size remains stable ($< 10\%$ change in size) from the pregestational period to the end of pregnancy.[6] In spite of this, some studies report an increase in size during pregnancy.[8] Besides, larger fibroids (> 5 cm in diameter) are more likely to grow, whereas smaller fibroids are more likely to remain stable in size.[4] Fibroids may cause pregnancy loss but there is a lack of consensus in the association between uterine fibroids and recurrent miscarriages among the medical community.[9] Depending on the size and location, fibroids may alter the contour of the intrauterine cavity, leading to decidual atrophy or distortion of the vascular architecture of the decidua and affect implantation, placentation, and ongoing pregnancy.[10]

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Myomectomy during the course of cesarean section (CS) is questionable because of an increased risk of intrapartum and short-term postpartum complications, especially bleeding. However, many authors agree that myomectomy is a safe procedure during CS.[11] The recent literature advocates elective or opportunistic myomectomy in well-selected cases during CS.[12]

Although there were various studies about pregnancies with fibroids in the literature, the number of studies on the effect of small fibroids on pregnancy was limited. Therefore, in the present study, we aimed to evaluate the obstetric outcomes of singleton high-risk pregnancies with a uterine fibroid < 5 cm.

Methods

The present retrospective cohort study was conducted among high-risk pregnant women who were followed-up by a single surgeon (M. S. B.) at the Division of Perinatology, Department of Obstetrics and Gynecology from the Hacettepe University Hospital between August 2016 and December 2019. Women with uterine anomaly, those with multiple pregnancies, and pregnant women with fibroids > 5 cm in diameter or multiple fibroids were excluded. In the remaining 172 patients, pregnant women with preconceptionally diagnosed small/medium size (< 5 cm) single uterine fibroids (study group) were compared with pregnant women without uterine fibroids (control group). The required data were obtained from the patients' files and the electronic database of our institution. The study protocol was approved by the Ethics Committee of Hacettepe University with the reference number of GO 19/1064, and informed consent was obtained from all participants.

Pregnancies with poor obstetric history, chronic inflammatory diseases, autoimmune disorders, metabolic and/or inflammatory risk factors for placenta-mediated pregnancy complications were defined as high-risk pregnancy in this study. All high-risk pregnancies were included in a special antenatal care program for the optimal management of their risk factors. Pregnancy follow-up consisted of serial ultrasonography to evaluate fetal growth, aneuploidy screening (combined or triple test), fetal anatomy scanning at the 20^{th} to 24^{th} gestational weeks, oral glucose challenge test, and a non-stress test performed according to national and international guidelines. The iron supplement (30 mg) was given to all pregnant women daily.

The study and control groups were compared in terms of maternal age, gravidity, parity, Beksac Obstetric Index pregnancy (BOIp), miscarriage rate, hemoglobin (Hb) level at the first trimester, gestational age at birth, birth weight, 5^{th} minute Apgar score, fetal presentation, postdelivery Hb (8 hours after delivery), and delta Hb levels (the difference between the postdelivery and first trimester Hb levels). The BOI is a special obstetric index for the assessment of risk levels in pregnancies depending on their previous obstetric histories [(number of alive children + (n/10))/Gravida]. The BOI value calculated in the preexisting pregnancy was defined as BOIp.[13] Beksac Obstetric Index is used widely in the literature for the comparison of risk levels for different patient groups. This index is used in many studies regarding various types of maternal risk factors.[14,15] Furthermore, characteristics of the uterine fibroid (size, type, and location), the growth rate of the fibroid during pregnancy, location of the placenta, obstetric complications due to fibroids, cesarean myomectomy rate, and delta fibroid size (the difference between the size of the fibroid during delivery and at the preconceptional period) were evaluated in the study group.

Statistical analyses were performed using the IBM SPSS statistics software, version 22.0 (IBM Corp., Armonk, NY, USA). Variables were investigated using visual (histograms, probability plots) and analytical methods (Shapiro-Wilk test) to determine the normality of distribution. As the data were not normally distributed, the Mann-Whitney U-test was performed for the comparison of continuous variables, and the chi-square test was performed for comparing categoric variables between the groups. A two-tailed p-value < 0.05 was considered statistically significant.

Results

The present study included 172 high-risk pregnant women. There were 25 cases in the study group and 147 cases in the control group. Demographic features and clinical characteristics of both groups were summarized in ►**Table 1**.

Miscarriage rates were similar between the groups (16% and 17% for the study and control groups, respectively [$p = 0.84$]). There were no statistically significant differences between the groups in terms of gestational age at birth, birth weight, and 5^{th} minute Apgar score. There were no early preterm deliveries in the cohort. Five (20%) and 32 (21%) late preterm deliveries were detected in the study and control groups, respectively. Median BOIp was 0.657 for both groups ($p = 0.858$). Malpresentation rates were 4% and 4.1% for the study and control groups, respectively ($p = 0.841$). The number of patients who received a blood transfusion for postpartum anemia was 1 (4%) in the study group and 2 (1.4%) in the control group ($p = 0.351$).

Basic characteristics of the study group were presented in ►**Table 2**. None of the uterine fibroids was located in the cervix. Topographic locations of uterine fibroids were subserosal (68%), intramural (28%) and submucosal (4%). The mean size of uterine fibroids at preconception and birth was 2.16 cm ($\pm$0.75) and 2.54 cm ($\pm$0.77), respectively. Fifteen uterine fibroids (60% of the study group) were increased, and the others (40%) were stable in size during pregnancy. The mean delta fibroid size was 0.37 cm ($\pm$0.61).

Placental locations were anterior (32%), posterior (48%), and fundal (%20) in the study group. Placenta previa and placental abruption were not shown in the study group. Five patients from the study group (20%) had retroplacental myoma. Out of these five patients, only one was complicated with preterm delivery, and the remainders had no adverse pregnancy outcome. Miscarriage was shown in four cases in the study group. Two patients were hospitalized with pelvic pain due to degeneration of the fibroid, and three patients were hospitalized with vaginal bleeding in the first trimester. The frequency of preterm delivery was 20% among women

Table 1 Comparison of demographic features and clinical characteristics between groups

	Study group ($n = 25$) (median, min–max)	Control group ($n = 147$) (median, min–max)	*p*-value
Maternal age	35.00 (18–41)	33.00 (20–42)	0.055
Gravidity	3.00 (1–8)	3.00 (1–9)	0.522
Parity	2.00 (1–5)	2.00 (1–5)	0.819
BOIp	0.657 (0.22–1.31)	0.657 (0.15–1.31)	0.858
Miscarriage rate (n,%)	4 (16%)	25 (17%)	0.840
Hb level at 1st trimester	12.3 (7.6–14.8)	12.4 (8.4–14.8)	0.531
Gestational age at birth	37.00 (34–38)	37.00 (34–40)	0.782
Birth weight	2,930 (2,300–3,720)	2,970 (810–4,310)	0.602
5th minute Apgar score	9.00 (4–10)	10.00 (0–10)	0.693
Postdelivery Hb level	10.1 (5.6–12.2)	10.4 (6.3–13.6)	0.142
Delta-Hb level	2.0 (0.3–5.0)	1.8 (0.4–4.7)	0.263

Abbreviations: BOIp, Beksac Obstetric Index pregnancy; Hb, hemoglobin, min, minimum; max, maximum; n, number.

Table 2 Basic characteristics of the study group (25 pregnant women with uterine fibroids)

Parameter	N (%) or mean ± SD
Uterine fibroid location	
Anterior	15 (60)
Posterior	7 (28)
Fundal	3 (12)
Uterine fibroid topographic location	
Subserosal	17 (68)
Intramural	7 (28)
Submucosal	1 (4)
Uterin fibroid size preconception (cm)	2.16 ± 0.75
Uterin fibroid size at birth (cm)	2.54 ± 0.77
Modes of delivery	
Miscarriage	4
Vaginal delivery	2 (9.5‡)
CS without myomectomy	4 (19‡)
CS myomectomy	15 (71.4‡)

Abbreviations: CS, cesarean section; N, number; SD, standard deviation.
‡Rates are given after exclusion of cases with miscarriage.

with fibroids. In the study group, the CS rate was 90.5%, and none of the CS was performed due to uterine fibroids. Myomectomy was performed during CS in 15 cases (71.4%).

Discussion

Uterine fibroids are the most common benign uterine tumors, with an estimated incidence of 20 to 40% in women during their reproductive years. The association of myoma and pregnancy is becoming more frequent due to the advanced maternal age.[16] In our study, 14.5% of 172 pregnant women had uterine fibroids with a diameter < 5 cm.

Previous studies have shown a possible association between fibroids and increased risk of adverse pregnancy outcomes.[17–19] In 2008, Klatsky et al[18] reported an increased risk of miscarriage in women with uterine fibroids compared with women without fibroids. According to a study conducted by Navid et al,[20] the frequency of miscarriage among women with fibroids was 10%. In our study, we found that miscarriage rates were 16% and 17% in women with and without myomas, respectively, most probably due to the characteristics of our cases. Fetal malpresentation has also been reported to be more common among women with fibroids. Klatsky et al[18] reported a frequency of malpresentation of 16% among women with fibroids, ~ 2.5 times higher than in the general population. Similar results have been reported by Navid et al[20] In our study, malpresentation rates were 4% and 4.1% for the study and control groups, respectively. This may be explained by the inclusion of the patients with a smaller size of fibroids. This shows us that small fibroids do not affect the malpresentation rate. Shavell et al[21] showed that compared with women with no fibroids or small fibroids (≤ 5 cm), women with large fibroids (> 5 cm) delivered at a significantly earlier gestational age (38.6 versus 38.4 versus 36.5 weeks). According to our results, the preterm delivery rate was 20% in the study group, and there was no statistically significant difference between the groups in terms of gestational age at birth (median gestational age was 37.0 weeks for both groups). Placental abruption has been associated with uterine fibroids and seems to be related to fibroid location.[22] Placental abruption and placenta previa were not observed in our study group, most probably due to the size of the fibroids. Fetal growth does not appear to be affected by the presence of uterine fibroids, which we have also demonstrated in our study.[22] Degeneration occurs in around 10% of pregnant women with fibroids.[4] Likewise, two patients (8%) were hospitalized with pelvic pain due to degeneration in our study and none of these pregnancies complicated with any adverse event.

Risk factors for pregnancy complications appear to be the size and the location of fibroids, such as the large size of over 5 cm and retroplacental location and/or distortion of the uterine cavity.[17–23] In our study, we have demonstrated that fibroids < 5 cm did not provide an additional risk in terms of adverse pregnancy outcomes. The risk of uterine fibroid-related complications during pregnancy might be primarily correlated with the size of myomas.

Pregnancy-related increases in steroid hormone levels and uterine blood flow affect fibroid growth.[4] Aharoni et al[24] reported leiomyomas to be mostly unchanged during pregnancy (59%). It has also been reported that the size of the fibroids was increased in 22% of the patients and the growth percentage of these fibroids was found to be 25%.[24] In our study, the size of the fibroids was increased in 60% of the cases, and the growth percentage of the fibroids was also 25%.

Song et al[25] reviewed 9 case-control studies that included more than 1,000 women with fibroids, of whom 41% underwent cesarean myomectomy and 59% underwent CS alone. They could not demonstrate any difference between groups in terms of safety parameters.[25] Turgal et al[11] found no statistical difference in the adhesion formations between women who had previously undergone cesarean myomectomy for small fibroids and controls who had not undergone myomectomy during their previous CS. Cesarean sections of our patients were performed due to other obstetrical indications, and we have demonstrated that opportunistic cesarean myomectomy was convenient as a safe and viable option in well-selected cases. Thus, we may conclude that cesarean myomectomy may be safely performed in patients with a myoma < 5 cm by experienced physicians. However, appropriate case selection must still be performed and previously reported complications must be kept in mind.

The limitations of this study were the relatively small number of cases, retrospective design, and lack of information related to fibroid sizes throughout gestational trimesters. On the other hand, longitudinal follow-up of the cases and presentation of single surgeon experience are the strengths of this study.

Conclusion

In conclusion, small size uterine fibroids (< 5 cm) seem to have no adverse effect on pregnancy outcomes even in high-risk pregnancies, and cesarean myomectomy may be safely performed in properly selected cases.

Contributors

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

Conflict of Interests

The authors have no conflict of interests to declare.

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Women's Obstetric History and Midtrimester Cervical Length Measurements by 2D/3D and Doppler Ultrasound

História obstétrica e medida do comprimento do colo uterino de mulheres no segundo trimestre gestacional por ultrassonografia bi/tridimensional e Doppler

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Abstract

Objective The aim of the present study was to compare the obstetric history and both two- and tri-dimensional ultrasound parameters according to different cervical lengths.

Methods The present cross-sectional study analyzed 248 midtrimester pregnant women according to cervical length and compared the data with the obstetric history and 2D/3D ultrasound parameters. Patients were divided into 3 groups according to cervical length: The Short Cervix group for cervical lengths $\geq$ 15 mm and $<$ 25 mm ($n = 68$), the Very Short Cervix group for cervical lengths $<$ 15 mm ($n = 18$) and the Control group, composed of 162 pregnant women with uterine cervical lengths $\geq$ 25 mm.

Results When analyzing the obstetric history of only non-nulliparous patients, a significant association between the presence of a short cervix in the current pregnancy and at least one previous preterm birth was reported ($p = 0.021$). Cervical length and volume were positively correlated (Pearson coefficient $= 0.587$, $p < 0.0001$). The flow index (FI) parameter of cervical vascularization was significantly different between the Control and Very Short Cervix groups. However, after linear regression, in the presence of volume information, we found no association between the groups and FI. Uterine artery Doppler was also not related to cervical shortening.

Conclusion The present study showed a significant association between the presence of a short cervix in the current pregnancy and at least one previous preterm birth. None of the vascularization indexes correlate with cervical length as an independent parameter. Uterine artery Doppler findings do not correlate with cervical length.

Keywords
- cervix uteri
- cervical length measurement
- pregnancy trimester, second
- reproductive history
- pregnancy, high-risk

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Resumo

Objetivo O objetivo do presente estudo foi comparar a história obstétrica e os parâmetros bi- e tridimensionais ultrassonográficos de acordo com os diferentes comprimentos cervicais.

Métodos O presente estudo transversal analisou 248 gestantes no segundo trimestre de acordo com o comprimento cervical e comparou os dados com a história obstétrica e os parâmetros ultrassonográficos 2D/3D. As pacientes foram divididas em 3 grupos de acordo com o comprimento do colo uterino: grupo Colo Curto para comprimentos cervicais ≥ 15 mm e < 25 mm ($n = 68$), grupo Colo Muito Curto para comprimentos cervicais < 15 mm ($n = 18$) e grupo Controle, composto por 162 gestantes com comprimento cervical uterino ≥ 25 mm.

Resultados Ao analisar a história obstétrica apenas de pacientes não nulíparas, foi relatada uma associação significativa entre a presença de colo uterino curto na gravidez atual e pelo menos um episódio de parto prematuro anterior ($p = 0{,}021$). Comprimento e volume do colo uterino foram correlacionados positivamente (coeficiente de Pearson $= 0{,}587$, $p < 0{,}0001$). O parâmetro índice de fluxo (IF) da vascularização cervical foi significativamente diferente entre os grupos Controle e Colo Muito Curto. Entretanto, após regressão linear, na presença de informações de volume, não encontramos associação entre os grupos e o parâmetro IF. Também não foi encontrada relação entre o Doppler da artéria uterina e o encurtamento cervical.

Conclusão O presente estudo mostrou uma associação significativa entre a presença de colo uterino curto na gravidez atual e pelo menos um episódio de parto prematuro anterior. Nenhum dos índices de vascularização se correlaciona com o comprimento cervical como parâmetro independente, assim como o Doppler da artéria uterina também não está relacionado ao comprimento do colo uterino.

Palavras-chave

- colo do útero
- medida do comprimento cervical
- segundo trimestre da gravidez
- história reprodutiva
- gravidez de alto risco

Introduction

The primary mechanical function of the uterine cervix is maintaining pregnancy to term, and the cervix undergoes complex changes during gestation. Understanding the underlying mechanisms of these changes could provide earlier detection of the onset of some complex processes, such as cervical insufficiency and preterm birth.[1]

Cervical length determined by transvaginal ultrasound in the second trimester is currently the best predictor of preterm birth.[2] The risks of prematurity increase as the cervix decreases. For a cervical length of ≤ 25 mm, the risk of preterm delivery is between 25 and 30%, but for a cervix < 15 mm the risk is almost 50%.[3] However, the assessment of other cervical ultrasound parameters that are already available and that could even precede cervical shortening remains to be elucidated. Rovas et al[4] studied pregnancies longitudinally and found that 3D cervical vascular indices are stable during pregnancy. There are few data showing that these indexes are different comparing pregnancies in preterm labor and normal development. However, we do not know how these indexes behave in pregnancies of risk for prematurity related to short cervix.

There is evidence that angiogenic factors may also play a key role in cervical ripening.

Uterine artery Doppler sonography analyzes uteroplacental perfusion and may also participate in the remodeling of the cervix. Recent evidence suggests that defective placentation, with failure to transform the myometrial segment of spiral arteries, may be more frequently associated with spontaneous preterm deliveries.[5–7]

Therefore, the literature is not clear about the contribution of 3D parameters in the evaluation of the cervix during pregnancy and if it is different according to the cervical length. The objective of the present study was to compare the obstetric history and both bi- and tridimensional ultrasound parameters according to different cervical lengths.

Methods

Cross-sectional study performed in the Fetal Medicine Unit of the Obstetric Clinic of the Hospital das Clínicas of the Faculdade de Medicina da Universidade de São Paulo (FMUSP, in the Portuguese acronym) covering data from May 2014 to January 2018 from the PROPE Project (ClinicalTrials.gov Identifier NCT02511574). The present study is a branch of a main study that compares progesterone and Arabin Pessary for the prevention of preterm delivery in

pregnancies with a short cervix. An aleatory subset data of cervical length evaluation before randomization were selected for the present study. The main research project and the present study were approved by the Ethics Committee for the Analysis of Research Projects of the Hospital das Clínicas of the FMUSP (number 1.730.615). Patients (or legal representatives) allocated to Short Cervix and Very Short Cervix groups signed an informed consent form approved by the Ethics Committee for Research Projects Analysis of the hospital. Regarding the Control group, we requested permission to use database information.

Midtrimester pregnant women receiving second trimester anomaly ultrasounds from low- and high-risk clinics underwent a cervical transvaginal evaluation. Patients with cervical lengths < 25 mm were elected for the study and divided into three groups. The groups were divided according to cervical length considering the definition of short cervix when the cervix is < 25 mm and of very short cervix < 15 mm, because the latter group has a 3-fold risk for prematurity.[3] The groups were: The Short Cervix group for cervical lengths ≥ 15 mm and < 25 mm ($n = 68$), the Very Short Cervix group for cervical lengths < 15 mm ($n = 18$) and the Control group, composed of 162 pregnant women with uterine cervical lengths ≥ 25 mm. The number of patients in the Control group corresponded to the total number of pregnant women with ≥ 25 mm cervical length assessed during the study period and about whom we had proper information to compare with that of the other two groups.

The inclusion criteria were singleton living fetus pregnancy without malformations, between 20 and 23 weeks and 6 days of gestation established by ultrasound performed in the 1st trimester or 2 ultrasound screenings between 16 and 20 weeks and no history of cervical insufficiency/surgery or preterm rupture of membranes (PROM).

Uterine cervical length was assessed using the transvaginal ultrasound technique with the patient placed in the dorsal lithotomy position with an empty bladder. An ultrasound probe was introduced into the vagina, and care was taken to avoid undue pressure to the cervix. After a satisfactory sagittal image was taken, the transducer was slightly withdrawn until the image became blurred and returned to a perfect image showing the internal os, the cervical canal and the external os. The measurement was placed from the outer to the inner cervical os, including only the segment of the cervical canal that was bordered by the endocervical mucosa. The image occupied $\sim 75\%$ of the screen as described by To et al.[8] For 3D assessment of cervical volume and vascularization indices, we performed real-time screening with virtual organ computer-aided analysis (VOCAL) volumetric assessment. All cervical measurements were performed on multiplanar images, and the contour mode of VOCAL was set to manual, rotation steps at an angle of 30°, that is, six contours of the cervix were drawn manually using the roller ball cursor of the machine. Care was taken not to include the lower uterine segment or the vaginal wall. After all contours were drawn, the volume and power Doppler flow indexes of the cervix were computed automatically.[4] The following blood flow indices were obtained: vascularization index (VI), flow index (FI) and vascularization flow index (VFI). To assess the uterine artery, we used Doppler as recommended by the practical guidelines of International Society of Ultrasound in Obstetrics and Gynecology (ISUOG).[9] In each uterine artery, we assessed the resistance index (RI), pulsatility index (PI) and systolic/diastolic ratio (S/D). All examinations were performed by a single medical sonographer.

The tests were performed using Voluson E8 Expert TM equipment (GE Healthcare, Zipf Austria) with a 5 to 9 MHz transvaginal transducer with a 146° field of view (GE Healthcare, Zipf, Austria). The following identical preinstalled settings were used for all patients: a frequency between 3 and 9 MHz, a pulse repetition frequency of 0.6 kHz, a gain of 5.0, and a low wall motion filter of 1. All information was recorded in a computer database.

The patients were assessed according to their demographic characteristics, obstetric history and ultrasound parameters.

Quantitative variables are summarized through the mean, median, standard deviation (SD), minimum and maximum values. Qualitative variables are presented as the absolute frequency (n) and percentage (%).

A nonparametric Kruskal-Wallis test was used to compare the quantitative variables in the three groups. To make paired comparisons (multiple comparisons) after the Kruskal-Wallis test (in case of significant results), we considered the Dunn test. The Pearson chi-squared test or the Fisher exact test were used to correlate qualitative variables whenever appropriate. The analysis of linear correlation between two quantitative variables was performed by using the Pearson linear correlation coefficient.

To analyze the consistency of possible significant results of groups in ultrasound parameters, linear regression models were adjusted considering the control variables to evaluate whether the group would remain significant in the presence of any possible confounding variables.

The interclass coefficient was calculated as the intraobserver reproducibility comparing the difference between analyses in 2 different 3D acquisitions.

A 5% significance level was chosen, and the statistical analysis was conducted with IBM SPSS for Windows, Version 20.0 (IBM Corp, Armonk, NY, USA).

The present study was submitted to the Ethics Committee of the Department of Obstetrics and Gynecology of the FMUSP and the Ethics Committee for Research Project Analysis (CAPPesq, in the Portuguese acronym). Participating pregnant women (or legal representatives) signed the Informed Consent Form. To use data from the Control Group, an addendum to the research project was made and consent to use the database was requested.

Results

The final analysis was performed with 68 (27.42%) pregnant women in the Short Cervix group, 18 (7.26%) in the Very Short Cervix group and 162 (65.32%) in the Control group.

The median cervical length was 34.60 mm (variation, 26.20–54.70) for the Control group, 21.00 mm (variation, 15.10–24.50) for the Short Cervix group, and 10.45 mm (variation, 6.30–14.00) for the Very Short Cervix group.

Table 1 Demographic characteristics of pregnant women according to the transvaginal assessment of uterine cervical length between 20 and 23 weeks and 6 days

Demographic characteristics		Control	Short Cervix	Very Short Cervix	*p-value*
		(≥ 25 mm)	(≥ 15 mm and < 25 mm)	(< 15 mm)	
		n = 162	n = 68	n = 18	
Maternal age (years)	Median (minimum–maximum)	31 (14–47)	29.50 (13–41)	30.50 (15–40)	0.025*
Weight (kg)	Median (minimum–maximum)	69.30 (43–130.20)	66 (49–103)	68.20 (56–107.80)	0.464*
Height (cm)	Median (minimum–maximum)	161 (145–178)	162.50 (152–181)	164 (150–170)	0.114*
BMI (kg/m^2)	Median (minimum–maximum)	26.84 (17.55–48.93)	25.97 (18–39.13)	25.53 (20.57–39.12)	0.199*
Race Caucasian	n (%)	76 (46.9%)	37 (54.4%)	9 (50%)	0.037**
Mixed		62 (38.3%)	23 (33.8%)	2 (11.1%)	
Black		24 (14.8%)	8 (11.8%)	7 (38.9%)	
Smoking	n (%)	5 (3.1%)	3 (4.4%)	0 (0%)	0.836**
Gestational age at inclusion (weeks)	Median (minimum–maximum))	22.14 (20–23.86)	22.71 (20.29–23.86)	22.08 (20.14–23.86)	0.042*

*Kruskal-Wallis Test.
**Fisher Exact Test.

Table 2 Obstetric history of pregnant women according to the transvaginal assessment of uterine cervical length between 20 and 23 weeks and 6 days

Obstetric history	GROUP			*p-value**
	Control	Short Cervix	Very Short Cervix	
	(≥ 25 mm)	(≥ 15 mm and < 25 mm)	(< 15 mm)	
	n = 162	n = 68	n = 18	
First pregnancy	59 (36.4%)	29 (42.6%)	8 (44.4%)	0.593
Previous delivery **	90 (55.60%)	29 (42.6%)	8 (44.4%)	0.169
Abortion**	45 (27.8%)	24 (35.3%)	6 (33.3%)	0.508
Curettage**	27 (16.7%)	18 (26.5%)	5 (27.8%)	0.178
Bleeding***	45 (27.8%)	16 (23.5%)	6 (33.3%)	0.661

*Pearson chi-square test.
**At least one previous episode.
***At least 1 episode in the current pregnancy.

The groups differed in maternal age, ethnicity, and gestational age at inclusion (►**Table 1**).

According to previous obstetric history (presence of at least one previous episode of pregnancy, delivery, abortion, curettage and/or bleeding), there were no significant differences among the three studied groups (►**Table 2**).

When analyzing the obstetric history of only non-nulliparous patients, we observed a significant association between the presence of a short cervix in the current pregnancy and at least one previous preterm birth. In the Control group, only 22.2% of the non-nulliparous women had had previous preterm deliveries, whereas in the Short and Very Short Cervix groups, the rates were 48.3% and 37.5%, respectively ($p = 0.021$).

Regarding the sonographic parameters, we observed a moderate positive linear correlation between the volume and length of the cervix (Pearson coefficient = 0.587, $p < 0.0001$). The correlation between these two measures may be presented by the square equation in which expected volume = 12.214 + 0.968* length, that is, the expected volume of a case with null length is 12.214 cm^3. For each increase of one cervical length unit (mm), an increase of 0.968 volume units (cm^3) would be expected.

The Control, Short Cervix, and Very Short Cervix groups showed differences in the median volume (43. 8 versus 30.87 versus 19.57, respectively) (p = < 0.001) and median FI parameter of cervical vascularization (38.92 versus 39.32 versus 35.16, respectively) ($p = 0.027$), and the difference between the Control and Very Short Cervix groups was statistically significant. However, after linear regression, in the presence of volume information, we found no association between the groups and FI. There was no statistical correlation between the groups and the uterine artery Doppler results (►**Table 3**).

After adjusting the linear regression model to the FI index with covariables maternal age, race, gestational age at inclusion, history of at least one previous preterm delivery and volume, in addition to group, we noticed that only volume was significant (coefficient 0.14; standard error 0.027; $p < 0.001$), which means that, in the presence of volume information, there was no association between the groups and FI. In the Control and Short Cervix groups, cervical primigravidae had a shorter median volume compared no primigravidae women (Control group volume: 41.0 × 45.2cm^3, $p = 0.003$; Short Cervix group volume: 26.6 × 33.6cm^3, $p = 0.033$).

The intraclass coefficients for the intraobserver repeatability were 0.957 (95% confidence interval (CI): 0.893–0.983) for volume, 0.848 (95%CI: 0.622–0.939) for VI, 0.876 (95%CI: 0.693–0.951) for FI and 0.805 (95%CI: 0.515–0.922) for IVF.

Table 3 Ultrasound parameters according to the transvaginal assessment of uterine cervical length between 20 and 23 weeks and 6 days

Parameters	Group**	Median min–max	*p*-value*
Volume (cm3)	Control	43. 8 (23.10–100.87)	< 0.001
	Short Cervix	30.87 (7.58–69.04)	
	Very Short Cervix	19.57 (5.42–47.23)	
Vascularization Index (VI)	Control	4.87 (0.51–19.87)	0.656
	Short Cervix	4.10 (0.43–24.23)	
	Very Short Cervix	5.89 (0.41–11.67)	
Vascularization Index (FI)	Control	38.92 (29.02–69.39)	0.027
	Short Cervix	39.32 (28.45–52.44)	
	Very Short Cervix	35.16 (28.71–49.24)	
Vascularization Index (VFI)	Control	2.51 (0.15–7.51)	0.457
	Short Cervix	2.02 (0.13–21.13)	
	Very Short Cervix	2.17 (0.12–5.31)	
Right Uterine Artery (RI)	Control	0.59 (0.38–0.82)	0.075
	Short Cervix	0.59 (0.38–0.90)	
	Very Short Cervix	0.68 (0.41–1.46)	
Right Uterine Artery (S/D)	Control	2.46 (1.61–5.60)	0.197
	Short Cervix	2.53 (1.61–9.85)	
	Very Short Cervix	3.09 (1.71–6.82)	
Right Uterine Artery (PI)	Control	0.97 (0.43–2.39)	0.575
	Short Cervix	0.98 (0.48–3.26)	
	Very Short Cervix	1.05 (0.47–2.77)	
Left Uterine Artery (RI)	Control	0.62 (0.39–0.93)	0.356
	Short Cervix	0.63 (0.41–0.90)	
	Very Short Cervix	0.59 (0.43–0.83)	
Left Uterine Artery (S/D)	Control	2.61 (1.64–4.99)	0.247
	Short Cervix	2.63 (1.69–9.79)	
	Very Short Cervix	2.42 (1.74–5.88)	
Left Uterine Artery (PI)	Control	1.01 (0.51–2.14)	0.194
	Short Cervix	1.04 (0.55–3.94)	
	Very Short Cervix	0.97 (0.61–2.45)	

*Kruskal-Wallis Test.
**Group: Control (n = 162), Short Cervix (n = 68) Very Short Cervix (n = 18).
Abreviations: FI, flow index; VFI, vascularization flow index; RI, resistance index; S/D: systolic/diastolic ratio; PI, pulsatility index.

Discussion

Evaluation of cervical length in the second trimester of pregnancy identifies pregnant women with a high risk for preterm delivery; however, fewer than 20% of pregnant women with a short cervix will have preterm deliveries.[10] Thus, the identification of other findings related to cervical shortening may contribute to early diagnosis and improvement in accurately identifying short-cervix pregnant women who effectively have an increased risk of prematurity and are eligible for treatment.

In our study, transversally selected pregnancies that were screened for prematurity in the 2nd trimester by cervical length using a cutoff of < 25 mm were selected. Cervical length < 25 mm is defined as a short cervix and has a 3-fold higher risk for preterm delivery compared with cervix length ≥ 25 mm.[3] Obstetric history and 3D/4D ultrasound parameters were compared between the groups with short and normal lengths, dividing the short cervix groups into Very Short Cervix when the cervix was < 15 mm and Short Cervix when the measurement was between 15 and 24.9 mm. The option to create these two subgroups of short cervices was related to the fact that the shorter the cervix, the higher is the risk for prematurity, and the group with lengths < 15 mm represented the group with higher risk. In the Very Short Cervix group, the median cervical length observed was 10.45 mm, compared with 21 mm in the Short Cervix group. These two groups have completely different risks and therefore should be analyzed separately. The median cervical length in the control group, 34.60 mm, was similar to that reported in other studies.[3,11–13] There was a significant difference concerning ethnicity among the three groups, with a higher proportion of afrodescendant women in the Very Short Cervix group. The literature shows an increased incidence of preterm deliveries in afrodescendant women. However, two large studies have reported that when social and demographic factors are considered, ethnic origin is not significant.[14,15] A previous study performed in the Brazilian population has not shown differences in cervical length among afrodescendants and Caucasian women.[16] The present study could not clarify whether the shortening of the cervix in the 2nd trimester of pregnancy in afrodescendants was related to race itself or to social factors relevant to the majority of this race worldwide. Nevertheless, efforts should be made to elucidate this condition because if a short cervix is truly found more commonly in afrodescendants independently of the cause, this subgroup of pregnant women could have their cervical lengths monitored.

Concerning maternal age, the literature reports a greater incidence of short cervix and increased risk for prematurity in adolescents. It is suggested that this fact is due to social and behavioral factors and not intrinsic biological determinants of age.[16,17] In our study, the maternal age was statistically younger in the Short Cervix group, but in the Control and Very Short Cervix groups, there were no significant differences. This finding may be explained by the considerably smaller number of pregnant women in the Very Short Cervix group; however, the finding would also be possibly related to the increased risk of prematurity in young pregnant women reported in other studies.

We also found differences between the groups concerning gestational age at inclusion, but this factor was considered clinically irrelevant as it was assessed during a 1-week interval in all women during the screening period and may reflect only the dates the patients were referred for screening.

Even though the literature shows a higher incidence of short cervix and preterm deliveries in smokers, we did not notice differences among the study groups. This may have been due to the low incidence of smokers in the group or the omission of such information by the subjects.[16,18–20]

Concerning obstetric history, we found an association between pregnant women who had had at least one previous preterm delivery and short cervix in the current pregnancy. This finding confirms that an important risk factor of preterm delivery is a previous history of prematurity. It could be hypothesized that a woman with high risk due to a previous history of prematurity has an increased likelihood to be found with a short cervix in the next pregnancy, and therefore, two strong risk factors could potentialize recurrence.[21–25]

The use of 3D techniques is still recent, and there are only few data in the literature describing their use and benefits in the field. Thus, studies on cervical volume in normal pregnancy are still insufficient. In our study, the assessment of transvaginal cervical volumes by the 3D VOCAL technique showed a positive correlation between cervical length and volume, which is expected because a short cervix has a lower volume and the opposite is also true. Therefore, the use of VOCAL requires 3D software and machines that increase costs in medical assistance and probably do not contribute to better prediction, as these parameters are dependent. Our findings are in agreement with other studies that have attempted to increase accuracy in predicting preterm deliveries using the 3D technique to assess the uterine cervix.[26,27] These studies did not show any benefit of using 3D compared with 2D techniques in the field.[27–29]

Dilek et al[28] observed significantly lower values of length and cervical volume in pregnant women who had spontaneous preterm deliveries than in pregnant women with term deliveries. However, the measurement of cervical volume, calculated by the 2D technique in the referred study, did not add benefits to assessing cervical length for predicting preterm deliveries. Strauss et al[30] observed, in multiple pregnancies, a significant correlation between the mean cervical length assessed by 2D analysis and the mean cervical volume, both assessed abdominally.

Concerning 3D vascular indexes, we observed correlations of different cervical lengths only for FI, with lower FI indexes in the Very Short Cervix group than in the Control group, but the difference was no longer significant after the linear regression analysis. This finding is probably in agreement with other studies that showed that FI is not a perfusion indicator and cannot provide information about the blood volume pumped into vessels during a specific period. In fact, the literature reports that the actual meaning of FI is not clear and that it is less predictable than VI or VFI.[31]

It is inferred that the cervix should increase vascularization and flow in preparation for labor; however, studies have not agreed in their data. Rovas et al[4] demonstrated the constant distribution of vascular indices throughout normal pregnancy, and the values did not increase as the pregnancy progressed. De Diego et al observed an increase in VI and VFI in pregnant women with a history of treated preterm labor compared with asymptomatic women with the same cervical length. The FI was higher in asymptomatic women.[32]

Studies correlating uterine artery Doppler flow and preterm delivery have shown contradictory results. When assessed in the 1st and 2nd trimester, uterine artery Doppler flow did not present a significant correlation with spontaneous preterm delivery compared with maternal demographic characteristics and previous obstetric history.[33,34]

In our study, there was no significant correlation between uterine artery Doppler and cervical length; therefore, there is probably no association with preterm delivery due to a short cervix.

The present study was performed with a homogenous sample in a single center and showed the behavior of different ultrasound parameters according to uterine cervical length. Although the small sample was a limitation, the present study shows that the parameters analyzed could not be useful for the explanation of cervical shortening. The prediction of preterm delivery was not the objective of the present analysis. The scarce data available in the literature for comparison with our findings is also another difficulty. In the present study, only 3D cervical volume was related to cervical length, which is not new in the literature and is fully expected.

Conclusion

There is a significant association between the presence of a short cervix in the current pregnancy and at least one previous preterm birth. Cervical length and volume are positively correlated. None of the vascularization indices correlate with cervical length as an independent parameter. Uterine artery Doppler findings do not correlate with cervical length.

Contributors

All authors were involved in the design and interpretation of the analyses, contributed to the writing of the manuscript, read and approved the final manuscript.

Conflicts of Interests

The authors have no conflict of interests to declare.

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Epidemiological Profile of the Victims of Sexual Violence Treated at a Referral Center in Southern Brazil

Perfil epidemiológico das vítimas de violência sexual atendidas em um centro de referência do Sul do Brasil

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Abstract

Objective To characterize the sociodemographic profile of women victims of sexual violence treated at a university hospital in southern Brazil.

Method The present cross-sectional study included all female victims of sexual violence who attended the sexual violence unit at the Hospital de Clínicas de Porto Alegre (HCPA, in the Portuguese acronym) from April 18, 2000 to December 31, 2017. Data were extracted from the electronic record of the patients and stored in a standardized questionnaire database with epidemiological aspects of the victim, the perpetrators and the type of aggression. Statistical analysis was performed using the chi-squared test for trend and descriptive statistics with 95% confidence interval (CI).

Results During the length of the study, 711 women victims of sexual violence were treated. The mean age of the patients was 24.4 ($\pm$10) years old (range from 11 to 69 years old) and most of the victims were white (77.4%), single (75.9%) and sought care at the unit within 72 hours after the occurrence (80.7%). In most cases, violence was exerted by a single perpetrator (87.1%), who was unknown in 67.2% of cases. Victims $<$ 19 years old showed a higher risk of not using contraception (relative risk [RR] = 2.7; 95% CI = 1.9–3.6).

Conclusion Most victims of sexual violence were treated within 72 hours of the occurrence. The majority of these victims were white and young, and those $<$ 19 years old had a higher risk of not using contraception and to know the sexual perpetrator.

Keywords

- women's health service
- violence against women
- sexual violence
- rape

Resumo

Objetivo Caracterizar o perfil sociodemográfico de mulheres vítimas de violência sexual atendidas em um hospital universitário da região Sul do Brasil.

Métodos Estudo transversal de todas as mulheres atendidas na unidade de vítimas de violência sexual do Hospital de Clínicas de Porto Alegre (HCPA) entre 18 de abril de

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2000 a 31 de dezembro de 2017. Os dados foram extraídos a partir do registro eletrônico de um questionário padronizado envolvendo aspectos epidemiológicos da vítima, do agressor e do tipo de agressão. O teste qui-quadrado foi empregado para tendência e estatística descritiva com 95% de intervalo de confiança (IC) foram utilizados para análise estatística.

Resultados Foram atendidas 711 mulheres vítimas de violência sexual. A média da idade das pacientes foi de 24,4 (±10) anos, sendo que a maioria das vítimas era branca (77,4%), solteira (75,9%) e buscou atendimento na unidade dentro de 72 horas após a ocorrência (80,7%). Na maioria dos casos, a violência foi exercida por agressor único (87,1%), sendo este desconhecido em 67,2% dos casos. As vítimas < 19 anos mostraram um maior risco de não estarem usando algum método contraceptivo (risco relativo [RR] = 2,7; IC95% = 1,9–3,6).

Conclusão A maioria das vítimas de violência sexual foi atendida dentro de 72 horas da ocorrência. As vítimas sexuais eram, na sua maioria, brancas e jovens, sendo que as < 19 anos apresentavam um maior risco de não estarem utilizando algum método contraceptivo e de conhecerem o seu agressor.

Palavras-chave
- serviço de saúde da mulher
- violência contra a mulher
- violência sexual
- delitos sexuais
- estupro

Introduction

Violence against women is defined as "any act based on gender that causes death, harm or physical, sexual or psychological distress to women, whether in the public or the private sphere," or as "any sexual act, attempt to obtain a sexual act, unwanted sexual comments or advances, or acts to traffic, or otherwise directed, against a person's sexuality using coercion, by any person, regardless of their relationship to the victim, in any setting, including but not limited to home and work."[1,2] This type of violence has been a public health problem. Sexual violence can expose the victims to sexually transmitted infections, to unwanted pregnancy and to emotional problems in the short or long term, for instance, suicide and depression.[3] Twenty to 60% of the victims do not tell anyone or do not seek institutional help to report intimate partner violence.[4] The lack of official data and the underreporting problem are challenging for researchers in this area.[5] Data from specialized centers for the care of women victims of sexual abuse are scarce.[6]

Homicide rates against women in Brazil have been steadily increasing since 2007, reaching 4.8 cases of female homicides/100,000 inhabitants in 2013.[7] Data from the informatics department of the Brazilian Unified Health System (DATASUS), the official electronic database of the Brazilian Ministry of Health, revealed that 243,259 domestic, sexual and/or other violence were registered in Brazil in 2016, of which 22,648 rapes were reported.[8] Around 21.9 women seek health care services for sexual violence every day and there are 14.2 reports of women victims of rape daily.[9]

A study revealed that the number of police reports against women in the state of Rio Grande do Sul, Brazil, more specifically in the cities of Santa Maria, Erechim and Santana do Livramento, ranged from 66 to 361 cases between 2005 and 2009.[10] This variability in the number of police reports may be due to the systematic lack of data collection in a specialized unit for this activity. The gynecological emergency unit (GEU) of the Hospital de Clínicas de Porto Alegre (HCPA, in the Portuguese acronym) has been a reference center for the care of women victims of sexual violence since April 2000. This unit offers multidisciplinary care in emergency and outpatient settings. The staff of this unit comprises gynecologists, psychiatrists, nurses, psychologists, and social workers. The consultation for this type of victim is aimed at the prevention of sexually transmitted infections (STIs) and unwanted pregnancy. This first emergency contact is a great opportunity to offer emergency contraception for those who need it.[11] The GEU follows the Brazilian Ministry of Health protocols in this area and collects data from these victims in a systematic manner.[12] This systematic data collection may reveal some aspects of this population and the conditions in which sexual violence had occurred. The objective of the present study is to characterize the socioepidemiological profile of these victims of sexual violence who were treated at the HCPA, a university hospital in the southern region of Brazil. As a secondary objective, the average age was compared between women who were or were not using contraception at the time of violence.

Methods

Study Design and Setting

This is a cross-sectional study, conducted from April 1, 2000 to December 31, 2017, at the Gynecological Emergency Unit at the Hospital de Clínicas de Porto Alegre (GEU-HCPA, in the Portuguese acronym), Porto Alegre, Rio Grande do Sul, Brazil.

Participants

Women victims of sexual assault, aged ≥10 years old, who were referred to or came spontaneously to the GEU, and had an electronic medical record were included in the study. Those without electronic records and male victims were excluded.

Variables

Age (in years), ethnicity (by self-declaration), marital status, years of education, profession, characterization of sexual violence, that is, place where the violence occurred, number of perpetrators, characteristics of the perpetrator, whether or not there was a previous relationship between the perpetrator and the victim, form of intimidation, type of sexual assault, occurrence or not of ejaculation, first or repeated aggression, use of contraceptive method at the time of the violence, existence or not of police report and presumed age of the perpetrator were evaluated as study variables. The time elapsed between the sexual assault and the medical care and whether exams, prophylaxis, referrals for hepatitis B vaccination were provided or not were also evaluated.

Data Sources/Measurements

After direct interviews with the patient, data were entered into an electronic medical record. Data from the electronic medical records of the patients were obtained and transferred to a specific database developed for this purpose (GoogleForms, Google LLC, Mountain View, CA, USA). Data was collected for a period of 215 months. A training period of 3 months was performed to assure the consistency of the database input. No strategy for statistical analysis was applied for missing values.

Bias

Data were entered independently by two researchers (Marmontel M. and Santarem M. D.), which were later compared for reducing bias. Discrepancies were solved by reviewing the electronic medical record by a senior professional (Savaris R. F.) or reinterviewing the patient. Reinterview of the patient was performed either in the follow-up consultation, or by telephone by one of the authors (Marmontel M.), responsible for the outpatient clinic. In case of outdated telephone numbers, the social service of the hospital was activated.

Sample Size

The sample was for convenience and included all cases treated within 18 years.

Quantitative Variables

Quantitative variables were described as means and standard deviations (SD). The population was divided into 2 groups based on a cutoff of the age most likely of not using any contraceptive method.

Statistical Methods

Statistical analysis was descriptive using percentage and 95% confidence interval (CI), mean with SD. The identification of a

Table 1 Sociodemographic characteristics of women victims of sexual violence

Variable	Overall ($n = 711$)		$\leq$ 19 years old ($n = 262$)		$>$ 19 years old ($n = 449$)		*p-value*[*]
	n (%)	95%CI	n (%)	95%CI	n (%)	95%CI	
Ethnic group							
White	550 (77.4)	74.1–80.3	194 (74)	68.4–79.0	356 (79.3)	75.3–82.8	0.08
Non-white	154 (21.6)	18.8–24.8	64 (24.4)	19.6–3.0	90 (20)	16.6–24.0	
Ignored	7 (1.0)	0.5–2.1	4 (1.5)	0.6–4.0	3 (2.1)	0.2–2.1	
Marital Status							
Single	540 (75.9)	72.7–79.0	248 (94.7)	91.2–96.8	292 (65.0)	60.5–69.3	< 0.001
Married	100 (14.1)	11.7–16.8	7 (2.7)	1.3–5.5	93 (20.7)	17.2–24.7	
Separated or Widow	64 (9.0)	7.1–11.3	1 (0.4)	0.1–2.7	63 (14)	11.1–17.6	
Ignored	7 (1.0)	0.5–2.1	6 (2.3)	1.0–5.0	1 (0.2)	0–1.6	
Education							
Illiterate	9 (1.3)	0.7–2.4	2 (0.8)	0.2–3.0	7 (1.6)	0.7–3.2	< 0.001
$\leq$ 9 years	256 (36.0)	32.5–39.6	137 (52.3)	46.2–58.3	119 (26.5)	22.6–30.8	
10–12 years	299 (42.1)	38.5–45.7	96 (36.6)	31.0–36.6	203 (45.2)	40.7–49.9	
$\geq$ 13 years	87 (12.2)	10.0–14.9	2 (0.8)	0.2–3.0	85 (18.9)	22.8–15.6	
Ignored	60 (8.4)	6.6–10.7	25 (9.5)	6.5–13.8	35 (7.8)	5.6–10.7	
Employment status							
Unemployed	71 (10)	8.0–12.4	12 (4.6)	2.6–7.8	59 (13.1)	10.3–16.6	< 0.001
Employed	223 (31.4)	28.1–34.9	22 (8.4)	5.6–12.4	201(44.8)	40.2–49.4	
Student	218 (30.7)	27.4–34.2	154 (58.8)	52.7–64.6	64 (14.3)	11.3–17.8	
Ignored	199 (28.0)	24.8–31.4	74 (28.2)	23.1–34.0	125 (27.8)	23.9–32.2	

Abbreviation: CI, confidence interval.
[*]Chi-squared for trend comparing groups $\leq$ 19 and $>$ 19 years old only.

cutoff of age as the most likely of not using any contraceptive method was verified by the curve receiver operator characteristics (ROC). After identifying this cutoff, the sample was divided into 2 groups for further comparisons, using the chi-squared test for trend or the Mann Whitney test. Statistical analyses were performed using the Prism 8 software (GraphPad Software, San Diego, California, USA).

Ethical Aspects

The present study was submitted and approved by the Research Ethics Committee of the HCPA (CAAE = 84939318000005327).

Results

Participants

Between April 18, 2000 and December 31, 2017, a total of 711 female victims of sexual violence (100%) were screened for consultation and entered in the analysis. There were no exclusions.

Descriptive Data

The mean (SD) and median age of the studied population were 24.1 (±10) years old and 22 years old, respectively, ranging from 11 to 69 years old. Further details of the population characteristics, the characteristics of violence and the provided care given at the first visit are described in ►**Tables 1**, **2** and **3**, respectively.

Outcome Data

The median age of the victims using contraception ($n = 215$) was significantly higher compared with those not using any method ($n = 496$) (24 versus 20; $p < 0.0001$; Mann Whitney test). In the ROC curve analysis (►**Fig. 1**), the cutoff point for identifying women with a higher risk of not using contraception was 19 years old. From a total of 262 women ≤ 19 years old, only 61 were using some contraceptive method, (23.3%; 95%CI: 18.6–28.8%). In contrast, 449 women were >19 years old; from these, 173 were using some contraceptive method (38.5%; 95%CI: 34.0–43.2%). These figures give a relative risk (RR) = 2.7 (95%CI = 1.96–3.6).

Main Results/Other Analyzes

The subgroup analysis of the population revealed that most of the perpetrators were known by the victims ≤ 19 years old and the vaginal contact was more common in this subgroup, while those > 19 years old suffered more than one sexual contact and the majority of the women > 19 years old were married or with a previous relationship (►**Table 1**). Women ≤ 19 years old received more emergency contraception (69.1%; 95%CI= 63.2–74.4%). Most victims of violence sought

Table 2 Characteristics of the sexual violence in the studied population and by the age of 19 years old

Variable	Overall ($n = 711$)		≤ 19 years old ($n = 262$)		> 19 years old ($n = 449$)		*p-value**
	n (%)	95%CI	n (%)	95%CI	n (%)	95%CI	
First occurrence							
Yes	525 (73.8)	70.5–76.9	201 (76.7)	71.2–81.5	324 (72.2)	67.8–76.1	
No	37 (5.2)	3.8–7.1	16 (6.1)	3.8–9.7	21 (4.7)	3.1–7.1	0.1
Ignored	149 (21.0)	18.1–24.1	45 (17.2)	13.1–22.2	104 (23.2)	19.5–27.3	
Relationship with perpetrators							
Unknown	478 (67.2)	63.7–70.6	152 (58.0)	51.9–63.9	326 (72.6)	68.3–76.5	
Known	207 (29.1)	25.9–32.6	99 (37.8)	32.1–43.8	108 (24.1)	20.3–28.2	<0.001
Ignored	26 (3.7)	2.5–5.3	11 (4.2)	2.3–7.4	15 (3.3)	2.0–5.5	
Place of occurrence							
Street	87 (12.2)	10.0–14.9	27 (10.3)	7.2–14.6	60 (13.4)	10.5–16.8	
Residence	166 (23.3)	20.4–26.6	67 (25.6)	20.6–31.2	99 (22.0)	18.4–26.1	
Work	19 (2.7)	1.7–4.2	2 (0.8)	0.2–3.0	17 (3.8)	2.4–6.0	0.4
Other	44 (6.2)	4.6–8.2	13 (5.0)	2.9–8.4	31 (6.9)	4.9–9.7	
Ignored	395 (55.6)	51.9–59.2	153 (58.4)	52.3–64.2	242 (53.9)	49.3–58.5	
Number of perpetrators							
Single	619 (87.1)	84.4–89.3	232 (88.5)	84.1–91.9	387 (86.2)	82.7–89.1	
Multiple	73 (10.3)	8.2–12.7	20 (7.6)	5.0–11.5	53 (11.8)	9.1–15.1	0.8
Ignored	19 (2.7)	1.7–4.2	10 (3.8)	2.7–7.0	9 (2.0)	1.0–3.8	
Form of Aggression							
Physical	139 (19.5)	16.8–22.6	44 (16.8)	12.7–21.8	95 (21.2)	17.6–25.2	
Verbal	48 (6.8)	5.1–8.9	15 (5.7)	3.5–9.3	33 (7.3)	5.3–10.2	0.3
More than one type	16 (2.3)	1.4–3.6	4 (1.5)	0.6–4.0	12 (2.7)	1.5–4.7	
Ignored	508 (71.4)	68.0–74.7	199 (76.0)	7.4–80.8	309 (68.8)	64.4–72.9	

Table 2 (*Continued*)

Variable	Overall ($n = 711$)		≤ 19 years old ($n = 262$)		> 19 years old ($n = 449$)		*p-value**
	n (%)	95%CI	n (%)	95%CI	n (%)	95%CI	
Type sexual contact							
Oral	15 (2.1)	1.3–3.5	6 (2.3)	1.0–5.0	9 (2.0)	1.0–3.8	
Anal	22 (3.1)	2.0–4.7	9 (3.4)	1.8–6.5	13 (2.9)	1.7–4.9	
Vaginal	366 (51.5)	47.8–55.1	155 (59.2)	53.1–65.0	211 (47.0)	42.4–51.6	0.01
More than one type	244 (34.3)	30.9–37.9	70 (26.7)	21.7–32.4	174 (38.8)	34.3–43.4	
Ignored	64 (9.0)	7.1–11.3	22 (8.4)	5.6–12.4	42 (9.4)	7.0–12.4	
Ejaculation							
Yes	344 (48.4)	44.7–52.1	121 (46.2)	40.2–52.3	223 (49.7)	45.0–54.3	
No	25 (3.5)	2.4–5.2	7 (2.7)	1.3–5.5	18 (4.0)	2.5–6.3	0.2
Ignored	342 (48.1)	44.4–51.8	134 (51.1)	45.1–57.2	208 (46.3)	41.7–51.0	
Approximate age of the perpetrators							
≤ 20 years old	21 (3.0)	1.9–4.5	5 (1.9)	0.8–4.5	16 (3.6)	2.2–5.7	
21–30 years old	79 (11.1)	9.0–13.6	28 (10.7)	7.5–15.1	51 (11.4)	8.7–14.6	
31–40 years old	40 (5.6)	4.2–7.6	11 (4.2)	2.3–7.4	29 (6.5)	4.5–9.1	
41–60 years old	18 (2.5)	1.6–4.0	9 (3.4)	1.8–6.5	9 (2.0)	1.0–3.8	0.2
Ignored	553 (77.8)	74.6–80.7	209 (79.8)	74.5–84.2	344 (76.6)	72.5–80.3	
Police Report							
No	39 (5.5)	4.0–7.4	13 (5.0)	2.9–8.4	26 (5.8)	4.0–8.4	
Yes	515 (72.4)	69.0–75.6	203 (77.5)	72.0–82.1	312 (69.5)	65.1–73.6	0.1
Ignored	157 (22.1)	19.2–25.3	46 (17.6)	13.4–22.7	111 (24.7)	20.9–28.9	

Abbreviation: CI, confidence interval.
*Chi-squared for trend comparing groups ≤19 and > 19 years old only.

Table 3 Description of emergency care given to the women after sexual violence

Variable	Overall ($n = 711$)		≤ 19 years old ($n = 262$)		> 19 years old ($n = 449$)		*p-value**
	n (%)	95%CI	n (%)	95%CI	n (%)	95%CI	
Presence of physical injuries							
Yes	13 (1.8)	1.1–3.1	5 (1.9)	0.8–4.5	8 (1.8)	0.9–3.5	
No	527 (74.1)	70.8–77.2	187 (71.4)	65.6–76.5	340 (75.7)	71.5–79.5	0.2
Ignored	171 (24.1)	21.0–27.3	70 (26.7)	21.7–32.4	101 (22.5)	18.9–26.6	
Prophylaxis for sexually transmitted diseases dispensed							
Yes	612 (86.1)	83.3–88.4	232 (88.5)	84.1–91.9	380 (84.6)	87.7–81.0	
No	10 (1.4)	0.8–2.6	4 (1.5)	0.6–4.0	6 (1.3)	0.6–2.9	0.1
Ignored	89 (12.5)	10.3–15.2	26 (9.9)	6.8–14.2	63 (14.0)	11.1–17.6	
Prophylaxis for HIV dispensed							
Yes	621 (87.3)	84.7–89.6	231 (88.2)	83.7–91.6	390 (86.9)	83.4–89.7	
No	40 (5.4)	4.2–7.6	15 (5.7)	3.5–9.3	25 (5.6)	3.8–8.1	0.5
Ignored	50 (7.0)	5.4–9.2	16 (6.1)	3.8–9.7	34 (7.6)	5.5–10.4	
Referral for Hepatitis B Vaccine							
Yes	609 (85.7)	82.9–88	227 (86.6)	81.9–90.3	382 (85.1)	81.5–88.1	
No	52 (7.3)	5.6–9.5	19 (7.3)	4.7–11.1	33 (7.3)	5.3–10.2	0.4
Ignored	50 (7.0)	5.4–9.2	16 (6.1)	3.8–9.7	34 (7.6)	5.5–10.4	
Immunoglobulin Hepatitis B dispensed							
Yes	116 (16.3)	13.8–19.2	49 (18.7)	14.4–23.9	67 (14.9)	11.9–18.5	
No	545 (76.7)	73.4–79.6	197 (75.2)	69.6–80.1	348 (77.5)	73.4–81.1	0.1

(*Continued*)

Table 3 (*Continued*)

Variable	Overall ($n = 711$)		≤ 19 years old ($n = 262$)		> 19 years old ($n = 449$)		*p-value*[*]
	n (%)	95%CI	n (%)	95%CI	n (%)	95%CI	
Ignored	50 (7.0)	5.4–9.2	16 (6.1)	3.8–9.7	34 (7.6)	5.5–10.4	
Emergency contraception dispensed							
Yes	389 (54.7)	51.0–58.3	181 (69.1)	63.2–74.4	208 (46.3)	41.7–51.0	
No	272 (38.3)	34.7–41.9	65 (24.8)	19.9–30.4	207 (46.1)	41.5–50.7	<0.001
Ignored	50 (7.0)	5.4–9.2	16 (6.1)	3.8–9.7	34 (7.6)	5.5–10.4	
Victim was pregnant							
Yes	13 (1.8)	1.1–3.1	2 (0.8)	0.2–3.0	11 (2.4)	1.4–4.4	
No	454 (63.9)	60.2–67.3	162 (61.8)	55.8–67.5	292 (65.0)	60.5–69.3	0.09
Ignored	244 (34.3)	30.9–37.9	98 (37.4)	31.7–43.4	146 (32.5)	28.3–37.0	
Sought consultation within 72h of the violence							
Yes	574 (80.7)	77.7–83.5	214 (81.7)	76.5–85.9	360 (80.2)	76.2–83.6	
No	117 (16.5)	13.9–19.4	41 (15.6)	11.7–20.6	76 (16.9)	13.7–20.7	0.6
Ignored	20 (2.8)	1.8–4.3	7 (2.7)	1.3–5.5	13 (2.9)	1.7–4.9	
Referral to psychiatrist							
Yes	259 (36.4)	33.0–40.0	93 (35.5)	29.9–41.5	166 (37.0)	32.6–41.5	
No	272 (38.3)	34.7–41.9	96 (36.6)	31.0–42.7	176 (39.2)	34.8–43.8	0.3
Ignored	180 (25.3)	22.2–28.7	73 (27.9)	22.8–33.6	107 (23.8)	20.1–28.0	
Follow-up at the gynecology outpatient clinic							
Yes	497 (69.9)	66.4–73.2	181 (69.1)	63.2–74.4	316 (70.4)	66.0–74.4	
No	208 (29.3)	26.0–32.7	78 (29.8)	24.5–35.6	130 (29.0)	24.9–33.3	0.6
Ignored	6 (0.8)	0.4–1.9	3 (1.1)	0.4–3.5	3 (0.7)	0.2–2.1	

Abbreviation: CI, confidence interval.
[*]Chi-squared for trend comparing groups ≤19 and > 19 years old only.

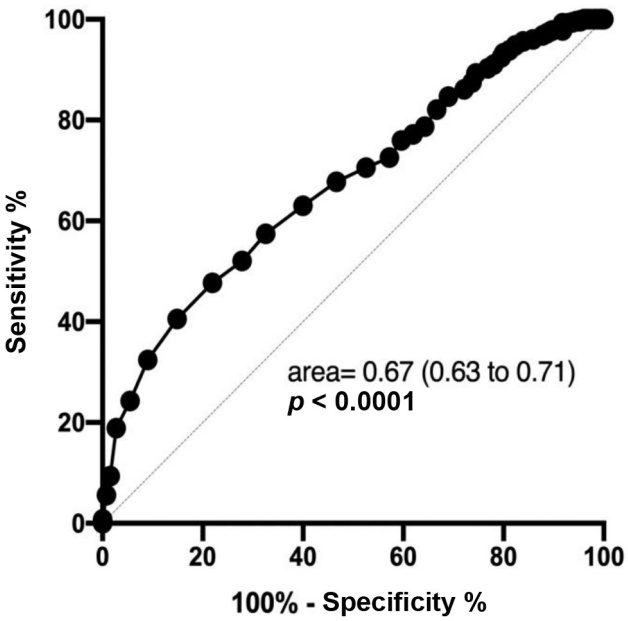

Fig. 1 ROC curve plotting age and use or not of any contraceptive method during the occurrence of sexual violence.

care within 72 hours of occurrence (574 out of 711 cases, 80.7%; 95%CI = 77.7–83.5%) and continued follow-up (497 out of 711 [69.9%]; 95%CI = 66.4–73.2%) at the gynecology outpatient clinic.

Discussion

The victims of sexual violence treated at the HCPA between 2000 and 2017 had a mean age of 24.4 years old. Those between 18 and 25 years old comprised 25.7% of the studied population (183 out of 711; 25.7%; 95%CI= 22.7–29.1%). Our data are different from the British data. Data from a referral center for sexual abuse cases in the UK showed that 50% (95% CI = 46.9–53.6%) of the cases were aged between 18 and 25 years old.[13] Our results also differ from those reported in DATASUS for 2017, either for Brazil (36.5%) or for the state of Rio Grande do Sul (32.5%). This discrepancy could be explained by the age distribution in the city of Porto Alegre, where 13% of the female population is between 15 and 29 years old.[14]

The main ethnic group in our cohort was white (77.4%; 95%CI = 74.1–80.3%). This finding follows the DATASUS (2017) data; the majority of victims of violence in the state of Rio Grande do Sul are white (78.4%; 16,962 out of 21,639).[15] This is explained by the epidemiological profile of women from our state; from a universe of 5.4 million women, 83.2% are white.[16]

From our data, it was possible to verify that only 31.1% (221 of 711; 95%CI = 27.7%–34.6%) of the victims of violence were using some contraceptive method. This information is relevant and there are scant data to be compared. Most of the studies use the numbers of unwanted pregnancies as proxy.[17–19]

Most victims of violence were assaulted by unknown perpetrators (67.2%; 95%CI = 63.7–70.6%) in their residence (23.3%; 95%CI = 20.4%–26.6% [►**Table 2**]), which is in line with data presented by Delziovo et al[20] in a sample of a public service in southern Brazil, in the state of Santa Catarina. Most victims of violence sought care within 72 hours after the occurrence (80.7%; 95%CI = 77.7–83.5% (►**Table 3**). There was a low incidence of physical injuries in these victims (►**Table 3**). These findings are different from other authors,[21] but they are in agreement with those found in a Danish cohort, where they reported a 2% incidence of physical injury.[22] The low incidence of physical injuries does not allow us to find a plausible explanation. Some authors explain it by the degree of resistance by the victim,[23] while others explain this finding by the paralysis presented by the victim during the sexual assault.[24] Both explanations seem valid but we are not able to perform such analysis.

Analysis of the ROC curve showed that abused women < 19 years old had a 2.7 higher risk of not using any contraceptive method, compared with older women. This information is new and reveals the importance, for health professionals, to evaluate the contraceptive method used by the victim. Patel et al[25] published that only 40% of emergency departments offer counseling and provision of emergency contraceptives.

After dividing the sample by the age of 19 years old, some significant differences were found, such as the type of sexual contact with the victims (►**Tables 1** and **3**). The majority of women > 19 years old had a previous or current relationship, had > 10 years of education and were employed. In contrast, most women ≤ 19 years old were single, had < 9 years of education and were students (►**Table 1**). These findings are expected, since these social events, for example, to be married, are more frequent in older women. According to the literature, the younger the women who suffered sexual assault, the higher the incidence of psychologic and physical abnormalities in the future.[26]

The prevalence of known perpetrators was higher among women ≤ 19 years old, compared with those > 19 years old (►**Table 2**). This finding is in accordance with the data provided by Rapee, Abuse & Incest (RAINN), an American anti-sexual violence organization (rainn.org). According to RAINN, 80% of the rapes are committed by someone known to the victim.[27] Similar results were presented by Sodipo et al[28] in Nigeria. Other authors have reported that rapists can be friends, colleagues or family members[29,30] but they do not mention a difference in age. Possible explanations for this association can be related to cultural aspects of the community and the abusive behavior of the perpetrator, associated with the economic dependency of the victim.[29] Further research is necessary on this topic.

The present study has some limitations. The sample is limited to one region in southern Brazil. A significant proportion of information, such as the location of the occurrence, the form of aggression, if ejaculation occurred, the age of the rapist and the form of violence (►**Tables 2** and **3**) were lacking, jeopardizing further analysis. Some variables, for instance, the age and number of rapists, were impossible to obtain from the history of the patient; many women were drugged or intoxicated and they were not able to recall the events. Others were traumatized and did not want to tell the details. However, although these variables were missing, others, from the same patient, were present, such as relationship with perpetrators and marital status, which had 99% of completeness. Thus, caution is required for interpreting our results on these variables.

A positive aspect of the present study is its 17-year span. This cohort presents data from the region of Porto Alegre, the city with the highest number of notifications in Rio Grande do Sul, according to the DATASUS.[15] Efforts were made to minimize the inherent biases of this type of study, such as double-checking the data and active search with the patient in outpatient follow-up.

Conclusion

The victims of violence seen at the HCPA were mostly white, with a mean age of 24.4 years old. Those < 19 years old had a higher RR: 2.7 (95%CI = 1.96–3.6) of not using contraception, and the majority of the perpetrators are known by these young women. Health professionals must provide emergency contraception to these victims, mainly to those < 19 years old. Emergency contraception is more effective before 72 hours and most victims seek care within 72 hours of the occurrence. Finally, the relationship with the perpetrator should be investigated and proper measures must be taken when the victim knows the perpetrator.

Contributions

All authors contributed to the writing of the article, relevant revision of the intellectual content and approved the final version submitted for publication.

Conflicts to Interests

The authors have no conflict of interests to declare.

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Preoperative Differentiation of Benign and Malignant Non-epithelial Ovarian Tumors: Clinical Features and Tumor Markers

Diferenciação pré-operatória de tumores ovarianos não epiteliais benignos e malignos: características clínicas e marcadores tumorais

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Abstract

Objective To evaluate the role of clinical features and preoperative measurement of cancer antigen 125 (CA125), human epididymis protein (HE4), and carcinoembryonic antigen (CEA) serum levels in women with benign and malignant non-epithelial ovarian tumors.

Methods One hundred and nineteen consecutive women with germ cell, sex cord-stromal, and ovarian leiomyomas were included in this study. The preoperative levels of biomarkers were measured, and then surgery and histopathological analysis were performed. Information about the treatment and disease recurrence were obtained from the medical files of patients.

Results Our sample included 71 women with germ cell tumors (64 benign and 7 malignant), 46 with sex cord-stromal tumors (32 benign and 14 malignant), and 2 with ovarian leiomyomas. Among benign germ cell tumors, 63 were mature teratomas, and, among malignant, four were immature teratomas. The most common tumors in the sex cord-stromal group were fibromas (benign) and granulosa cell tumor (malignant). The biomarker serum levels were not different among benign and malignant non-epithelial ovarian tumors. Fertility-sparing surgeries were performed in 5 (71.4%) women with malignant germ cell tumor. Eleven (78.6%) patients with malignant sex cord-stromal tumors were treated with fertility-sparing surgeries. Five women (71.4%) with germ cell tumors and only 1 (7.1%) with sex cord-stromal tumor were treated with chemotherapy. One woman with germ cell tumor recurred and died of the disease and one woman with sex cord-stromal tumor recurred.

Conclusion Non-epithelial ovarian tumors were benign in the majority of cases, and the malignant cases were diagnosed at initial stages with good prognosis. The measurements of CA125, HE4, and CEA serum levels were not useful in the preoperative diagnosis of these tumors.

Keywords

- non-epithelial ovarian tumors
- ovarian cancer
- biomarkers
- germ cell tumors
- sex cord-stromal tumors

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Resumo

Objetivo Avaliar o papel das características clínicas e a medida pré-operatória dos níveis séricos de CA125, HE4, e CEA em mulheres com tumores de ovário não epiteliais benignos e malignos.

Métodos Cento e dezenove mulheres consecutivas com tumores ovarianos de células germinativas, do cordão sexual-estroma, e miomas ovarianos foram incluídas neste estudo. Os níveis pré-operatórios dos biomarcadores foram medidos, a cirurgia e a análise histopatológica foram realizadas. Informações sobre tratamento e recorrência da doença foram obtidas dos prontuários médicos das pacientes.

Resultados Nossa amostra incluiu 71 mulheres com tumores de células germinativas (64 benignos e 7 malignos), 46 com tumores do cordão sexual-estroma (32 benignos e 14 malignos), e 2 com leiomiomas ovarianos. Entre os tumores benignos de células germinativas, 63 eram teratomas maduros, e, entre os malignos, quatro eram teratomas imaturos. Os tumores mais comuns do grupo do cordão sexual-estroma foram fibromas (benignos) e tumores de células da granulosa (malignos). Os níveis séricos dos biomarcadores não diferiram entre os tumores de ovário não epiteliais benignos e malignos. A cirurgia preservadora de fertilidade foi realizada em 5 (71,4%) mulheres com tumores malignos de células germinativas. Onze (78,6%) mulheres com tumores do cordão sexual-estroma malignos foram tratadas com cirurgia preservadora de fertilidade. Cinco (71,4%) mulheres com células germinativas e apenas 1 (7,1%) com tumor do cordão sexual-estroma foram tratadas com quimioterapia. Uma mulher com tumor de células germinativas recidivou e morreu da doença. Uma mulher com tumor do cordão sexual-estroma recidivou.

Conclusão Os tumores de ovário não epiteliais foram benignos na maioria dos casos e os malignos foram diagnosticados em estágios iniciais, com bom prognóstico. A medida dos níveis séricos de CA125, HE4, e CEA não foram úteis no diagnóstico pré-operatório desses tumores.

Palavras-chave

- tumores ovarianos não epiteliais
- câncer de ovário
- biomarcadores
- tumores de células germinativas
- tumores do cordão sexual-estroma

Introduction

Adnexal masses are commonly found on gynecological imaging in women of all ages.[1] It is estimated that 5 to 10% of women will be submitted to surgery to investigate an adnexal mass in their lifetime.[2] Despite the majority of them being benign, malignant tumors must be promptly diagnosed and treated.[3] Non-epithelial ovarian cancers are rare, accounting for approximately only 5% of ovarian malignancies encompassing germ cell tumors (3%) and sex cord-stromal tumors (2%).[4]

According to the last classification of World Health Organization (WHO),[5] germ cell tumors of ovary comprise dysgerminoma, yolk sac tumor, embryonal carcinoma, non-gestational choriocarcinoma, mature teratoma, immature teratoma, mixed germ cell tumor, monodermal teratomas and tumors with malignant transformation arising from a dermoid cyst. Mature teratoma, is the most common benign ovarian neoplasia, most occur during reproductive years, with a peak incidence between 20 and 40 years of age.[6] Benign mature teratomas comprise 95% of all germ cell tumors, and only 5% of germ cell tumors are malignant.[6]

The WHO last classification for ovarian sex cord-stromal tumors shows that these tumors have been reclassified into the following clinicopathologic entities: pure stromal tumors, pure sex cord tumors, and mixed sex cord-stromal tumors. Ovarian fibroma, thecoma, Leydig cell tumor are pure stromal tumors. Adult granulosa cell tumor, Juvenile granulosa cell tumor and Sertoli cell tumor are pure sex cord tumors, while Sertoli-Leydig cell tumor is mixed sex cord-stromal tumor.[5,7]

In clinical practice, women undergo surgery to diagnose and treat an adnexal mass according to findings on clinical exam, transvaginal ultrasound and tumor biomarker. More specific biomarkers such as β-subunit of human chorionic gonadotropin (β-hCG), α fetoprotein, lactic dehydrogenase (LDH) may be useful for diagnosing malignant non-epithelial tumors.[8] On the other hand, there is scarce information in the current literature about the role of routinely measured biomarkers cancer antigen 125 (CA125) and carcinoembryonic antigen (CEA); and also more recently discovered biomarker Human Epididymis Protein 4 (HE4) in the preoperative diagnosis of non-epithelial ovarian tumors.

The objective of our study was to evaluate, the role of clinical features and preoperative determination of CA125, HE4 and CEA serum levels in the differentiation of benign from malignant non-epithelial ovarian tumors.

Methods

Patients

This is a cross-sectional study that was conducted at Hospital da Mulher Prof. Dr. José Aristodemo Pinotti at Universidade Estadual de Campinas (Unicamp), from February 2010 to December 2015. The study and was approved by the research ethics committee of the institution (Protocol 1092/2009). Women referred to the pelvic oncology clinic, due to adnexal masses detected in ultrasound or other imaging exam, were invited to

Table 1 Clinical features by tumor type

Characteristics	Germ cell tumors ($n = 71$)			Sex cord-stromal tumors ($n = 48$)			
	Benign n = 64 (%)	Malignant n = 7 (%)	P1	Benign n = 34 (%)	Malignant n = 14 (%)	P2	P3
Age (years)							
< 35	29 (45.3)	6 (85.7)		4 (11.8)	4 (28.6)		
35–50	17 (26.6)	0	0.110	6 (17.6)	5 (35.7)	0.125	0.0001
> 50	18 (28.1)	1 (14.3)		24 (70.6)	5 (35.7)		
Menopausal status							
Premenopausal	48 (75)	6 (85.7)	0.528	9 (26.5)	9 (64.3)	0.024	0.0001
Postmenopausal	16 (25)	1 (14.3)		25 (73.5)	5 (35.7)		
Body mass index (kg/m^2)							
< 30	44 (68.7)	4 (57.1)		23 (67.7)	8 (57.1)		
30–35	14 (21.9)	2 (28.6)	0.816	8 (23.5)	4 (28.6)	0.842	0.963
> 35	6 (9.4)	1 (14.3)		3 (8.8)	2 (14.3)		
Close relatives with cancer (breast/ovary)							
No	31 (48.4)	2 (28.6)	0.437	16 (47.1)	9 (64.3)	0.232	0.478
Yes	33 (51.6)	5 (71.4)		18 (52.9)	5 (35.7)		
Laterality							
Unilateral	53 (82.8)	6 (85.7)	0.845	29 (85.3)	14 (100)	0.117	0.301
Bilateral	11(17.2)	1 (14.3)		5 (14.7)	0		
Stage							
I		7 (100)			13 (92.9)		
II							
III					1 (7.1)		
IV							
Histological subtype							
Mature teratoma	63 (98.4)						
Struma ovarii	1 (1.6)						
Immature teratoma		4 (57.1)					
Carcinoid		1 (14.3)					
Dysgerminoma		1 (14.3)					
Yolk sac tumor		1 (14.3)					
Fibroma				26 (76.5)			
Thecoma				5 (14.7)			
Ovarian leiomyoma				2 (5.9)			
Sclerosing stromal tumor				1 (2.9)			
Granulosa cell					10 (71.4)		
Steroid cell tumor					1 (7.1)		
Sertoli-Leydig cell tumor					2 (14.3)		
Gynandroblastoma*					1 (7.1)		

Abbreviations: P1, including only germ cell tumors; P2, including only sex cord-stromal tumors; P3, including germ cell and sex cord-stromal tumors.
*currently known as sex cord-stromal tumor, not otherwise specified; which is a subtype of the mixed sex cord-stromal tumors group.

participate. Patients were consecutively included after signing a consent form and were submitted to the study protocol. On the first visit, patients were submitted to physical exam, and blood was collected to measure biomarker levels. In addition, transvaginal ultrasound was scheduled. When indicated, women underwent surgery for disease diagnosis and treatment. The indication of surgery was based on clinical exam, preoperative biomarkers, and ultrasound scan. The medical files of the patients obtained, which were from the hospital's digital filing system, were reviewed to obtain information about treatment, disease recurrence, and patient status. Women were considered postmenopausal when they had >1 year of amenorrhea or were >50 years old in case of previous hysterectomy. In premenopausal women, tumorectomy or unilateral adnexectomy with contralateral ovarian preservation without hysterectomy was considered fertility-sparing surgery.

Ultrasound (US)

The following ultrasound parameters were used to decide which women should undergo surgical treatment: largest diameter of the lesion; maximum diameter of the largest solid part; if unilocular or multilocular; presence of wall irregularity; ascites; acoustic shadows; number of papillary projections; color Doppler blood flow.[9] When surgery was not indicated, women were scheduled for clinical follow-up. From 869 women enrolled in the study, we excluded 361 who were not operated, 237 women with epithelial ovarian tumors, 128 with non-neoplastic and non-ovarian tumors, and 24 with ovarian metastases. One hundred and nineteen consecutive women with benign and malignant non-epithelial ovarian tumors were included in the study. Women had their surgery indicated according to their clinical exam, ultrasound results (simple rules by international ovarian tumor analysis [IOTA]),[9] and serum biomarkers. In the present study, 72 women had their ultrasound analyzed with IOTA simple rules. Among them, 9 had malignant tumors as per histology diagnosis, but the IOTA simple rules were malignant in 8 cases and benign in 1 case of granulosa cell tumor. Among the remaining 63 cases that had a benign tumor histology diagnosis, the IOTA simple rules were benign in 54 women, indeterminate in 1 case (ovarian fibroma), and malignant in 8 women (2 with fibroma, 1 with thecoma, 1 with ovarian leiomyoma, 1 with struma ovarii, and 3 with teratomas).

Histopathology

Histopathological diagnosis was the gold standard parameter, performed by pathologists specialized in gynecologic pathology, following the last "WHO classification of tumors of female reproductive organs."[5] Women with bilateral tumors with one of them presenting epithelial histology were excluded from the study. Our sample comprises 71 women with germ cell tumors (64 benign and 7 malignant), 46 with sex cord-stromal tumors (32 benign and 14 malignant), and 2 with ovarian leiomyomas.

CA125 and CEA

Serum levels of CA125 and CEA were determined by the CA125 II and CEA tests, respectively, both biomarkers through the chemiluminescence technic in the automatic analyzer Cobas e411 (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's instructions, with CA125 expressed in U/ml and CEA in ng/ml.

Human Epididymis Protein 4 (HE4)

The concentrations of HE4 were measured according to manufacturer's instructions using the ARCHITECT HE4 assay (Abbott Diagnostics, Abbott Park, IL, USA), with HE4 expressed in pmol/L.

Statistical Analysis

Data were analyzed using the R Environment for Statistical Computing software (R Foundation for Statistical Computing, Vienna, Austria).[10] According to the histopathological diagnoses, tumors were classified as benign or malignant germ cell or sex cord-stromal tumors. Two patients with ovarian leiomyoma had their tumors grouped with sex cord-stromal tumors for statistical purposes. Women's clinical features, serum biomarker levels and surgical treatment were compared using the Chi-square test for categorical variables and the Kruskal-Wallis test for the continuous variables. Statistical calculations were performed using 95% confidence intervals (95% CIs) considering $p < 0.05$ as significant. For missing data reason, we excluded 19 cases without CA125, 18 cases without HE4, and 4 without CEA for the biomarkers' analysis only. Follow-up time (in months) was considered from the date of diagnostic surgery to last hospital visit or date of death in the case of one patient.

Results

In ►**Table 1**, among 119 women, 98 (82.4%) presented benign tumors and 21 (17.6%) malignant. Seventy-two (60.5%) were premenopausal and 47 (39.5%) were postmenopausal. Germ cell tumors were significantly more frequent in premenopausal women, and those younger than 50 years old, compared with women with sex cord-stromal tumors. Neither body mass index nor history of close relatives with breast or ovarian cancer were related to tumor malignancy. Benign ovarian tumors were bilateral in 16 (16.3% of benign tumors) women. Almost all women with malignant germ cell and sex cord-stromal tumors presented at the initial stage of the disease: 20 (95.2%) with stage I, of note, 15 (71.4%) were stage Ia. Among benign germ cell tumors, 63 (98.4%) were mature teratomas, and, among malignant, only 4 (57.1%) were immature teratomas. Fibromas were the most common tumors among the patients in the benign sex cord-stromal group, and in the malignant counterpart, the most common was granulosa cell tumor.

In **table 2**, mean CA125 and HE4 were higher in malignant germ cell tumors, although without statistical significance. Among them, a postmenopausal patient with carcinoid tumor presented an HE4 value of 211.2 pmol/l. There was no difference in the expression of these markers in women with benign or malignant sex cord-stromal tumors, regarding mean serum levels. The analysis of biomarkers concentration by cutoff points showed that women with malignant

Table 2 Mean serum levels of CA125, HE4, and CEA and distribution by cutoff points according to histopathological diagnosis

Biomarkers	Germ cell tumor $n = 71$			Sex cord-stromal tumors $n = 48$		
	Benign n = 64	Malignant n = 7	*p*-value	Benign n = 34	Malignant n = 14	*p*-value
CA 125 (U/ml)	63.8	376	0.37	90.9	65.8	0.53
	(11–29.3)	(89.8–518)		(13–33.9)	(9.2–63.3)	
HE4 (pmol/L)	46.5	114.0	0.44	64.3	53.5	0.47
	(33.9–54.6)	(67.5–167.5)		(47.3–78.8)	(45.1–59.5)	
CEA (ng/ml)	4.4	3.9	0.46	2.6	1.8	0.49
	(1.2–2.9)	(1.6–5.8)		(1.2–3.0)	(1.1–2.6)	
Biomarkers						
CA 125						
< 35 (U/ml)	46	2	0.0002	22	7	0.1889
≥ 35 (U/ml)	7	5		6	5	
HE4						
Premenopausal						
< 70 (pmol/L)	39	2	0.00002	5	8	0.3747
≥ 70 (pmol/L)	1	4		2	1	
Postmenopausal						
< 140 (pmol/L)	13	0	0.0001	20	5	0.6187
≥ 140 (pmol/L)	0	1		1	0	
CEA						
< 5 (ng/ml)	47	4	0.028	28	14	0.1662
≥ 5 (ng/ml)	6	3		4	0	

Abbreviations: CA125, cancer antigen 125; CEA, carcinoembryonic antigen; HE4, human epididymis protein.
Missing data - CA125 for 19 women, HE4 for 18 women and CEA for 4 women.

Table 3 Women's treatment and follow-up

	Germ cell tumor			Sex cord-stromal tumor			
	Benign n = 64	**Malignant n = 7**	**P1**	**Benign n = 34**	**Malignant n = 14**	**P2**	**P3**
Surgical type							
Laparoscopy	28 (43.7)	2 (28.6)	0.595	10 (29.4)	3 (21.4)	0.4916	0.077
Laparotomy	36 (56.3)	5 (71.4)		24 (70.6)	11 (78.6)		
Surgical treatment							
Fertility sparing surgery	47 (73.4)	5 (71.4)	0.909	12 (35.3)	11 (78.6)	0.013	0.0034
HT + BSO/staging	17 (26.6)	2 (28.6)		22 (64.7)	3 (21.4)		
Chemotherapy							
Yes		5 (71.4)			1 (7.1)		
No		2 (28.6)			13 (92.9)		
Recurrence							
Yes		1 (14.3)			1 (7.1)		
No		6 (85.7)			13 (92.9)		

Abbreviations: HT + BSO, total hysterectomy and bilateral salpingo-oophorectomy; P1, including only germ cell tumors; P2, including only sex cord-stromal tumors; P3, including germ cell and sex cord-stromal tumors.

germ cell tumors presented significantly elevated CA125, HE4, and CEA levels.

In **table 3**, there was no statistical difference related to surgical type, performed in women with benign and malignant tumors. Fertility-sparing surgery was the treatment of choice in 47 (73.4%) patients in benign germ cell tumor group and in 5 (71.4%) in malignant group. As related to sex cord-stromal tumors, 12 (35.3%) of the patients in the benign group and 11 (78.6%) of those in the malignant group were treated with fertility-sparing surgery. According to data verified on March 22, 2019 in the digital files of patients, the mean follow-up time of those 21 patients with malignant tumors was 44.2 months. Besides, one patient with germ cell tumor recurred and died of the disease, and one patient with sex cord-stromal tumor recurred.

A 21-year-old patient with yolk sac tumor was submitted to unilateral salpingo-oophorectomy (tumor stage was Ic) and adjuvant chemotherapy. After 16 months, she presented serum α fetoprotein elevation and imaging exam showed bladder implant, perigastric, splenic and mesenteric lymph nodes disease. She was treated with chemotherapy, and since tumor presented partial response; she was submitted to laparotomy 29 months after the 1st treatment. Biopsies were negative but after 5 months, imaging exam revealed intestinal disease progression. Once more, chemotherapy was used; however, the patient succumbed to the disease after 51 months from the diagnostic surgery.

A 53-year-old patient with gynandroblastoma was initially treated with total hysterectomy with bilateral salpingo-oophorectomy (HT + BSO) and pelvic and paraortic lymphadenectomy. Tumor stage was Ia. She recurred 19 months after it, and she was submitted to a laparotomy to resect a pelvic tumor (this time an adult granulosa cell tumor) and remained without disease until April 2017 when she was discharged from the hospital. Gynandroblastoma is currently classified as a sex cord-stromal tumor, not otherwise specified; which is a subtype of mixed sex cord-stromal tumor group.

Discussion

In this single center study, we evaluated 119 benign and malignant non-epithelial ovarian tumors, as related to women's clinical features, preoperative CA125, HE4, and CEA serum levels, surgical and chemotherapy treatment, and disease recurrence. The majority of tumors were benign, mainly of germ cell origin (mature teratomas), and most of malignant tumors were diagnosed in the initial stage.

Among sex cord-stromal tumors, we detected a higher incidence of fibromas. Ovarian fibroma tumors account for ~ 4% of all ovarian tumors. Fibromas can occur at any age, affecting adolescents and young women, although the mean age of occurrence is in the late forties. Interestingly, ~ 10 to 15% of fibromas present with ascites, and less than 1% appear with both ascites and hydrothorax, known as Meigs syndrome, mimicking advanced ovarian cancer.[7,11] Fibromas usually present as solid adnexal mass on transvaginal ultrasound and, if CA125 is elevated, suspicion of malignancy increases. Shen et al showed that elevated serum CA125 level was found in 66 of 580 (11.3%) of patients with ovarian fibroma/fibrothecoma. Elevated serum CA125 level was significantly correlated with tumor diameter ≥ 10cm, ascites, and hydrothorax.[11]

Women with benign tumors presented similar mean serum levels of CA125, HE4, and CEA when compared with women with malignant tumors. However, when we analyzed biomarker concentration by cutoff points, women with malignant germ cell tumors were significantly associated to elevated CA125, HE4, and CEA levels. Due to the rarity of non-epithelial ovarian cancer, there are limited data regarding the role of CA125, HE4, and CEA in the preoperative diagnosis of these rare tumors. In a previous study from our group, we found that women with non-epithelial ovarian cancer did not express elevated CA125 and HE4 levels such as women with epithelial ovarian cancer.[12]

In our present study, fertility-sparing surgery was performed in 47 (73.4%) women with benign and in 5 (71.4%) women with malignant germ cell tumors. Preconized surgical treatment for young women is conservative (cystectomy or tumorectomy) with maintenance of ovarian parenchyma. Maintained cortical tissue contains follicles that are able to supply hormonal function and fertility.[13] In malignant germ cell tumors, conservative surgeries were performed, followed by adjuvant chemotherapy in 5 (71.4%) cases, with satisfactory response, except for the patient with yolk sac tumor. Fertility-sparing surgery was associated to chemotherapy in only one woman with malignant sex cord-stromal tumor, because of the poor response of this tumor to systemic therapeutics.[14] Recurrence was a relatively rare event for women with malignant non-epithelial ovarian tumors.

Surgeons should take into account the possibility of a synchronous or asynchronous bilateral benign ovarian tumor and focus on conservative surgery in young women. Although uncommon, even benign ovarian tumors can recur, for example, mature teratomas present ~ 3 to 4% postsurgical recurrence.[15] On the other hand, postmenopausal women are safely treated with HT + BSO.[16]

Conclusion

In conclusion, mature teratomas were the germ cell ovarian tumors more frequently found in our casuistic. Among sex cord-stromal tumors, fibromas were the most common in our sample. Malignant cases were diagnosed at initial stages with good prognosis. Serum determination of CA125, HE4, and CEA levels were not useful for the preoperative diagnosis of malignancy in women with non-epithelial ovarian tumors.

Contributors
All authors were involved in the design and interpretation of the analyses, contributed to the writing of the manuscript, read and approved the final manuscript.

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

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SARS-CoV-2 and Pregnancy: A Review of the Facts

SARS-CoV-2 e gestação: uma revisão dos fatos

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Abstract

Objective The present comprehensive review aims to show the full extent of what is known to date and provide a more thorough view on the effects of SARS-CoV2 in pregnancy.

Methods Between March 29 and May, 2020, the words *COVID-19*, *SARS-CoV2*, *COVID-19 and pregnancy*, *SARS-CoV2 and pregnancy*, and *SARS and pregnancy* were searched in the PubMed and Google Scholar databases; the guidelines from well-known societies and institutions (Royal College of Obstetricians and Gynaecologists [RCOG], American College of Obstetricians and Gynecologists [ACOG], International Society of Ultrasound in Obstetrics & Gynecology [ISUOG], Centers for Disease Control and Prevention [CDC], International Federation of Gynecology and Obstetrics [FIGO]) were also included.

Conclusion The COVID-19 outbreak resulted in a pandemic with $>$ 3.3 million cases and 230 thousand deaths until May 2nd. It is caused by the SARS-CoV2 virus and may lead to severe pulmonary infection and multi-organ failure. Past experiences show that unique characteristics in pregnancy make pregnant women more susceptible to complications from viral infections. Yet, this has not been reported with this new virus. There are risk factors that seem to increase morbidity in pregnancy, such as obesity (body mass index [BMI] $>$ 35), asthma and cardiovascular disease. Current reports describe an increased rate of preterm birth and C-section. Vertical transmission

Keywords
- SARS-CoV-2
- pregnancy
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is still a possibility, due to a few reported cases of neonatal positive real-time polymerase chain reaction (RT-PCR) in nasal swab, amniotic fluid, and positive immunoglobulin M (IgM) in neonatal blood. Treatments must be weighed in with caution due to the lack of quality trials that prove their effectiveness and safety during pregnancy. Medical staff must use personal protective equipment in handling SARS-CoV2 suspected or positive patients and be alert for respiratory decompensations.

Resumo

Objetivo A presente revisão detalhada busca fornecer dados objetivos para avaliar o que se sabe até o momento e possibilitar uma visão mais ampla dos efeitos do SARS-CoV2 na gravidez.

Métodos Entre 29 de março e 2 de maio de 2020, foi realizada uma busca nos bancos de dados PubMed e Google Scholar com as palavras *COVID-19*, *SARS-CoV2*, *COVID-19 e gravidez*, *SARS-CoV2 e gravidez*, e *SARS e gravidez*. As recomendações dos principais órgãos sobre o tema também foram acessadas.

Conclusão O surto de COVID-19 resultou em uma pandemia com $>$ 3.3 milhões de casos e 230 mil mortes até 2 de maio. É uma condição causada pelo vírus SARS-CoV2 e pode levar ao acometimento pulmonar difuso e à falência de múltiplos órgãos. Características únicas da gestante tornam essa população mais propensas a complicações de infecções virais. Até o momento, essa tendência não foi observada para esse novo vírus. Os fatores que parecem estar associados à maior morbidade materno-fetal são obesidade (índice de massa corporal [IMC] $>$ 35), asma e doença cardiovascular. Há descrição de aumento de parto prematuro e parto cesáreo. Não se pode descartar a possibilidade de transmissão vertical da doença, devido a relatos de positividade de reação em cadeia de polimerase (RT-PCR) de swab nasal, RT-PCR de líquido amniótico e imunoglobulina M (IgM) de recém-nascidos. Tratamentos devem ser analisados caso a caso, dada a falta de qualidade de estudos que comprovem a sua eficácia e segurança na gravidez. O corpo clínico deve utilizar equipamentos de proteção individual (EPI) ao manusear pacientes suspeitos ou confirmados e ficar atento aos sinais de descompensação respiratória.

Palavras-chave
- SARS-CoV-2
- gravidez
- recomendações
- fisiologia
- tratamento

Introduction

In December 2019, SARS-CoV-2 was first identified in Wuhan, China; it was the beginning of an outbreak.[1] The virus belonged to the well-known family *Coronaviridae* and mostly caused the common cold. However, this strain proved to be much more infectious than other viruses from this family such as MERS-CoV (Middle East Respiratory Syndrome) and SARS-CoV (Severe Acute Respiratory Syndrome).[1] The high rate of infectivity associated with the morbidity and mortality[2] created a world health crisis and on March 11, 2020, the World Health Organization declared a pandemic of this new disease, now named COVID-19.[3] In May 2, 2020, there were $>$ 3.3 million confirmed cases and $>$ 230,000 deaths caused by this outbreak.[4] Pregnancy results in unique physiological changes specifically to the immune and respiratory systems that make pregnant women more susceptible to viral infections.[5] The knowledge about the impact of SARS-CoV-2 infection in this vulnerable patient population is still limited. To address this gap, we will review the evidence available on viral characteristics, its association with pregnancy, and current management guidelines. We hope to provide resources and practical recommendations to aid in perinatal care practices.

Methods

A search in the PubMed and Google Scholar databases was conducted daily between March 29 and May 2, 2020, with the words: *COVID-19*, *COVID-19 and pregnancy*, *SARS-CoV2 and pregnancy*, and *SARS and pregnancy*; the guidelines focusing on pregnancy from major societies and institutions (Royal College of Obstetricians and Gynaecologists [RCOG], American College of Obstetricians and Gynecologists [ACOG], International Society of Ultrasound in Obstetrics & Gynecology [ISUOG], Centers for Disease Control and Prevention [CDC], International Federation of Gynecology and Obstetrics [FIGO]) were also reviewed. The references for the main articles were thoroughly reviewed to provide a broader comprehension of the specifics of pregnancy physiology, the pathophysiology of the virus, the main treatments, and their possible effects on pregnancy.

Pathophysiology

Coronaviruses (CoVs) are a group of enveloped, single stranded, positive sense RNA viruses that use surface spike (S) glycoprotein on the envelope to attach host cells and mediate membrane fusion during infection. The S protein includes two regions: S1 (host cell receptor binding) and S2 (membrane fusion). For SARS-CoV, the receptor binding domain (RBD) is located in the C-Terminal Domain-1 (CTD1) of the S1 region. It has been suggested that SARS-CoV-2 infect human cells through the binding of the RBD domain to the human Angiotensin II (ACE-2) receptor; the molecular mechanism of the binding between the RBD protein and the ACE2 receptor is still unknown.[6] Two different types of SARS-CoV-2 were identified, type L (60%) and type S (30%) and we still do not know the clinical implications of this finding.[7] The transmission of SARS-CoV-2 occurs through respiratory droplets, direct contact, or fomites. Once in contact with the nasopharyngeal mucosa and pulmonary tissue, the virus enters the host-cell attaching to ACE-2 receptors and starts its replication, similar to SARS-CoV. In response, the body presents the viral antigens by antigen presenting cells (APCs) to the defense system, resulting in the production of proinflammatory cytokines and chemokines that increase the vascular permeability and lead to alveolar edema. In more severe cases, there is an overproduction of these cytokines, resulting in a cytokine storm that triggers the immune system to attack the body causing acute respiratory distress syndrome (ARDS) and multiple organ failure.[8] The CoVs have a high affinity for respiratory, enteric, hepatic, neurologic and myocardial tissues and lead to a variety of symptoms depending on the affected organ.[9] The severity of the disease can range from a common cold to severe respiratory failure, which could lead to end-organ failure and death. In the previous experiences with SARS-CoV and MERS-CoV, pregnant women had more chances of developing serious disease when compared with the general population; higher rates of adverse pregnancy outcomes (pre-eclampsia, preterm birth and fetal distress) were also identified.[10] The current evidence available on SARS-CoV-2 suggests that it does not follow this pattern, and pregnancy has not shown to increase the severity of cases.[11]

Clinical Presentation, Diagnosis, and Epidemiology

Commonly reported symptoms of COVID-19 are cough, fever, myalgia, and less frequently dyspnea, diarrhea, vomit, hemoptysis, anosmia and dysgeusia.[12,13] A systematic review by Zaigham et al[14] included 108 cases of COVID-19 in pregnancy. The main presenting symptoms were fever (68%), cough (34%), malaise (13%), dyspnea (12%) and diarrhea (6%). This presentation seems to be no different than in nonpregnant patients.[14]

A suspect case is defined as the combination of symptoms and possible exposure. Currently, the gold standard test is a real-time polymerase chain reaction (RT-PCR) on respiratory samples (throat swab/ nasopharyngeal swab/ sputum), with test sensitivity estimated between 56–83%.[15] Elderly patients or those with comorbidities including diabetes, hypertension, obesity, or cardiovascular disease are at higher risk for morbidity and mortality. In a retrospective cohort, Garg et al[16] analyzed 14 US states in March 2020 and found a total of 48 hospitalized patients aged between 18 and 49 years old due to COVID-19. In this younger population, the most common comorbidities were obesity (59%), chronic pulmonary disease (36.4%), chronic metabolic disease (21.7%), and hypertension (17.5%). There were also 3 (9.9%) pregnant patients.[16]

Physiological Predisposition to Infection in Pregnancy

Unique physiological changes occur in the maternal body to allow for a healthy pregnancy. Immunologically, there are three stages in pregnancy: in the 1st trimester, there is a complex proinflammatory chain that ensures the adequate trophoblastic invasion with no recognition of the paternal antigen; in the 2nd stage (13 to 27 weeks), an anti-inflammatory response is necessary for adequate fetal growth and to prevent spontaneous initiation of labor; then, in the 3rd trimester, the stimulus shifts back to a proinflammatory state for delivery. Each of these stages is a fine equilibrium that can be broken by viral infections, leading to maternal and fetal complications.[17] In theory, during the proinflammatory stages, pregnant patients would be more prone to develop cytokine storm, which is an indicator of severity in SARS-CoV-2 infection.[5] The pulmonary physiology during pregnancy suffers hormonal and functional changes that make pregnant women less tolerant to hypoxia. From the beginning of pregnancy, the levels of progesterone act on the brainstem increasing the respiratory rate and the tidal volume, the chest wall compliance decreases and so does airway resistance.[18] In the last trimester, the uterus restricts the diaphragm, which lowers the total lung capacity.[19] These respiratory adaptations associated with the immunological changes place pregnant patients at risk of developing more severe respiratory infections, as previously seen in influenza infections.[20] The hypoxemia that arises from a pulmonary infection can lead to vasoconstriction and intrauterine growth restriction (IUGR).[21]

Experience with Previous Coronaviruses during Pregnancy

There were two previous outbreaks of viruses from the *Coronaviridae* family: MERS and SARS. With little information available on SARS-CoV-2, specialists initially turned to these earlier experiences as a source of comparable data. The MERS outbreak in April 2012 lead to 2,494 confirmed cases and was responsible for 858 deaths.[22] The mortality rate was 20% amongst the population < 60 years old. Even though it belongs to the same family as SARS-CoV-2, this virus binds to a different receptor Dipeptidyl peptidase-4 (DPP4) in the alveolar cells and shares only 50% of the SARS CoV-2 genome.[23] In a retrospective study conducted in Saudi Arabia with 660 patients, there were only 11 cases of infection during pregnancy.[24] Seven (64%) of these were admitted in the ICU, there were 3 (27%) maternal deaths and 3 (27%) stillbirths; there was no evidence of vertical transmission.[24] The SARS outbreak in 2003 infected $>$ 8,000 people and lead to 919 deaths.[25] This virus is more similar to SARS-CoV-2, sharing 80% of its genome and the same ACE-2 receptor for cell entry, although it binds with 20 times less affinity. To date, the pathophysiology is

described as very similar to SARS-CoV-2, but the mortality rate was higher (11%). The pregnant population was particularly susceptible to severe forms of the disease.[26] Wong et al[27] reported on 12 cases of pregnant women in several hospitals in southern China with SARS. Seven were infected in the 1st trimester, of which 4 had miscarriages (57%). The other 5 were infected between weeks 26 to 32; 4 had preterm births (80%) and two had fetal growth restriction (40%), there was no evidence of vertical transmission.[27]

SARS-CoV-2 Impacts on Pregnancy: Reported Cases

Based on the experience of past Coronavirus outbreaks, the unique immune response and higher morbidity associated with pulmonary infections, Liu et al[5] suggest that pregnant women might be prone to more severe forms of COVID-19. However, the available data does not support this prediction so far. The first to report COVID-19 in pregnancy, Chen et al,[28] suggested there was no increased risk of vertical transmission. But the small number of patients did not allow a definite conclusion. Breslin et al[29] did a retrospective cohort with 43 SARS-CoV-2 positive pregnant women in 3 institutions in New York; 29 (67.3%) patients presented with symptoms and the remaining 14 were asymptomatic and routinely screened before delivery.[29] Overall, 37 (86%) presented with none or mild symptoms, 4 (9.3%) had moderate symptoms and 2 (4.7%) had severe symptoms, classified with the criteria proposed by Wu et al[30]: mild disease was defined as no or mild pneumonia; severe was defined as respiratory rate > 30, SatO2 $\leq 93\%$, pO2/FiO2 < 300 and infiltrates $> 50\%$ of the lung; and critical disease as respiratory failure, septic shock and end-organ failure.[30]) There was resolution of pregnancy in 18 patients, of which 10 (56%) were normal deliveries; 2 patients had worsening symptoms right after delivery, and 1, 6 days after delivery. There was only 1 preterm with 34 weeks 6/7. Nasal swab polymerase chain reaction (PCR) test for SARS-CoV-2 was negative in all tested newborns. No serology was made. Even though this study showed no evidence of increased maternal or fetal risk, they proposed screening for all pregnant women due to the high rate of initially asymptomatic cases (22.7%) It is important to point out that all the cases that presented with severe symptoms happened in women with body mass index (BMI) > 35. A systematic review by Zaigham et al[14] included 108 cases of COVID-19 in pregnancy. A total of 86 deliveries were reported, 79 (92%) cesarean and 7 (8%) vaginal deliveries. The main indication for cesarean was fetal distress, although the criteria used for this diagnosis is not clear in most studies. Lymphocytopenia was reported in 59% of the cases. The main comorbidity associated with higher morbidity was obesity. A total of two neonatal deaths were reported, both had additional risks of prematurity and cesarean. Common findings in the neonates included thrombocytopenia and lymphopenia. In this review, there were no cases with evidence of vertical transmission, although the paper points out to two case reports that described positive neonatal immunoglobulin M (IgM) and immunoglobulin G (IgG). In both cases, the nasal swab RT-PCR was negative. However, the reliability of antibody testing has been questioned since its sensitivity and specificity vary by disease, and the possibility of false-positives and cross-reactivity exists.[31] Another report described a 28-year-old obese woman with miscarriage at 19 weeks of gestation and positive PCR for SARS-CoV-2 in the placenta. No other cause for the fetal death was found, but other explanations such as spontaneous preterm birth or cervical insufficiency cannot be excluded. Even with positive PCR, fetal autopsy did not show any malformation.[32] Elshafeey et al[33] conducted a systematic review that included 385 cases of COVID-19 in pregnancy; of these, 109 (28.3%) were infected in early pregnancy. The main presenting symptoms were fever (67.3%) and cough (65.7%), and 7.5% were asymptomatic. In this review, 252 births were reported, 175 cesareans (69.4%) and 77 vaginal (30.6%). A total of 368 (95.6%) cases were classified as mild, 14 (3.6%) as severe and 3 (0.8%) were critical; 17 (4.4%) required ICU and all but 1 recovered. There were 256 newborns, 39 (15.2%) were preterm, 20 (7.8%) had low birthweight and 20 (7.8%) suffered fetal distress; 3 (1.2%) cases of neonatal death were reported.[33] It is important to mention that, on average, preterm birth rates vary from 9.3 (high income countries) to 11.8% (low income countries).[34] Regarding vertical transmission, according to Elshafeey et al,[33] 4 (1.6%) had positive RT-PCR on nasopharyngeal swab, 3 (1.2%) had positive IgM, and 6 (2.3%) had positive IgG. Polymerase chain reaction for SARS-CoV2 in cord blood (30 patients), amniotic fluid (23 patients) and placenta (12 patients) were all negative. This review contains the largest number of patients so far; however, they fail to correlate the data to its original study, generating some confusion. The higher number of vaginal deliveries is expected as more cases are reported outside of China since no official guideline recommends cesarean due to SARS-CoV-2 infection. Currently, one case of maternal death due to respiratory failure from SARS-CoV-2 infection has been reported, 11 days after delivery. The same patient had positive RT-PCR for SARS-CoV-2 in the amniotic fluid and the newborn, who initially tested negative, had a positive result on the second test, 24 hours later.[35] There have been few reports on maternal complications. A case report by Gidlöf et al[36] described a pregnant woman, with BMI > 35 and pre-eclampsia bearing twins, that evolved to eclampsia after being infected by SARS-CoV-2. Additionally, Koumoutsea et al[37] brought attention to 2 cases with a possible link between 3rd-trimester SARS-CoV-2 infection and progressive coagulopathy.

Current Instructions on Obstetric Management: What do the Guidelines Say?

Multiple guidelines directed to health professionals in obstetric care have been published by different professional societies and international institutions. There is consensus regarding most recommendations, such as adopting telehealth when possible, use of corticosteroids if indicated even with confirmed infection, keeping route of delivery according to obstetric indications and maintenance of breastfeeding. The RCOG[38] guideline, updated on April 17, alerts for differential diagnosis that might mimic COVID-19, such as other infections and pulmonary embolism. The remaining recommendations include cardiotocography (due to the

reported risk of fetal distress), isolation of all confirmed cases, use of surgical mask by SARS-CoV-2 positive patients, use of personal protective equipment by all staff and administration of low molecular weight heparin postpartum, given the low risk of hemorrhage. The use of pools during labor is contraindicated due to the risk of fecal transmission. The guideline highlights the possibility of rapid escalation of disease severity at postpartum, thus signs of deterioration such as respiratory rate > 30, saturation $< 94\%$, FiO2 $> 40\%$ and decreased urine output must be assessed and dealt with swiftly. There is no contraindication to vaginal birth.[38] The ACOG[39] recommends screening in all suspicious cases. In case of infection in late pregnancy, postpone delivery until negative results should be attempted if no other medical indications arise. The same society recommends expedited discharge if possible (1 day for vaginal delivery and 2 days for cesarean).[39] The FIGO guidance takes into consideration the severity of the disease, dictated by symptoms and comorbidities; in suspected or confirmed cases, they recommend postpartum separation if the mother appears acutely ill and use of a dedicated breast pump instead of direct breastfeeding to avoid contact.[40] The ISUOG does not advise against the induction of labor in case of a favorable cervix, although it alerts to the lower threshold regarding fetal distress, and points out the use of negative-pressure in delivery and neonatal rooms. There is indication of chest computed tomography (CT) as a part of the workup in pregnant women. A chest CT scan may be considered as a tool for the detection of COVID-19, taking into account that it exposes the patient to a low-dose of radiation; fetal growth restriction and microcephaly have been described in high-dose exposures. The ISUOG guidance recommends that informed consent should be acquired, and a radiation shield needs to be applied over the uterus. The same institution suggests that pregnant women with suspected SARS-CoV-2 infection or with mild symptoms should be monitored with 2 to 4 weekly ultrasounds for fetal growth, amniotic fluid volume and umbilical artery Doppler if necessary.[41] The CDC recommendations regarding hospital care, last updated on April 6, determine that the number of visitors should be minimal and all should wear face masks; symptomatic women should be tested preferentially, skin to skin contact and breast-feeding in SARS-CoV-2 patients should be allowed with the use of face shield and the neonates of positive patients should be considered positive for precaution sake.[42]

Impacts of Possible Treatments in Pregnancy

The evidence on possible treatments for SARS-CoV-2 infection is still scarce. Consequently, the use of drugs needs to be taken with caution, especially in pregnancy. There have been some considerations by LaCourse et al[43] supporting the inclusion of pregnant and breastfeeding women in trials to draw more conclusions regarding this population. So far, the main pharmacotherapies described are hydroxychloroquine (HCQ), antivirals and anti-interleukines. When caring for pregnant patients, it is important to keep in mind that changes in the physiology decrease drug concentration; therefore, the dose of the medication should be adjusted accordingly.[44] Hydroxychloroquine is known to have antiviral effects; however, mechanisms found in vitro for viruses such as Chikungunya, Zika and Dengue have not been observed in vivo.[45] There has been evidence of HCQ antiviral effects against SARS-CoV-2 in vitro but there is paucity of high-quality data of these effects in vivo.[46] Although a recent clinical trial demonstrated a small benefit with the use of HCQ, issues with study design and execution bring the validity of these results into question: the unblinded and nonrandomized nature of the trial; the small number of patients included in the study ($n = 36$); significant loss to follow-up in the intervention group ($n = 6$); and use of a lower threshold of viral load to diagnose the disease.[47] When used in pregnant patients, there is evidence that HCQ crosses the placenta; the drug and its metabolites have been found in cord blood and neonatal urine.[48] Nevertheless, the risk posed by the drug is outweighed by the risk posed by Malaria (stillbirth, low weight at birth, premature birth) and Systematic lupus erythematosus (SLE) (pre-eclampsia, HELLP syndrome, premature birth), being classified as safe in pregnancy by the CDC.[49] To date, there is no significant evidence of the effects of SARS-CoV2 in pregnancy or of the efficacy of HCQ in the treatment of COVID-19 to justify the use of HCQ in infected pregnant women. Remdesivir inhibits RNA synthesis; it was developed for the Ebola outbreak and has been tested for other RNA viruses, such as SARS-CoV-2. Grein et al[50] conducted a multicenter study for its compassionate use in 53 severe COVID-19 hospitalized patients. Clinical improvement was observed in 36 patients (68%) and mortality was 13%. In China, the mortality rate in patients with similar conditions ranged from 22 to 66%, making these results look promising.[50] A more recent randomized, double blinded, placebo controlled study with 237 enrolled patients did not show significant reduction in overall mortality or clinical improvement.[51] During the Ebola outbreak, 6 cases of Remdesivir use in pregnant women were described and no adverse effects were reported. This course of action was only chosen due to the high mortality rate associated with Ebola, which drove the benefits of using the drug to outweigh the possible risks to pregnancy.[52] However, the number of cases is too small to draw any reliable conclusion regarding its effect on pregnancy. Tocilizumab is an anti-IL-6 monoclonal antibody. Xu et al[53] reported its use in 21 severe or critical patients and 19 (90.5%) had improvement of the overall clinical condition and were discharged. Once again, more data in less biased double-blinded randomized trials is necessary to draw any conclusion. The review by Hoeltzenbein et al[54] on 299 cases with use of Tocilizumab did not show increased risk of congenital abnormalities; there was an increased risk for stillbirth and preterm birth. There are reports of the drug crossing the placenta and of its presence in breast milk.[55]

Impacts in Mental Health

The Covid-19 outbreak is associated with adverse mental health consequences. Anxiety, depression and self-reported stress are common psychological reactions symptoms to the COVID-19 pandemic.[56] It is important that future research includes the impact on women's mental health during pregnancy and postpartum.[57]

Conclusion

The unique physiological immune state and the low tolerance to hypoxemia make pregnant women prone to more severe forms of pulmonary infections. The group was a high-risk cohort in previous Coronavirus outbreaks, such as SARS and MERS. However, this has not been observed in the COVID-19 outbreak, with symptoms and severity being described as similar to those of the general population. Whether this is because of the small number of cases that have been reported or if it reflects a unique pathophysiology of SARS-CoV2 remains uncertain. Considering the available data, pregnant women with BMI $>$ 35, pre-eclampsia, asthma, chronic metabolic and cardiovascular disease should be managed with greater caution. In addition, patients with confirmed SARS-CoV-2 must receive special attention after delivery because of the risk of sudden worsening of pulmonary function. There is recent evidence on the possibility of vertical transmission, although there is no indication of teratogenic effects of SARS-CoV-2. The current treatment options for COVID-19 still need more research to prove efficacy and benefit; their use in pregnancy should be weighed in with caution.

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

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Practical Recommendations for the Management of Benign Adnexal Masses

Recomendações práticas para o tratamento de massas anexiais benignas

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Abstract

Objective To perform a comprehensive review to provide practical recommendations regarding the diagnosis and treatment of benign adnexal masses, as well as information for appropriate consent, regarding possible loss of the ovarian reserve.

Methods A comprehensive review of the literature was performed to identify the most relevant data about this subject.

Results In total, 48 studies addressed the necessary aspects of the review, and we described their epidemiology, diagnoses, treatment options with detailed techniques, and perspectives regarding future fertility.

Conclusions Adnexal masses are extremely common. The application of diagnosis algorithms is mandatory to exclude malignancy. A great number of cases can be managed with surveillance. Surgery, when necessary, should be performed with adequate techniques. However, even in the hands of experienced surgeons, there is a significant decrease in ovarian reserves, especially in cases of endometriomas. There is an evident necessity of studies that focus on the long-term impact on fertility.

Keywords

- adnexal masses
- ovarian cysts
- ovarian surgery
- ovarian reserve
- infertility
- fertility preservation

Resumo

Objetivo Realizar uma revisão abrangente para fornecer recomendações práticas sobre o diagnóstico e tratamento de massas anexiais benignas, bem como informações para um consentimento adequado com relação à possível perda da reserva ovariana.

Métodos Uma revisão abrangente da literatura foi realizada para identificar os dados mais relevantes sobre o assunto.

Resultados No total, 48 estudos abordaram os aspectos necessários da revisão, e descrevemos sua epidemiologia, diagnósticos, opções de tratamento com técnicas detalhadas, e perspectivas sobre fertilidade futura.

Conclusões As massas anexiais são extremamente comuns. A aplicação de algoritmos de diagnóstico é obrigatória para excluir a malignidade. A maioria dos casos pode ser manejada conservadoramente. A cirurgia, quando necessária, deve ser realizada com técnicas adequadas. No entanto, mesmo nas mãos de cirurgiões experientes, há diminuição significativa da reserva ovariana, principalmente nos casos de endometriomas. Há uma evidente necessidade de estudos que enfoquem o impacto das massas anexiais benignas na fertilidade em longo prazo.

Palavras-chave

- massas anexiais
- cistos ovarianos
- cirurgia ovariana
- reserva ovariana
- infertilidade
- preservação da fertilidade

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Introduction

Benign adnexal masses are extremely common during a woman's life. Up to 10% of them will undergo surgery due to some adnexal mass throughout their lifetime.[1] Because it is a benign disease, the surgical treatment may seem deceptively simple. How can we properly inform patients who are concerned about fertility?

Despite the high prevalence of this condition and the number of surgical procedures, a significant part of the patients does not seem to receive enough information for appropriate consent regarding possible loss of the ovarian reserve.[2] There is evidence of negative impact on ovarian reserve due exclusively to the presence of cysts[3,4] and perhaps more markedly in endometriotic cysts.[5] In addition, a considerable proportion of these patients will undergo surgery that could potentially compromise even more the ovarian function.[6]

It is extremely important that the attending physician has a critical view of the difficulties in assessing adnexal masses, the consequences of the clinical and surgical treatments, and the current possibilities of gauging the ovarian reserve, since the treatments and the different techniques may interfere on fertility in the long term.

The objective of the present review is to provide the gynecological surgeon with fundamental elements for a better understanding of the decision-making process in the treatment of adnexal pathologies and the best possible counseling for women about the risks and benefits of these treatments in their reproductive future. The establishment of appropriate surgical routines that consider the preservation of fertility is of major importance.

Methods

The data were obtained through a bibliographic research in the Medline, LILACS and Scielo databases. We performed the search using the terms "*ovarian cyst*," "*adnexal mass*," "*ovarian reserve*," "*ovarian surgery*," "*infertility*" and "*fertility preservation*." All identified articles were published in English in the past 15 years (between January 2004 and April 2019). The articles that had as their central topic benign ovarian pathologies and their relationship with alterations in the ovarian reserve and preservation of fertility were included.

Results

A total of 48 articles published between 2004 and 2019 fulfilled the inclusion criteria. The information was analyzed for the consistency of the data, the year of publication, and the quality of the study. Articles that did not address directly the review objectives were excluded.

Discussion

Epidemiology

The ovarian cyst is defined as a structure that contains fluid and has more than 30 mm in diameter.[1] A significant part of the ovarian cysts is asymptomatic, which can lead one to underestimate the real incidence. It is estimated that, in the United States, 250 thousand women per year are hospitalized due to adnexal masses.[7]

According to a population-based cohort with 11,595 patients from 1991 to 2014,[8] the incidence of ovarian cysts increases exponentially with age. There is an incidence plateau around the age of 26, reaching 152 cases per 100 thousand women per year at 35 years old, which is maintained throughout the menacme.[8]

Just over a third of the benign masses were epithelial lesions (35.1%). Almost a third were tumor like lesions (32.8%), being functional cysts and endometriotic cysts. 29.8% were germ-cell tumors (almost entirely mature teratomas), and a small fraction of 2.3% were stromal tumors (mostly fibromas/tecomas). The exact proportions are shown in ►**Fig. 1**.

At menacme, most of the masses are benign, and the chance of developing malignancy of the symptomatic cysts is around 1: 1 thousand.[1] The incidence of borderline malignancies and tumors follows the same behavior with regard to the incidence plateau; however, it is of around 8 cases per 100 thousand women per year. Therefore, the proportion of malignancies among all ovarian neoplasms is of $\sim$ 3%.[8] In the pediatric range, the common symptoms are acute and chronic abdominal pain, presence of abdominal mass, and abdominal distension. Germ-cell tumors are more common, with teratomas being the main representatives. Physiological cysts in premenarchal girls are rare, and it is estimated that the prevalence of malignancy does not exceed 15%.[9]

Diagnostics

We can conclude from the previous section that, in fact, the chance of facing malignant adnexal pathologies is relatively low. Despite this, the identification of malignant neoplasms is mandatory. The difficulty in establishing a reasonable means of screening for ovarian malignancies is widely known. Most ovarian cancers are not diagnosed in the early stages (15% in stage I), even in the menopausal period, when the incidence of this type of malignancy increases.[10]

Many models have been proposed to screen patients for appropriate treatment, but none of them was able to be unanimously accepted. The details of the various models are beyond the scope of the present review, but they may include: the Risk of Malignancy Index (RMI); the National Institute for Health and Care Excellence (NICE) Guidelines; the Risk of Ovarian Malignancy Algorithm; Logistic Regression (LR); and methods based on ultrasound criteria proposed by the International Ovarian Tumor Analysis (IOTA): "Simple Rules" (SRs); Simple Rules Risk (SRR); and Assessment of Different Neoplasms in the Adnexa (ADNEX).[11]

Despite some modifications over the years after the creation of the RMI, it remains as the alternative with the best validation.[1] It consists of the product between the level of carcinoembryonic antigen 125 (CA-125), hormonal status (M) and ultrasound scoring (U): RMI = CA-125 x M x U (►**Table 1**).

In order to create an adequate screening workup, the use of a specific set of ultrasound characteristics to predict malignancy of the adnexal masses named the "Simple Rules"

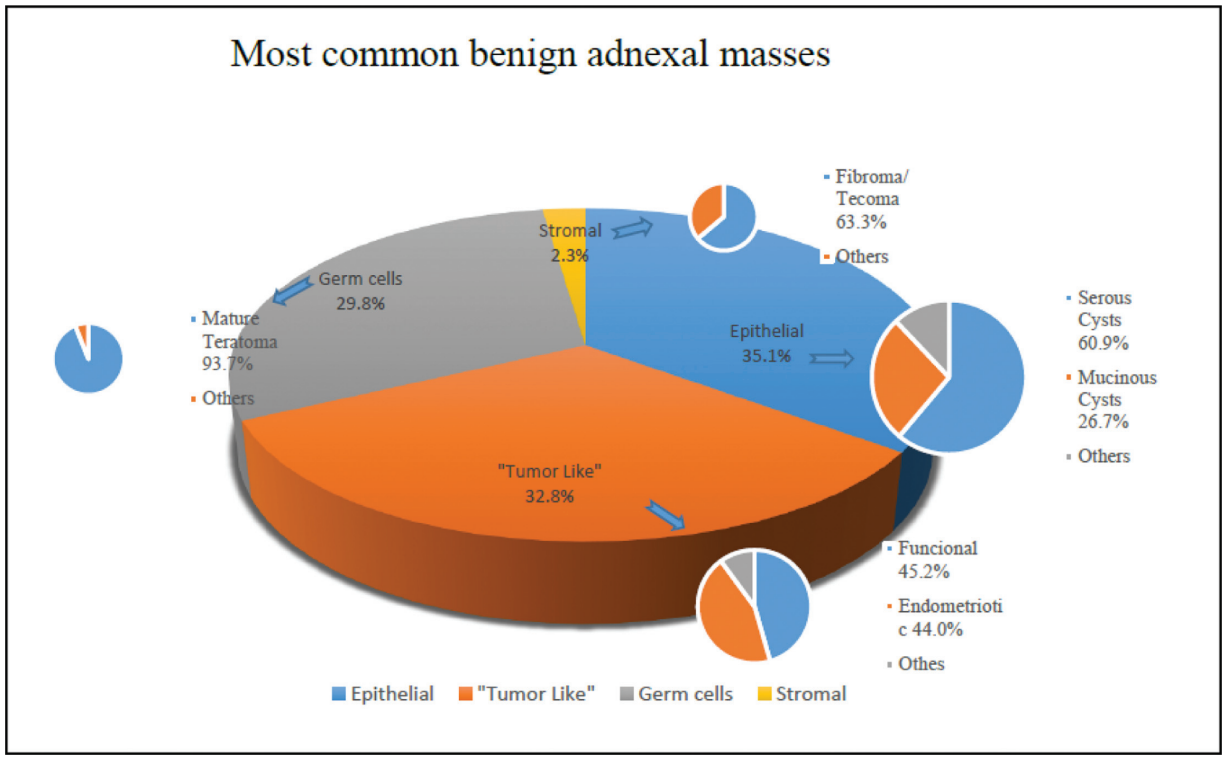

Fig. 1 Most common benign adnexal masses.

Table 1 Risk of Malignancy Index (RMI)

RMI CRITERIA	SCORE
MENOPAUSAL STATUS (M)*	
Premenopausal	1
Postmenopausal	3
ULTRASOUND IMAGING (U)	
Multiloculated	1 (if 1 feature)
Solid areas	3 (if 2 or more features)
Bilaterality	
Ascites	
SERUM CA-125	Absolute value in IU/mL

Box 1 International Ovarian Tumor Analysis (IOTA) "Simple Rules"

IOTA "SIMPLE RULES"	
Benign (B)	Malign (M)
1- Unilocular cyst	1- Irregular solid tumor
2- Solid component, but < 7 mm	2- Ascites
3- Acoustic shadows	3- At least 4 papillary structures
4- Smooth multilocular tumor < 100 mm	4- Irregular multilocular tumor > 100 mm
5- No blood flow	5- Very strong flow

(SRs) was recently proposed.[12] The concept is based on the identification of basic benign and malignant echography features (**Box 1**).

Eight years later, in 2016, a large multicenter cross-sectional study[13] involving 22 research centers with 4,848 patients aimed to evaluate the efficacy of the SRs in the prediction of malignancy of adnexal masses. For the 1% risk cutoff, the sensitivity was of 99.7%, the specificity was of 33.7%, the LR was + 1.5 and -0.010, the positive predictive value (PPV) was of 44.8%, and the negative predictive value (NPV) was of 98.9%. For the 30% risk cutoff, the sensitivity was of 89.0%, the specificity was of 84.7%, the LR was + 5.8 and -0.13, the PPV was of 75.4%, and the NPV was of 93.9%.[13]

The use of SRs was subsequently validated considering their performance in the diagnosis of early ovarian malignancies, even when compared with the other models proposed by the IOTA. At this point, we highlight the high NPV (98.9%) of the SRs in scenarios of low risk of malignancy.[13]

After the application of the screening methods, the patients whose initial evaluation reveals high risk for malignancy should ideally be treated in specialized centers with a multidisciplinary team, maximizing the oncological results and making it possible to discuss options to preserve fertility.[14]

Ovarian Reserve

There is currently no ideal method to predict the ovarian reserve, and some important aspects should be considered. Estimates of the ovarian reserve are performed mainly by the measurement of the antimullerian hormone (AMH) and the antral follicle count (AFC). The AMH is produced by granulosa cells from active follicles, and can be dosed in the peripheral blood. The production of AMH is stable throughout the menstrual cycle, and is the first to change with advancing

age. The levels of AMH are related to some outcomes of assisted reproductive technology (ART), such as the number and the quality of yielded oocytes and the live-birth rate (LBR).[15,16] The diversity of laboratory kits available for AMH dosage generates distortions and differences in reference values, which can cause bias in the interpretation of results. In addition, since the AMH is produced by both ovaries simultaneously, the actual impact of the surgical procedures may be underestimated in cases of unilateral disease.[17]

The AFC consists of the sum of the 2- to 10-mm ovarian follicles found between the 2nd and 4th days of the menstrual cycle, and it is also related to ART outcomes.[17]

It has already been proposed that the association of methods (dosage of AMH and AFC) may contribute to reduce the risk of misunderstandings. In the event that the levels of AMH are higher than expected given an AFC, the presence of polycystic ovarian syndrome should be considered. And levels of AMH lower than expected for a given AFC may be an early sign of ovarian failure.[18]

Some of the studies mentioned in the present review also used other methods such as the follicle-stimulating hormone (FSH), ovarian volume measurement and ovarian peak systolic velocity (PSV), but they are less reliable.[19]

Treatment

Surveillance

A significant proportion of the benign ovarian masses will present spontaneous resolution. Therefore, the expelling conduct may be of extreme validity, avoiding unnecessary surgeries, and, consequently, additional damage to healthy ovarian tissue. Functional cysts or simple ovarian cysts (anechogenic, thin-walled and smaller than 50 mm) usually resolve after 3 menstrual cycles without the need for any intervention.[1]

Management of the Risk of Adnexal Torsion

After the decision regarding surveillance, the risk of adnexal torsion remains a concern. In an international prospective cohort, among the patients selected for conservative management and surveillance, the overall risk for torsion was of around 4%.[20]

A case series[21] with 360 patients showed that the main pathologies associated were dermoid cysts (36%), follicular cysts (16.1%), corpus luteum cysts (9.9%), and serous cystadenoma (9.9%), with an overall mass size ranging from 8 cm to 15 cm. Functional cysts were successfully treated mainly with detorsion.[21]

An interesting proposal in the symptomatic pediatric/adolescent range is a composite score of risk. It consists of identifying and scoring the presence of independent risk factors: absence of vomiting (zero points) or presence of vomiting (2 points); ovarian volume higher than 17 mL (premenarchal; 2 points) or 105 mL (menarchal; 2points); adnexal ratio (volume of the affected ovary divided by the contralateral ovary) higher than 21 (2 points). For scores ≥ 4, surgical treatment is recommended. Even with scores between 2 and 3, until 10% of the patients presented with torsion.[22]

Regarding Endometriomas

A study[23] monitored 1,199 cycles of 244 patients with unilateral endometriomas, comparing ovulation between the healthy and the affected ovaries. Documented ovulation did not differ (49.7% versus 50.3% respectively), even with cysts with more than 6 cm in diameter. In total, 43% of the patients conceived spontaneously during the study period of 4 years.[23] There is no relevant data on the literature that supports that systematic surgical removal of cysts smaller than 4 cm prior to assisted reproduction procedures. Expectant behavior is also justified in this scenario.[24] Other aspects regarding the management of endometriomas will be further discussed, but surveillance seems to be the main approach.

Oral Contraceptives

A systematic review[7] that analyzed eight randomized trials concluded that, although widely used in the clinical practice, the prescription of oral contraceptives does not influence the resolution of functional cysts. The outcomes are the same for both spontaneous cysts and those caused by ovulation-induction processes. Persistent cysts tend to be pathological rather than physiological.[7]

Surgical Approach - Technical Considerations

The indication of surgery occurs when: there is uncertainty regarding the suspicion of malignancy; the size of the adnexal mass increases the risk of pain and torsion episodes; the augmentation of the mass might compromise the ovarian follicles; and, in cases of endometriotic cysts, when there is a progressive increase in volume and pelvic pain due to endometriosis.[25] Once the need for intervention is defined, one should consider several technical details that can minimize the impact on the ovarian reserve and improve the overall outcome of the surgery.

Laparoscopy

The body of evidence in favor of the laparoscopic approach is significant when there is a need for surgery. Laparoscopic cystectomy is often the rule, to minimize potential complications such as ruptures in malignant situations, and to optimize fertility preservation. This technique is well established as the gold standard in this set of pathologies.[1,25,26]

Comparison of Etiologies

Despite the fact that the multitude of etiologies of the ovarian masses and the surgical practice demonstrate evident technical differences among the different types of cysts, the damage to the ovary is evident and unavoidable in every situation.

The comparison of the levels of AMH, FSH, AFC, ovarian volume and vascularization did not show significant differences when comparing the group with bilateral endometriomas ($n = 21$), unilateral endometriomas ($n = 29$), other benign cysts ($n = 20$), and the control group without cysts ($n = 20$), when the laparoscopic surgery was performed with hemostatic sutures. The small difference observed was in the first postoperative month, but did not remain after 12 months.[27]

Comparing the levels of AMH and the amount of remaining follicles in the surgical specimen, no differences were

found between patients with endometriomas ($n = 68$) and other benign cysts ($n = 32$). Bilaterality was the only risk factor associated with greater loss of ovarian reserve.[28]

In a study[29] with 71 patients, the final volume was lower (2.41 mL versus 2.23 mL, $p = 0.49$), as compared with the non-operated ovary, as well as the AFC (3.45 versus 2.43, $p = 0.11$), regardless of the fact that there were endometriotic cysts or not. Ovarian volume and CFA differences were not dependent on the size of the cysts.[29]

Contrasting this scenario, in a study[30] comparing the AMH levels of patients with endometriomas, other benign cysts and patients with infertility of tubal cause, endometriomas show a different behavior from the other benign cysts, since AMH levels may be lower than in the other conditions (1.53 ng/mL, 2.20 ng/mL, and 2.82ng / ml respectively). Surgery significantly decreases the levels of AMH in the case of endometriomas (worse if bilateral) compared with other pathologies.[30]

In a study[4] with 75 patients (33 teratomas, 25 endometriomas, 9 functional cysts, and 8 cystadenomas) the reduction in the levels of AMH was different, depending on the histological diagnosis of the mass. Patients with endometriomas had a faster and longer lasting reduction in AMH levels: a 51-% mean reduction 6 months after surgery ($p = 0.007$). Patients with teratomas presented a 25-% reduction ($p = 0.009$). In the other patients, the reduction was of 34% ($p = 0.059$).[4]

In a study[31] with 22 patients, 12 with endometriomas and 10 with non-endometriotic cysts, there was a reduction in the levels of AMH postsurgery (5.48 ng/mL before and 2.56-ng/mL after; $p < 0.05$), but without changes in the AFC, estradiol and ovarian volume. This decrease occurred at the expense of the group of patients with endometriomas. A technique of bipolar hemostasis associated with hemostatic suture was used.[31]

A retrospective study[3] of 97 patients aged between 20 and 39 years showed that AMH levels are lower in patients with endometriomas compared with other benign cysts (4.12 -ng/mL versus 6.02 ng/mL; $p < 0.001$). The mean level of AMH was also lower the larger the diameter of the non-endometriotic mass.[3]

In a case-control study[32] with 56 patients with endometriomas and 16 patients with other benign cysts, there was a significant decrease in AMH levels after surgery (stripping cystectomy with bipolar hemostasis) in the group with endometriosis (4.3 ng/mL versus 2.8 ng/mL; $p < 0.001$), but the same did not occur in the group of other benign cysts (5.6 ng/mL versus 4.9 ng/mL; $p = 0.251$). This drop was also more significant in the group with endometriosis of stages III to IV (4.26 ng/mL versus 2.62 ng/mL; $p < 0.001$) when compared with the group with endometriosis of stages I to II (4.38 ng/mL versus 3.34 ng/mL; $p = 0.66$).[32]

Another retrospective study[33] with 138 women submitted to salpingectomy, 36 submitted to unilateral salpingo-oophorectomy, 40 who underwent excision of an endometrioma, and 41 who underwent cystectomy due to other causes showed no difference in the levels of AMH ($p = 0.33$), AFC ($p = 0.59$) and FSH ($p = 0.21$) between the salpingectomy group and the group who did not undergo surgery. The group submitted to unilateral salpingo-oophorectomy had lower levels of AMH (-54%; $p = 0.001$). Women with endometrioma also had lower levels of AMH (-66%; $p = 0.002$), but this did not affect the AFC ($p = 0.22$) and FSH ($p = 0.28$).[33]

Recently, a study performed in patients[34] with endometriomas ($n = 34$) and other benign masses ($n = 18$) showed that, 6 months after surgery, the levels of AMH were reduced by 59.3% ($p < 0.12$) when compared with baseline values in the group with endometriomas, and it was reduced by 29.5% ($p < 0.2$) in the group with other benign masses. This reduction was not related to the number of follicles inadvertently removed during the procedure ($p < 0.669$). It is very important to note that, in this study, all procedures were performed by a single specialist surgeon, which indicates that postoperative damage to the levels of AMH is evident, even for surgeons with extensive experience.[34]

In addition, a retrospective study[35] revealed that there are no differences in ovarian stimulation response (measured through retrieved oocytes) in in vitro fertilization (IVF) cycles when there is an evident ultrasound diagnosis of dermoid cyst.[35]

Endometriomas - Options of Surgical Techniques and Hemostasis

Several years ago, some advantages were associated with the excision of an endometriotic cyst when compared with several types of ablative processes. There was an assumption that the excision of the cyst capsule was associated with a lower recurrence of pain symptoms (dysmenorrhea, dyspareunia and acyclic pelvic pain) and less need for further surgeries. In addition, it was associated with a higher rate of spontaneous gestation after the procedure. It was still unclear whether excision was superior to ablative procedures for ART outcomes.[26]

In 2011, a randomized study[36] performed with 48 patients with bilateral endometriomas compared cystectomy and coagulation and found, after cystectomy, a lower antral follicle count (3.67 versus 4.75; $p = 0.001$), lower ovarian volume (6.27 mL versus 9.87 mL; $p = 0.005$) and fewer oocytes collected after ovarian hyperstimulation (3.08 versus 3.86; p 0.01) compared with coagulation alone.[36]

In a study[37] with 25 patients with endometriomas, using only stripping, without coagulation, there was no difference in presurgical AMH levels and 3 cycles after surgery (3.61 ng/mL versus 3.00 ng/mL respectively; $p = 0.62$).[37]

In another study[38] with 99 patients who underwent surgery for endometriomas, the comparison between cystectomy and bipolar vaporization showed a decrease of more than 50% in AMH levels after surgery. There was no difference between the techniques.[38] It is imperative, however, to highlight some limitations of the mentioned study. It was not randomized, did not make a clear separation of the groups, and did not present any follow-up data.

In yet another study,[39] 45 patients with unilateral endometriomas were treated with laparoscopy and cystectomy with striping and hemostasis with a dual-wavelength laser (Biolitec Ceralas HPD, wavelength of 980 nm and 1470 nm, model 120 W). The mean level of AMH before surgery was of 3.01 ng/mL; 4 to 6 weeks after surgery, it was of 2.41 ng/mL;

and 6 to 9 months after, it was of 2.7 ng/mL. The decrease was statistically significant ($p < 0.05$).[39] However, the technique was not compared with stripping alone or with other techniques.

The use of hemostatic sealants was compared with bipolar coagulation in a non-randomized study.[40] The rate of decline in AMH levels was lower using the sealants (15.4%) compared with bipolar coagulation (41.2%; $p = 0.003$).[40] The levels were measured in 129 patients, without randomization, a follow-up of only 3 months, and other ovarian reserve parameters were not measured.

In a more recent study,[41] 207 patients who underwent excision of endometriomas were followed up for 12 months. The levels of FSH, AMH, the AFC and the PSV were compared regarding 3 different hemostasis techniques: bipolar cauterization ($n = 69$), ultrasonic scalpel ($n = 69$) and suture ($n = 69$). Throughout the period up to the 12th month, the levels of FSH were higher, and the levels of AMH were lower, in the first 2 groups ($p < 0.05$). At the 12th month, the AFC and PSV were also lower in the first 2 groups ($p < 0.05$). The authors concluded that bipolar cauterization and the use of ultrasonic scalpel cause more damages to the ovaries when compared with hemostatic suture.[41]

Recently, the laparoscopic stripping of endometriotic cysts became the standard procedure, since it favors a lower recurrence of symptoms and increases pregnancy rates.[42]

Despite this, one cannot deny that surgical damage to ovarian tissue is evident. The histological analysis of the endometrioma capsules revealed the presence of normal ovarian follicles, in a larger quantity the younger the patient and the smaller the cyst diameter.[43]

Those analyses suggest that the intervention leads to the decrease in the ovarian reserve, although the literature is controversial and heterogeneous, especially considering the different methods of hemostasis.[44,45] The evidence points to a tendency to believe that suture is less harmful to the ovarian reserve.

Additional Relevant Technical Details

Following cystectomy, removal of ovarian tissues from the abdomen should preferably be performed through the umbilical portal and wrapped in a protective pouch. This decreases the chance of eventual contamination of the abdominal cavity with the contents of the cyst, and causes less postoperative pain and a shorter recovery time. Transverse minilaparotomy should be considered for the cases of masses with a larger volume (higher than 7 cm in diameter).[1]

The phase of the menstrual cycle for the surgery does not seem to influence the results regarding blood loss and variations in AMH levels. In yet another study,[46] 84 patients in the follicular phase and 71 in the luteal phase were compared after cystectomy for surgical blood loss ($p = 0.984$) and AMH levels before and 3 months after surgery ($p = 0.945$); no differences were found by the authors.[46]

During the surgical approach, one should take into consideration the anatomical position of the vascularization of the ovary, aiming at the protection of the pelvic infundibulum from surgical trauma. Interestingly, in a study,[47] the comparison between the excision of dermoid cysts with a mesial approach (33 patients) and an anti-mesial approach (34 patients) showed a higher maintenance of the mean number of antral follicles, a larger mean ovarian diameter, and a higher mean PSV in the ovaries of patients treated with the mesial approach.[47]

Fertility as the Endpoint

Interestingly, only one article[48] addressed the main objective of fertility, translated as the birth rates after ovarian surgery. The follow-up of 60 women for 24 months after ovarian surgery demonstrated a significant decrease in AMH levels (2.7 mcg/l to 1.1 mcg/l; $p = 0.001$). In total, 36 women tried to conceive, 18 became pregnant, and there were 12 live births. It was possible to determine the behavior of the AMH levels in 34 women who attempted to conceive, and it decreased in both groups (pregnant: 3.3 mg/l to 1.0 mg/l; $p = 0.057$; not pregnant: 3.2 mg/l to 2.0 mg/l, $p = 0.003$), but this decrease was not different between the 2 groups ($p = 0.112$).[48]

Conclusion

We conducted a comprehensive review of the literature for the identification of relevant factors regarding the practical recommendations for the treatment of benign adnexal masses and the insights for fertility preservation. The discussion of the subject is extensive, somewhat controversial, but with some points of convergence. In the menacme, after the diagnosis of an adnexal mass, the incidence of cancer is not high, and the use of magnetic resonance imaging (MRI) and SRs is satisfactory to predict the risk of developing malignancy. Expectant management can be a valid alternative, avoiding unnecessary procedures, surgical complications, and ovarian changes caused by traumatic injuries. The use of anovulatory medications is, in most cases, unnecessary. Dermoid cysts are more associated with torsion, and masses ranging from 8 cm to 15 cm are more common in this kind of complication. Detorsion is a valid option in cases of functional cysts. The use of composite scores of risk factors in the pediatric/adolescent scenario can aid in the decision for surveillance or surgical treatment. When surgery is necessary, some technical aspects are somehow clearer. The use of videolaparoscopy is well established, in which stripping cystectomy shows better results if we consider all types of masses together. Surgery can be performed at any stage of the cycle. Materials should be removed from the abdomen in protective pouches and, preferably, through the umbilical scar incision. Minilaparotomy is acceptable for masses larger than 7 cm. The mesial approach should be considered in cases of teratomas. The use of bipolar electrocautery appears to have an even more negative impact on AMH levels and the AFC after cystectomies, which may persist for 12 months after the surgical procedure, and should be avoided. Suture is preferable. However, caution should be exercised with such an assertion, given the heterogeneity of the available studies. We emphasize the need for a precise standardization of future studies that involve comparing new hemostasis techniques (when to apply them and if they are necessary at all).

Specifically in the case of endometriomas, the evidence is unclear, but, apparently, there are no changes in the primary ovulatory function of the affected ovaries, but they may be associated with decreased ovarian reserve caused by the disease itself. In addition, the evidence regarding decreased ovarian reserve after the surgical treatment is very strong. Moreover, in view of the recurrence of endometriomas, the second surgery is even more harmful to the AFC. The precise indication and technical quality of the first surgery is fundamental, and successive surgeries should be considered with great caution. Now, there are no standardized protocols to address endometriomas, especially considering the size as the mark of the decision. In regards to fertility, surveillance seems to be the best alternative. Despite some proposals on this subject, the need for future research is evident. Regarding the ovarian reserve, the current difficulties of using markers that are more reliable are clear. Apparently, estimates may be more accurate when counting the antral follicles (which show the direct impact of the affected ovary) in relation to AMH levels (which reflect the pattern of the two ovaries simultaneously). There is a lack of long-term follow-up studies that can elucidate these differences more clearly. Nevertheless, despite the evidence of the decrease in the parameters of evaluation of the ovarian reserve, the question remains: what is the impact of the adnexal masses and their treatments on the real chances of gestation? The data suggest that ovarian reserve evaluations purely based on AMH levels or the AFC may not satisfactorily reflect the actual risks of infertility. It has been suggested that, although objective assessments of the ovarian reserve are of extreme value, it is necessary to prioritize the focus on long-term studies that present the rate of live births as their endpoint. Therefore, we suggest great caution and care when clarifying the best possible evidence for patients with adnexal masses, revealing our limitations. In this way, we will be able to offer the necessary data about the reproductive future and the adequate information for the correct decision making regarding the patients who need treatment for adnexal pathologies.

Conflicts of Interest

The authors have none conflict to interests to declare.

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Characterization of Placental Infection by Zika Virus in Humans: A Review of the Literature

Caracterização da infecção placentária pelo vírus zika em humanos: Uma revisão da literatura

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Abstract

Objective The aim of the current review is to present a systematic evaluation of reported human placental findings in cases of zika virus (ZIKV) infection.

Data sources We reviewed the EMBASE, PUBMED, and SCIELO databases until June 2019, without language restrictions.

Selection of studies The search terms *placenta* AND *zika virus* were used. The inclusion criteria of the studies were studies that reported placental findings in humans. Experimental studies, reviews, notes or editorials were excluded. A total of 436 studies were retrieved; after duplicate exclusion, 243 articles had their titles screened, and 128 had their abstract read; of those, 32 were included in the final analysis (18 case reports, 10 case series, and 4 cohorts)

Data collection We collected data concerning the author, year of publication, study design, number of participants, number of placental samples, onset of symptoms, perinatal outcomes, and main findings on histological analysis.

Data synthesis The placental pathologic findings were described as mild and nonspecific, similar to those of other placental infections, including chronic placentitis, chronic villitis, increased Hofbauer cells, irregular fibrin deposits, increased mononuclear cells in the villus stroma, villous immaturity, edema, hypervascularization, stromal fibrosis, calcification, and focal necrosis of syncytiotrophoblasts.

Conclusion Zika infection presents unspecific placental findings, similar to other infections in the toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes (TORCH)group. Characterizing and standardizing placental findings after zika virus infection is key to understanding the mechanisms of congenital diseases.

Keywords

- Zika virus
- ZIKV
- placenta
- Hofbauer cells
- TORCH

Resumo

Objetivo O objetivo desta revisão é apresentar uma avaliação sistemática dos achados relacionados à infecção por zika vírus (ZIKV) na placenta humana.

Fontes de dados As bases de dados EMBASE, PUBMED, e SCIELO foram pesquisadas, até junho de 2019, sem qualquer restrição de língua.

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Seleção dos estudos Os termos *placenta* E *zika virus* foram utilizados na busca. Foram incluídos estudos que reportassem achados placentários de infecção em seres humanos, enquanto estudos experimentais, revisões, notas e editoriais foram excluídos. Um total de 436 estudos foram identificados, e 243 tiveram seus títulos lidos após a exclusão de duplicatas. Cento e vinte e oito artigos tiveram seus resumos avaliados, dos quais 32 foram incluídos na análise final (18 relatos de caso, 10 séries de casos, e 4 estudos de coorte).

Dados obtidos Foram pesquisados dados relativos ao autor, ano da publicação, desenho do estudo, número de participantes, número de amostras de placenta, início dos sintomas, desfechos perinatais, e principais achados histológicos.

Síntese dos dados Os principais achados placentários descritos foram leves e inespecíficos, similares a outras infecções placentárias, incluindo infecção placentária crônica, vilosite crônica, aumento das células de Hofbauer, depósitos irregulares de fibrina, aumento das células mononucleares no estroma viloso, imaturidade vilosa, edema, hipervascularização, fibrose estromal, calcificação, e necrose focal dos sincicitrofoblastos.

Conclusão Infecções por ZIKV têm achados placentários inespecíficos, similares aos de outras infecções do grupo toxoplasmose, rubéola, citomegalovírus e herpes (TORCH). Caracterizar e padronizar os achados placentários após infecção por ZIKV é fundamental para entender o mecanismo das infecções congênitas.

Palavras-chave
- Zika vírus
- ZIKV
- placenta
- células de Hofbauer
- TORCH

Introduction

Zika virus (ZIKV) is a flavivirus much similar to other arboviruses of relevance, such as dengue, West Nile, yellow fever, and Japanese encephalitis viruses. It is transmitted mostly by *Aedes aegypti* mosquitoes, and was first recognized in humans in Uganda in 1952, with two main previous outbreaks, in Yap, Micronesia, in 2007 and in the French Polynesia, in 2013.[1,2] The ZIKV may also be transmitted to humans according to other routes non-vector reliant, such as blood transfusion, sexual transmission, or maternal-fetal transmission.[3]

Brazil had the most significant and recent outbreak of ZIKV, with major relevance not only due to the total number of cases reported (over 200 thousand), but also because of its severity and association to fetal malformations.[4] The fetal consequences were further defined as Congenital Zika Syndrome (CZS), which includes a spectrum of congenital defects (not only microcephaly).[5] These conditions are similar of those caused by "TORCH" pathogens. The TORCH acronym stands for: ***T**oxoplasma gondii* infection, **O**ther (*Treponema pallidum, Listeria monocytogenes, parvovirus* B-19, and human immunodeficiency virus (HIV), amongst others), **R**ubella, **C**ytomegalovirus (CMV), and **H**erpesviruses (HSV) 1 and 2. After the Brazilian zika outbreak, some authors have suggested the inclusion of ZIKV among the group "others" in the acronym or even a more direct inclusion such as TORCHZ.[6]

The precise mechanisms of placental infection and maternal-fetal transmission during pregnancy, not only in ZIKV but in the other TORCH infections as well, remains unclear. Described routes include: ascending infection, direct crossing or infection of syncytiotrophoblasts (SYN), infection of extravillous trophoblasts through maternal microvasculature, and trafficking of and/or signaling from maternal immune cells.[6]

The SYN layer is the outer layer of the placental villus, of multinucleated, terminally-differentiated cells in direct contact with the maternal blood. The extravillous trophoblasts (EVTs) anchor cells to the uterine wall. Both of these are differentiated from the cytotrophoblast layer (CTB) throughout pregnancy.[7] Hofbauer cells (HCs) are placental macrophages of fetal origin, existent in the chorionic villus throughout the entire gestation.[8] Hofbauer cells have been associated to ZIKV infection, with description of hyperplasia of such cells in the placenta.[9]

The study of placentas of suspected cases of ZIKV is recommended, as part of optimum healthcare for these women and newborn. Histopathologic examination of the placenta, with ZIKV ribonucleic acid (RNA) testing (via reverse transcription-polymerase chain reaction [rRT-PCR]), may confirm fetal infection, since viral detection in the serum is time-sensitive and the window for ZIKV detection might be missed.[4]

The aim of the present review is to present an integrative evaluation of reported placental findings in human studies on ZIKV infection during pregnancy.

Methods

We performed a review of the literature to identify studies that assessed placental findings in human with ZIKV infection during pregnancy. The time end-point of this review was June 2019, including publications of the EMBASE, PUBMED, and SCIELO databases, without language restrictions. We

used the following Medical Subject Heading (MeSH) search terms: *placenta* AND *zika virus*. The inclusion criterion of the studies was reporting of placental findings in humans, while studies that did not report placental findings, experimental studies, reviews, notes or editorials were excluded. The current study followed all recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. In the first step of this review, two independent reviewers performed a title screening of all studies identified in the database search; in the second step, the remaining studies were evaluated considering their abstracts by two independent reviewers and further full text, for inclusion. Discordances between the primary reviewers were solved by a third senior reviewer. After the final selection of the studies that were included in this review, each study was evaluated, and the following characteristics for each study were obtained: author, year of publication, study design, number of participants, number of placental samples, onset of ZKV infection symptoms, perinatal outcomes, and main findings on histological analysis. Those results were stored in a Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA, USA) and further organized in a table with detailed description of data.

Results

A total of 436 articles were retrieved in the databases search (PubMed = 164; EMBASE = 270 and SCIELO = 2); of those, 193 were duplicated articles, so 243 had their title screened. One hundred and fifteen articles were excluded after title screening, and the remaining 128 studies had their abstract read. After that, 96 studies were excluded (27 reviews, 45

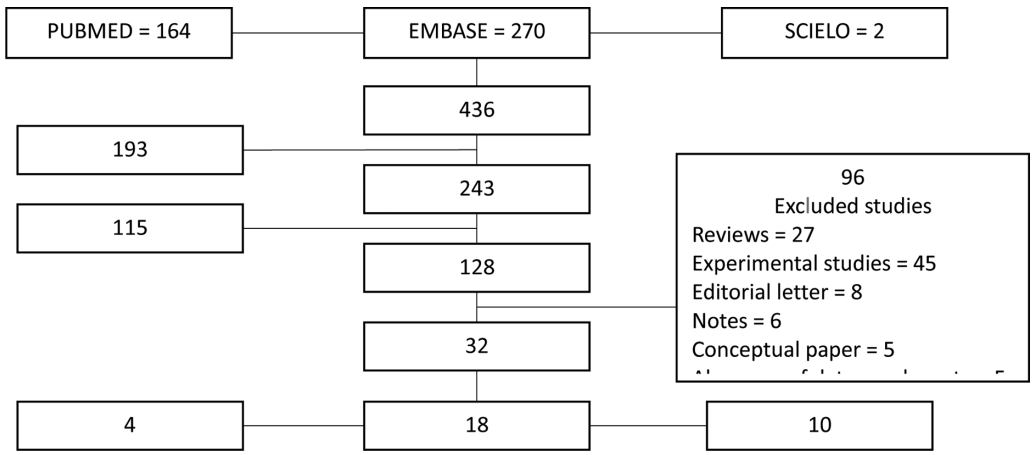

Fig. 1 Inclusion flowchart of studies in the present review.

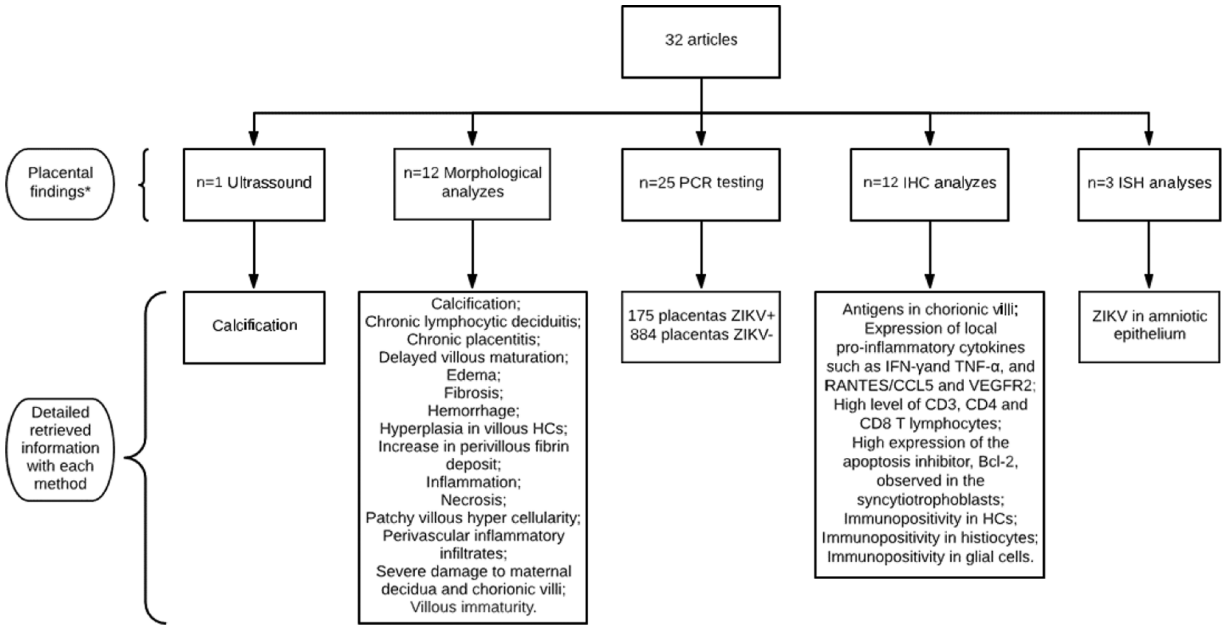

Fig. 2 Inclusion flowchart of studies.

Table 1 Characteristics, number of cases, and main findings on placental evaluation of the included studies

Author, year	Type of study	Participants/ placentas sampled	Onset of symptoms (trimester)					Perinatal outcomes			Main findings on placental evaluation and overall findings
			1st	2nd	3rd	N/A	A	B	C	D	
Driggers et al (2016)[14]	Case report	1/1	1	–	–	–	–	–	1	–	High viral load found in placenta, fetal membranes and umbilical cord by RT-PCR. ZIKV RNA in Amniotic fluid, fetal brain, liver, lung and spleen.
Martines et al (2016)[11]	Case report	4 / 4	2	–	2	–	2	–	–	2	Placenta with fibrosis, calcification, and deposits of fibrin. Material consistent with third trimester gestation = RT-PCR negative. Two abortions, one had dense and heterogeneous chorionic villitis with calcification, sclerosis, edema, increased perivillous fibrin deposition, and patchy lympho histiocytic intervillositis and the other had minute fragments of placental. Both placental RT-PCR positive for ZIKV.
Martines et al (2016)[12]	Case series	5/2	1	–	–	4	2	–	2	1	RT-PCR ZIKV positive in all samples. IHC: ZIKV antigens in chorionic villi of a first trimester placenta.
Melo et al (2016)[15]	Case series	11/11	9	1	–	1	–	–	3	8	PCR ZIKV performed in nine placentas, two positives.
Mlakar et al (2016)[16]	Case report	1/1	1	–	–	–	–	1	–	–	Ultrasound scan performed at 29 weeks showed microcephaly with brain and placental calcification. RT-PCR ZIKV positive in fetal brain tissue
Noronha et al (2016)[13]	Case report	5/3	3	–	1	1	1	–	–	4	RT-PCR ZIKV positive in all samples. Main pathological findings: chronic placentitis, hyperplasia in villous HCs. IHC with the 4G2 anti-flavivirus monoclonal antibody analysis showed: immunopositivity in HCs and some histiocytes in intervillous spaces, diffusely distributed immunopositivity in some glial cells.
Sarno et al (2016)[17]	Case report	1/1	–	–	–	–	–	–	1	–	RT-PCR ZIKV negative in placental sample.
van der Eijk et al (2016)[18]	Case report	1/1	1	–	–	–	1	–	–	–	Placental histopathological and IHC investigation: no inflammation markers. RT-PCR ZIKV positive in the amniotic fluid, fetal and placental tissue. In situ hybridization (ISH) only found ZIKV in amniotic epithelium.
Acosta-Reyes et al (2017)[19]	Case report	2/2	1	1	–	–	1	–	–	–	Placental ZIKV RT-PCR positive in one case. Histological analysis: increase in perivillous fibrin deposit, chronic lymphocytic deciduitis in both cases.
Bhatnagar et al (2017)[20]	Case series	44/44[H]	19	24	–	1	11	3	3	27	ZIKV RT-PCR positive in 32 placental samples. ISH positive in 16 of the cases positives by RT-PCR.
Chen et al (2017)[21]	Case report	1/1	–	1	–	–	–	–	–	1	RT-PCR ZIKV negative in placental sample.
Mattar et al (2017)[22]	Case report	1/1	–	1	–	–	–	–	–	1	RT-PCR ZIKV positive in placental sample. ZIKV not found in umbilical cord or serum.
Rabelo et al (2017)[23]	Case report	1/1	–	–	–	1	–	–	–	1	IHC revealed presence of ZIKV antigens. Severe damage to maternal decidua and chorionic villitis, with large areas of fibrinoid necrosis and perivascular inflammatory infiltrates. Dense and heterogenous calcification observed.
Reagan-Steiner et al (2017)[24]	Case series	627/627	131	153	–	343	81	–	–	546	Of 546, 60 placental sample RT-PCR ZIKV positives. In 81 samples of pregnancy losses, 18 placental sample RT-PCR ZIKV positives. IHC performed in 91 placentas from livebirths and 7 had evidences of ZIKV infection.
Ritter et al (2017)[10]	Case report[E]	4/2	2	–	–	2	1	–	1	–[F]	One sample, histological analysis showed: patchy villous hypercellularity, focal perivillous fibrin deposition, increased HCs and focal calcification.
Rosenberg et al (2017)[9]	Case report	1/1	1	–	–	–	–	1	–	–	RT-PCR ZIKV positive in the placenta and fetal brain. Placenta demonstrated focally stromal edema,

Table 1 (*Continued*)

Author, year	Type of study	Participants/ placentas sampled	Onset of symptoms (trimester)			Perinatal outcomes			Main findings on placental evaluation and overall findings
			1st	2nd	3rd	N/AA	BCD		
									hydropic chorionic villi with hyperplasia and focal proliferation of HCs. prominent hypercellularity of the villous stroma. IHC with inflammatory markers (CD163 and CD8) found in HCs. ISH positive for ZIKV demonstrated scattered, strongly positive staining cells within the villous stroma of the chorionic villi, which were presumably HCs.
Schaub et al (2017)[25]	Case series	8/8	6[I]	–	–	–	3	– – 1[F]	RT-PCR ZIKV positive in three samples.
Schwartz (2017)[26]	Case series	12/12	–	–	–	12	–	– – 12	Placentas from fetuses with congenital ZIKV infection didn't present placental inflammation. IHC: special stains reveal proliferation and prominent hyperplasia of HCs, in the chorionic villi of infected placentas. ZIKV infection present in HCs from second and third trimester placentas.
Noronha et al (2018)[27]	Case series	24/24	5	8	6	5	1	– – 23	Villous immaturity was the main histological finding. IHC: Hyperplasia of HCs observed in the third trimester in placental tissues. HCs were the only ZIKV-positive fetal cells found in placentas that persisted until birth. 33% of women infected during pregnancy gave birth to babies with congenital anomalies. No pattern correlating the gestational stage in the infection, the positivity of HCs in the placenta due to IHC and the presence of congenital malformations at birth.
Esquivel et al (2018)[28]	Cohort	3/6	1	2	1	–	–	– – 3	Patient 1: Placental PCR negative, but both twins were PCR-positive. Patient 2: Both placentas and twins were PCR-positive at birth. Patient 3: One twin and associated placenta PCR-positive, the second twin and placenta PCR-negative. All six placentas with villous immaturity and other placental histopathologic findings distinct in each placental pair. These results suggest that each twin should be evaluated individually for Zika infection as ZIKV may not transmit equally to each fetus.
Maykin et al (2018)[29]	Cohort	29/29	2	22	1	4	–	– – 29	PCR ZIKV positive in 25 placentas. Ten placental pathological findings: delayed villous maturation, chronic deciduitis, stromal fibrosis and HC hyperplasia.
Mletzko e Schildgen (2018)[30]	Cohort	301/121	–	–	–	300	180	– – 121	RT-PCR ZIKV negative in all placentas and tissues from spontaneous abortions.
Rabelo et al (2018)[31]	Case report	1/1	1	–	–	–	1	– – –	Histological analyses of the placenta and fetal organs revealed different types of tissue abnormalities: inflammation, hemorrhage, edema and necrosis in placenta, as well as tissue disorganization in the fetus. IHC: Increased cellularity (HCs and TCD8+ lymphocytes), expression of local pro-inflammatory cytokines such as IFN-γ and TNF-α, and other markers, such as RANTES/CCL5 and VEGFR2, supported placental inflammation and dysfunction.
Sassetti et al (2018)[32]	Case report	1/1	1	–	–	–	–	– – 1	RT-PCR ZIKV negative in Placenta and blood. RT-PCR positive in the newborn urine sample collected on day 1 after birth.
Turley et al (2018)[33]	Case series	4/4	–	–	–	4	–	– – 4	All 4 cases demonstrated positive placental testing by multiple modalities. IHC: tissues were stained against E glycoprotein of the ZIKV envelope with 4G2 monoclonal antibody

(*Continued*)

Table 1 (*Continued*)

Author, year	Type of study	Participants/ placentas sampled	Onset of symptoms (trimester)				Perinatal outcomes		Main findings on placental evaluation and overall findings
			1st	2nd	3rd	N/AA		BCD	
									revealing strong but localized signal in the chorionic villus parenchyma and villous lumen. PCR amplicons of the ZIKV genome were amplified by RT-PCR from placenta in all cases. Bioanalyzer assessment of RT-PCR product confirmed the highest amounts of ZIKV in placenta and verified amplicon size.
Wongsurawat et al (2018)[34]	Case report	1/1	1	–	–	–	1	– – –	PCR ZIKV positive in the placenta and brain.
Felix et al (2017)[35]	Case report	2/2	2	–	–	–	–	– – 2	PCR ZIKV negative in placenta fragments, blood and urine. ZIKV serology performed only showed presence of IgG antibodies of maternal origin.
Merriam et al (2019)[36]	Cohort	70/70	–	–	–	70	–	4 – 63	PCR positive in 1 placenta. PCR positive in urine and serum in five and nine women respectively, and two women had both positive urine and serum PCR.
Rodó et al (2019)[37]	Case series	72/72	16	41	14	–	–	– – –	RT-PCR ZIKV positive for 10 placentas. Sorological assay positive for the other 62 women. 2 cases of central nervous system anomalies and 1 miscarriage, all in women with first trimester infection.
Santos et al (2020)[38]	Case report	1/1	1	–	–	–	–	– – 1	Deciduitis present on maternal surface of the placenta, with a prevalence of lymphocytes associated with vasculitis. IHC: HCs found in placental tissue, specific-ZIKV protein found in placental cells. IHC with high level of CD3 T lymphocytes present in addition to CD4 and CD8 cells. High expression of the apoptosis inhibitor, Bcl-2, observed in the syncytiotrophoblasts.
Seferovic et al (2019)[39]	Case series	4/4	2	2	–	–	–	– – 4	RT-PCR ZIKV performed on placenta, membrane and cord samples. ZIKV was detected in all placental specimens in cases 1, 2 and 3 (affected by CZS), but not by case 4 (unaffected). ZIKV detected in the membranes and cord of cases 2 and 3, but not in cases 1 and 4. Histological and IHC examination of placentas reveals evidence of ZIKV infection and active in cases 1, 2 and 3. ISH positive in cases 1, 2 and 3.
Yarrington et al (2019)[40]	Case report	1/1	–	–	–	–	–	– – 1	RT-PCR ZIKV positive in placental sample. Evaluation for other causes of microcephaly negative.

Abbreviations: Bcl-2, B-cell lymphoma-2; CZS, congenital Zika syndrome; HCs, Hofbauer cells; IDC, immunohistochemistry; IFN-γ, interferon-gamma; ISH, in situ hybridization; RANTES, regulated on activation, normal T expressed; RNA, ribonucleic acid; RT-PCR, reverse transcription-polymerase chain reaction; TNF-α, tumor necrosis factor-alpha; VEGFR2, vascular endothelial growth factor receptor 2; ZIKV, Zika virus.
A, abortion; B, termination; C, stillbirth; D, liveborn; E, case reports + review of the literature; F - data not detailed on all considered cases; G, asymptomatic case; H - 8 cases of children with microcephaly, without placental samples; I, two cases were asymptomatic.

experimental studies, 8 editorials, 6 notes, 5 conceptual articles, and 5 articles with no data on placental findings), and 32 studies were included in the final analysis: 18 case reports, 10 case series, and 4 cohort studies. ►**Fig. 1** shows the inclusion flowchart for the present study.

The majority of studies included placental testing for ZIKV with RT-PCR as part of diagnostic procedures, and some studies presented detailed data on abnormal morphological findings and immunohistochemistry (IHC) studies (►**Fig. 2**).

►**Table 1** summarizes the main findings on the selected studies, published from 2016 (first reports on the subject) to June 2019, containing the results of 1,244 women with ZIKV infection during pregnancy. The majority of women presented symptoms in the first trimester of pregnancy. Different methods for ZIKV infection diagnosis were performed. Placental pathologic findings were described as mild and nonspecific, including chronic placentitis (TORCH type), chronic villitis, increased HCs, variable perivillous fibrin

and mononuclear cells, villous immaturity, stromal fibrosis and calcification, increased vascularity, and also lymphocytic deciduitis and focal syncytiotrophoblast necrosis.[10–13]

Most of the detailed cases represented first-trimester infection, with symptomatic disease, leading to significant cases of abortions, stillbirth, or neonatal death.[9–13,18–21,25] The ZIKV was found to induce fetal disease and/or adverse pregnancy outcomes well beyond the first trimester, even late during pregnancy.[41,42]

Among the reported studies, the largest case series considered[15] focused on ZIKV-specific RT-PCR amplification products from placenta with no details on IHC findings. Nevertheless, a few studies have presented interesting IHC results, with evidence of ZIKV infection in HCs within the placental villi.[12,13,20]

Discussion

The current review evaluated studies that reported placental findings among women with ZIKV infection during pregnancy. Placental pathological findings are mostly mild and nonspecific, suggesting an important role for HCs within the villi. These findings are consistent with the effects of other viruses in the placenta, such as human CMV,[43,44] leading to proinflammatory responses, impaired remodeling of spiral arteries in the decidua, and cell death; ultimately compromising suitable utero-placental blood-flow.[45] The amount of placental inflammation is associated to the severity of fetal findings.[46]

The present review points toward an important role of HCs, which are of fetal origin, monocytic derived, and part of the normal component of the stroma of the chorionic villi, shown to appear very early in gestation. Hofbauer cells have been described as alternatively activated macrophages[9,47] responsible for the phagocytosis of fluids and apoptotic materials, antigen presentation, and perhaps an angiogenic role in early placental vasculogenesis, placental water balance, and endocrine function. Hyperplasia of the HCs has been previously reported in other maternal-fetal infections, such as those in the TORCH group and its proliferation within the chorionic villous stroma is also confirmed.[9,48,49]

The placenta is an important virus reservoir, that can confirm the diagnosis when infection was not confirmed during the acute phase, due to limitations on adequate and timely sample collection, which is a serious concern in ZIKV infection.[4]

There is a worldwide variation regarding antenatal screening availability and follow-up for women with fetal congenital abnormalities. In Latin America, many countries, including Brazil, consider abortion or termination of pregnancy due to fetal congenital abnormalities illegal or highly restricted.[50] Both factors help explain the sparsity of tissue samples from earlier gestational ages reported in the literature. A possible bias from our results is that the placental tissues evaluated were from late-pregnancy infection or infections in apparently unaffected neonates.[50]

Another important point our review highlights is that there is no standardized description of placental findings related to ZIKV. A common global pattern of description of those findings would be helpful to gather results from different groups, settings and countries, allowing researchers to empower results and provide more robust conclusions. It would also help clinicians to justify the importance of histological analysis of placental tissue in suspect or confirmed cases of ZIKV during pregnancy.

Conclusion

Characterizing placental infection is key for understanding the severity of the disease and fetal malformations. The ZIKV presents similar features to other TORCH infections, with a significant role of HCs. Missed opportunities of such evaluation are evident when considering the limited number of studies included in the present review. However, it is very important to address the need for adequate sampling and evaluation of placental findings during an outbreak, among suspected and confirmed cases of ZIKV infection. For that, specific evaluation on different placental layers, combined with studies on RNA detection and standardization of results presentation is fundamental.

Contributions

Venceslau E. M. and Guida J. P. S. contributed by collecting data and writing the first draft; Amaral E. and Modena J. L. P. reviewed the first draft; and Costa M. L. had the original idea for the present study and coordinated it, supervised the data collection, and reviewed the first draft.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Why Is Preeclampsia still an Important Cause of Maternal Mortality Worldwide?

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According to the World Health Organization, ~ 810 women died per day from preventable causes related to pregnancy in 2017. Most of these deaths occurred in low/lower middle-income countries and in low-resource settings. The maternal mortality rate worldwide is still high, even though it dropped by 38% between 2000 and 2017.[1]

As highlighted in the latest report of the American College of Obstetricians and Gynecologists, preeclampsia is responsible for 50,000 to 60,000 deaths/year and ~ 50 to 100 maternal near-misses for every preeclampsia-related death. Despite of the advances in the understanding of preeclampsia, the clinical practice does not seem to be progressing at the same rate.[2]

Hypertensive disorders, including preeclampsia, are very common complications of pregnancy, with an incidence of 5 to 10%.[3] However, this incidence might be underestimated due to underreporting. Health professionals at all levels of medical care need to know the clinical and laboratory manifestations to diagnose this disease. That is why protocols are required to guide physicians to know how to deal with hypertension in pregnancy and achieve better maternal and perinatal outcomes, especially in the developing countries.[4]

In the last few years, there has been a decrease in the rates of complications related to preeclampsia in the developed countries, but this is not being observed in the developing ones, probably due to the lack of hospital resources and failure of medical and prenatal care.[5] Besides that, the incidence of preeclampsia has increased by 25% in the United States in the past 20 years for unknown reasons.[2]

Stroke, HELLP syndrome (Hemolysis, Elevated Liver Enzymes, Low Platelets), eclampsia, hemorrhage, and cardiopulmonary and renal complications are the main causes of maternal mortality associated with preeclampsia. Clinical warning signs, high blood pressure, and laboratory abnormalities are important variables that need to be consistently observed to improve the immediate treatment.[6] Hopefully, due to the widespread use of magnesium sulfate and the improved prenatal care, the rate of eclampsia has decreased.[7]

A difficulty in the medical care of women with hypertension is that, when they have signs or symptoms of severe preeclampsia, the disease may progress rapidly to clinical worsening or death, and this may occur during pregnancy, labor, or even in the postpartum period.[8] For this reason, an online calculator was recently developed to predict severe maternal outcomes, called full preeclampsia integrated estimate of risk (PIERS) calculator. This tool provides the percentage of risk of having adverse maternal outcomes within 48 hours up to a week after assessment by analyzing gestational age, presence of dyspnea or chest pain, O_2 saturation, levels of serum creatinine, and liver transaminases.[9]

Currently, only the use of calcium and low-dose aspirin are considered effective for preventing preeclampsia. Therefore, the adequate prenatal care is an important preventive measure allowing clinicians to prescribe these medications at the appropriate time and detect risk factors such as previous personal or family history of preeclampsia, chronic hypertension, kidney disease, diabetes, autoimmune disorders of connective tissue, thrombophilia, black ethnicity, obesity, and primigravida.[8]

In conclusion, preeclampsia is still an important cause of maternal mortality, acute and long-term complications worldwide, and this is an alert for physicians. Aiming to improve maternal and perinatal outcomes, protocols are essential in the health services to guide professionals for the care of pregnant women with arterial hypertension. This measure may optimize early detection, treatment and prevention of the disease, especially in developing countries.

Conflict of Interests

The authors have no conflict of interests to declare.

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FEBRASGO POSITION STATEMENT

Outpatient care for pregnant and puerperal women during the COVID-19 pandemic

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

Key-points:

- The COVID-19 pandemic remains a rapidly evolving situation, and as new research and data become available, clinical care recommendations should be refined to reflect the most current information.
- Importance of maintaining outpatient care for pregnant and postpartum women during the pandemic period due to the new coronavirus
- Provide care so that consultations do not become a place of risk for contamination of users and health professionals. This care must involve the physical space, use of PPE, guidance from professionals and pregnant and postpartum women
- Importance of vaccination of pregnant women for influenza, thus facilitating the differential diagnosis of respiratory syndromes
- Provide strategies for health education in prenatal care and postpartum care using new technologies
- The more expanded the testing for COVID-19, the more it provides protection for professionals and patients

Recommendations

- During the pandemic and, as long there is a risk of contamination by COVID-19, outpatient care for pregnant and puerperal women needs to be maintained, however additional strategies need to be implemented;
- Restructure health services in order to screen symptomatic individuals, provide adequate use of Personal Protective Equipment (PPEs) by health professionals;
- Promote social distancing without leaving aside the welcoming and humanization aspect of the care for pregnant and postpartum women;
- Think new ways to carry out groups of pregnant women minimizing risk of contamination, using educational videos, mobile phone applications, online groups;
- Whenever possible, universal screening promotes greater security for women, newborns and health professionals and should be done;

Background

On March 11th, 2020, the World Health Organization (WHO) decreed a pandemic state for the coronavirus 19, named COVID-19. The rapid evolution of the outbreak, which spread across all continents, generated universal concern, not only for the number of deaths, but also for the worldwide impact in the most diverse spheres.[1] In order to prevent further spread of the epidemic, people are advised to stay at home, avoid crowds and promote social distancing, which poses a dilemma for many women during the pregnant puerperal cycle about the possibility of going to hospitals, doctors's offices, laboratories or primary health care units.

Prenatal care is known to be important throughout pregnancy, to identify risk, prevention and management of pregnancy-specific diseases or pre-existing pathological conditions, patient education and health promotion.[2]

And the same risks and questions apply to outpatient postpartum consultations, a period in a woman's

life that even under normal conditions is neglected. Currently, the postpartum period has been the focus of many new studies due to its importance in caring for women, not only in the immediate postpartum period, but also in the long term, considering reproductive planning, mental health, self-care and also in the follow-up guidance for comorbidities.

So far, there are disagreements about what is the risk for pregnant women,in terms of susceptibility or adverse results in SARS-CoV-2 infection (severe acute respiratory syndrome by coronavirus) compared to the general population. Some respiratory diseases, such as H1N1, have been associated with worse results in pregnant women, but initial studies on COVID-19 infection among pregnant women have not shown this increased risk.[3,4] However, we need to cite national data with a significant increase in maternal mortality from infection with the new coronavirus.[5]

More recent data show a greater concern among affected pregnant women. Serious manifestations of the disease, admission to the ICU and mechanical ventilation were more frequent among pregnant women, although there is no description of increased mortality rates so far.[6] Adverse perinatal results such as increased rates of prematurity and fetal death have also been reported.[7] However, the mortality data should be revised and adjusted by age, and may bring new results in the future.

Pregnant women with chronic diseases (hypertension, diabetes) or obesity should be considered at higher risk for complications of COVID-19 infection as well as the general population.[5]

However, it is known that prenatal and postnatal follow-up should not be suspended, given the importance of monitoring and following-up in decreasing maternal-fetal, neonatal and puerperal risks.

How to structure the changes in outpatient care for pregnant and puerperal women while there is a risk of infection for COVID-19?

The risk of going to health units, doctor's offices or just leaving home should be considered at each scheduled prenatal visit. Alternative approaches in providing antenatal care have been proposed as a strategy in the effort to control the spread of COVID-19 among patients, caregivers and staff. Even if evidence is limited in relation to the safety and effectiveness of these approaches, several international entities recognize the need to implement innovative strategies during this rapidly evolving public health emergency, considering the differences in the care environments and the population's risks.

Thus, consultations should be used in the best possible way with the greatest amount of clarification and guidance that can be carried out. We must consider grouping the components of the treatment (for example, vaccines, blood glucose tests, ultrasound examinations, etc.) However, for some situations of high-risk pregnant women and in the third trimester, there is no way to guide waiving or spacing of prenatal visits. Frequent situations such as those of pregnant women with any form of hypertension, diabetes, fetal growth restriction cannot be left without qualified outpatient follow-up as it could increase the risk of perinatal morbidity and mortality. In addition to these, other conditions also cannot go without close monitoring, as social vulnerability and serious illnesses (heart disease, autoimmune diseases, neoplasms).

The burden of this unprecedented situation we are experiencing can be somehow minimized with the organization of health services that assist pregnant and postpartum women.

Since the beginning of the pandemic, numerous service protocols have been created and updated at a unique speed that makes it difficult to stay updated on the topic. However, some precautions are consensus both in the structuring of services and in individual care. It is recommended to review the existing flows for early identification and immediate care in a specific location for "COVID care" for symptomatic pregnant and postpartum women, optimizing care. And, in a general way for all pregnant and postpartum women to reduce their stay in Health Units.[8]

What changes in the structuring of services should be implemented?

- If possible, previously telephone contact the patient to ask about covid-19 signs and symptoms: fever, cough, runny nose, body pain, diarrhea, abdominal pain. If symptoms are present, advise seeking specific care for patients at risk of covid-19 and not going to the routine prenatal/ postpartum outpatient service to avoid contact with other pregnant/postpartum women;
- Pre-service screening for every pregnant and puerperal woman arriving at outpatient clinic service with questions about the signs and symptoms described above and temperature measurement;
- To favor the social distancing between users of the health service, with the delimitation of the physical space used and the marking of armchairs / chairs in the waiting room. To avoid a greater number of people in the same place, during this period the routine presence of a companion should be avoided, which can be reviewed in special situations;
- And that health services have different entrances, physical space and work teams for the care of pregnant and puerperal women with and without symptoms and signs suggestive of SARS-Cov2.

Thus, it is essential to reorganize the health service to provide adequate care for pregnant and puerperal women.

What changes in individual care should be made?

- The doctor should wash his hands before and at the end of the consultation, in the absence of a suitable place for hand washing, hand sanitizer with alcohol gel can be used.[5]
- The use of medical masks (surgical and N95 / PPF2) is a preventive measure that limit the spread of respiratory diseases, including COVID-19. However, the use of a mask alone is not sufficient to provide the appropriate level of protection. Other equally relevant measures must be adopted. When using masks, this measure must be combined with hand hygiene and other preventive measures to prevent COVID-19 person-to-person transmission. Cloth masks, homemade, with common and low-cost materials should be used by pregnant women as an additional voluntary public health measure.[9]
- Use of eye protection (Faceshield / protection glasses) by health professionals throughout outpatient care. This material must be reused after cleaning and disinfection. We emphasize that ordinary glasses for refractive corrections do not replace the recommended eye protection.[5]
- Guide and reinforce the importance of influenza vaccination during prenatal care.
- Evaluate the possibility of extending the interval between consultations, as long as it does not compromise clinical and obstetric issues.
- Optimize collection of laboratory exams, ultrasounds and other subsidiary exams, so that they are carried out on the same days as the consultations, within the possibilities of the services, avoiding, whenever possible, leaving the home and excessive exposure of pregnant women and postpartum.
- Due to the impossibility of keeping the distance safe, there is a great risk of contamination during ultrasound (USG). Therefore, ultrasound examinations should be reduced to the essential minimum and patients should attend without companions. For the pandemic period, the following are recommended: USG in the first trimester between 11 and 13 weeks (to date pregnancy and the first trimester morphological exam); 18 to 24 weeks USG (for second trimester morphological assessment). The third trimester exam should only be performed if there is a clinical indication. In pregnancies with maternal or fetal pathologies, strict monitoring with the minimum necessary frequency is justified. In pregnant women with infection confirmed by COVID 19, ultrasound exams should be postponed as much as possible to reduce the spread of the virus.[10]

How to manage some medications used frequently in pregnancy?

Below are some guidelines on the use of some medications that may be needed during prenatal care and what changes if you suspect or confirm a COVID-19 infection:

- Betamethasone: - the Center for Disease Control and Prevention (CDC) initially recommended avoiding glucocorticoids in pregnant women positive for COVID-19, because an association with increased risk of mortality in influenza patients (coronavirus infection in MERS-CoV) has been shown. Due to the neonatal benefits of prenatal administration of betamethasone for fetal lung maturation between 24 + 0 and 33 + 6 weeks, when there is a risk of preterm birth, the American College of Obstetrics and Gynecology (ACOG) continues recommending its use for the standard indications for pregnant patients even those with suspected or confirmed for COVID-19.[11] However, these decisions can be individualized, always weighing the neonatal benefits with the risks of possible harm to the pregnant woman.
- Low dose aspirin - For pregnant women without COVID-19, ACOG advises maintaining the use of low dose aspirin as clinically indicated (for example, prevention of pre-eclampsia). For those with suspicion or confirmation of COVID-19 with indication of low-dose aspirin, the decision to continue the drug must be individualized, and it is usually possible. Given the lack of data, the European Medicines Agency and the World Health Organization do not recommend avoiding NSAIDs in patients with COVID-19 when clinically indicated.[12]

Asymptomatic obstetric patients and universal testing - What do we know?

In the first study in the USA testing COVID-19 in 100% of pregnant women (n = 215), 1.9% were symptomatic and tested positive for COVID-19, among asymptomatic 84.6% tested negative and 13.5 % tested positive for COVID-19. This study was in parturient women, but probably the proportion among pregnant women in prenatal care is similar.[13] Also in the USA, another study drew attention to the low prevalence of COVID-19 (2.7% [5/188]) in universal testing among pregnant women and puerperal women, and among asymptomatic, only 2 positive cases, which were negative in the 2nd sample.[14] However, in a study in Japan, the percent-

age of positive tests among asymptomatic obstetric patients was 4%.[15]

So far, we do not have universal testing data in Brazil, but national studies are being carried out for this purpose. While we do not have all data, everyone, health professionals and pregnant/puerperal women must protect themselves and prevent the spread of the virus.[16]

How to innovate in antenatal education and mental health care?

Social distancing makes it impossible to carry out groups pregnant women. Antenatal education groups have been increasingly valued, due to the possibility of different orientations by a multidisciplinary team, not only about the evolution of pregnancy and childbirth. These groups deal with issues that are important for women and that are usually superficially addressed in individual medical appointments, due to lack of time or other difficulties. Rights of pregnant women, possibilities of contraception in the immediate postpartum or postpartum consultation, nutritional aspects, domestic violence, depression and anxiety, physical activity, breastfeeding and care for newborns are topics that need to be discussed during prenatal care , so that women feel more empowered and have a positive experience in their pregnancy and postpartum period.(2)

It is necessary to think of new ways to reinvent the activities carried out in groups for pregnant women, through the use of educational videos, mobile phone applications, online groups, in short, all types of educational / informational material that could be offered without risk of contamination. In addition to making the most of individual consultation time for these approaches.

Another differential of this pandemic period is the increase in anxiety, sadness and fear. The uncertain scenario related to the disease, pregnant and puerperal women infected or not with COVID-19 may be experiencing intense psychological suffering, which can cause serious consequences in terms of mental health. (17) It would be interesting for pregnant and puerperal women to have a way of communicate with health professionals in case of psychological distress or to resolve doubts during this period.

Studies have shown poor sleep quality in pregnant women and it is observed that sleep disorders seem to worsen throughout pregnancy, which may have impacts on labor, maternal and fetal health. Poor sleep quality can be even greater in these pandemic periods with social distancing, reduced leisure activities and anxiety.(18,19)

All these details in outpatient care must include women in pregnancy in the postpartum period. We cannot neglect women in the postpartum period, as it is known that most maternal deaths occur in the puerperium and are related to delay or difficulty in accessing health services after the woman's hospital discharge.

Final considerations

The priority today is to reduce the public health burden of COVID-19. We obstetricians and gynecologists have an obligation to help implement simple measures to make pregnant women and postpartum women aware of safe practices such as hand hygiene, wearing masks, social distancing, cough etiquette, staying at home whenever possible and disinfecting surfaces often. For as long as there is no vaccine, these precautions are what can reduce contamination and save lives. We cannot refrain from offering qualified care focused on the needs of each woman, and try to provide, even in times of exception like this pandemic, a positive and safe experience during pregnancy, childbirth and the puerperium as recommended by the WHO good practices.

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