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Editorial

RBGO - First Impact Factor: 1.2

Marcos Felipe Silva de Sá[1]

[1] Editor RBGO

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RBGO - Revista Brasileira de Ginecologia e Obstetrícia is proud to announce the achievement of its first Impact Factor. This accomplishment supports RBGO's position as the leading Gynecology and Obstetrics journal in Latin America.

Having a high-quality ObGyn journal published in Brazil has been the goal of Brazilian researchers so that the high-quality science produced here could be increasingly disseminated internationally. As a Society that proposes to support the training and education of professionals in Gynecology and Obstetrics, the Brazilian Federation of the Association of Gynecology and Obstetrics – FEBRASGO- also understood this need and did its utmost to offer our Brazilian researchers, residents, postgraduate students, and professionals a high-level and internationally competitive journal.

In the last seven years, RBGO has been completely reformulated: an English edition was made available, it became an "open access" journal, its board of associate editors was restructured, it is now indexed in the main databases of international scientific literature and the periodicity was regularized. All these improvements made it an international journal that is offered cost free to the authors. The indicators below (►**Fig. 1**) demonstrate the positive effect of the measures taken by RBGO. The main goal was to achieve the Impact Factor which has a special meaning since it places the journal on the list of the widely disseminated journals internationally.

Finally, this June, RBGO was awarded an Impact Factor of 1.2 by Clarivates after a rigorous evaluation during the past 5 years. We take advantage of this historic moment to invite

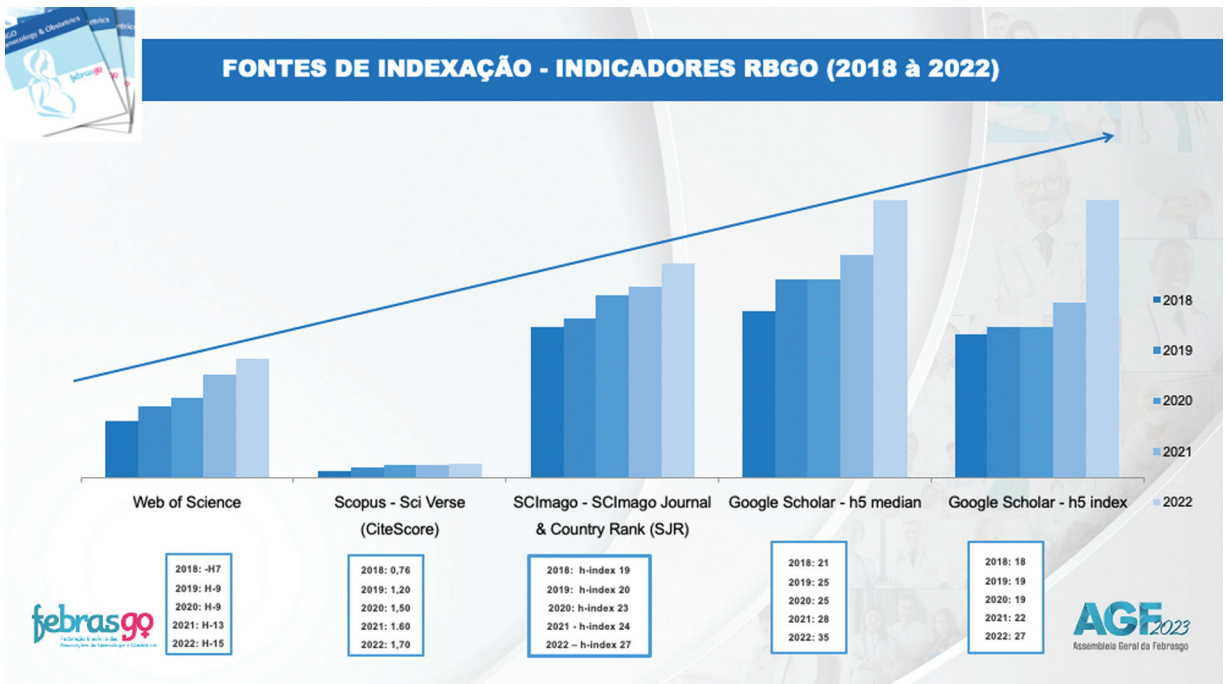

Fig. 1 RBGO performance in the previous five years according to international indicators.

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all authors to join our academic community! There are many benefits of publishing in RBGO which, from now on, gains greater importance and competitiveness in the dissemination of works published in the journal. Our great challenge in the future is to maintain this "status" with a pretentious desire to ascend.

We thank the authors who submitted their manuscripts to RBGO, the Associate Editors and "anonymous" reviewers, the Editorial Office team and Febrasgo collaborators. A special thanks to the Executive Board of Febrasgo, who believed in the proposal of the NEW RBGO and offered their unconditional support to the Editors.

Increased Cesarean Section Rates during the COVID-19 Pandemic: Looking for Reasons through the Robson Ten Group Classification System

Aumento das taxas de cesárea durante a pandemia de COVID-19: procurando explicações por meio da Classificação de Robson

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Abstract

Objective To compare cesarean section (CS) rates according to the Robson Ten Group Classification System (RTGCS) and its indications in pregnant women admitted for childbirth during the first wave of the coronavirus disease 2019 (COVID-19) pandemic with those of the previous year.

Materials and Methods We conducted a cross-sectional study to compare women admitted for childbirth from April to October 2019 (before the pandemic) and from March to September 2020 (during the pandemic). The CSs and their indications were classified on admission according to the RTGCS, and we also collected data on the route of delivery (vaginal or CS). Both periods were compared using the Chi-squared (χ^2) test or the Fisher exact test.

Results In total, 2,493 women were included, 1,291 in the prepandemic and 1,202 in the pandemic period. There was a a significant increase in the CS rate (from 39.66% to 44.01%; $p = 0.028$), mostly due to maternal request (from 9.58% to 25.38%; $p < 0.01$). Overall, groups 5 and 2 contributed the most to the CS rates. The rates decreased among group 1 and increased among group 2 during the pandemic, with no changes in group 10.

Conclusion There was an apparent change in the RTGSC comparing both periods, with a significant increase in CS rates, mainly by maternal request, most likely because of changes during the pandemic and uncertainties and fear concerning COVID-19.

Keywords

- cesarean section rates
- COVID-19
- Robson classification

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Resumo

Objetivo Comparar as taxas de cesárea segundo a Classificação de Robson, assim como suas indicações, em mulheres admitidas para parto durante a primeira onda de doença do coronavírus 2019 (*coronavirus disease 2019*, COVID-19, em inglês), com as do ano anterior.

Materiais e Métodos Conduzimos um estudo transversal que comparou as mulheres admitidas para parto entre abril e outubro de 2019 (pré-pandemia) e entre março e setembro de 2020 (durante a pandemia). As cesarianas e as suas indicações foram classificadas conforme o sistema proposto por Robson, e obteve-se a via de parto (vaginal ou cesárea). Ambos os períodos foram comparados usando-se os testes do Qui quadrado ou o exato de Fisher.

Resultados Ao todo, 2.943 mulheres foram incluídas, das quais 1.291 antes da pandemia e 1.202 durante a pandemia. A taxa de cesárea aumentou significativamente (de 39.66% para 44,01%; $p = 0{,}028$), principalmente devido a desejo materno (de 9,58% para 25,38%; $p < 0{,}01$). Os grupos 5 e 2 foram os que mais contribuíram para as taxas de cesárea. Durante a pandemia, o grupo 1 reduziu sua frequência, enquanto o grupo 2 a aumentou.

Conclusão Houve uma aparente mudança nas características da população conforme a classificação de Robson. Observou-se significativo aumento nas taxas de cesárea, principalmente por desejo materno, o que reflete possíveis incertezas e medos relacionados à COVID-19.

Palavras-chave

- taxas de cesárea
- COVID-19
- classificação de Robson

Introduction

In 2020, the world faced a new and challenging situation: the coronavirus disease 2019 (COVID-19) pandemic, as declared by the World Health Organization (WHO) on March,[1] with significant consequences and increased maternal mortality rates.[2] Brazil, a country with heterogeneous social and economic conditions, was one of the most affected in terms of the rates of infections and mortality among pregnant women.[3]

During pregnancy and the postpartum period, COVID-19 is associated with a high risk of developing severe acute respiratory syndrome (SARS); however, it also affects maternal anxiety due to the fear of complications during pregnancy and childbirth.[4] In addition, companions have experienced restrictions in the delivery rooms, leaving pregnant women with less support during delivery.[5] Regardless of the risks and fear, COVID-19 infection, especially in mild cases, is not an indication for cesarean delivery.[5–7]

The WHO states that "there is no justification for any region to have a cesarean rate higher than 10-15%."[8] However, there has been a progressive increase in cesarean rates around the world.[9] In 2016, the WHO, concerned about the global increase in cesarean rates and the negative consequences on maternal and child health, recommended the implementation of a universal classification to compare cesarean rates in different hospitals, cities or regions, and even within the same place, in different time frames, and proposed the use of a 10 group classification, known as the Robson Ten Group Classification System (RTGCS), which has been previously validated.[9,10]

In Brazil, cesarean section (CS) rates (CSRs) have significantly increased in recent decades, at an alarming pace, from 38% in 1994 to 50% in 2009, reaching 57% in 2018.[11,12] There is a concern that the COVID-19 pandemic may have increased even more such rates.

The present study intends to evaluate the impact of the COVID-19 pandemic on the CSRs at a secondary public hospital in Southeastern Brazil. We also aimed to compare the pandemic period to the previous year, as well as to describe the contribution of each Robson group and the main indications for CS in the two periods.

Materials and Methods

The present was a retrospective, cross-sectional study in which we reviewed the medical charts of all women admitted for childbirth at Hospital Estadual Sumaré (HES) from March to September 2020 (during the COVID-19 pandemic) and from April to October 2019 (before the pandemic). We determined the overall CSRs in both periods and the ten groups of the RTGCS, which considers the following obstetric characteristics: parity, previous CS, gestational age, onset of labor, fetal presentation, and the number of fetuses. These characteristics are mutually exclusive, fully inclusive, and clinically relevant, leading to a simple classification and enabling comparisons over time within a unit and among different units (►**Chart 1**).

Data were inserted into a Microsoft Office 2019 Excel (Microsoft Corp., Redmond, WA, United States) spreadsheet and analyzed with the Epi Info (Centers for Disease Control and Prevention, Atlanta, GA, United States) software, version

Chart 1 Robson Ten Group Classification System[10]

Group	Description
1	Nulliparous, singleton, cephalic, ≥ 37 weeks of gestation, in spontaneous labor
2	Nulliparous, singleton, cephalic, ≥3 7 weeks of gestation, induced labor or cesarean section before labor
3	Multiparous (excluding previous cesarean section), singleton, cephalic, ≥ 37 weeks of gestation, in spontaneous labor
4	Multiparous without a previous uterine scar, with singleton, cephalic pregnancy, ≥ 37 weeks of gestation, induced or cesarean section before labor
5	Previous cesarean section, singleton, cephalic, ≥ 37 weeks of gestation
6	All nulliparous with a single breech
7	All multiparous with a single breech (including previous cesarean section)
8	All multiple pregnancies (including previous cesarean section)
9	All women with a single pregnancy in transverse or oblique lie (including those with previous cesarean section)
10	All singleton, cephalic, < 37 weeks of gestation (including previous cesarean section)

7.2.5. We initially considered the overall CSR in both periods, determined and compared the frequency of all RTGCS groups, the contribution of each group to the CSRs, and the indication for the CS. The results using the RTGCS were presented as recommended by the WHO.[12]

To estimate the sample size, we considered that the population covered by the maternity hospital was of 286 thousand inhabitants, and supposed that CSR would be of around 40%. For a confidence interval (CI) of 99.99%, the minimum number of included cases would be 1,413.

Differences between groups and over the considered periods were presented using the Chi-squared (χ^2) test to determine the statistical significance of the data collected during the two periods, with values of $p < 0.05$ considered significant. We also obtained prevalence ratio (PR) and CIs to compare the two periods.

As the present is a retrospective study, without any clinical intervention, with the review of medical records and also considering that there is no postpartum follow-up at the institution, the informed consent form was waived by the local ethics committee, which approved the research protocol under CAAE 26439119.3.0000.5404. All the principles defined in the Declaration of Helsinki and in Resolution no. 466/12 of the Brazilian National Health Council were respected.

Results

A total of 2,493 deliveries were considered, 1,202 during the pandemic and 1,291 before it (►**Fig. 1**). ►**Table 1** presents the overall distribution of deliveries and CSs during both periods. Group 3 was the most frequent in the sample, with 547 deliveries, followed by groups 5 (546 deliveries) and 1 (474 deliveries). There were 244 (9.79%) preterm deliveries during the period.

The overall CSR was of 41.76% ($n = 1{,}041$). Groups 5, 2 and 10 were the most important contributors to the rate (►**Table 1**).

►**Table 2** shows that there were important differences regarding the frequency of each RTGCS in the two periods evaluated. The prevalence among groups 2 and 5 increased during the pandemic, from 12.01% to 15.31% (PR: 1.275; CI: 1.045–1.555; p-value = 0.02) and from 20.29% to 23.63% (PR: 1.164; CI: 1.004–1.350; p-value = 0.04) respectively. In the other hand, the prevalence in group 1 decreased from 20.91% to 16.97% (PR: 0.811; CI: 0.688–0.956; p-value = 0.01).

The overall CSR increased from 39.66% before the pandemic to 44.01% during it (PR: 1.110; CI: 1.011–1.217; p-value = 0.03). Data are presented in ►**Table 3**. The CSR increased in almost every group, except groups 4 and 8. It presented a marked increase in group 5, in which the rate rose from 66.41% to 73.24% (PR: 1.103; CI: 0.987–1.232; p-value = 0.08). It also significantly increased among women undergoing induction of labor (groups 2 and 4), among whom the combined CSR increased from 32.92% to 47.02% (PR: 1.428; CI: 1.186–1.719; p-value < 0.01).

To better understand the reasons behind the increase in the CSR, we observed the three major indications for CS in both periods, according to the medical charts. Before the pandemic, fetal distress (26.95%) was the leading indication, followed by repeated CS (15.63%) and maternal request (9.18%). During the pandemic, maternal request reached the first position (25.33%; PR: 2.759; CI: 2.025–3.759; p-value < 0.01), while

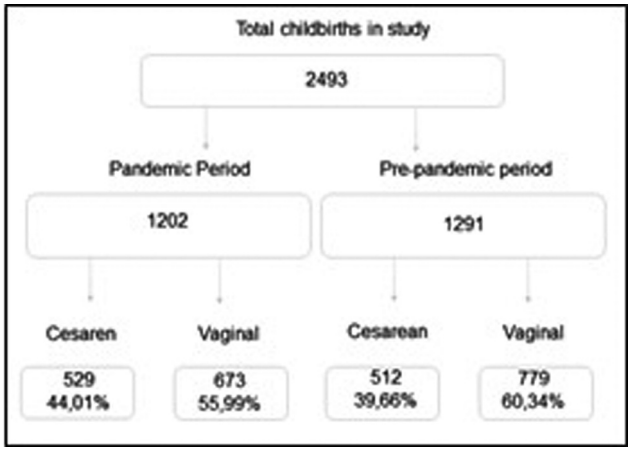

Fig. 1 Flowchart of the women included in the present study.

Table 1 Overall distribution of deliveries and cesarean sections (CSs) in a Brazilian maternity during a two-year period

Group	Number of CSs	Number of women	Percentage of women	CS rate (%)	Absolute group contribution to overall CS rate	Relative contribution of group to overall CS rate
1	90	474	19.01%	18.99%	3.61%	8.65%
2	221	339	13.60%	65.19%	8.86%	21.23%
3	32	547	21.94%	5.85%	1.28%	3.07%
4	69	219	8.78%	31.51%	2.77%	6.63%
5	382	546	21.90%	69.96%	15.32%	36.70%
6	23	23	0.92%	100.00%	0.92%	2.21%
7	48	51	2.05%	94.12%	1.93%	4.61%
8	41	47	1.89%	87.23%	1.64%	3.94%
9	3	3	0.12%	100.00%	0.12%	0.29%
10	132	244	9.79%	54.10%	5.29%	12.68%
Total	1.041	2.493	100.00%	41.76%		100.00%

Table 2 Frequency of each group in the Robson Ten Group Classification compared before and during the pandemic

Group	Prepandemic: n (%)	Pandemic: n (%)	Prevalence ratio (confidence interval)	*p*-value
1	270 (20.91)	204 (16.97)	0.811 (0.688–0.956)	0.01
2	155 (12.01)	184 (15.31)	1.275 (1.045–1.555)	0.02
3	289 (22.39)	258 (21.46)	0.958 (0.827–1.112)	0.58
4	118 (9.14)	101 (8.40)	0.919 (0.713–1.185)	0.52
5	262 (20.29)	284 (23.63)	1.164 (1.004–1.350)	0.04
6	17 (1.32)	6 (0.50)	0.379 (0.150–0.958)	0.03
7	30 (2.32)	21 (1.75)	0.752 (0.433–1.306)	0.30
8	30 (2.32)	17 (1.41)	0.609 (0.337–1.10)	0.09
9	1 (0.08)	2 (0.17)	2.148 (0.195–23.66)	0.52
10	119 (9.22)	125 (10.40)	1.128 (0.889–1.432)	0.32
1 to 4	832 (64.45)	747 (62.15)	0.964 (0.901–1.024)	0.23
2 and 4	285 (23.71)	273 (21.15)	1.121 (0.969–1.300)	0.12
1 and 3	559 (43.33)	462 (38.44)	0.888 (0.807–0.967)	0.01

Table 3 Overall and per Robson Ten Group Classification rates of cesarean section compared before and during the pandemic

Group	Prepandemic: n (%)	Pandemic: n (%)	Prevalence ratio (confidence interval)	*p*-value
1	49 (18.15)	41 (20.10)	1.101 (0.783–1.608)	0.59
2	101 (65.16)	120 (65.22)	1.001 (0.856–1.170)	0.99
3	15 (5.19)	17 (6.59)	1.269 (0.647–2.490)	0.49
4	38 (32.20)	31 (30.69)	0.953 (0.643–1.412)	0.81
5	174 (66.41)	208 (73.24)	1.103 (0.987–1.232)	0.08
6	17 (100.00)	6 (100.00)	NS	NS
7	28 (93.33)	20 (95.24)	1.020 (0.891–1.168)	0.78
8	16 (94.12)	25 (83.33)	0.885 (0.725–1.080)	0.29
9	1 (100.00)	2 (100.00)	NS	NS
10	64 (53.78)	68 (54.40)	1.011 (0.803–1.275)	0.92
1 to 4	203 (24.40)	209 (27.98)	1.147 (0.971–1.354)	0.10
2 and 4	134 (32.92)	134 (47.02)	1.428 (1.186–1.719)	< 0.01
1 and 3	64 (11.45)	58 (12.55)	1.097 (0.786–1.530)	0.59
Total	512 (39.66)	529 (44.01)	1.110 (1.011–1.217)	0.03

Table 4 The three major indications for cesarean section before and during the pandemic

Indication	Prepandemic: n (%)	Pandemic: n (%)	Prevalence ratio (confidence interval)	*p*-value
Maternal request	47 (9.18)	134 (25.33)	2.759 (2.025–3.759)	< 0.01
Fetal distress	138 (26.95)	111 (20.98)	0.778 (0.626–0.968)	0.02
Repeated cesarean section	80 (15.63)	78 (14.74)	0.944 (0.708–1.258)	0.69

fetal distress decreased its contribution (20.98%; PR: 0.778; CI: 0.626–0.968; *p*-value = 0.02). ►**Table 4** summarize these findings.

We observed that the frequency of CSs due to maternal request increased significantly among women undergoing induction of labor. In group 2, maternal request for CS increased from 11.80% to 36.70% (PR: 3.091; CI: 1.733–5.552; *p*-value < 0.01). It also increased in group 4 (from 10.50% to 33.33%; PR: 3.173; CI: 1.105–9.105; *p*-value = 0.021). Among women with at least 1 previous CS, who were included in group 5, the maternal request rose from 14.90% to 34.30% (PR: 2.297; CI: 1.543–3.431; *p*-value < 0.01).

Discussion

During the pandemic, there was an overall increase in CSRs, mainly due to increased maternal request, in addition to an increase in the number of primiparous women admitted for induction of labor or elective CS (group 2), as well as a reduction in the admission of primiparous women in spontaneous labor (group 1).

Comparing data from our hospital with data from the Southeastern region of Brazil in a study[13] conducted from 2014 to 2016 regarding the distribution in the Robson groups, some differences were observed before the pandemic, especially in groups 1 (20.91% versus 14.4%) and 2 (12.01% versus 20.3%), which became more similar during the pandemic, when we noticed a decrease in group 1 (16.97%) and an increase in group 2 (15.31%).

A Brazilian study[14] among pregnant women reported that only 1/3 (27.6%) preferred CS at the beginning of antenatal care; however, 73.2% of those with a previous CS performed in the private health care system wanted a new cesarean, and fear of vaginal birth was the most mentioned factor for this choice, especially among primiparous women. On the other hand, most of the questioned obstetricians confirmed that they performed CSs through defensive medicine, concerned with the risk of judicialization.[15] These two issues, together with the lack of prior information about childbirth, can help explain the rate of cesarean deliveries in Brazil.

A study[16] comparing 3 months of the pandemic with the previous year showed an increase in nulliparous pregnant women (9% versus 12.5%) and pregnant women who arrived at the hospital in a more advanced stage of labor (26.8% versus 40%) during the pandemic. Another retrospective and comparative study[17] conducted in the United Kingdom, no significant differences were found in the frequency of cesarean births (31.2% versus 29.4%; *p*-value = 0.039). These results are different from our findings, since our data showed a decrease in the number of women admitted in spontaneous labor and an increase in CSs. This suggests that fear of exposure to COVID-19 and its potential risks may have delayed access to health care for women in labor; nevertheless, it could also have led to earlier requests for CS, prior to labor.

An important confounding factor in our results was the institution of a state law that guaranteed pregnant women the right to choose the mode of delivery, without the necessary explanation of the risks and benefits of the procedure during prenatal care. The impact of this law may have contributed, concurrently to the pandemic, to the increase in CSRs observed in the present work.

Important issues, such as the impossibility of having a companion, the length of stay for induction until delivery, reduction in medical and healthcare staff due to absences related to COVID-19 and even structural changes in the hospital may have led many pregnant women and doctors to choose CS. Continuous support during childbirth, by a person chosen by the woman, has significant benefits for the parturient and her children.[18] During the pandemic at our institution, not even patients without COVID had companions during childbirth.

The present study has several limitations, the retrospective data collection through medical chart reviews; however, we consider that this problem is partially mitigated, since all deliveries that occurred at the facility are audited weekly, and data on parity, mode of delivery, and the Robson Classification are reviewed, and divergences are prospectively corrected. In the other hand, we believe that the present is the first study that evaluated CSRs using the Robson's Classification during the COVID-19 pandemic in Brazil.

The hospital in which the present study was conducted was not a referral center for COVID-19 during pregnancy and universal screening was not implemented, with no data on the prevalence of the infection among women admitted for childbirth. However, it was a referral for COVID-19 among adults, and that supported many of the structural changes with impact on obstetric care, such as those aforementioned.

Conclusion

Our results show that there was an increase in inductions among primiparous women and in the overall CSR during the analyzed period, with increased maternal requests for the procedure, especially among patients with a previous CS.

Contributions

CEBS performed data collection, wrote the first draft of the manuscript, and reviewed its final version. JPSG had the original idea, performed the statistical analysis, and reviewed the final version of the manuscript. MLC also had the original idea, coordinated the group, and reviewed the final version of the manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

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A Study of the Current Scenario of the Obstetrics and Gynecology Residency during the COVID-19 Pandemic

Um estudo do cenário atual da residência em obstetrícia e ginecologia durante a pandemia de COVID-19

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Abstract

Objective To analyze the impact of the COVID-19 pandemic on the residency of gynecology and obstetrics in São Paulo.

Methods Cross-sectional study developed by representatives of residents of the Association of Gynecology and Obstetrics of the State of São Paulo (SOGESP, in the Portuguese acronym). Data were collected from questionnaires applied to gynecology and obstetrics residents registered on the SOGESP website in February 2022. The interviewees answered about the repercussions of the pandemic on medical residency and whether they had technical and psychological support during the period.

Results A total of 247 questionnaires were collected from residents of gynecology and obstetrics. The residents had an age of 28.3 ± 3 years old, and most of them were female (88.4%). The displacement to COVID care was reported by 62.34% of the students, but only 35.6% reported completely adequate personal protective equipment and only 7.7% reported complete theoretical and technical instruction to support these patients. Almost all of the interviewees stated that the gynecology sector was the most affected. The majority of the interviewees considered that the second-year residents had the greatest loss, and more than half of the residents in the 1st and 2nd

Keywords
- internship and residency
- gynecology
- COVID-19
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year said they wished to give up their residency during the pandemic. More than 80% of the residents reported online theoretical classes and/or presentation of articles, reinforcing the fact that virtual activities gained a greater space within the medical residency.

Conclusion The pandemic impacted the residency in greater proportion in outpatient clinics and gynecological surgeries, also interfering with the physician's desire to continue with the program.

Resumo

Objetivo Analisar o impacto pandemia de COVID-19 sobre a residência de ginecologia e obstetrícia do Estado de São Paulo.

Métodos Estudo transversal desenvolvido por representantes dos residentes da Associação de Ginecologia e Obstetrícia do Estado de São Paulo (SOGESP). Foram coletados dados de questionários aplicados aos residentes de ginecologia e obstetrícia cadastrados no site da SOGESP em fevereiro de 2022. Os entrevistados responderam sobre repercussões da pandemia sobre a residência médica e se tiveram suporte técnico e psicológico durante o período.

Resultados Foram levantados 247 questionários de residentes de ginecologia e obstetrícia. Os residentes apresentaram idade de $28{,}3 \pm 3$ anos, sendo a maioria do sexo feminino (88,4%). O deslocamento para "covidários" foi referido por 62,34% dos avaliados, porém somente 35,6% referiram equipamento de proteção individual completamente adequado e apenas 7,7% referiram instrução completa teórica e técnica para o suporte destes pacientes. Quase a totalidade dos entrevistados afirmou que o setor de ginecologia foi o mais afetado. A maioria dos entrevistados considerou que o os residentes do segundo ano foram os que tiveram maior prejuízo, sendo que mais da metade dos residentes do 1° e 2° ano afirmou ter desejado desistir da residência durante a pandemia. Mais de 80% dos residentes referiram aulas teóricas e/ou apresentação de artigos online, reforçando o fato de que as atividades virtuais ganharam um espaço maior dentro da residência médica.

Conclusão A pandemia impactou nas residências em maior proporção nos ambulatórios e cirurgias ginecológicas, interferindo também sobre o desejo do médico de seguir com o programa.

Palavras-chave
- residência médica
- ginecologia
- COVID-19
- educação médica

Introduction

The worldwide pandemic of COVID-19, which surprised the world in the year 2020, was a landmark in practically all professional branches. Several companies had to close their doors or move their activities to "home-office," while a minority continued to work face-to-face, as in the case of healthcare professionals. As for medical residency, the reality varied depending on the specialty, due to the cancellation of elective surgeries and outpatient clinics considered non-essential. In addition, many resident doctors were allocated to areas of exclusive care of patients with COVID-19. In the case of gynecology and obstetrics, it was no different. Although more than a year has passed since the beginning of the pandemic, it is still not possible to assess the impact of the pandemic on residents from an academic, physical, and psychological point of view.

The medical residency has proven to be the most effective method for medical training, with Brazil currently being the third country with the highest percentage of specialist doctors in gynecology and obstetrics. In 2019, of the 53,776 resident physicians in training, 4,609 were in gynecology and obstetrics. Of these, 1,243 were in their 1st year and were directly impacted by COVID-19 in the following two years of residency. It is important to emphasize that 33.9% of all resident physicians are concentrated in the state of São Paulo, which represents approximately one-third of the national total. Within the expected workload, according to the National Commission of Medical Residency (CNRM, in the Portuguese acronym), residents of gynecology and obstetrics should have 48 hours in practical activities and 12 hours in theoretical activities weekly, and the residency should include the clinical and surgical areas, with competencies that contribute to the effective management of situations, problems, and dilemmas in the specialty, besides developing a critical-reflexive thought in regard to the medical literature, making residents progressively more accountable and independent. It is not known, however,

whether or not physicians were trained in all the recommended skills during the pandemic.[1,2]

In a study with 148 residents from 18 countries, published by the American Confederation of Urology in 2020, for example, 82% responded that activities within the urology department were significantly reduced and 15% responded that activities were completely canceled. In addition, 75% responded that their surgical training was completely affected by the pandemic. On the other hand, a North American study that assessed the impact of the pandemic on emergency medical education identified the impacts on clinical training, teaching education, and concentration and emotional mental states. In the case of gynecology and obstetrics, the activities include theoretical and practical content within various subspecialties, with modules of care considered essential, such as the obstetrics and oncology sector, as well as services considered non-essential, such as climacteric, family planning, and urogynecology outpatient clinics, for example.[3,4]

Considering a broad view of the situation, it is still unclear what the impacts of the pandemic are on the training of gynecologists and obstetricians. There are still no large-scale studies within this specialty in the country. The Obstetrics and Gynecology Association of the state of São Paulo has been supporting the residencies through monthly virtual educational content in nine regional offices, in addition to changing the format of congress from the traditional face-to-face to an electronic format. Considering the residents in training, the purpose is to map out the repercussions of the pandemic period on this public, including physical, structural, academic, and psychic aspects, as well as to establish a profile of this population.

The main objective of the present study was to analyze the impact of the COVID-19 pandemic period in the academic, physical, and psychological domains of first, second, and third-year obstetrics and gynecology residents in the state of São Paulo. The second objective was to profile the residents evaluated, as well as the percentage of residents who were affected by COVID-19.

Methods

A cross-sectional analytical study was performed by researchers representing gynecology and obstetrics residents belonging to the Obstetrics and Gynecology Association of the State of São Paulo (SOGESP, in the Portuguese acronym). All data were collected from questionnaires administered to first, second, and third-year residents of the Gynecology and Obstetrics residency program in the state of São Paulo who answered a virtual questionnaire during the stipulated period in February 2022.

Its high social relevance is emphasized for addressing the impacts of the pandemic on the training of professionals who will enter the medical market.

The data of the participants was kept secret and confidential. At no time will the name be disclosed in any phase of the research, which guarantees anonymity, and the results will be disclosed in such a way as not to identify the individuals.

Participants from all years of the medical residency program in obstetrics and gynecology, whose institutions belong to the state of São Paulo, and whose residency program coordination authorized the administration of the questionnaires were included.

Participants who had already graduated or who had not initiated specialization were excluded, as well as participants of medical residency in specialties other than gynecology and obstetrics, or who are not attending residency registered in the state of São Paulo. Additionally, residents of institutions whose coordination did not authorize the implementation of the questionnaire were excluded, thus totaling 45 institutions of residency in obstetrics and gynecology out of the 63 listed in the state of São Paulo.

In February 2022, questionnaires were administered to gynecology and obstetrics residents regarding the impact of the COVID-19 pandemic on residency programs and the clinical data of the residents.

The study was performed virtually, through the Website and the Associação de Ginecologia e Obstetrícia do Estado de São Paulo (http://sogesp.com.br). The resident registered at SOGESP received an invitation by e-mail beforehand to answer the survey.

The questionnaire comprised a total of 24 questions, in which data were recorded, such as whether the resident had COVID during the pandemic, classifying it as mild, moderate, or severe. The physician was asked whether the resident was assigned to care for patients with COVID-19 in adult emergency rooms (labeled as "Covidarium") or intensive care units (ICUs). The participant classified the impact of the pandemic on medical residency as "None," "Minimal," "Partial" or "Total" considering outpatient care, gynecological surgeries, obstetric procedures, and lectures. Residents were asked which year had the greatest losses as a result of the pandemic in residency (first, second, or third year), and if he/she is in favor of an additional year for residents most affected by the pandemic. From an academic point of view, the resident was also asked if there was a proposal to make up for the lost activities in the residency due to the pandemic. Once these considerations were made, the participant was asked about their intention to subspecialize and if this was influenced by the period experienced.

Considering the psychological domain, the participant was asked if they received psychological support for issues other than the pandemic and if they considered quitting the residency during the pandemic. In addition, the participant was asked about their vacation time from the medical residency program, whether it was affected in any way by the COVID-19 pandemic, and whether there was any proposal for replacement as well as for the case of elective internships.

From the standpoint of COVID-19 patient care, residents were asked whether the medical residency supplied adequate personal protective equipment (PPE) to care for contaminated patients and whether theoretical and technical preparation was provided, which was classified as "None," "Minimal," "Partial," or "Total". In line with the rationale of

protection from exposure to the virus, we asked about the provision of vaccination against COVID-19 by the institution.

Following the investigation of academic repercussions during the pandemic period, the participant answered whether they have a preference between face-to-face and virtual congress. In addition, the resident was asked about their participation in the development of any scientific article during the pandemic and whether they consider that the pandemic interfered with their scientific production.

Finally, the resident answered if they consider that their specialization was more affected in the obstetrics or gynecology sector, ending with an open question for suggestions to make up for the damage caused by the pandemic in medical residency.

The present study included the questionnaires answered by the resident physicians who met the selection criteria (convenience sample). The characteristics of the participants were presented descriptively (minimum values, maximum values, numbers, percentages, median, and standard deviation [SD]).

Data were distributed using the Kolmogorov-Smirnov test. Chi-squared, Fisher, or Student *t*-tests were used depending on the nature of the variables. For non-normal distribution data, nonparametric tests were used. P values < 0.05 were considered statistically significant.

The data obtained were organized in electronic spreadsheets of Microsoft Excel 2018 version 1910 software (Microsoft Corporation, Redmond, WA, USA).

The present study was approved by the research ethics committee of the *Centro de Estudos e Pesquisas Dr. João Amorim* - CEJAM (CAAE 50512821.9.0000.9107).

Results

Considering the inclusion criteria, 248 questionnaires from gynecology and obstetrics residents were included and 1 questionnaire was excluded as it belonged to a medical residency that was not from the state of São Paulo, resulting in 247 remaining questionnaires, which would correspond to 19.4% of the $\sim$ 1,274 residents of the specialty in the state of São Paulo during the year 2021. The physicians were distributed according to the regional offices of SOGESP in the state. The majority of respondents belonged to medical residency programs in the city of São Paulo (Headquarters) (46.5%), compared with the regions of ABC Paulista (15.9%), Campinas (13.8%), Santos (8.1%), Ribeirão Preto (7.7%), Midwest (4.0%), Vale do Paraíba (1.6%), São José do Rio Preto (1.6%) and Presidente Prudente (0.8%). The residents were 28.3 years old and most of them were female (88.4%). Regarding residency year, 86 people were in their 1st year (34.8%), 80 people were in their 2nd year (32.4%), and 81 people were in their 3rd year of residency (32.8%). Among the physicians evaluated, 153 participants (61.9%) reported having had COVID during the pandemic. Among the physicians who had a confirmed diagnosis, 53.4% classified the disease as "mild" and 8.5% of those evaluated classified it as "moderate." It is important to emphasize that none of the residents approached reported having had a severe form of COVID, and $\sim$ 90% of the interviewees reported that the vaccine was available during their residency. Assignments within the residency to care for patients affected by COVID-19 were confirmed by 62.34% of those evaluated. In addition, 42.9% reported direction to care for patients in the ICU affected by COVID-19. Considering the technical preparation for this type of care with the supply of PPE, the residents were questioned according to ►**Fig. 1**.

The residents were evaluated regarding their intention to give up their medical residency during the pandemic according to the year of their residency, as shown in ►**Fig. 1**. It is noteworthy that among the physicians who reported that they had wished to give up their residency during the pandemic, 73.6% reported that their residency had no psychological support service.

Within the scope of the impact of the pandemic on medical residency, the questionnaires were stratified according to the regions of SOGESP in the state of São Paulo, according to ►**Fig. 2**. When asked, 96.3% of the interviewees stated that residency was more affected in the gynecology sector compared with obstetrics.

It is emphasized that only 31% of the residents reported that there was a proposal for making up for the lost activities. Still, 94.7% of those surveyed expressed the desire to subspecialize, and only 18.1% of those interviewed said that the pandemic interfered with their choice. When asked, 79.3% expressed the desire to work in obstetrics after the conclusion of medical residency, 94.7% expressed the desire to maintain contact with gynecology and 64.0% expressed the desire to work with both areas. Within the lost theoretical-practical content, almost 80% of the residents who have the possibility of doing the optional external internship reported that there was a loss regarding this benefit. Considering the activities performed remotely, in video classes on the computer, in 82.5% of the residencies there was a reference to theoretical classes and/or presentation of articles online. Although virtual classes were a convenient format, 60.3% of the physicians said they preferred the face-to-face format. However, this number increased to 80.5% when they were asked about their preference regarding congresses (►**Fig. 3**).

Discussion

First of all, when analyzing data, it is noteworthy that the great majority of interviewees belonged to the city of São Paulo. This is consistent with the fact that most medical residences in the state of São Paulo are currently concentrated in the capital of the state or neighboring cities (27%), not to mention large cities such as ABC Paulista (which ranked second in the questionnaires, or Campinas [which ranked third]).

Regarding the gender identity of the evaluated residents, women predominated in the present study with 88.4%. These data are compatible with the number found in other gynecology and obstetrics medical residences around the world; for example, with an English study from 2022, finding 85% of female residents, while another Italian study from 2020

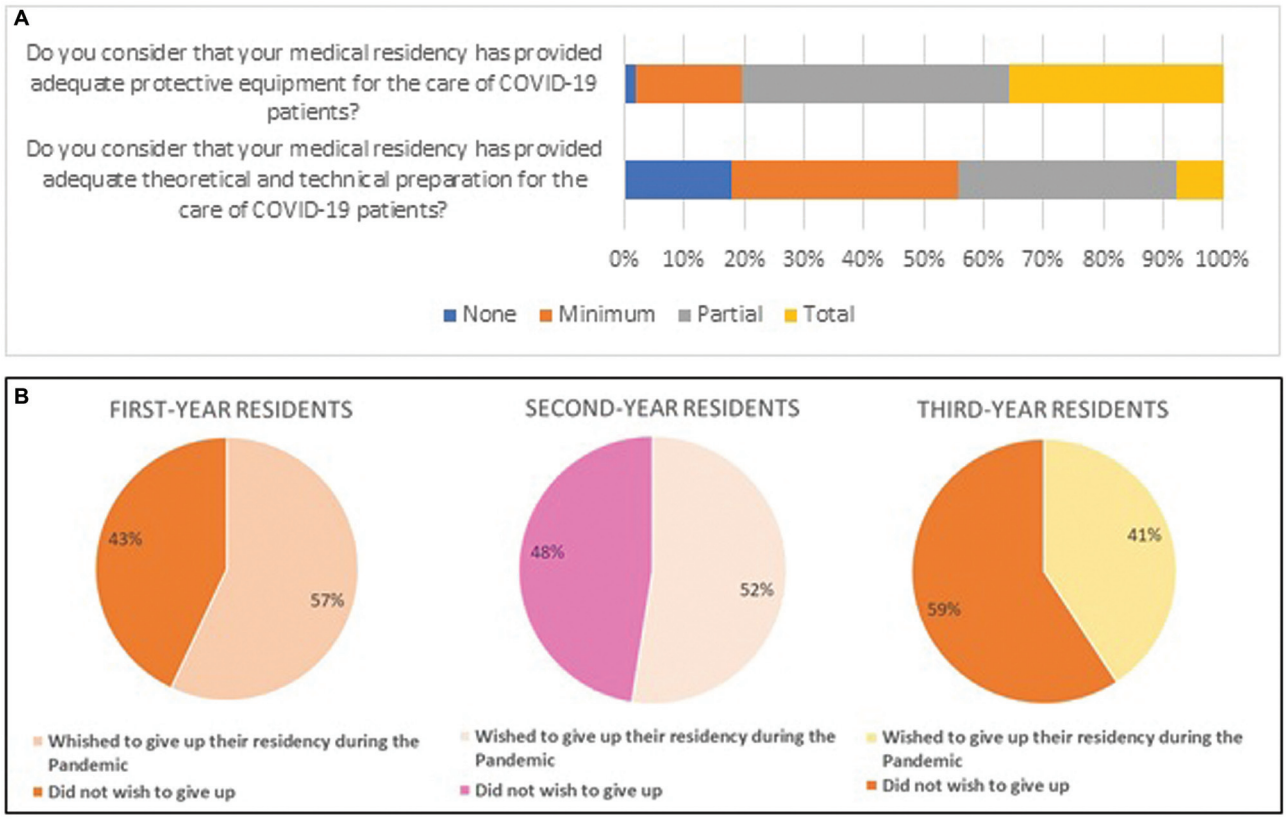

Fig. 1 (A) Analysis of residents' preparation for care of patients with COVID-19. (B) Analysis of residents according to desire to quit residency program during the pandemic.

found 81%. What is the reason for this majority of female doctors within gynecology? There are still no articles in the literature assessing this fact and the studies show no preference on the part of patients regarding the gender of the attending physician. It is worth mentioning here that Brazil is undergoing a process of feminization of medicine and that among the physicians who currently practice the profession, the majority are still male, but among those who are $\leq$ 29 years old, the majority are now female. The age found among the interviewees was consistent with other studies, emphasizing that while in Brazil the medical residency in gynecology and obstetrics lasts 3 years, in other countries it can take up to 5 years.[5–9]

The pandemic required great resilience from the medical staff, directly affecting the education of obstetrics and gynecology residents, who had to balance the clinical care of patients while learning specialty skills. Among the significant findings of the present study, $>$ 60% of those evaluated reported having had the disease, and none of the residents reported a severe form of COVID. This can be accounted for the fact that the medical population was one of the first to receive the vaccination (emphasizing that almost all of the interviewees reported receiving the vaccine through their residency). Moreover, another point attributable to the good response to the disease could be related to the young age of this population, 28.3 years old, which is known to relate to better outcomes within COVID infection, considering the lower rate of associated comorbidities for this group.[10]

Among the main factors responsible for the impact of the pandemic on medical residency, we can highlight the cancellation of elective surgeries and the reassignment of residents to clinical departments, the so-called "covidariums," which may have compromised both theoretical and surgical learning. In a study of general surgery residents in Greece, for example, it was found that 54.8% of physicians who were reassigned to clinical areas reported that their surgical skills were negatively affected by the pandemic, a figure that fell to 24.7% of residents who were not reassigned.[11]

In the present study, it was identified that 62.34% of those evaluated were directed to this type of care, while only 35.6% of the interviewees reported having received completely adequate PPE, and only 7.7% reported complete theoretical and technical instruction to care for these patients. This result was below the results of a study performed with gynecology and obstetrics residents in Italy, in which 56.1% reported having received adequate safety equipment, and 79.6% reported having been well informed about prevention and management protocols for these patients.[6]

Regarding the impact of the pandemic on the psychological condition of residents, the correlation between the vulnerability to psychological pathologies and the frequency of contact with patients affected by COVID-19 is well known, resulting in physicians even considering dropping out of residency. When we asked this question, we expected a good number of 3rd-year residents to have expressed this intention, since they experienced the pandemic in the 2nd and 3rd years of residency, in 2020 and 2021, which are the

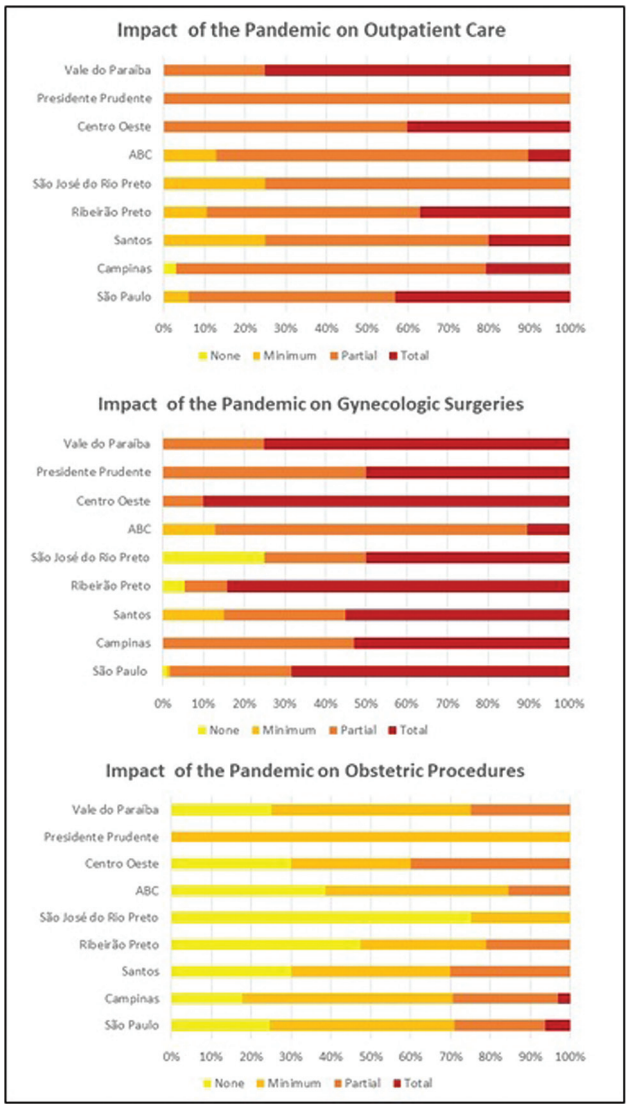

Fig. 2 Analysis of the impact of the pandemic on outpatient care, gynecological surgeries and obstetric procedures.

two years of most surgical practice, especially in the field of gynecology. However, the majority of the interviewees (44.5%) considered that 2nd-year residents were the ones who suffered the greatest loss academically due to COVID-19, behind 1st-year residents (39.7%) and 3rd-year residents (15.8%). It is emphasized that for 1st- and 2nd-year residents, more than half of the respondents stated that they wished to quit residency during the pandemic, while in the case of 3rd-year residents, the rate was lower. It is worth pointing out here that it is not only the pandemic that affects the resident's intention to quit training, but also the pressure of the work itself. The first year of residency is the most affected at this point. These results reinforce the fact that medical residency programs should ensure healthy communication to promote mental health for physicians by providing psychological support in or out of pandemic situations.[12–14]

Regarding the impact of the pandemic on teaching practices, as seen in ►**Fig. 2**, it can be said that the conflict was bigger within gynecologic surgery and outpatient clinics compared with obstetric procedures, considering all regions of the state, which was expected to some extent. Considering that we cannot stop obstetric procedures even in adverse conditions, such as in the pandemic, 96.3% of the interviewees affirmed that residency was more affected in the Gynecology sector than in Obstetrics. In all regional offices of SOGESP, $\geq$ 70% of the residents considered the impact of the pandemic on outpatient clinics to be partial to total, and more alarmingly, in 8 of the 9 regional offices evaluated, half or more of the respondents considered the impact on gynecological surgeries to be total. This interference of the pandemic may have practical repercussions, creating professionals lacking the confidence to perform surgical procedures in their postresidency practice. According to the residents, repercussions on theoretical activities were lower than on practical ones, which was unanimous among the interns during the 3-year internship; however, 50% of the interviewees considered that the impact was from partial to

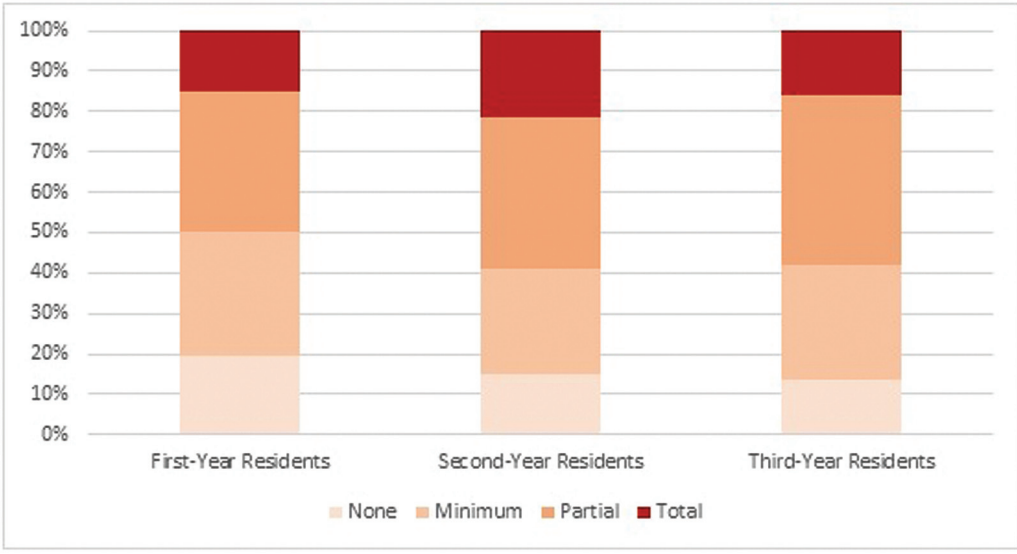

Fig. 3 Analysis of the impact of the pandemic on theoretical classes.

total. This was largely due to the online platforms that emerged in the pandemic, which was reported by 82.5% of the respondents, and in some cases, these activities continued online even after the global situation improved. Despite the pandemic and COVID-19 interfering with teaching practices, only 18% of the respondents reported that this period interfered with their intention to pursue subspecialty training, a number close to the 20% found in a study of London obstetrics and gynecology residents who reported an impact of the pandemic on career choice. The number of residents willing to continue working in obstetrics (79.3%) was below the 84% observed in the Canadian study and lower than the 94.7% found for gynecology.[5,15,16]

The weaknesses of the present study are: it is a cross-sectional study, with all the limitations attributed to it; the survey was performed only with residents from the state of São Paulo, with no possibility of extending these results to other states or even countries. The strengths of the study are a large number of interviewees, from different regions of the state, with this being one of the first studies on the impact of the pandemic on obstetrics and gynecology residents in Brazil.

Conclusion

The pandemic had an impact on gynecology and obstetrics residency in the state of São Paulo. It was greater on practical activities such as outpatient clinics and gynecological surgeries than on obstetrics and theoretical classes. It also affected the mental health of residents.

Contributors

All authors contributed to the design of the study and were involved in the data collection, data analysis and/or interpretation. All authors also contributed to manuscript writing/substantive editing and review and approved the final draft of the manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

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Geographical Health District and Distance Traveled Influence on Clinical Status at Admission of Patients with Gestational Trophoblastic Disease

A influência do distrito de saúde e da distância viajada sobre o estado clínico na apresentação de pacientes com doença trofoblástica gestacional

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Abstract

Objective To assess the potential relationship of clinical status upon admission and distance traveled from geographical health district in women with gestational trophoblastic disease (GTD).

Methods This is a cross-sectional study including women with GTD from the 17 health districts from the São Paulo state (I–XVII), Brazil, referred to the Botucatu Trophoblastic Disease Center (specialized center, district VI), between 1990 and 2018. At admission, hydatidiform mole was assessed according to the risk score system of Berkowitz et al. Gestational trophoblastic neoplasia was evaluated using the International Federation of Gynecology and Obstetrics / World Health Organization (-FIGO/WHO) staging/risk score. Data on demographics, clinical status and distance traveled were collected. Multiple regression analyses were performed.

Results This study included 366 women (335 hydatidiform mole, 31 gestational trophoblastic neoplasia). The clinical status at admission and distance traveled significantly differed between the specialized center district and other districts. Patients referred from health districts IX ($\beta = 2.38$ [0.87–3.88], $p = 0.002$) and XVI

Keywords
- gestational trophoblastic disease
- geographical health district
- distance traveled
- clinical status
- referral center

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(β = 0.78 [0.02–1.55], $p = 0.045$) had higher hydatidiform mole scores than those from the specialized center district. Gestational trophoblastic neoplasia patients from district XVI showed a 3.32 increase in FIGO risk scores compared with those from the specialized center area (β = 3.32, 95% CI = 0.78–5.87, $p = 0.010$). Distance traveled by patients from districts IX (200km) and XVI (203.5km) was significantly longer than that traveled by patients from the specialized center district (76km).

Conclusion Patients from health districts outside the specialized center area had higher risk scores for both hydatidiform mole and gestational trophoblastic neoplasia at admission. Long distances (>80 km) seemed to adversely influence gestational trophoblastic disease clinical status at admission, indicating barriers to accessing specialized centers.

Resumo

Objetivo Avaliar a possível relação entre estado clínico na apresentação e distância percorrida a partir do distrito de saúde em mulheres com doença trofoblástica gestacional.

Métodos Estudo transversal incluindo mulheres com doença trofoblástica gestacional dos 17 distritos de saúde do estado de São Paulo (I–XVII), Brasil, encaminhadas ao Centro de Doenças Trofoblásticas de Botucatu (distrito VI), entre 1990 e 2018. Na admissão, avaliaram-se mola hidatiforme pelo sistema de pontuação de risco de Berkowitz et al. e neoplasia trofoblástica gestacional pelo escore de risco/estadiamento Federação Internacional de Ginecologia e Obstetrícia / Organização Mundial da Saúde (FIGO/OMS). Coletaram-se dados demográficos, clínicos e distância percorrida e análises de regressão múltipla foram realizadas.

Resultados Este estudo incluiu 366 mulheres (335 mola hidatiforme, 31 neoplasia trofoblástica gestacional). O estado clínico na apresentação e distância percorrida diferiram significativamente entre o centro especializado e demais distritos. Nas pacientes encaminhadas pelos distritos IX (β = 2,38 [0,87–3,88], $p = 0,002$) e XVI (β = 0,78 [0,02–1,55], $p = 0,045$), os escores de mola hidatiforme foram maiores que no centro especializado. As pacientes com neoplasia trofoblástica gestacional do distrito XVI apresentaram escores FIGO 3,32 vezes maior que no centro especializado (β = 3,32, 95% CI = 0,78–5,87, $p = 0,010$). A distância percorrida pelas pacientes dos distritos IX (200km) e XVI (203,5km) foi significativamente maior do que a percorrida pelas pacientes do centro especializado (76km).

Conclusão Pacientes de distritos de saúde fora da cobertura do centro especializado apresentaram escores de risco mais alto para mola hidatiforme e para neoplasia trofoblástica gestacional na admissão. Longas distâncias (>80 km) pareceram influenciar negativamente o estado clínico da doença trofoblástica gestacional na apresentação, indicando barreiras no acesso a centros especializados.

Palavras-chave
- doença trofoblástica gestacional
- distrito de saúde
- distância viajada
- estado clínico
- centro de referência

Introduction

Gestational trophoblastic disease (GTD) is the term given to a group of rare tumors that arise during pregnancy, which are associated with abnormal proliferation of trophoblastic cells and increased secretion of human chorionic gonadotropin (hCG). Hydatidiform mole (HM), also known as pre-malignant GTD, can be either complete (no embryonic/fetal tissue is present) or partial (some embryonic/fetal tissue develops). Gestational trophoblastic neoplasia (GTN), is the malignant form of GTD that encompasses different histopathological types (invasive mole, choriocarcinoma, placental-site trophoblastic tumor, and epithelioid trophoblastic tumor).

The clinical characteristics of GTD patients at presentation at a specialized center are considerably influenced by social and economic factors, as well as barriers to healthcare access, which lead to patient presentation at later stage disease.[1–3] A potential cause for a less favorable outcome may be the distance required to travel to a specialized center.[3,4] Given the rarity of GTD, centralizing care for this condition has been internationally promoted as a means to improve care. However, disadvantages such as longer travel times are not usually taken into account.

To ensure universal health coverage and equity in the country, Brazil has implemented the regionalization of

health services.[5] The Botucatu Trophoblastic Disease Center (BTDC) of the São Paulo State University (UNESP), provides tertiary care primarily to residents in the state Health District-VI, which encompasses 68 municipalities and covers an area of 26.790,1 km^2, with an estimated population of 1.8 million inhabitants. Nonetheless, women with GTD from other localities are also treated at BTDC, regardless of their home residence.

Regionalizing health care, however, has not guaranteed equity in the treatment of GTD in Brazil because the disease cases of a region must be treated within the patient's own region of residence, and not all regions have a center specialized in GTD. Consequently, women with GTD are often referred to centers very far from where they live. Additionally, the efficiency of the referral system relies on the first physician seeing the patient being able to identify GTD.[1] Since this is not always the case, the patient may be subjected to a pilgrimage from service to service before being referred to a specialized center. This is a very bureaucratic and time-consuming process that has economic implications to the patient who cannot always pay the costs of transportation and lodging.

Within this framework, the objective of this study was 3-fold:

to determine the residence of the GTD patients referred to BTDC;
to compare the health districts referring GTD patients to our center regarding patient demographic characteristics, clinical status at admission, and distance traveled;
to assess the potential association between clinical status at admission and distance traveled among patients with HM or GTN (gestational trophoblastic neoplasia) referred to BTDC.

Methods

This cross-sectional study included women with GTD referred for initial treatment to the Botucatu Trophoblastic Disease Center (BTDC) from health districts in the state of São Paulo, Brazil, between 1990 and 2018. Although women from all over the country can be referred to our center, those from other Brazilian states were not included.

The BTDC is affiliated with a public state university, and as such, provides multimodality treatment, and follow-up with multidisciplinary management, as well as chemotherapy drugs, all free of charge to women with GTD. This study was approved by the Research Ethics Committee of the Botucatu Medical School, UNESP (CAAE: 96348318.5.0000.5411).

The clinical diagnosis of HM was based on ultrasound findings suggestive of complete hydatidiform mole (CHM) or partial hydatidiform mole (PHM), and pre-uterine evacuation hCG level. The clinical diagnosis of CHM was based on ultrasound images showing a heterogeneous uterine mass with cystic spaces, vesicles, or hydropic villi,[6] while PHM was diagnosed when ultrasound findings indicated the presence of a thick placenta with several anechoic cystic lesions and, in some cases, ovular membrane and fetal growth restriction, and multiple malformations inherent to triploidy.[7] After evacuation, the sonographic diagnosis was confirmed by histopathological analysis[8,9] and immunohistochemical staining with p57 (KIP2).[10]

The diagnosis of GTN was established according to the International Federation of Gynecology and Obstetrics (FIGO) criteria:[11] hCG plateau $\pm$ 10% for 4 measurements over 3 consecutive weeks (days 1,7,14, and 21); hCG level rise $>$ 10% for 3 consecutive weekly measurements over at least 2 weeks (days 1, 7, and 14); hCG elevated for $\geq$ 6 months after evacuation or histologic diagnosis of choriocarcinoma.

Demographics, data on clinical status at admission, and health district of the patients' residence were collected from paper-based and electronic medical records.

The distance (km) traveled to reach the BTDC was estimated using Google Maps (Google LLC., Mountain View, CA, USA), considering the documented residential address of the patient and the address of the Botucatu Medical School Hospital, where the center is located.

According to the National Council of Health Secretaries,[5] the state of São Paulo is subdivided into 17 health districts. Thus, the health district of residence of all GTD patients was identified at admission based on each patient's municipality of residence.

The clinical status of patients with HM and GTN upon admission were considered as outcome variables. The HM level was assessed according to the molar pregnancy risk score system proposed by Berkowitz et al.,[12] which is based on clinical, laboratory and radiologic findings (S1). The risk score for molar pregnancy included the following parameters: ultrasound diagnosis, uterine size for gestational age, pre-evacuation hCG, longitudinal (larger) diameter of the ovary, patient age, and presence of clinical complications. Based on the score assigned to each of these parameters, the clinical status of the patient with HM at admission was quantified using a point system ranging from 0 to 15. Patients with HM were classified as low-risk HM (score $<$ 4) or high-risk HM (score $\geq$ 4) for developing GTN.

The clinical status at admission of patients referred for GTN treatment was assessed using the FIGO/WHO staging classification system and risk score (S2). The FIGO staging is performed according to the anatomical distribution of the neoplasm (stages I, II, III, and IV), and the risk scoring system uses prognostic factors for resistance to single-agent chemotherapy. A value of 0, 1, 2, or 4 is given for each risk factor, resulting in scores ranging from 0 to 25 points. Depending on the score obtained, the condition of the patient with GTN was categorized into low-risk ($\leq$ 6 points) or high-risk GTN ($\geq$ 7 points).

The following variables were considered as potential confounders: age (years), race (white/non-white), parity (total number of viable pregnancies), education level (elementary, high school, college/university, postgraduate), marital status (partner/no partner), employment (yes/no), and prior knowledge of GTD (yes/no).

The geographical distribution of the participants according to residence (health district) and clinical status at admission were plotted on a map of the state of São Paulo

subdivided into its 17 health districts (shapefile obtained through the package geobr). Using the latitude and longitude coordinates of the study participants' home addresses provided by Google Maps, each one was scored on the map of the state of São Paulo. The thematic map according to clinical status at admission was built using the ggplot2 package. Both geobr and ggplot2 packages were used through the R software (R Foundation for Statistical Computing, Vienna, Austria) version 3.4.3.

The Chi-square, Fisher exact, or Kruskall-Wallis tests were used to compare demographic data, clinical status at admission, and traveled distance among patients from health districts VI, IX, and XVI, followed by the Dunn test for multiple comparisons. Associations of clinical status at admission of patients with HM and GTN by health district (VI, IX, and XVI) were made using multiple regression models, adjusted for confounding factors. The significance level was set at $p < 0.05$. Analyses were performed using the Statistical Package Social Sciences (SPSS, IBM Corp. Armonk, NY, USA) version 21.0, and the R software 3.4.3.

Results

During the study period, 470 patients were registered at BTDC. Of these, 366 met this study's inclusion criteria, and 104 were considered ineligible due to history of nonmolar pregnancy ($n = 13$), residence outside the state of São Paulo ($n = 4$), or missing data ($n = 87$). Thus, the final study population consisted of 366 women: 335 with HM and 31 with GTN (►**Fig. 1**).

Of the 17 health districts in São Paulo State, 8 referred patients to BTDC. Approximately 30% of the patients referred resided in health districts outside the area covered by this center (HD VI). Furthermore, HD VI (73.5%), HD XVI (19.1%), and HD IX (4.1%) accounted for the largest number of referrals. Among GTD cases, 8.5% were referred for GTN treatment and 91.5% for molar evacuation. Notably, of the 335 patients with HM, 197 (58.8%) had the high-risk form (score ≥ 4). Among GTN patients, 22.6% were scored as high risk (≥ 7) (S3). ►**Fig. 2** shows that the majority of the patients referred to the BTDC resided in the areas covered by health

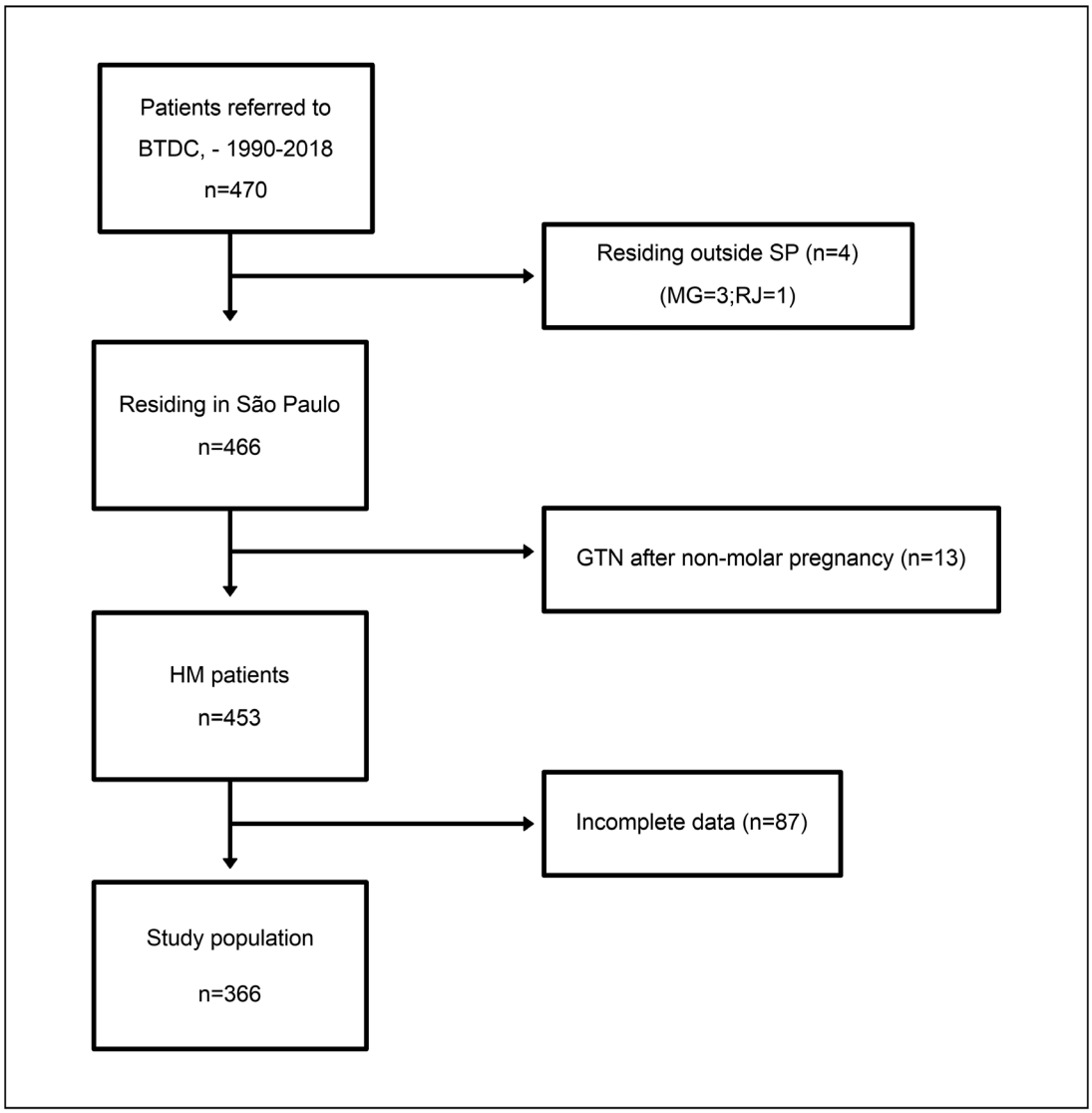

Fig. 1 Patient flow chart.

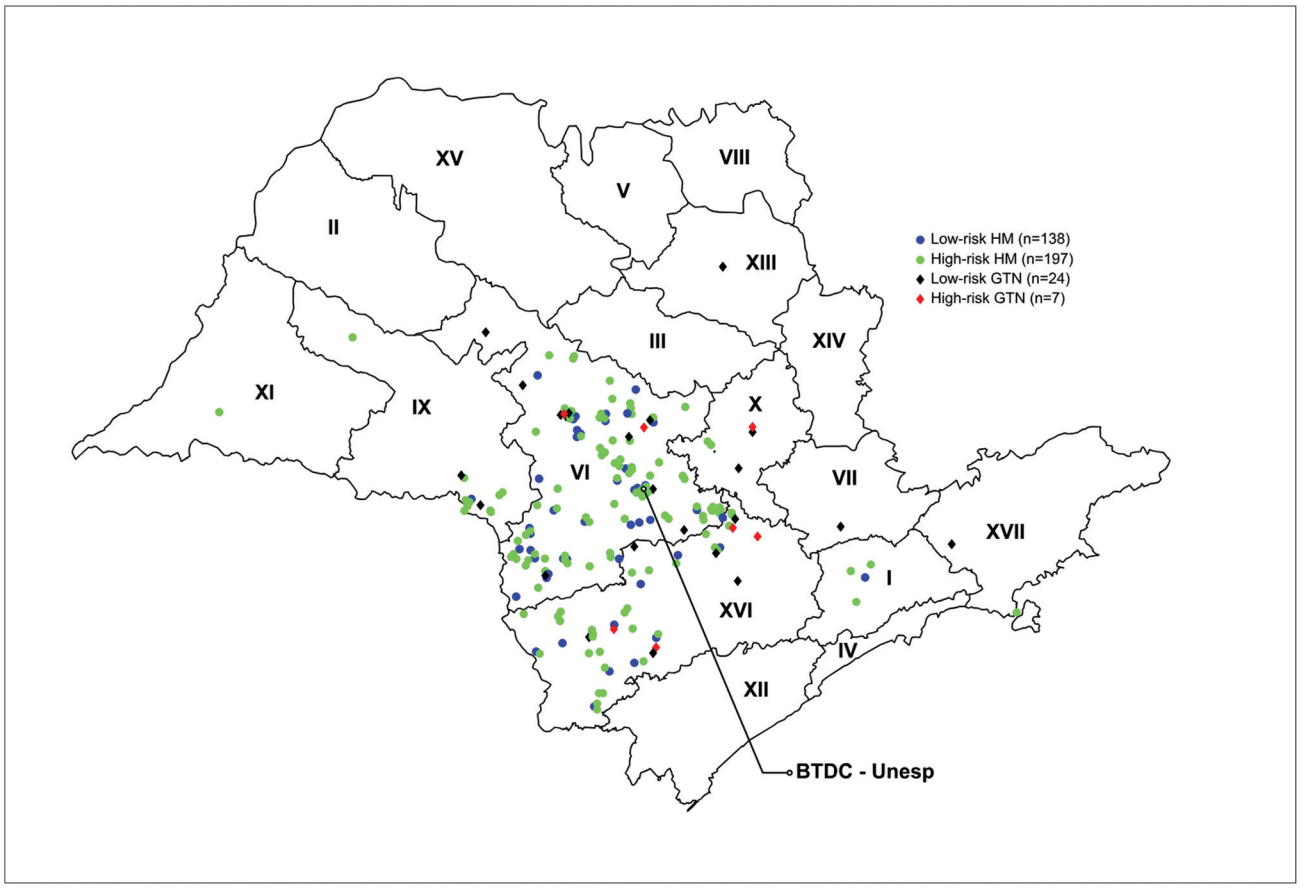

Fig. 2 Thematic map showing the residence of the patients reffered to BTDC and their GTN status.

districts VI, XVI, and IX, and that the number of women with high-risk HM was greater in health district IX.

Given that only a small number of patients were from health districts I, VII, X, XII, and XIII, all the analyses presented from this point on are based on data from health districts VI, IX, and XVI, where 96% (354/366) of the study population resided.

►**Table 1** indicates that, overall, women from the health districts accounting for the largest number of referrals (VI, IX, and XVI) were young (median age = 23 years, min–max, 13–52), white ($n = 263$; 74.5%), nulliparous ($n = 180$; 50.8%), had a low education level (primary education; $n = 179$; 51.0%), and lived with a partner ($n = 275$; 77.9%). About 30% (107) of these women were adolescents, as per the definition of the World Health Organization.[13] Among nonadolescents ($n = 247$), less than half (49.6%) had a job. In general, prior knowledge of GTD (as assessed per the BTDC's protocol) was poor (3/354; 0.8%).

Regarding clinical status at admission, the median HM risk score was 4 (min–max, 0–11) and the median GTN risk score was 3 (min–max, 1–14). The median distance traveled to reach the BTDC was 92 km. More than 50% of the patients (209/354; 59%) lived at a distance > 80 km from the BTDC. No significant differences in demographic data were observed, except for age ($p = 0.017$). Nonetheless, clinical status at admission and distance traveled significantly differed between women from the area covered by the BTDC (health district VI) and those residing outside this area. The median HM risk score was significantly higher in health district IX than in the others ($p = 0.048$). The median distance traveled by patients from health districts IX and XVI was significantly longer compared with patients from health district VI ($p < 0.001$). Furthermore, the percentage of long-distance travelers (> 80 km) was higher in health districts IX and XVI than in health district VI ($p < 0.001$) (►**Table 1**).

►**Table 2** shows the multiple linear regression analysis of the association of HM clinical status at admission with health district (VI, IX, and XVI), adjusted for confounders. Patients referred from health districts IX ($\beta = 2.38$ [0.87–3.88], $p = 0.002$) and XVI ($\beta = 0.78$ [0.02–1.55], $p = 0.045$) had higher HM scores than those from health district VI.

Notably, the rate of high-risk HM was nonsignificantly 33% higher among women from health district VI who resided more than 80 km far from BTDC (long-distance travelers) (RR = 1.33; 95% confidence interval [CI] = 0.96–1.86, $p = 0.088$; Poisson regression) (S4). The association between long distance and high-risk HM was not calculated for health districts IX and XVI because nearly all patients from those districts lived farther than 80 km from BTDC.

►**Table 3** shows the multiple linear regression analysis adjusted for confounders of the association of the GTN

Table 1 Demographics, clinical status at admission and distance traveled according to health district

Variable	Overall ($n = 354$)	HD			*p*-value
		HD VI ($n = 269$)	HD XVI ($n = 70$)	HD IX ($n = 15$)	
Age (years)	23 (13–52)	22 (13–47)	25 (15–52)	19 (13–45)	0.017
10–19	107 (30.2%)	86 (32%)	12 (17.1%)	9 (60%)	
20–39	225 (63.6%)	169 (62.8%)	51 (72.9%)	5 (33.3%)	0.005
≥ 40	22 (6.2%)	14 (5.2%)	7 (10.0%)	1 (6.7%)	
Race					
White	263 (74.5%)	203 (75.7%)	48 (68.6%)	12 (80%)	0.452
Non-white	90 (25.5%)	65 (24.3%)	22 (31.4%)	3 (20%)	
Parity	0 (0–8)	0 (0–8)	0.5 (0–5)	1 (0–2)	0.551
Nulliparous	180 (50.8%)	139 (51.7%)	35 (50%)	6 (40%)	
Primiparous	103 (29.1%)	81 (30.1%)	17 (24.3%)	5 (33.3%)	0.505
Multiparous	71 (20.1%)	49 (18.2%)	18 (25.7%)	4 (26.7%)	
Education					
Elementary school	179 (51%)	144 (53.9%)	27 (39.1%)	8 (53.3%)	
Highschool	147 (41.9%)	108 (40.4%)	33 (47.8%)	6 (40%)	0.103
College / Post-graduation [a]	25 (7.1%)	15 (5.6%)	9 (13%)	1 (6.7%)	
Had a partner	275 (77.9%)	203 (75.7%)	60 (85.7%)	12 (80.0%)	0.187
Employed (age > 19 years)	122 (49.6%)	89 (48.6%)	29 (50.9%)	4 (66.7%)	0.434
Knowledge of GTD	3 (0.8%)	2 (0.7%)	0 (0.0%)	1 (6.7%)	0.130
HM Score ($n = 329$)	4 (0–11)	4 (0–11)	5 (0–11)	7 (2–10)	0.048
HM classification ($n = 329$)					
Low risk	137 (41.6%)	115 (44.9%)	19 (31.7%)	3 (23.1%)	0.07
High risk	192 (58.4%)	141 (55.1%)	41 (68.3%)	10 (76.9%)	
FIGO score	3 (1–14)	3 (1–7)	4 (2–14)	1.0 (1–2)	0.085
FIGO classification ($n = 25$)					
Low risk	19 (76%)	11 (84.6%)	6 (60%)	2 (100%)	0.373
High risk	6 (24%)	2 (15.4%)	4 (40%)	0 (0%)	
Distance traveled (km)	92 (2–325)	76.1 (2–244)	203.5 (70.9–325)	200 (159–315)	0.001
Distance traveled > 80 km	209 (59%)	125 (46.5%)	69 (98.6%)	15 (100%)	0.001

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; GTD, gestational trophoblastic disease; GTN, gestational trophoblastic neoplasia; HD, health district; HM, hydatidiform mole. **Notes:** Data are expressed as median (min–max) or n (%). [a] Only 4 patients were post-graduated; Fisher exact test, Chi-square and Kruskal-Wallis; HD XVI > HD VI > HD IX regarding age ($p < 0.05$); HD IX > HD XVI > HD VI regarding HM risk score ($p < 0.05$).

patients' clinical status at admission with health district of residence (VI, IX, and XVI).

The GTN patients referred from health district XVI showed a 3.32 increase in FIGO risk scores when compared with those from district VI ($\beta = 3.32$, 95% CI = 0.78–5.87, $p = 0.010$). No woman with GTN had any previous knowledge about the disease, so it was not possible to estimate its effect on the risk score.

Discussion

This study indicates that geographical residence influenced the clinical status of the GTD patients referred to BTDC. Considering the demographic characteristics associated with worse outcome, we observed that GTD patients referred from health districts outside the area covered by our specialized center were mostly long-distance travelers (> 80 km) and had a higher risk score compared with those residing in the BTDC (health district VI) coverage area.

Irrespectively of the health district of residence, there was no difference in demographic characteristics in the population studied. Most women were young, had no or only 1 child, had a low educational level, and were unemployed. Such unfavorable sociodemographic status has also been reported by other centers in developing countries.[2,14–17]

Among the patients with HM referred to our center, 58.8% were at high-risk of molar pregnancy (score ≥ 4). Compared with women residing in the specialized center

Table 2 Adjusted multivariate analysis of the association between HM clinical status at admission and health district of residence (VI, IX and XVI)

Variable	β	95%CI		*p*-value
Health district (Ref: HD VI)				
XVI	0.78	0.02	1.55	0.045
IX	2.38	0.87	3.88	0.002
Age (years)	-0.03	-0.08	0.02	0.244
Parity	0.1	-0.21	0.41	0.516
Non-white	0.2	-0.48	0.87	0.569
Education (Ref: Elementary school)				
Secondary school	-0.65	-1.28	0.01	0.045
College/Postgraduation	-0.12	-1.43	1.19	0.86
Had a partner	-0.36	-1.09	0.33	0.326
Employed	0.2	-0.47	0.9	0.544
Knowledge of GTD	-1.68	-4.78	1.41	0.287

Abbreviations: CI, confidence interval; GTD, gestational trophoblastic disease; HD, health district; HM, hydatidiform mole.

district, women from other districts had a significantly higher molar pregnancy score. This might have resulted from the fact that despite advances in the early diagnosis of HM worldwide,[18–21] ultrasound exams and hCG assays are not always readily available in developing countries. As a result, women may be diagnosed with HM by the end of the first trimester or during the second trimester of pregnancy, when many have already developed medical complications.[2,17]

A substantial number of GTN patients referred to our center (22.6%) had a high-risk score ($\geq$ 7) (high-risk GTN), particularly patients from health district XVI, which is not in the area covered by our center (VI). In the patients from health district XVI, risk scores were significantly higher (mean of 3.32 points) than in those from district VI. Notably, this 3.32 increase in the risk score is enough to change the categorization of GTN from low to high risk.

Whereas the rate of high-risk GTN among our patients was 22.6%, Maestá et al.[22] found that in South American (Brazil and Argentina) trophoblastic disease centers, 15% of the women with GTN had the high-risk form of the disease. Both of these rates are high compared with those reported by trophoblastic centers in developed countries (2.7–6.3%).[23,24]

Regarding residence, approximately ⅓ of the patients referred to the BTDC were from health districts outside the area covered by our center. The visualization of the thematic map shows that districts IX and XVI were the ones who most referred GTD patients, and both border district VI, where BTDC is located. The greater influx of patients from these districts could be easily explained as the result of a shorter

Table 3 Adjusted multivariate analysis of the association between GTN clinical status at admission and health district of residence (VI, IX and XVI)

Variable	β	95% CI		*p*-value
Health district (Ref: HD VI)				
XVI	3.32	0.78	5.87	0.01
IX	-1.51	-5.72	2.7	0.481
Age (years)	0.16	0	0.33	0.048
Parity	-1.56	-2.87	-0.03	0.046
Nonwhite	-0.37	-3.03	2.31	0.783
Education (Ref: Elementary school)				
Secondary school	0.83	-1.78	3.43	0.534
College/Postgraduation	-3.24	-6.97	0.5	0.089
Had a partner	-2.37	-6.5	1.76	0.26
Employed	0.16	-2.14	2.45	0.892
Knowledge of GTD	–	–	–	–

Abbreviations: CI, confidence interval; IFGO, International Federation of Gynecology and Obstetrics; GTN, gestational trophoblastic neoplasia.
Notes: No GTN patient had any previous knowledge of the disease.

distance to be traveled by the patients. However, these districts are quite large, and the median distance covered by patients to obtain care at the specialized center is 200 km, which makes them long-distance travelers. Virtually all patients residing outside the coverage area of the specialized center and about half (HD VI: 46.5%) of those residing in the coverage area of the specialized center were long-distance travelers (> 80km).

Several studies have shown that long distance travel constitutes a barrier to treatment among cancer patients.[25–27] Travel time to health care services has also been shown to influence access, utilization and outcomes among patients with various malignancies.[28–30] In women with GTN, a single study evaluating the effect of distance traveled showed that long-distance travelers were significantly more likely to present with high-risk disease (relative risk [RR] = 2.4; 95% CI = 1.1–5.2).[3] Feltmate et al.[4] also noted that a distance greater than 20 miles from the patient's home to the trophoblastic disease center was associated with failure to complete hCG follow-up ($p = 0.001$). Furthermore, the impact of distance traveled is stronger for patients of lower socioeconomic status.[25,26]

Among South American women with GTN, long distances, social and economic disparities, inefficiency of the referral system, and limited GTD training may lead to late referral to a specialized center.[22] Very often, patients are not referred to an hCG follow-up program upon hospital discharge after molar evacuation, and when they are referred to the primary healthcare system, the results of postmolar serum hCG level are very frequently delayed, and misinterpretation of hCG regression curves may delay referral to a specialized center. Furthermore, patients living far away from a specialized center may cause them to postpone seeking care because of transportation issues and reluctance to miss days of work.[3]

It is worth noting that the high growth fraction of the placental trophoblast causes GTD to rapidly develop. Therefore, the timely management of patients with GTD in a specialized center can reduce morbidity and mortality. Moreover, the inefficiency of the referral system, as well as the gaps in GTD training, can lead to late referral to a specialized center. However, Brazilian regulations still do not consider it an urgent/emergency condition, which leads to delays in referral. Efforts should be made to change these referral/counter-referral regulations, as well as to allow the remote management of these patients through consultation with specialists when referral to a specialized center is not possible.

The limitations of this study were those inherent to its retrospective design and possible referral bias. As our study was conducted in a tertiary center for the treatment and follow-up of women with GTD, the data collected may overrepresent the incidence of high-risk HM and GTN at presentation. Additionally, the small number of patients from each health district might have limited statistical analysis of the effects of demographic characteristics and distance traveled on clinical status at admission.

In summary, this study showed that 1) a considerable proportion of patients with GTD (~ 30%) referred to BTDC came from health districts outside the center's geographical area of coverage; 2) women attending this center were characterized by low socioeconomic and education level, as well as unemployment status regardless of region of residence; 3) patients from health districts outside the area covered by the specialized center had higher risk scores for both HM and GTN at admission; 4) long distances (> 80 km) seemed to adversely influence the clinical status of GTD patients at admission, indicating barriers to accessing specialized centers.

Conclusion

Patients from health districts outside the specialized center area had higher risk scores for both HM and GTN at admission. Long distances (>80 km) seemed to adversely influence GTD clinical status at admission, indicating barriers to accessing specialized centers. Further studies are warranted to determine the potential impact of geographic location and travel distance on obtaining care in a specialized center among women with GTD.

Contributions

da Silva VAR – reviewed the literature, collected and managed data from the databases of Botucatu Trophoblastic Disease Center (São Paulo State University), wrote the initial draft of the manuscript. Maestá I – conceived and designed the study, contributed to and revised the manuscript; audited data collected from Botucatu Trophoblastic Disease Center database (São Paulo State University). Costa RAdeA – contributed to data analysis and interpretation, reviewed the literature for discussion. Campos AdeA – reviewed the literature, collected and managed data from the databases of Botucatu Trophoblastic Disease Center (São Paulo State University), wrote the initial draft of the manuscript. Braga A – contributed to data management and analysis and revised the manuscript. Horowitz NS – contributed to data analysis and interpretation and revised the manuscript. Elias KM – conceived the analysis strategy, contributed to the manuscript. Berkowitz RS – supervised the study and revised the manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

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Effect of Endometriosis on Cumulus ATP, Number of Mitochondria and Oocyte Maturity in Cumulus Oocyte Complex in Mice

Efeito da endometriose no cumulus ATP, número de mitocôndrias e maturidade oocitária no complexo oocitário cumulus em camundongos

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Abstract

Objective Endometriosis causes a decrease in oocyte quality. However, this mechanism is not fully understood. The present study aimed to analyze the effect of endometriosis on cumulus cell adenosine triphosphate ATP level, the number of mitochondria, and the oocyte maturity level.

Methods A true experimental study with a post-test only control group design on experimental animals. Thirty-two mice were divided into control and endometriosis groups. Cumulus oocyte complex (COC) was obtained from all groups. Adenosine triphosphate level on cumulus cells was examined using the Elisa technique, the number of mitochondria was evaluated with a confocal laser scanning microscope and the oocyte maturity level was evaluated with an inverted microscope.

Results The ATP level of cumulus cells and the number of mitochondria in the endometriosis group increased significantly ($p < 0.05$; $p < 0.05$) while the oocyte maturity level was significantly lower ($p < 0.05$). There was a significant relationship between ATP level of cumulus cells and the number of mitochondrial oocyte ($p < 0.01$). There was no significant relationship between cumulus cell ATP level and the number of mitochondrial oocytes with oocyte maturity level ($p > 0.01$; $p > 0.01$). The ROC curve showed that the number of mitochondrial oocytes (AUC = 0.672) tended to be more accurate than cumulus cell ATP level (AUC = 0.656) in determining the oocyte maturity level.

Conclusion In endometriosis model mice, the ATP level of cumulus cells and the number of mitochondrial oocytes increased while the oocyte maturity level decreased. There was a correlation between the increase in ATP level of cumulus cells and an increase in the number of mitochondrial oocytes.

Keywords
- endometriosis
- ATP
- cumulus cells
- mitochondria
- oocyte
- reproductive health

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Introduction

Endometriosis is defined as the presence of endometrial-like tissue outside the uterine cavity, which induces a chronic inflammatory reaction.[1] Approximately 30 to 50% of women with endometriosis have infertility and 25 to 50% of infertile women have endometriosis.[2]

Although numerous potential explanations have been documented, the precise mechanism by which endometriosis results in infertility is not entirely understood. According to studies, endometriosis-affected women who undergo in vitro fertilization (IVF) had lower rates of fertilization and oocyte division than endometriosis-free women.[3] Oocyte quality in endometriosis also decreases. It has been demonstrated that GDF-9, a growth factor released by oocytes, is decreased in the follicular fluid of infertile endometriosis patients.[4] This is caused by inflammatory factors in the female pelvic area, where there is an increase in the concentration of inflammatory cytokines such as TNF-α which leads to impaired function or quality of oocytes indirectly through cumulus cells.[3] This is confirmed by a study by Nakahara et al.,[5] which discovered that cumulus cells of endometrioma patients experienced a much higher rate of apoptosis than in patients without endometrioma.

Apoptosis in cumulus cells is believed to interfere with its function to support oocyte growth, which can eventually result in impaired oocyte maturation. As a result, essential nutrients like adenosine triphosphate (ATP) are primarily produced by cumulus cells to be supplied to oocytes[6] during oocyte maturation.

The nucleus and cytoplasm of the oocyte mature during the maturation process. The process of nuclear maturation involves the resumption of meiosis I, the ejection of the first polar body (Polar Body I), and the progression to the metaphase II (MII) stage.[7] Organelles like mitochondria are more numerous and are distributed differently in the cytoplasm.[8] Mitochondrial oocyte is the mitochondria present in the germ cell, oocyte, characterizing in oocytes by its rounder appearance and fragmented network.[9] Because mitochondria are not replicated during the cleavage stage of the embryo, the presence and quantity of mitochondria in mature oocytes are crucial for ensuring the survival of each blastomere that will obtain its mitochondria from the oocyte.[10] In both human and experimental animals, abnormal mitochondrial quantity is associated with poor oocyte quality.[11–13]

One of the most crucial organelles in determining the quality of an oocyte is the mitochondria, which control the potential of oocyte growth through a variety of routes including ATP synthesis, Ca^{2+} regulation, and maintenance of intracellular redox potential (IRP). The fact that mitochondrial oocytes grow in quantity, display extraordinary mobility, and cluster in a specific area, which is assumed to fulfill high energy demands during oocyte maturation is evidence for the crucial function that mitochondria play in oocyte and embryo development.[9] To divide, mitochondria require ATP compounds, which are taken from the cytoplasm. Oocytes use a large amount of their energy source (ATP) derived from cumulus cells for their maturation process and also increase the number of mitochondria during the maturation process because mitochondrial oocytes are in a "quiet" metabolic state or low activity to reduce their oxidant production.[14] The quantity of mitochondrial oocytes is believed to be affected by the decline in ATP supply from cumulus cells.

The aim of the present study was to analyze the effect of endometriosis on cumulus cell ATP level, the number of mitochondria and the oocyte maturity level. The present study used oocytes in mice as endometriosis model since studying the effect of endometriosis on oocytes in humans has ethical constraints.

Methods

The present study had received ethical clearance from the Animal Care and Use Committee Faculty of Veterinary Medicine Universitas Airlangga, Surabaya, Indonesia (number 2. KE.134.12.2021). All procedures done in the present study were conducted in accordance to the United Kingdom Animal Act 1986. All surgeries were conducted under anesthesia and all efforts were made to minimize the suffering.

The present study had a true experimental design conducted in the laboratory on mice (*Mus musculus*). All experimental animals were randomly selected so that they had the same opportunity to receive treatment and had a control group. The sample size was determined using the Lemeshow formula (with a significance level of $\alpha = 0.05$). Considering the average count of the control and treatment groups and the possibility of dropping out, the sample size was 16 mice per group.

The mice were obtained from a mouse breeder center for research purposes from the Integrated Research and Testing Laboratory (Laboratorium Penelitian dan Pengujian Terpadu, LPPT), Gadjah Mada University, Yogyakarta, Indonesia. Mice used in the study were healthy mice aged $\pm$ 12 weeks old, never pregnant, with a weight ranging from 20 to 30 g. Healthy mice are mice that based on clinical examination have bright eyes, no dirt, the fur is clean, not dull and not easy to fall off, no wound, and not aggressive.

In the present study, the experimental animal studies were prepared first. The mice were acclimatized for 1 week in a clean cage, with enough air, light, and homogeneous food and drink. Then, the mice were randomly divided into 2 groups, the control group (P0) and the endometriosis group (P1). To determine the sample size, the Lemeshow formula was used, with the result that each group consisted of 16 mice.[15]

The making of endometriosis model mice was in accordance with what was done in the study by Hendarto.[16] In the present study, the presence of endometriosis was confirmed by the formation of endometriotic lesions and visually visible hypervascularization of the peritoneal tissue at surgery. Another visible sign was the attachment of the uterus and digestive tract or other organs. The mice were given an injection of cyclosporin A with the aim of suppressing their immune status, which was done intramuscularly on the thighs of the mice. The drug preparation available in

Indonesia was Sandiimun produced by Novartis in 1 ampoule containing 50 mg/mL. The required dose was 10 mg/kg. In the present study, the weight of the mice ranged from 20 to 30 g, so the dose of cyclosporin A given must be adjusted. After calculating the dosage of the preparation, each mouse received a conversion dose of 1.8 mg/mouse so that the dose after dilution with water for injection was 0.2 mL of Sandiimun for each mouse. Endometriosis is induced by injecting endometrial tissue intraperitoneally and then by injecting estrogen to stimulate its growth. Endometrial tissue was taken from benign tumor uterine material, which was stored in phosphate buffered saline (PBS). Washing was performed 2 × with a centrifugal device with a rotation of 2,500 rpm. The supernatant was discarded and then PBS, penicillin 200 IU/ml and streptomycin 200 µg/ml were added. Then the wet endometrial tissue was taken with a 3 ml syringe. The dose given to mice was 0.1 ml. In addition, 54 IU estrogen injections (equivalent to 5.4 ug) were also given on days 1 and 5. In the control group, the mice received distilled water injections.

After 2 weeks, all groups of mice were given an injection of 5 IU Pregnant Mare Serum Gonadotropin (PMSG) hormone and 48 hours later they were injected with Human Chorionic Gonadotropin (hCG) and mixed with vasectomized male mice for ovulation induction. Seventeen hours after the mice mated, vaginal plug examination was performed. Female mice with positive vaginal plugs were terminated. Then, preparations for removing the fallopian tube organs were performed. The cumulus oocyte complex (COC) was collected by tearing the fertilization sac of the fallopian tube, which was done by observing the fallopian tube under a microscope. The COC was collected and the separation was performed using 0.1% hyaluronidase.

Adenosine triphosphate level on the cumulus cells obtained was then examined using the Elisa technique according to the instructions of the manufacturer. Measurement of ATP level was performed using Mouse Adenosine Triphosphate ELISA Kit, (Cat. No. E0665Mo, Bioassay Technology Laboratory) and it was performed with absorbance readings at a wavelength of 450 nm. The oocytes obtained were then examined for the number of mitochondria using the mito-tracker green (MTG) FM 50 µg from Invitrogen (then measured with a confocal laser scanning microscope (CLSM). The data obtained were then processed using special software Olympus Fluoview Ver.4.2a in a computer. The oocyte maturity level was evaluated using an inverted microscope with 200x magnification. The sign of oocyte maturity was determined when it reached the Metaphase II stage with polar body I removed.

All statistical analyzes were performed using IBM SPSS Statistics for Windows version 26 (IBM Corp., Armonk, NY, USA). Data distribution was assessed by the Kolmogorov-Smirnov normality test. To determine the difference between the endometriosis group and the control group, a continuous dataset that was not normally distributed used the two-tailed Mann-Whitney U test and data that were normally distributed used the *t*-test. Correlation analysis of each variable used the Spearman or Pearson test, depending on the distribution of the data. A p-value < 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was performed to determine the sensitivity, specificity, and limit value of cumulus cell ATP levels or the number of oocyte mitochondria to oocyte maturation level (►**Fig. 1**).

Results

All 16 mice from the P0 group and 16 mice from the P1 group were found to have ovulation. All COC were collected, and oocytes were separated from cumulus cells that surrounded them (►**Table 1**) (►**Fig. 2**).

The ATP level of all mice cumulus cells obtained was measured. The results of the *t*-test on ATP level of the two groups showed a significant difference ($p < 0.05$) with ATP level of the control group significantly lower than that of the treatment group (endometriosis) with the mean in the control group of 25.84 ng/ml and in the endometriosis group of 30.15 ng/ml (►**Table 1**). We counted the number of mitochondria from oocytes taken from cumulus cells using CSLM. The Mann-Whitney test results on the number of mitochondria in the two groups revealed a significant difference ($p < 0.05$), with the number of mitochondria in the control group significantly lower than that in the treatment group (endometriosis), with the means of the two groups being 208,875 and 406,503.25, respectively (►**Table 1**). We also assessed the oocyte maturity using an inverted microscope. According to the results of the *t*-test on the maturity level of the two groups, the oocyte maturity level in the control group was significantly higher ($p < 0.05$) than that in the treatment group (endometriosis), with the mean in the control group being 36.27% and that in the endometriosis group being 19.91% (►**Table 1**). Then, using correlation test, we examined the relationship between these variables. We first examined the relationship between the ATP level in cumulus cells and the number of mitochondrial oocytes. The Spearman correlation test results revealed a significant relationship ($p < 0.01$) between the ATP level in cumulus cells and the number of mitochondrial oocytes, in which the ATP level in cumulus cells had 46% influence on the number of mitochondrial oocytes (►**Table 2**).

Second, we examined the correlation between the number of mitochondrial oocytes and the level of oocyte maturity. According to the results of the Spearman correlation test ($p > 0.01$), there was no significant correlation between the number of mitochondrial oocytes and the level of oocyte maturity (►**Table 2**). The correlation between the ATP level in cumulus cells and the oocyte maturity was then examined. The findings of the Pearson correlation test revealed that there was no significant correlation between the number of mitochondrial oocytes and ATP levels in the cumulus cells ($p > 0.01$) (►**Table 2**). Finally, we also performed further analyses to assess the diagnostic value of cumulus cell ATP level or mitochondrial number or oocyte maturity level. The results of the ROC curve revealed no significant correlation between ATP level in cumulus cells or the number of mitochondrial oocytes on the level of oocyte

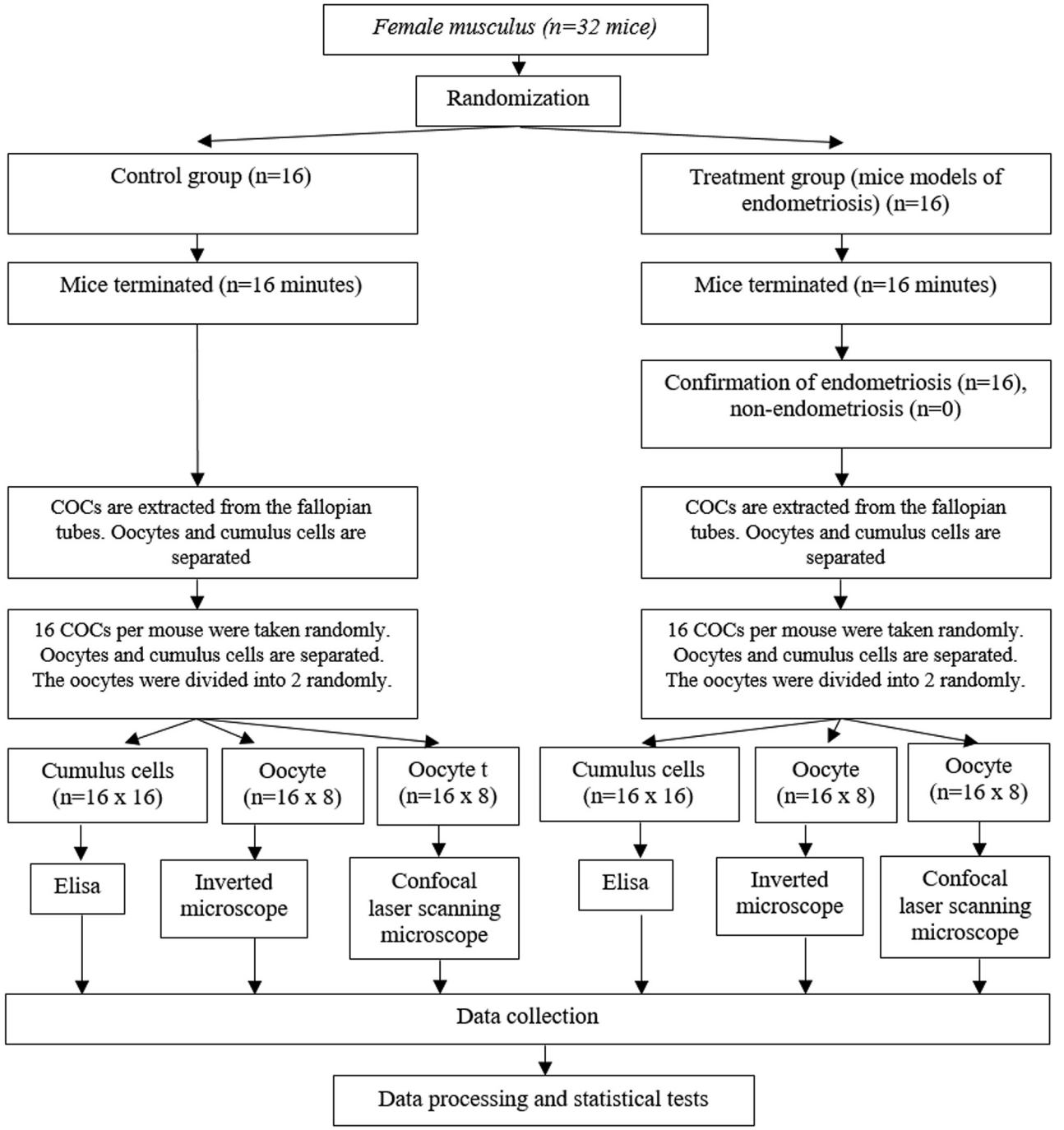

Fig. 1 Research flow.

Table 1 Differences between the endometriosis group and the control group

	Group	Mean	SD or mean rank	*p-value*
ATP Level of mice cumulus cell in each group	P0	25.84	1.97*	0.000
	P1	30.15	1.76*	
The number of mitochondria in each group.	P0	208,875	10.19**	0.000
	P1	406,503	22.81**	
Oocyte maturity level	P0	36.27	0.18*	0.006
	P1	19.91	0.16*	

Abbreviations: ATP, adenosine triphosphate; SD, standard deviation.
** Mean rank.

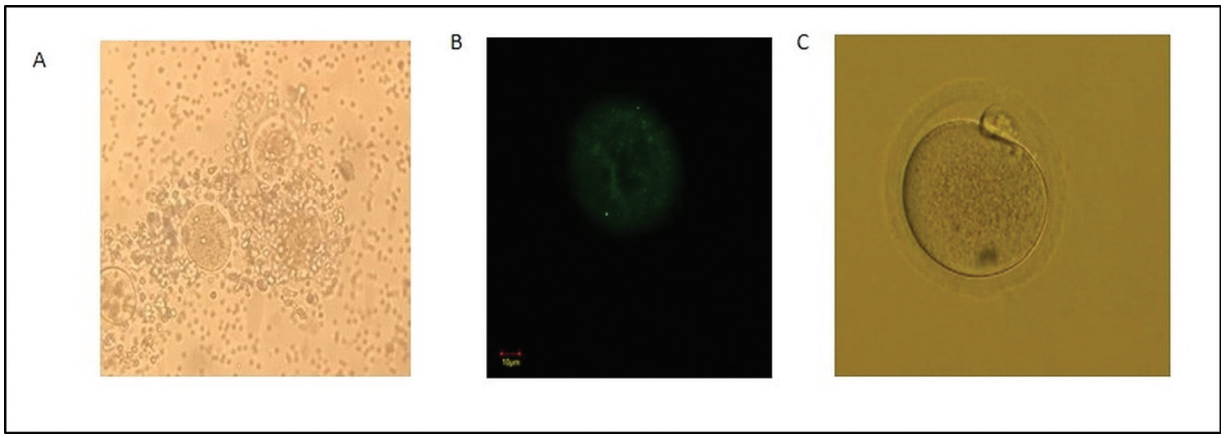

Fig. 2 (A) Mice cumulus-oocyte complex (microscope magnification 40x). (B) Mitochondria on examination with CLSM (marked in green) (C) Mature oocytes on examination with an inverted microscope (200x magnification).

Table 2 The effect of ATP level in cumulus cell on the number of mitochondrial oocytes, the effect of the number of mitochondrial oocytes on oocyte maturity level, and the effect of cumulus cell ATP level on the oocyte maturity level

	r	*p-value*
Effect of cumulus cell ATP levels on the number of oocyte mitochondria	46%	0.008
Effect of the number of oocyte mitochondria on the level of oocyte maturity.	–	0.102
Effect of cumulus cell ATP levels on oocyte maturity level.	–	0.381

Abbreviations: ATP, adenosine triphosphate.

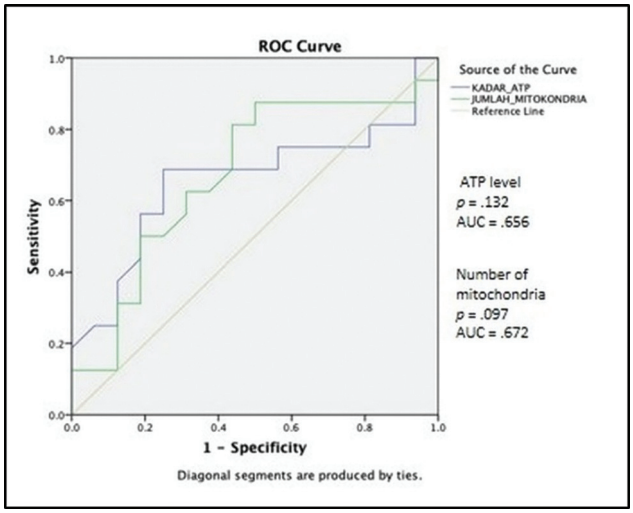

Fig. 3 ROC curve of cumulus cell ATP level and the number of mitochondrial oocytes on the oocyte maturity level.

maturity. However, the number of mitochondrial oocytes (AUC = 0.672) was more accurate in predicting the oocyte maturity level than the ATP level of cumulus cells (AUC = 0.656) (►**Fig. 2**).

►**Fig. 3** shows the ROC curve of cumulus cell ATP level and the number of mitochondrial oocytes on the oocyte maturity level. The sensitivity and specificity of the cumulus cell ATP level and the number of mitochondrial oocytes were plotted using ROC analysis between the endometriosis group and the control group. The area under the curve (AUC) and the p-value are shown. The cumulus cell ATP level or the number of mitochondria were not proven to significantly differentiate the oocyte maturation level of the endometriosis group and that of the control group ($p = 0.132$ and 0.097).

Discussion

The results showed that ATP level in the endometriosis group significantly increased compared with that in the control group ($p < 0.05$). This result is different from the study by Hsu et al., where the ATP levels of cumulus cells were lower in the endometriosis group.[17] This might be because this study was conducted in animal models where exposure to endometriosis was given in a shorter time, in contrast with women with endometriosis, who may take longer without knowing for sure when the exposure to endometriosis started. Another possibility is that the apoptosis that occurred in cumulus cells was incomplete or still at an early stage when the viability of cumulus cells was still > 50%.[18]

Apoptosis is a form of cell death that requires energy. This is supported by a study by Zamareva et al.[18] Apoptotic stimuli, like TNF-α, cause cytoplasmic ATP levels to rise significantly. Excess cytoplasmic ATP triggers apoptotic execution events including caspase activation and DNA fragmentation. Therefore, an elevated level of cytoplasmic ATP is a prerequisite for apoptotic cell death. According to a study by Zamaraeva et al.,[18] while cell viability remained at 50%, ATP signaling in the population of cells that underwent apoptosis returned to levels similar to those of the control group. Subsequently, cytoplasmic ATP signaling gradually decreased, which was accompanied by an increase in the number of dead cells.[15] The fact that cumulus cells naturally proliferate throughout the process of folliculogenesis under the influence of FSH, estradiol,[19] and growth factors generated by oocytes supports this explanation even more (GDF9,

BMP15).[20] In a study by Hendarto et al.,[4] it was discovered that patients with endometriosis had lower levels of GDF-9 in their follicular fluid. This suggests that cumulus cell proliferation may be declining, which confirms the finding of the study that the apoptotic process increased ATP levels.

The findings of our study also showed that there were significantly more mitochondrial oocytes in the endometriosis group than in the control group ($p < 0.05$). This could be as a result of an increase in ATP supply from cumulus cells, which during the oogenesis process stimulates an increase in the number of mitochondria in the oocyte.

Oocytes in the germinal vesicle (GV) stage during follicular development interact closely with granulosa cells via transzonal projections (TZPs). It is well known that the oocyte lacks the enzymes for glycolysis, cholesterol biosynthesis, and receptors for specific amino acids, thus the metabolism of granulosa cells is modulated to meet the needs of the oocyte (through oocyte-derived factors, the GDF9, BMP15, and FGF8B). Adenosine triphosphate, pyruvate, amino acids, and cholesterol must therefore be captured or produced by granulosa cells and supplied to oocytes.[6,21] An essential molecule for mitochondrial division, DYNAMO1, known as the mitochondrial division machine (MD), is also involved in the process of increasing the number of mitochondrial oocytes at this stage. During mitochondrial division, DYNAMO1 uses cytoplasmic ATP as an energy source for membrane cleavage.[22] Therefore, the oocyte receives a larger energy supply along with an increase in ATP level in cumulus cells. This could activate the mitochondrial cleavage machinery to promote mitochondrial replication inside the oocyte.

Furthermore, cells with a high demand for energy, like neuron and muscle cells, tend to have greater numbers of mitochondria.[23] Since mature oocytes show a remarkable increase in the number of mitochondria, this suggests that the oocyte maturation process requires a large amount of energy. The consequence is that higher free radicals will be formed as a side effect of oxidative phosphorylation, which can trigger oxidative stress and be harmful to these cells.[24] However, it seems that the oocyte develops a protective mechanism by using most of its energy source (ATP) derived from cumulus cells for its maturation process so that the mitochondria of the oocyte are in a "quiet" metabolic state or low activity to reduce their oxidant production.[1] However, it is known that oxidative stress occurs in endometriosis, which is considered to be the cause of a decrease in oocyte quality, but the mechanism is not widely understood.[25] As a consequence, oocytes are thought to require greater energy needed to repair themselves than for the maturation process. However, further studies are needed to confirm this.

The findings of the present study were different from those of Sanchez et al., who claimed that the number of mitochondrial oocytes in the endometriosis group was lower than that in the group with infertility caused by factors other than the endometrium.[26] It should be emphasized that a decrease in the amount of mtDNA molecules – which are a component of the mitochondria and can contain several mtDNA molecules – confirmed the findings of this paper. In contrast to this study, the measurements were made based on the binding of MTG with certain compounds in the mitochondrial matrix that supported the alkylation of thiol groups available in this subcellular compartment.

Another possible explanation for the aforementioned differences was the presence of polymorphisms in mitochondria. Polymorphisms often occur in mitochondria and mitochondrial polymorphisms influence the pathophysiology of various diseases by influencing mitochondrial matrix pH and intracellular calcium dynamics.[26,27] Free thiols are six times more reactive in the mitochondria than in the cytosol because the pH in the mitochondrial matrix is higher than in the cytosol (7.8–8 versus 7.2).[28] Changed pH in the matrix has the potential to affect the results of the study. However, further studies are required to confirm this polymorphism.

We used a correlation test to see whether there was a relationship between an increase in the ATP level of cumulus cells and an increase in the number of mitochondrial oocytes. The results revealed a significant correlation ($p < 0.01$) between the two variables. As a result, it is possible to infer that the ATP level in cumulus cells affects how many mitochondrial oocytes are present. The number of mitochondrial oocytes increases along with the ATP concentration of the cumulus cells. The higher the ATP content of the cumulus cells, the higher the number of mitochondrial oocytes. This supports the notion that mitochondria utilize the ATP present in the cytoplasm around them as a source of energy for reproduction.[22]

The oocyte maturity level in the endometriosis group was significantly lower than that in the control group ($p < 0.05$). This was highly contradictory when compared with the results of the aforementioned study that found an increase in the number of mitochondrial oocytes. With the abundance of mitochondria in the endometrial oocyte, the oocyte should have sufficient and independent resources to continue its maturation once its relationship with cumulus cells is damaged following the luteinizing hormone (LH) surge. This may be because there was a quantitative, instead of qualitative, increase in the number of mitochondria. This was supported by the correlation test we conducted between the number of mitochondrial oocytes and the maturity level of oocytes with the result that there was no significant relationship between the number of mitochondrial oocytes and the oocyte maturity level ($p > 0.01$).

A possible explanation related to the aforementioned results is the emergence of free radicals as a side effect of ATP formation in cumulus cells. Free radicals (ROS) are a side effect of oxidative phosphorylation in the mitochondrial cells that are actively producing ATP.[29] Endometriosis can trigger destructive apoptosis and increased ROS through mitochondrial dysfunction of cumulus cells.[30] Mitochondrial ROS can damage DNA by producing various DNA damages such as oxidized bases and DNA chain severance.[30,31] Thus, in addition to ATP, ROS formed in cumulus cells also increased and consequently was distributed into oocytes through TZPs and caused damage to mtDNA. Therefore, when the mitochondrial oocyte is active, it cannot function properly to support the final maturation process of meiosis II and also the early development of the embryo, which requires energy. From this, oocyte mitochondrial dysfunction that initially does not

appear to predispose to early oogenesis (before the LH surge) may eventually impair oocyte maturation, leading to infertility.[32–34] However, further studies are required to confirm this.

Another possible explanation is that there was an increase in free radicals in endometriosis due to iron overload that exceeds the storage capacity of macrophages.[35] According to Carlberg et al.,[3] the peritoneal fluid of women with endometriosis contains inflammatory substances that can diffuse into the ovarian follicles. These free radicals will diffuse into the follicles, which contain the oocytes, exposing the mtDNA and causing damage.

An interesting concept was presented by Chiaratti et al., who stated that mitochondrial oocytes are in a "quiet" metabolic state or low activity.[9] Thus, why do oocytes store so many mitochondria if they are not required for oogenesis? The function of these organelles during the late maturation and early embryogenesis periods can, at least in part, provide an explanation for this. During early oogenesis, mitochondrial oocytes are relatively unnecessary because their cooperation with granulosa cells is sufficient to support the needs of the oocyte. As is widely known, the process of oxidative phosphorylation in mitochondria has a side consequence of free radical generation, and this incidence demonstrates the significance of protecting mitochondria from oxidative damage that results in mutations in mitochondrial DNA (mtDNA).[36] Given that mitochondria are inherited exclusively by the mother, oocytes with mtDNA mutations can cause disease in their offspring. Thus, to compensate for the expansion of mutations, oocytes have developed special mechanisms to protect the mtDNA molecule from damage.[2]

Additionally, the correlation between cumulus cell ATP level and oocyte maturity level was also examined in the present study, and no significant correlation was found. This confirmed the theory that granulosa cells promote oocyte maturation prior to the LH surge. After the LH surge, the oocyte continues to mature on its own, using its own organelles. This was also confirmed in the present study, although there was no significant correlation between ATP level of cumulus cells or the number of mitochondrial oocytes with oocyte maturity level, the results of ROC curve for cumulus cell ATP levels or the number of mitochondrial oocytes on oocyte maturity level indicated that the number of mitochondrial oocytes (AUC = 0.672) tends to be more accurate than cumulus cell ATP level (AUC = 0.656) in determining the oocyte maturity level.

However, the limitation of the present study is the use a mouse model of endometriosis that was treated for 2 weeks. Endometriosis is a disease that induces a chronic inflammatory reaction. This research might be more suitable if the inflammatory conditions that occur are made longer.

Conclusion

There was an increase in cumulus cell ATP level and in the number of mitochondrial oocytes in endometriosis model mice and a decrease in oocyte maturity level in endometriosis model mice. The increase in ATP level of cumulus cells corresponded to an increase in the number of mitochondrial oocytes. There was no significant relationship between cumulus cell ATP level and the number of mitochondria on the oocyte maturity level in metaphase II (PbI) although the number of mitochondrial oocytes tended to be more accurate in determining oocyte maturity level than ATP level of cumulus cells.

Contributions

MYAW, WW, and HH designed this research. MYAW, WW, and HH conducted a survey and took samples at the samples field. All authors examined samples in the research laboratory. All authors compiled, read, revised, and approved the final manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

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Clinical Characteristics and Outcomes of a High-grade Endometrial Cancer Cohort Treated at Instituto Nacional de Câncer, Brazil

Características clínicas e desfechos de uma coorte de câncer endometrial de alto grau tratada no Instituto Nacional de Câncer, Brasil

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Abstract

Objective To analyze the outcomes of a cohort of patients with high-risk histologies of endometrial cancer (EC) treated at Instituto Nacional de Câncer (National Cancer Institute, INCA, in Portuguese), in Brazil.

Materials and Methods We reviewed the medical records of patients with high-risk histologies of EC in any stage registered at INCA between 2010 and 2016 to perform a clinical and demographic descriptive analysis and to evaluate the outcomes in terms of recurrence and survival.

Results From 2010 to 2016, 2,145 EC patients were registered and treated at INCA, and 466 had high-grade histologies that met the inclusion criteria. The mean age of the patients was 65 years, 44.6% were Caucasian, and 90% had a performance status of 0 or 1. The most common histology was high-grade endometrioid (31.1%), followed by serous carcinoma (25.3%), mixed (20.0%), carcinosarcoma (13.5%), and clear cell carcinoma (9.4%). Considering the 2018 Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics, FIGO, in French) staging system, 44.8%, 12.4%, 29.8%, and 12.9% of the patient were in stages I, II, III or IV respectively. Age (> 60 years), more than 50% of myoinvasion, higher stage, poor performance status, serous and carcinosarcoma histologies, and adjuvant treatment were independent factors associated with recurrence-free survival (RFS) and overall survival (OS) in the multivariate analysis.

Conclusion The current findings reinforced the international data showing poor outcomes of these tumors, especially for serous and carcinosarcomas and tumors with advanced stages, with shorter survival and high recurrence rates in distant sites, independently of the FIGO stage. Adjuvant therapy was associated with better survival.

Keywords

- endometrial cancer
- endometrial cancer therapy
- endometrial cancer pathology
- demographic analysis

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Resumo

Objetivo Analisar os desfechos de uma coorte de pacientes com câncer de endométrio (CE) e histologias de alto risco atendida no Instituto Nacional do Câncer (INCA) entre 2010 e 2016.

Materiais e Métodos Foram revisados prontuários de pacientes com histologias de alto risco de CE em qualquer estágio cadastradas no INCA entre 2010 e 2016 para realizar uma análise descritiva clínica e demográfica e avaliar os resultados em termos de recorrência e sobrevida.

Resultados De 2010 a 2016, 2.145 pacientes com CE foram cadastradas e atendidas no INCA, e 466 tinham histologias de alto grau e atendiam aos critérios de inclusão. A média de idade das pacientes foi de 65 anos, 44,6% eram brancas, e 90% tinham *performance status* de 0 ou 1. A histologia mais comum foi endometrioide de alto grau (31,1%), seguida de carcinoma seroso (25,3%), misto (20,0%), carcinossarcoma (13,5%) e carcinoma de células claras (9,4%). Considerando o estadiamento da Fédération Internationale de Gynécologie et d'Obstétrique (Federação Internacional de Ginecologia e Obstetrícia, FIGO, em francês) de 2018, 44,8%, 12,4%, 29,8% e 12,9% apresentaram estágios I, II, III ou IV, respectivamente. Idade ($>$ 60 anos), mais de 50% de mioinvasão, estágio avançado, *performance status* ruim, histologias serosas e carcinossarcoma, e tratamento adjuvante foram fatores independentes associados à sobrevida livre de recorrência e sobrevida global na análise multivariada.

Conclusão Os achados atuais reforçam os dados internacionais que demonstram o prognóstico ruim desses tumores, principalmente para as histologias serosas e carcinossarcomas e para estágios avançados, com menor sobrevida e altas taxas de recorrência à distância, independentemente do estágio da FIGO. A terapia adjuvante foi associada a melhor sobrevida.

Palavras-chave

- câncer de endométrio
- terapia para câncer de endométrio
- patologia câncer de endométrio
- análise demográfica

Introduction

Endometrial cancer (EC) is the most common gynecological cancer in developed countries and the third most common gynecological cancer in Brazil. Approximately 6,500 new cases were expected in Brazilian women per year from 2020 to 2022 and it caused 1,823 deaths in 2020.[1] The worldwide incidence is expected to increase in upcoming years, since obesity and aging, which are important risk factors to develop EC, are increasing.[2]

In 1983, Bohkman[3] performed a prospective study dividing EC into two major subgroups, in a classification that was used for decades. The first subgroup, named type I, was characterized by lower-grade histology, less aggressive behavior, metabolic syndrome, and a better response to progestins. The second, type II, with more aggressive behavior, is more commonly diagnosed in the advanced stage and is less responsive to progestins. At that time, Bohkman[3] did not know the different histologies described years later with the classification by the World Health Organization (WHO): endometrioid, serous, clear-cell, and undifferentiated carcinomas.[4] It is well known that serous carcinoma, clear-cell carcinoma (CCC), and carcinosarcoma (CCS) have a poorer prognosis compared with endometrioid tumors, and they are classified as type-II tumors.[5,6] However, high-grade endometrioid tumors are more heterogeneous and sometimes can show intermediate or similar prognosis to that of serous carcinomas and CCCs.[5–8] In recent years, this dualist vision of EC has been replaced by a more accurate molecular profile. In this system, developed by The Cancer Genome Atlas (TCGA) using next-generation sequencing, patients with endometrioid and serous carcinomas were classified in one of the four molecular subgroups: those with mutations in the *POLE* gene (called "POLE ultramutated", the subgroup with good prognosis); those with *p53* gene mutation (called "copy number high", the subgroup with poor prognosis), those with mutations in the *MLH1*, *MSH2*, *MSH6* or *PMS2* genes (called "microssatelite instability"), and those without a characteristic gene mutation (called "copy number low"), both with an intermediate prognosis.[9]

There is a paucity of information about the prognosis and outcomes of EC patients in the Brazilian population. Thus, the present study aimed to analyze demographic and prognostic characteristics of a high-grade EC cohort treated in a tertiary cancer center in Brazil.

Materials and Methods

The present is a retrospective study conducted at Instituto Nacional de Câncer (National Cancer Institute, INCA, in Portuguese). The medical records of EC patients registered at INCA between 2010 and 2016 were reviewed. The

inclusion criteria were patients over 18 years of age with high-grade endometrioid carcinomas, serous carcinomas, CCCs, CCSs or undifferentiated adenocarcinomas, regardless of the stage (I-IV) according to the 2018 Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics, FIGO, in French) staging system, who underwent the whole treatment at INCA. The exclusion criteria were patients with other synchronous or metachronous primary tumors, non-epithelial histologies, and low-grade histologies. Sociodemographic (age and race) and clinical variables (histology type, stage, treatment received, recurrence, type of recurrence, death) were collected.

The primary objective of the present study was to perform a clinical and demographic descriptive analysis and to evaluate the outcomes in terms of recurrence and survival of this cohort. Pelvic recurrences included vaginal and local recurrences (including to the pelvic lymph nodes and local spread to the rectum and bladder); recurrences outside the pelvis consisting of peritoneal carcinomatosis or omental metastasis were classified as abdominal recurrences; distant hematogenous recurrences include lung, liver, bone, and brain metastases, as well as non-pelvic or para-aortic lymph node involvement. Simultaneous pelvic and abdominal recurrences were classified as abdominal recurrence; simultaneous abdominal and distant recurrences were considered distant recurrence; and simultaneous locoregional and distant recurrences were also considered distant recurrence. Recurrence-free survival (RFS) was defined as the time from diagnosis to the date of recurrence confirmed by imaging or clinically (local or distant), or death, with censoring of patients alive without recurrence. Overall survival (OS) was defined as the time from diagnosis to death, regardless of the cause, with censoring of patients alive on the date of the last follow-up.

Statistical analyses were performed using the R (R Foundation for Statistical Computing, Vienna, Austria) software. Patient and tumor characteristics were compared with the *t*-test for continuous variables and with the Chi-squared (χ^2) or Fisher exact tests for categorical variables. Rates of distant and locoregional recurrences, and RFS and OS were analyzed by the Kaplan-Meier method and log-rank test from the date of diagnosis, with censoring of patients who were alive and recurrence-free on the date of the last follow-up. For the RFS analysis, all recurrences (locoregional and distant) were considered an event; for OS, all deaths regardless of the cause were considered an event. All statistical tests were two-sided and values of $p < 0.05$ were considered statistically significant.

The present study was approved by the institutional ethical committee (under number 26543019.5.0000.5274) and is in accordance with the Good Clinical Practice.

Results

From 2010 to 2016, 2,145 EC patients were registered and treated at INCA. Of these, 466 had high-grade histologies and met all the inclusion criteria. Their mean age was 65 years (standard deviation [SD]: ± 11.5), 44.6% were Caucasian, and 90% had a performance status (PS) of 0 or 1. The most common histology was high-grade endometrioid carcinoma (145; 31.1%) followed by serous carcinoma (118; 25.3%), mixed carcinoma (93; 20.0%), CCS (63, 13.5%), and CCC (44; 9.4%). Regarding stage, 44.8%, 12.4%, 29.8% and 12.9% were in 2018 FIGO stages I, II, III and IV respectively, and 48.8% presented more than 50% of myoinvasion.

The surgery route was an open laparotomy for 90.3% of the patients. Most underwent total hysterectomy plus salpingooforectomy and lymphadenectomy (33.8%) or in addition to omentectomy (34.8%); 31.4% were not submitted to lymph node assessment (they underwent only total hysterectomy with or without salpingooforectomy). Minimally-invasive surgery was barely used (laparoscopy: 5.7%; and robotic: 1.7%). Adjuvant treatment was administered to 77.6% of the cohort. Chemotherapy (mostly carboplatin plus paclitaxel) with or without any radiation therapy (external or brachytherapy) was prescribed to 50% of the patients; exclusive external beam radiotherapy and/or brachytherapy were performed in 27.1%. The mean number of cycles of systemic therapy was of 5.7, and the mean doses of external beam radiotherapy and brachytherapy were of 4,800 cGy and 2,675.4 cGy respectively. ►**Table 1** summarizes the main characteristics of the patients.

The median follow-up was of 74.9 months. As expected, recurrence was quite common in this high-risk cohort, with a rate of 43.8%. For the whole population, the recurrence pattern was most common in distant sites (44.1%), followed

Table 1 Clinical characteristics of the study cohort

Variables		n (%); N =466
Age	Mean (± standard deviation)	65.9 (11.5) years
Age group	< 60	118 (25.3) years
	≥ 60	348 (74.7) years
Race	White	208 (44.6)
	Black	89 (19.1)
	Non-white/black	169 (36.3)
Histological subtype	AEG3	145 (31.1)
	USC	118 (25.3)
	CCC	44 (9.4)
	CCS	63 (13.5)
	Mixed	93 (20.0)
	NOS	3 (0.6)
Type of surgery	TAH	14 (3.0)
	TAH + BSO	132 (28.4)
	TAH + BSO + LFN (PLNs or PALNs)	157 (33.8)
	TAH + BSO + LFN + omentectomy	162 (34.8)
Route of surgery	Open	420 (90.3)
	Laparoscopic	25 (5.4)
	Transvaginal	12 (2.6)
	Robotic	8 (1.7)

(*Continued*)

Table 1 (*Continued*)

Variables		n (%); N =466
ECOG-PS	0	116 (25.3)
	1	297 (64.8)
	2	33 (7.2)
	3	12 (2.6)
2018 FIGO	IA	148 (31.8)
	IB	61 (13.1)
	II	58 (12.4)
	IIIA	35 (7.5)
	IIIB	6 (1.3)
	IIIC1	63 (13.5)
	IIIC2	35 (7.5)
	IVA	2 (0.4)
	IVB	58 (12.4)
2018 FIGO	I	209 (44.8)
	II	58 (12.4)
	III	139 (29.8)
	IV	60 (12.9)
Myoinvasion	No invasion	24 (5.2)
	Less than 50%	214 (46.0)
	More than 50%	227 (48.8)
Chemotherapy	No	231 (49.6)
	Yes	235 (50.4)
Type of chemotherapy	Adjuvant	225 (95.7)
	Neoadjuvant	10 (4.3)
Cycles of chemotherapy	Mean (± standard deviation)	5.7 (1.1)
Adjuvant radiotherapy	No	313 (67.3)
	Yes	152 (32.7)
Radiotherapy dose (cGY)	Mean (± standard deviation)	4,800 (2,600)
Adjuvant brachytherapy	No	326 (70.1)
	Yes	139 (29.9)
Brachytherapy dose (cGY)	Mean (± standard deviation)	2,675.4 (350.6)
Any type of treatment[a]	No	104 (22.4)
	Yes	361 (77.6)
Type of treatment	No treatment	104 (22.4)
	Chemotherapy with or without EBR/BT	235 (50.5)
	EBR and/or BT	126 (27.1)
Disease recurrence	No	261 (56.1)
	Yes	204 (43.9)
Site of recurrence	Pelvis	60 (29.4)
	Abdomen	54 (26.5)
	Distant	90 (44.1)
Death	No	200 (42.9)
	Yes	266 (57.1)

Abbreviations: BSO bilateral salpingooforectomy; BT, brachytherapy; CCC, clear-cell carcinoma; CCS; carcinosarcoma; EBR, external beam radiotherapy; ECOG-PS, Eastern Cooperative Oncology Group's Performance Status scale; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics, in French) staging system; G3EA, grade-3 endometrioid adenocarcinoma; LFN, lymphadenectomy; x Mixed, mixed epithelial tumors; NOS, not otherwise specified; PALNs, paraaortic lymph nodes; PLNs, pelvic lymph nodes; TAH, total abdominal hysterectomy; USC, uterine serous carcinoma.
Note: [a]Includes chemotherapy and/or radiotherapy and/or brachytherapy.

by abdominal (26.5%) and pelvic (29.4%). Focusing on the recurrence pattern by stage or histology, these findings were not different, with most recurrences occurring in distant sites (►**Tables 1** and **2**).

The mean RFS and OS were of 36.8 and 52.8 months respectively. As expected, poor PS was associated with worse outcomes (OS of 131, 90, 64, and 48 months for PS 0,1, 2 and 3 respectively) as well as higher stages (for patients in stages I, II, III, and IV the RFS and OS were of 118 and 122; 37.5 and 48.5; 20.4 and 29.9; and 9.4 and 18 months respectively). Regarding histology, CCS and serous carcinoma had the worse prognosis, followed by CCC, mixed and high-grade endometrioid carcinomas. Age > 60 years, more than 50% of myoinvasion, higher stage, poor PS, serous and CCS histologies, and adjuvant treatment were independent factors associated with RFS and OS in the univariate and multivariate analyses (►**Tables 3** and **4**).

Discussion

The diagnosis of EC is usually established in patients with less aggressive histologies and early-stage disease (type I tumors), which leads to a high chance of cure with surgery alone. The incidence is increasing worldwide due to the increasing rate of obesity and the aging of the population.[2] In Brazil, the incidence is higher in more developed areas, such as the Southeastern region, and is also expected to increase.[1] Type-II EC, such as the histologies analyzed in this cohort, has long been known for its poor prognosis, and multimodality treatment is usually recommended by major international guidelines.[10,11]

Important insights can be drawn based on the present retrospective and descriptive analysis. First, we were able to reinforce the international data regarding the poor prognosis of high-risk histologies and the prognostic impact of higher stages.[5] Although we did not collect data about low-grade endometroid tumors (FIGO stages I and II), we could conclude the poorer outcome of our cohort compared with the former based on the international literature. In the present analysis, serous carcinoma and CCS retained a poor prognosis compared with high-grade endometrioid carcinoma. This

Table 2 Patterns of recurrence

		Pelvic – n (%)	Abdominal – n (%)	Distant – n (%)	Total – n (%)	*p*
2018 FIGO	IA	11 (37.9)	5 (17.2)	13 (44.8)	29 (100)	0.537
	IB	3 (25.0)	3 (25.0)	6 (50.0)	12 (100)	
	II	11 (42.3)	2 (7.7)	13 (50.0)	26 (100)	
	IIIA	6 (31.6)	5 (26.3)	8 (42.1)	19 (100)	
	IIIB	3 (60.0)	1 (20.0)	1 (20.0)	5 (100)	
	IIIC1	10 (24.4)	14 (34.1)	17 (41.5)	41 (100)	
	IIIC2	5 (20.0)	8 (32.0)	12 (48.0)	25 (100)	
	IVA	0 (0.0)	0 (0.0)	1 (100.0)	1 (100)	
	IVB	11 (23.9)	16 (34.8)	19 (41.3)	46 (100)	
2018 FIGO	I	14 (34.1)	8 (19.5)	19 (46.3)	41 (100)	0.179
	II	11 (42.3)	2 (7.7)	13 (50.0)	26 (100)	
	III	24 (26.7)	28 (31.1)	38 (42.2)	90 (100)	
	IV	11 (23.4)	16 (34.0)	20 (42.6)	47 (100)	
Histological subtype	G3EA	9 (21.4)	12 (28.6)	21 (50.0)	42 (100)	0.551
	USC	17 (25.0)	18 (26.5)	33 (48.5)	68 (100)	
	CCC	4 (22.2)	5 (27.8)	9 (50.0)	18 (100)	
	CCS	15 (36.6)	11 (26.8)	15 (36.6)	41 (100)	
	Mixed	15 (42.9)	8 (22.9)	12 (34.3)	35 (100)	
Myoinvasion	No invasion	5 (50.0)	3 (30.0)	2 (20.0)	10 (100)	0.343
	Less than 50%	24 (33.3)	16 (22.2)	32 (44.4)	72 (100)	
	More than 50%	31 (25.6)	34 (28.1)	56 (46.3)	121 (100)	
	(Missing)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100)	
Myoinvasion	No or less than 50%	29 (35.4)	19 (23.2)	34 (41.5)	82 (100)	0.320
	More than 50%	31 (25.6)	34 (28.1)	56 (46.3)	121 (100)	
	(Missing)	0 (0.0)	1 (100.0)	0 (0.0)	1 (100)	

Abbreviations: CCC, clear-cell carcinoma; CCS; carcinosarcoma; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics, in French) staging system; G3EA, grade-3 endometrioid adenocarcinoma; Mixed, mixed epithelial tumors; USC, uterine serous carcinoma.

Notes: Pelvic recurrences included vaginal and pelvic recurrences (including pelvic lymph nodes and local spread to the rectum and bladder); recurrences outside the pelvis consisting of peritoneal carcinomatosis or omental metastasis were classified as abdominal recurrences; distant recurrences include lung, liver, bone, and brain metastases, as well as non-pelvic or paraaortic lymph node involvement. Simultaneous locoregional and abdominal recurrences were classified as abdominal recurrence; simultaneous abdominal and distant recurrences were considered as distant recurrence, and simultaneous locoregional and distant recurrences were considered as distant recurrence.

finding contrasts with those of some studies, but it is also in line with those of many others.[5–8] In an analysis done by the Canadian High-Risk Endometrial Cancer (CHREC) Consortium with 1,260 women with high-risk histologies (grade-3 endometrioid adenocarcinoma [G3EA], CCC, CS, CCS),[5] the distribution of FIGO stages was similar to that of our cohort (49.3% versus 44.8% for stage I; 10.6% versus 12.4% for stage II; 27.4% versus 29.8% for stage III; and 12.7% versus 12.9% for stage IV). Regarding adjuvant treatment, 74.5% of the patients in the Canadian study and 77% in the present analysis underwent one treatment modality, with similar use of chemotherapy (54.8% versus 50% respectively). In both studies, CCS had the worse prognosis, with shorter OS and RFS among the high-risk histologies.[5] In our cohort, we observed more recurrences than in the Canadian cohort (43.9% versus 31.5% respectively), but the distribution was similar, with most recurrences in distant sites. A second point must be made regarding surgical aspects. International prospective randomized clinical trials[12–14] have highlighted the safety and lower morbidity of the minimally-invasive surgery (MIS) for EC, and have also showed safety in subgroup analyses for high-grade histologies. Although these trials included mainly low-grade endometrioid tumors (stage I), MIS was seldom used in our cohort despite the rate of 45% of patients in stage I. There is only one robotic platform at INCA, which was installed in 2012, and only one platform for laparoscopic surgery at the Gynecologic Oncology Unit. The low rates of MIS can also be explained by the fact that not every surgeon is certified to perform robotic surgery and by the frequent lack of surgical supplies. In addition, although lymph node assessment is recommended for any EC with myoinvasion, with sentinel lymph node being the standard of care for the uterine confined disease, about a third of the patients did not undergo any lymph node assessment. Unfortunately, we could not collect data regarding the use of sentinel lymph node. Third, the importance of

Table 3 Univariate and multivariate analyses for overall survival (OS)

Variable – OS		All – n (%)	HR (95%CI; *p*-value) –univariate analysis	HR (95%CI; *p*-value) –multivariate analysis
Age at diagnosis (in years)	Mean (± SD)	65.9 (11.5)	1.04 (1.02–1.05; $p < 0.001$)	–
Age group (in years)	< 60	118 (25.3)	–	–
	≥ 60	348 (74.7)	2.37 (1.71–3.29; $p < 0.001$)	2.05 (1.45–2.89; $p < 0.001$)
Race	White	208 (44.6)	–	–
	Black	89 (19.1)	1.37 (1.00–1.89; $p = 0.053$)	–
	Non-white/black	169 (36.3)	1.23 (0.94–1.61; $p = 0.139$)	–
Race	White	208 (44.6)	–	–
	Non-white	258 (55.4)	1.28 (1.00–1.63; $p = 0.050$)	–
2018 FIGO	I	209 (44.8)	–	–
	II	58 (12.4)	2.26 (1.52–3.36; $p < 0.001$)	2.85 (1.88–4.31; $p < 0.001$)
	III	139 (29.8)	3.08 (2.27–4.16; $p < 0.001$)	4.81 (3.21–7.19; $p < 0.001$)
	IV	60 (12.9)	5.37 (3.75–7.70; $p < 0.001$)	8.03 (5.07–12.73; $p < 0.001$)
ECOG-PS	0	116 (25.3)	–	–
	1	297 (64.8)	3.26 (2.26–4.70; $p < 0.001$)	2.28 (1.55–3.35; $p < 0.001$)
	2	33 (7.2)	5.40 (3.25–8.98; $p < 0.001$)	3.20 (1.87–5.46; $p < 0.001$)
	3	12 (2.6)	8.63 (4.35–17.10; $p < 0.001$)	4.03 (1.90–8.55; $p < 0.001$)
Myoinvasion	No invasion	24 (5.2)	–	–
	Less than 50%	214 (46.0)	1.40 (0.71–2.77; $p = 0.338$)	–
	More than 50%	227 (48.8)	2.76 (1.40–5.41; $p = 0.003$)	–
Myoinvasion	No or less than 50%	238 (51.2)	–	–
	More than 50%	227 (48.8)	2.04 (1.59–2.60; $p < 0.001$)	1.55 (1.18–2.04; $p = 0.002$)
Histological subtype	G3EA	145 (31.1)	–	–
	USC	118 (25.3)	1.90 (1.37–2.64; $p < 0.001$)	1.56 (1.10–2.22; $p = 0.013$)
	CCC	44 (9.4)	1.47 (0.94–2.30; $p = 0.095$)	1.18 (0.73–1.88; $p = 0.500$)
	CCS	63 (13.5)	2.97 (2.04–4.32; $p < 0.001$)	2.35 (1.56–3.52; $p < 0.001$)
	Mixed	93 (20.0)	1.06 (0.72–1.56; $p = 0.769$)	0.92 (0.61–1.38; $p = 0.674$)
	NOS	3 (0.6)	0.00 (0.00–Inf; $p = 0.991$)	0.00 (0.00–Inf; $p = 0.992$)
Treatment	No treatment	104 (22.4)	–	–
	Chemotherapy with or without EBR/BT	235 (50.5)	0.75 (0.56–1.00; $p = 0.052$)	0.30 (0.20–0.44; $p < 0.001$)
	EBR and/or BT	126 (27.1)	0.46 (0.32–0.66; $p < 0.001$)	0.56 (0.38–0.83; $p = 0.004$)

Abbreviations: 95%CI, 95% confidence interval; BT, brachytherapy; CCC, clear-cell carcinoma; CCS; carcinosarcoma; EBR, external beam radiotherapy; ECOG-PS, Eastern Cooperative Oncology Group's Performance Status scale; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics, in French) staging system; G3EA, grade-3 endometrioid adenocarcinoma; HR, hazard ratio; Mixed, mixed epithelial tumors; NOS, not otherwise specified; SD, standard deviation; USC, uterine serous carcinoma.

treating patients according to guidelines is well described in the literature.[10,11,15,16] The cohort of the present study was composed of high-risk patients, to whom the adjuvant treatment is almost always recommended, especially chemotherapy, and 22% percent of the patients did not undergo any kind of adjuvant treatment. Undergoing any type of adjuvant treatment was associated with better survival than observation in the present analysis. Intriguingly, most recurrences were in distant or abdominal sites, which puts into question the role of adjuvant external beam radiation for these patients.

The present analysis has several limitations, mainly based on its inherent retrospective nature, with many confounding factors that cannot be addressed, for it involved a single-center population and issues regarding the accuracy of the data collection. There were also limited data on comorbidities, which could have impacted the survival, and we were not able to classify the patients based on the new molecular classification. The strength of the study is that it involved a large number of patients with high-risk histology.

Conclusion

We retrospectively reviewed a cohort of patients with high-risk histologies treated at INCA between 2010 and 2016. We reinforced the international data showing the poor outcomes of these tumors, especially for serous carcinoma and CCS and tumors with advanced stages, with shorter survival and high

Table 4 Univariate and multivariate analysis for recurrence-free survival (RFS)

Variable – RFS		All – n (%)	HR (95%CI; *p*-value) –univariate analysis	HR (95%CI; *p*-value) –univariate analysis
Age at diagnosis (in years)	Mean (± SD)	65.9 (11.5)	1.03 (1.02–1.04; $p < 0.001$)	–
Age group (in years)	< 60	118 (25.3)	–	–
	≥ 60	348 (74.7)	2.14 (1.56–2.92; $p < 0.001$)	1.87 (1.35–2.60; $p < 0.001$)
Race	White	208 (44.6)	–	–
	Black	89 (19.1)	1.32 (0.97–1.82; $p = 0.081$)	–
	Non-white/black	169 (36.3)	1.20 (0.92–1.56; $p = 0.187$)	–
Race	White	208 (44.6)	–	–
	Non-white	258 (55.4)	1.24 (0.98–1.57; $p = 0.078$)	–
2018 FIGO	I	209 (44.8)	–	–
	II	58 (12.4)	2.18 (1.47–3.25; $p < 0.001$)	2.65 (1.75–4.01; $p < 0.001$)
	III	139 (29.8)	3.31 (2.46–4.45; $p < 0.001$)	4.67 (3.17–6.86; $p < 0.001$)
	IV	60 (12.9)	7.01 (4.91–10.01; $p < 0.001$)	9.75 (6.22–15.29; $p < 0.001$)
ECOG-PS	0	116 (25.3)	–	–
	1	297 (64.8)	2.80 (1.99–3.95; $p < 0.001$)	1.90 (1.33–2.72; $p < 0.001$)
	2	33 (7.2)	4.13 (2.53–6.75; $p < 0.001$)	2.29 (1.36–3.84; $p = 0.002$)
	3	12 (2.6)	6.62 (3.39–12.95; $p < 0.001$)	2.83 (1.36–5.87; $p = 0.005$)
Myometrium invasion	No invasion	24 (5.2)	–	–
	Less than 50%	214 (46.0)	1.18 (0.63–2.20; $p = 0.600$)	–
	More than 50%	227 (48.8)	2.33 (1.26–4.30; $p = 0.007$)	–
Myoinvasion	No or less than 50%	238 (51.2)	–	–
	More than 50%	227 (48.8)	2.01 (1.58–2.55; $p < 0.001$)	1.53 (1.17–2.00; $p = 0.002$)
Histological subtype	G3EA	145 (31.1)	–	–
	USC	118 (25.3)	1.95 (1.41–2.68; $p < 0.001$)	1.53 (1.09–2.17; $p = 0.015$)
	CCC	44 (9.4)	1.43 (0.92–2.23; $p = 0.110$)	1.10 (0.69–1.74; $p = 0.696$)
	CCS	63 (13.5)	2.81 (1.94–4.08; $p < 0.001$)	2.19 (1.47–3.27; $p < 0.001$)
	Mixed	93 (20.0)	1.13 (0.78–1.64; $p = 0.533$)	0.99 (0.66–1.47; $p = 0.946$)
	NOS	3 (0.6)	0.00 (0.00–Inf; $p = 0.990$)	0.00 (0.00-Inf; $p = 0.992$)
Treatment	No treatment	104 (22.4)	–	–
	Chemotherapy with or without EBR/BT	235 (50.5)	0.82 (0.62–1.09; $p = 0.178$)	0.31 (0.22–0.46; $p < 0.001$)
	EBR and/or BT	126 (27.1)	0.44 (0.31–0.63; $p < 0.001$)	0.48 (0.32–0.70; $p < 0.001$)

Abbreviations: 95%CI, 95% confidence interval; BT, brachytherapy; CCC, clear-cell carcinoma; CCS; carcinosarcoma; EBR, external beam radiotherapy; ECOG-PS, Eastern Cooperative Oncology Group's Performance Status scale; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique (International Federation of Gynecology and Obstetrics, in French) staging system; G3EA, grade-3 endometrioid adenocarcinoma; HR, hazard ratio; Mixed, mixed epithelial tumors; NOS, not otherwise specified; SD, standard deviation; USC, uterine serous carcinoma.

recurrence rates in distant sites, independently of the FIGO stage. Also, as recommended by the guidelines, adjuvant therapy was associated with better survival.

Author's Contributions

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

Conflict of Interests

The authors have no conflict of interests to declare.

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The Automation of Breast Ultrasonography and the Medical Time Dedicated to the Method

A automatização da ultrassonografia mamária e o tempo médico dedicado ao método

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Abstract

In this integrative review, we aimed to describe the records of time devoted by physicians to breast ultrasound in a review of articles in the literature, in order to observe whether the automation of the method enabled a reduction in these values. We selected articles from the Latin American and Caribbean Literature in Health Sciences (LILACS) and MEDLINE databases, through Virtual Health Library (BVS), SciELO (Scientific Electronic Library Online), PubMed, and Scopus. We obtained 561 articles, and, after excluding duplicates and screening procedures, 9 were selected, whose main information related to the guiding question of the research was synthesized and analyzed. It was concluded that the automation of breast ultrasound represents a possible strategy for optimization of the medical time dedicated to the method, but this needs to be better evaluated in comparative studies between both methods (traditional and automated), with methodology directed to the specific investigation of this potentiality.

Keywords

- mammary ultrasonography
- breast ultrasonography
- diagnostic imaging
- breast neoplasms
- three-dimensional imaging

Resumo

Na presente revisão integrativa, objetivamos descrever os registros de tempo dedicado pelos médicos à ultrassonografia mamária em revisão de artigos da literatura, visando observar se a automação do método possibilitou redução destes valores. Selecionamos artigos nas bases de dados Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) e MEDLINE, através da Biblioteca Virtual em Saúde (BVS), *Scientific Electronic Library Online* (SciELO), PubMed e Scopus. Obtivemos 561 artigos e, após a exclusão de artigos duplicados e procedimentos de triagem, foram selecionados 9 artigos, cujas informações principais relativas à pergunta norteadora da pesquisa foram sintetizadas e analisadas. Foi concluído que a automação da ultrassonografia mamária representa uma possível estratégia de otimização do tempo médico dedicado ao método; porém, essa conclusão necessita ser melhor avaliada em estudos comparativos entre ambos os métodos (tradicional e automatizado), com metodologia direcionada à investigação específica desta potencialidade.

Palavras-chave

- ultrassonografia mamária
- diagnóstico por imagem
- neoplasias da mama
- imageamento tridimensional

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Introduction

The optimization of the medical workflow, while maintaining the accuracy of diagnostic methods, has been observed among the objectives of studies related to breast ultrasound. In its traditional form, breast ultrasound requires a medical time that is usually considered long.[1–3]

In this context, automated breast ultrasound was developed, initially aiming at reducing the medical time for evaluating the ultrasound images, transferring the acquisition time of the same to a radiology technician, with specific training, allowing the use of the method on a large scale, for breast cancer screening.[1,4,5]

The automated breast ultrasound device has a larger transducer than the conventional one, coupled to a mechanical arm, performing an automatic and standardized scan of the entire breast. The images obtained are transferred to a workstation where they are available for medical interpretation.[6,7] Three images are obtained (anteroposterior, lateral and medial of each breast), forming three planes or views for interpretation: coronal, sagittal, and transverse.[8,9]

Factors such as the learning curve of the automated method, the physicians' experience with each of the methods, the number of findings, the size of the breasts (since a greater amount of breast tissue may require acquisition of additional views in the automated method and represents greater tissue volume to be evaluated also in the conventional method), interfere in this measure of time in an already established way.[3,8,10,11]

The evaluation of the coronal view only, with the objective of reducing the time required for the physician to interpret the automated images, was analyzed by Schiaffino et al. Therefore, the multiplanar evaluation is mandatory, that is, all images must be obtained for a good diagnostic performance.[12]

The use of computer algorithm systems to help detect changes in images obtained by automated ultrasound (computer-aided detection [CAD] system) is another strategy that has also been analyzed in some studies, with a reduction in medical interpretation time using these algorithms.[7,13]

Thus, we aimed to describe the records of time dedicated by physicians to breast ultrasound in a review of literature articles, in order to observe whether the automation of the method made it possible to reduce these values.

Methods

This is an integrative literature review, developed observing the following steps: elaboration of the research question, selection of literature articles, data extraction and critical analysis of the included articles, presentation and discussion of the results obtained, and establishing the conclusion of the authors.[14]

To define the question to be answered with the search for articles, the patient, intervention, comparison, and outcomes (PICO) strategy was used.[15] Our research object was the medical time required for breast evaluation using the automated way of obtaining the images. The intervention was defined as the use of the automated method of ultrasound of the breasts and our comparison was established with the conventional method of performing this exam, with the expectation as an outcome to reduce this medical time with the use of the automated method. Thus, we used the following question to guide our review: How long does the physician need to evaluate the automated ultrasound images of the breasts? Would this time be shorter than the time required to perform a conventional (non-automated) ultrasound of the breasts?

The selection of articles was made in July and August of 2022 in the Latin American and Caribbean Literature in Health Sciences (LILACS) and MEDLINE databases, through the Virtual Health Library (BVS), Scientific Electronic Library Online (SciELO), PubMed, and Scopus. As descriptors, in Health Sciences (DeCS) and Medical Subject Headings (MeSH), we used *mammary ultrasonography*, *breast ultrasonography*, *diagnostic imaging*, *breast neoplasms*, and *three-dimensional imaging*.

We applied language filters, selecting articles in English and Portuguese, with full text available, and selected screening, diagnosis, prognosis, evaluation, and observational studies in the areas of medicine, imaging, gynecology, and radiology as the type of studies.

Results

We obtained 561 articles from the databases, and, using the Rayyan application (Qatar Computing Research Institute, Ar-Rayyan, Qatar)[16], 45 duplicate articles were found, leaving 516 articles for analysis. Of these, 453 were excluded and 63 were included by reading the title. Of the 63 included, 22 were excluded, and 41 were included after reading the abstract. These 41 included articles were then considered for full text reading. After reading the full text, 32 were excluded, 12 of which did not present the measurement of the medical time spent interpreting the images obtained by automated breast ultrasound (reason 1), 10 in relation to the time to perform the conventional breast ultrasound (reason 2) and 6 for both methods (reason 3), and 4 for being narrative review articles (reason 4). The remaining 9 articles provided data for the composition of ►**Charts 1**, **2**, and **3**.[1,2,10,11,13,17–19,21] ►**Figure 1** summarizes these results in the PRISMA 2020 flowchart.[22]

Discussion

Considering the guiding question of this review, the medical time dedicated to the two methods of breast evaluation by ultrasound, we observed with the data from the studies included in this review that less medical time was spent on the automated method in most studies, but with few studies directly comparing both methods regarding the specific question of medical time dedicated to each one of them.[1,2,10,11,13,17,19,21,23]

Of the nine selected studies, seven brought only time information for one of the methods, either because the measurement of this time had not been included in the methodology of these studies or because the comparison

Chart 1 Summary of comparative studies of medical time in both methods

Authors Characterization	Philadelpho et al.	Tutar et al.
Article title	Comparison of Automated Breast Ultrasound and Hand-Held Breast Ultrasound in the Screening of Dense Breasts	Comparison of automated versus hand–held breast US in supplemental screening in asymptomatic women with dense breasts: is there a difference regarding woman preference, lesion detection and lesion characterization?
Country/year of publication	Brazil/2021	Turkey/2020
Type of study/level of evidence	Cross-sectional study/level 4	Cross-sectional study/level 4
Sample/inclusion criteria	440/asymptomatic women with dense breasts on mammography	340/women with dense breasts and normal mammograms
Exclusion criteria	Women with breast surgery for cancer or benign causes (including implants) and/or breast radiotherapy in the last 12 months	Women at high risk and/or with suspicious clinical findings and/or with a history of breast cancer
Objectives	Comparing conventional ultrasonography with ultrasonography automated breasts in breast cancer screening	Compare ABUS and HHUS in terms of workflow, patient preference, effectiveness in detecting and characterizing lesions
Metodology	HHUS first and ABUS next (independent evaluation) HHUS: breast radiologists (n = 13) and non-specialized (n = 17) ABUS: breast radiologists only (n = 6)	ABUS first and HHUS in the sequence HHUS: breast radiologists only (n = 2) bilateral breast and underarm examination ABUS: assessment by both breast radiologists in consensus
Conclusions	Compared to HHUS, ABUS allowed adequate complementary study in the breast cancer screening	No significant differences in lesion detection, lower PPV with ABUS, more than 50% of patients prefer HHUS
Time HHUS Breast Radiologists	7 min e 45 s	12.5 min
Time HHUS non-specialist radiologists	4 min e 15 s	————————
Time ABUS breast radiologists	4 min e 25 s	14.5 min
p-value	$p < 0.001$ *	————————

*Student t-test (difference between mean time of breast radiologists for HHUS and ABUS).

Chart 2 Summary of non-comparative studies that reported the medical time spent using the automated method

AUTHOR/ YEAR	TYPE OF STUDY/ LEVEL OF EVIDENCE	SAMPLE/ INCLUSION CRITERIA	EXCLUSION CRITERIA	METHODOLOGY	AVERAGE TIME ABUS
Skaane et al., 2015	Retrospective study/ level 4	90 included symptomatic patients or those with clinical or mammographic alterations	Did not restrict patient participation	ABUS evaluated by 5 breast radiologists	9 min
Wilczek et al., 2016 (Easy Study)	Randomized clinical trial/ Level 2	1,668 included patients aged ≥ 40 years, asymptomatic, with dense breasts	Pregnant or lactating women with a history of breast surgery and/or diagnosis and/or treatment of breast cancer in the last 12 months were excluded.	The ABUS images were analyzed by 5 breast radiologists, after evaluating the corresponding mammography	5–7 min
Vourtsis e Kachulis 2017	Non-randomized clinical trial/ level 3	1,886 patients symptomatic or not, with dense breasts	Did not restrict patient participation	ABUS images evaluated after respective mammograms, when available according to the case, by 2 breast radiologists	3 min
Jiang et al., 2018	Retrospective study/ level 4	185 patients with dense breasts	Patients submitted to previous breast interventions	18 breast radiologists interpreted the ABUS images twice (with and without the aid of computer-CAD systems)	3.5 min (without CAD) 2 min and 24 s (with CAD)

Chart 3 Summary of non-comparative studies that reported the medical time spent using the conventional method

AUTHOR/YEAR CHARACTERIZATION	Berg et al., 2008 (ACRIN 6666)	Chang et al., 2015	Phalak et al., 2018
Type of study/level of evidence	Randomized clinical trial/2	Retrospective study/4	Cross-sectional study/4
Sample/ inclusion criteria	2,725 women at high risk for breast cancer with at least heterogeneously dense breasts in at least 1 quadrant. Patients undergoing breast cancer follow-up could be included	1,526 asymptomatic women	100 patients with a history of lobular neoplasia
Exclusion criteria	excluded women with signs or symptoms of breast cancer, with surgery, or breast intervention procedures or breast exams less than 11 months ago, pregnant women, breastfeeding women, with breast implants, with metastatic cancer	Women with a personal or family history of breast cancer and/or suspicious MMG findings	Patients with $>20\%$ risk for breast cancer by risk models and/or with breast cancer
Methodology	USG performed by radiologists. Axillary assessment could be included and added to the total exam time	USG performed by breast radiologists. Axillary assessment routinely included in the exam and added to the total exam time	USG performed by technologists and images reviewed by radiologists. If necessary, a breast radiologist would redo the exam
HHUS average time	19 min	15–20 min	20 min

between the two methods was not the objective of these researches.[1,10,13,17,19,21,23]

The two studies that presented the time for both methods differed in their conclusions regarding medical time.[11,18] Tutar et al. included 340 patients in a cross-sectional study in which the average time for interpretation of automated ultrasound images was 14.5 minutes, greater than the average of 12.5 minutes observed for conventional ultrasound, with data reported descriptively. The authors attributed this result to the fact that they recorded all the lesions observed and analyzed all the images of the coronal, transverse, and longitudinal planes of each of the views (anteroposterior, lateral, and medial) obtained for each of the breasts in the automated ultrasound.[18]

However, a similar analysis was cited in the methodology of studies that measured medical time for interpretation of automated images.[10,13,17,21,23] The study by Skaane et al. stands out, with results that reinforce the observation that the number of findings interferes with the time required for image analysis. For the analysis of the images of both breasts, they obtained, on average, 9 minutes, and, considering the time of each breast individually, normal breasts or breasts with cysts required an average of 4 minutes, while breasts with probably benign nodules required 4.8 minutes, and breasts with suspicious findings for cancer required an average of 5.3 minutes.[10]

The other study that uses time data for both methods also has a cross-sectional design, including 440 patients. This study brings in its methodology the particularity of the different time of execution of conventional ultrasound by breast radiologists (average time of 7 minutes and 45 seconds) and by radiologists not specialized in breast imaging (average time of 4 minutes and 15 seconds). Automated ultrasound data were interpreted only by breast radiologists, in an average time of 4 minutes and 25 seconds. The difference between the means of the breast radiologists was analyzed for both methods using the t-Student test and was considered statistically significant ($p < 0.001$).[11]

Philadelpho et al. (2021) and Tutar et al. (2020) included patients with dense breasts in breast cancer screening in their studies. High-risk patients and those who had already been diagnosed and were being followed up were excluded, thus sampling a population whose exams tend to present fewer findings. Therefore, Philadelpho et al. (2021) obtained data similar to those of Wilczek et al. (2016) (Easy Study) and Jiang et al. (2018), who also sampled low-risk populations for breast cancer.[11,13,18,21]

Skaane et al. (2015) and Vourtsis and Kachulis (2017) did not restrict the participation of patients and, thus, sampled more heterogeneous populations, with the possibility of a greater number of ultrasound findings; however, they obtained very different time means. Skaane et al. (2015) describes an average of 9 minutes among 90 participants, while Vourtsis and Kachulis (2017) describe a much lower average of 3 minutes, but with a much larger number of participants, 1,886.[10,17]

For conventional ultrasound, low- and high-risk women were represented, in a non-comparative way with the automated method, in only 3 studies, which described similar time averages, between 15 and 20 minutes. However, Berg et al. (2008) and ACRIN 6666, and Chang et al. (2015) bring into their methodology the axillary evaluation as part of the exam, this time being added to the total time of the conventional exam, similar to the evaluation made by Tutar et al.

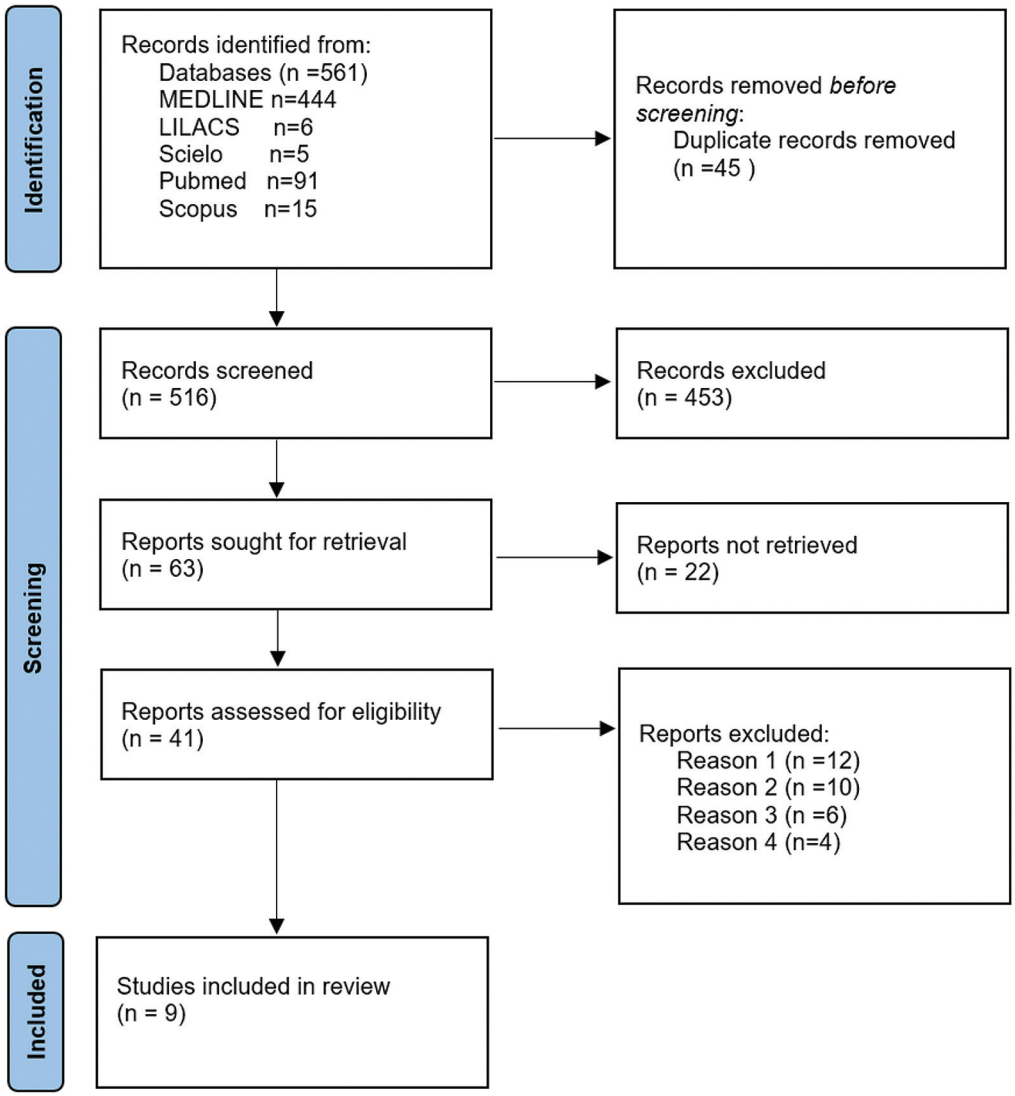

Fig. 1 PRISMA 2020 flowchart with database search results. *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

(2020).[1,18,19] However, Phalak et al. (2018) obtained an average of 20 minutes without axillary evaluation, with the particularity of the examination being performed by technologists and reviewed by radiologists, as authorized in Texas, the state where the study was carried out.[2]

Thus, we observed that even considering only the time variable, many factors are associated and interfere with its measurement, probably explaining the variability of data obtained in the literature for both conventional and automated methods of breast ultrasound evaluation.

As a limitation of this review, we have the small number of studies that evaluated the medical time in both methods, the fact that they are studies with a lower level of evidence, level 4, and the question that only one of them included a statistical analysis of the difference between the averages obtained for the time variable.

These observations suggest that the comparison of the times spent by the physician with each of the methods needs to be better evaluated in experimental studies, with a larger number of patients, which could allow a better evaluation of the potential of automated ultrasound in optimizing medical time.

Conclusion

In our integrative literature review, the automation of breast ultrasound represents a possible strategy for optimizing the medical time dedicated to the method, but it needs to be better evaluated in comparative studies between both methods, with a methodology aimed at the specific investigation of this potentiality.

Conflict of Interests

The authors have no conflict of interests to declare.

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Weaknesses in the Continuity of Care of Puerperal Women: An Integrative Literature Review

Fragilidades na continuidade do cuidado de puérperas: Revisão integrativa de literatura

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Abstract

The aim of the present study was to identify how the transition of care from the hospital to the community occurs from the perspective of puerperal women at risk. An integrative literature review was performed, with the question: "How does the transition of care for at-risk puerperal women from the hospital to the community occur?" The search period ranged from 2013 to 2020, in the following databases: PubMed, LILACS, SciELO, and Scopus. MESH, DeCS and Boolean operators "OR" and "AND" are used in the following crossover analysis: *patient transfer* OR *transition care* OR *continuity of patient care* OR *patient discharge* AND *postpartum period*, resulting in 6 articles. The findings denote discontinuity of care, given the frequency of non-adherence to the puerperal consultation. Transition studies of care in the puerperium were not found, which requires proposing new studies.

Keywords

- transitional care
- postpartum period
- continuity of patient care

Resumo

O objetivo do presente estudo foi identificar como ocorre a transição do cuidado do hospital para a comunidade na perspectiva de puérperas de risco. Foi realizada uma revisão integrativa da literatura, com a questão: "Como ocorre a transição do cuidado das puérperas de risco do hospital para a comunidade?" A pesquisa foi realizada com recorte temporal de 2013 a 2020, nas bases de dados: PubMed, LILACS, SciELO e Scopus. Utilizou-se MESH, DECS e operadores booleanos "OR" e "AND" resultando nos seguintes cruzamentos: *patient transfer* OR *transition care* OR *continuity of patient care* OR *patient discharge* AND *postpartum period*, com análise final de 6 artigos. Os achados denotam descontinuidade do cuidado, visto a frequência de não adesão à consulta puerperal. Estudos de transição do cuidado no puerpério não foram encontrados, o que requer que novos estudos sejam propostos.

Palavras-chave

- cuidado transicional
- período pós-parto
- continuidade da assistência ao paciente

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Introduction

Care transition (CT) is understood as a set of actions aimed at ensuring care continuity at different points of healthcare and or between different sectors of the same place. In addition, it encompasses a comprehensive care plan and should be performed by well-prepared professionals, whether in user and family education and their engagement as active subjects in decisions, or in the proper transfer of information between transition professionals.[1] In this context, maternity CT, after delivery, for primary health care (PHC), is a fundamental strategy.

The puerperium begins immediately after delivery, and lasts roughly 6 weeks, being its termination unforeseen, because it is related not only to anatomical and physiological changes, but to a framework of psychosocial issues that include self-esteem and reorganization of personal and family life.[2] Another author considers the variability of time that comprises this period, which can be from 8 months to 1 year.[3]

On the other hand, the risk postpartum period is characterized by situations in which postpartum women present complications in their health condition, due to preexisting diseases or intercurrences generated by both organic and socioeconomic unfavorable factors.[4] In this period, women undergo physical, psychological, social, and cultural changes; thus, quality care aims to maintain maternal health and act early in the event of complications, to minimize or treat associated comorbidities.[5]

Thus, aiming at the continuity of postpartum care, professionals and users/family members articulated in health services share information that contributes to the development of a care management plan both in the assistance provided in health services and in the promotion of supported self-care. From this, care continuity is the result of a joint, articulated, reflective, negotiated, singular and shared action.[6] In this perspective, inadequate CT can negatively affect treatment adherence, medication errors, low quality of life and increased risks for hospital readmissions.[7,8]

In this context, the assistance to the puerperium covers several points of the Health Care Network (HCN), starting, first, in maternity, when the woman is oriented on care to her health, identification of warning signs and symptoms that indicate the need for reassessment in health services.[9] At this point of attention, it is recommended that qualified processes for the immediate postpartum be guaranteed, and the development of a care plan for the puerperal woman and the newborn (NB) and mechanisms of communication and integration with PHC for care continuity.[10]

For this, the attention to the puerperium is complex and requires attention and continuity in the various points of attention of the HCN. The subject requires exploring the literature, and the development of the present study aims to identify how the transition from hospital care to the community occurs from the perspective of at-risk postpartum women.

Methods

This is an integrative literature review study. The study consisted of six stages: 1) 1st stage: identification of the theme and selection of the research question; 2nd stage: establishment of inclusion and exclusion criteria; 3rd stage: Identification of preselected and selected studies; 4th Stage: Categorization of the selected studies; 5th stage: Analysis and interpretation of the results, and 6th stage: Presentation of the review/synthesis of knowledge.[11]

The development was based on the following question: "How does the transition from the care of at-risk mothers from hospital to community occur?" For the construction of the research question, the PICO strategy (population, phenomenon of interest and context) was used, being possible, in this way, to elaborate a delimited and well-founded question that initiated the investigation.[12] The searches were based on Medical Subject Headings (MESH) and Health Sciences Descriptors (DeCS) and Boolean operators "OR" and "AND," resulting in the following crossings: *patient transfer* OR *transition care* OR *continuity of patient care* AND *charge* OR *patient discharge* AND *postpartum period*.

The selection of articles took place from June 2021 to June 2022, in the following databases: National Library of Medicine National Institutes of Health (PubMed), Latin American and Caribbean Health Sciences Literature (LILACS), Scientific Electronic Library Online (Scielo) and SciVerse Scopus (Scopus).

The process of searching and analyzing the studies was performed jointly by four researchers, aiming at data reliability. The inclusion criteria were: primary studies, in Portuguese, English and Spanish, in the period from 2013 to 2020, moment when the World Health Organization (WHO) launches the 2nd update of guidelines for postnatal care focusing on mothers and newborns in countries with limited resources, with the aim of reducing maternal and neonatal deaths from the review of evidence-based best practices.[13] The exclusion criteria were: review studies, theses, dissertations, editorials, case studies, and manuals.[11]

The searches in the aforementioned databases resulted in 482 studies, 127 from SciELO, 238 from PubMed, 109 from Scopus, and 8 from LILACS. Thus, to organize the references found, an online tool called ENDNOTE was used, which allowed, mainly, the identification of duplicate articles. After the exclusion of duplicate articles, the titles and abstracts of the 387 remaining articles were read, of which 10 met the inclusion criteria and were fully read. The reading was performed separately by the four researchers and the disagreements in the analysis were discussed in a meeting of experts. Thus, eight studies were part of the corpus of the research (►**Fig. 1**).

Given the extraction of data from the results, an instrument adapted from the literature by the authors was used, which includes characteristics of article identification (title, authors, year, country of publication, type of study, main contributions). The results were arranged through charts and the analysis of articles was performed descriptively, with the synthesis of evidence from each publication.

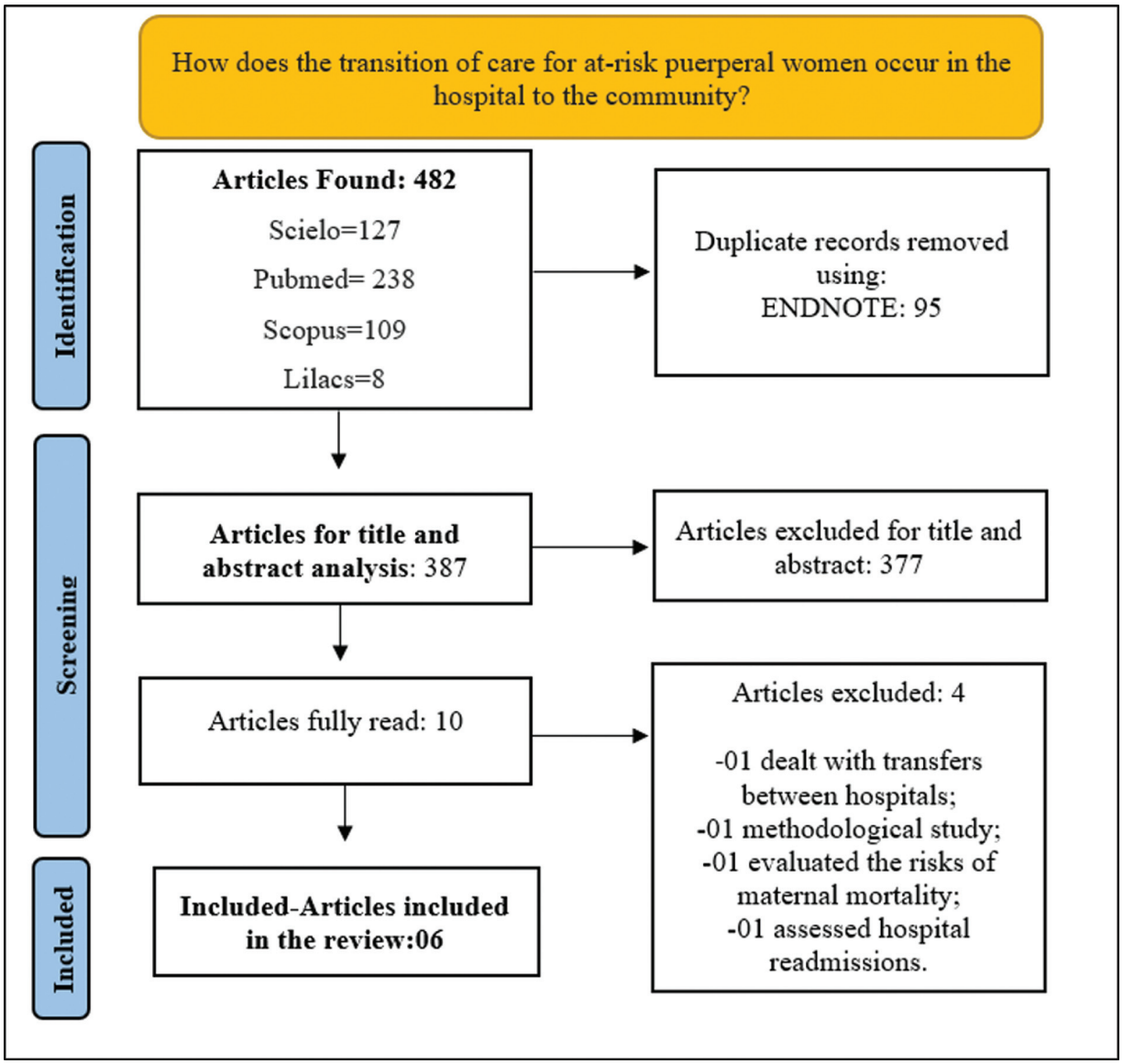

Fig. 1 PRISMA Flowchart.

Results

Of the six studies included, five belonged to the PubMed database and one to the SciELO database. Of these, five articles are in English and one in Portuguese. According to the years of publication, two were published in 2016, one in 2017, and three in 2020. The countries of origin were: Australia, Turkey, United States of America, Ethiopia, Sweden, and Brazil, with one article each. The number of participants was 22,777 women. The studies are described and listed in ►**Chart 1**.

The first study used a qualitative method through semi-structured interviews, and sought to know the perceptions of women about forms of postpartum care. It was held in Australia and involved 15 women. The study highlighted an important gap in the postpartum period characterized by lack of information and psychosocial care, both in the public and private sectors. However, it still showed that women who gave birth in the public sector had a better follow-up, all received home visits or a phone call within 10 days and a guarantee that they had someone to examine them and take care of them. The highest levels of satisfaction were women who opted for home birth, who had a midwifery follow-up in the prenatal, childbirth and postpartum periods and did not report concern or insecurity.

From this perspective, the second study adopted a mixed methodology; it was conducted in Stockholm, Sweden, and involved 363 women. It investigated the satisfaction perceived by mothers regarding prenatal care, postpartum care, and child healthcare in the first two postpartum weeks. Child and postpartum health support were considered equally satisfactory, while prenatal support was classified as much less satisfactory. The chances of being satisfied with postpartum support were twice as high for mothers who did not have emergency consultations after delivery when compared with those who had emergency visits. Mothers who

Chart 1 Presentation of included studies

First Author, Year, Country and Title	Type of study and number of participants	Contribution of the study
1. WOODWARD, B.M. 2016. Australia. Beyond birth: Women's concerns about post-birth care in an Australian urban community.[14]	Qualitative study, through semi-structured interviews. 15 participants.	There is a gap in the postpartum period characterized by a lack of information and psychosocial care, both in the public and private sectors, to guarantee the continuity of care. The highest levels of satisfaction occurred in women who opted for home birth.
2. BARIMANI, M. 2016. Sweden. Support and continuity during the first 2 weeks postpartum.[15]	Cross-sectional study, with mixed methodology. 363 participants.	Part of the puerperal women pointed out the lack of continuity, the insufficient support in relation to the physical and emotional health of the women. The level of satisfaction was related to the time the women stayed in the hospital, that is, they were given direct postpartum care. Mothers who sought emergency care showed lower satisfaction with puerperal care. The assistance sought in the emergency triggered the need for support and continuity of care.
3. YANIKKEREM, E. 2017. Turkey. Factors affecting readiness for discharge and perceived social support after childbirth.[16]	Descriptive and cross-sectional method, cross-sectional study. 610 participants.	The information provided by professionals about postpartum care and social support is important for women and their families. Especially for the primiparous group, women who had complications during or after childbirth or who for some reason could not attend childbirth classes. Women in socially vulnerable conditions have less information about the postpartum period and were not prepared for hospital discharge. There is a need for special intervention programs that inform this population about postpartum care
4. WEN, T. 2020. United States. Fragmentation of postpartum readmissions in the United States.[17]	Cohort study, retrospective 21,789 participants.	Reducing care fragmentation can represent an important objective to improve postpartum care and reduce the risk of severe morbidity, high costs, and long hospital stays.
5. ASRATIE, M.H. 2020. Ethiopia. Completion of maternity continuum of care among in the post-partum period: Magnitude and associated factors in the north west, Ethiopia.[18]	Cross-sectional study 819 participants	Fragility in the continuity of maternity care, with less than half of the women having a puerperal consultation. As associated factors, we identified the fact that the majority live in rural areas and low schooling.
6. BITTENCOURT, S.D.A. 2020. Brazil. *Nascer no Brasil*: continuity of care during pregnancy and postpartum period for women and newborns.[19]	Cross-sectional, quantitative study 16,220 participants.	Only 32.2% of the study population had a postpartum consultation. The coordination of care is still a challenge in the health care of women and children in the pregnancy-puerperal period, especially in the north and northeast states.

remained in the hospital for $\geq$ 3 days were 3 times more satisfied with postpartum support compared with those who remained for 2 days.

The third study was conducted in Turkey in 2015 and aimed to assess readiness for hospital discharge and the perception of social support received in the postpartum period. It involved 610 participants and used an instrument divided into three parts, Readiness for Hospital Discharge Scale – New Mother Form (RHD-NMF), which was developed by Weiss et al.[20] that evaluates whether the woman is ready to be discharged from hospital and the third part included the "Multidimensional Scale of Perceived Social Support" (MSPSS) that was developed by Zimmet in 1988 to assess social support. Most women (94.3%) reported being ready to go home. In this sense, evaluating the factors that lead to readiness for hospital discharge, it was found that 85.9% received information about hospital discharge and that most of these were provided by doctors and nurses.

Regarding the fourth study, this was a retrospective cohort study, conducted in the United States, from 2010 to 2014, with 21,789 participants. This study aimed to characterize the risk and results associated with postpartum fragmentation in readmissions where the readmission hospital was different from the delivery hospital. As a result, evaluating the indications for readmission, fragmentation was more likely for heart failure (28.6%), thromboembolism (28.4%), and respiratory infections (33.9%). Less likely causes include hypertension (11.1%), wound complications (10.7%), and uterine infections (11.0%). Thus, it was concluded that discontinuity of postpartum care was associated with increased risk of severe morbidity.

The fifth study, in turn, was conducted in the city of Motta (northwest Ethiopia, Africa) in 2019. At the time, it sought to evaluate the completion of continuing maternity care, the Continuum of maternity care, that is, the continuation of care from pregnancy to the postpartum period. In this study, 77.4% of women lived in rural areas, 69.6% without formal education and 63% started prenatal consultations in the 2nd trimester of pregnancy. Of the 819 participants, 283 had home births and only 10 received postpartum care by health professionals. Overall, of the 819 women, 346 (47%) had postpartum appointments.

The sixth study was conducted in Brazil, from 2011 to 2012, consisting of a cross-sectional and quantitative study that aimed to estimate the adequacy of the healthcare line during pregnancy and postpartum in puerperal and newborn users of the Brazilian Unified Health System (SUS, in the Portuguese acronym). Of this, 16,220 women participated. It was found that the southeastern (41.7%) and northeastern (29.4%) regions concentrated most of the births. Of the total participants, 74.8% of the women started prenatal care until the 16th week of pregnancy and only 32.2% underwent the puerperal consultation. The study revealed that there is a lower chance of care continuity in women living in the northeast, north, and midwest regions. In multivariate analysis, considering schooling, parity, and place of residence, the North and Northeast regions presented a seven to ten times greater chance of inadequate care than the South region. These findings indicate that the coordination of care is still a challenge in the healthcare of women and children in the puerperal pregnancy period.

Discussion

Of the six studies included, two showed more subjective issues involving women's perception and satisfaction in the postpartum period; one addressed readiness for hospital discharge, one involved readmission issues in the postpartum period and associated risk factors; a study on the *continuum* of maternity care, and finally, a study involving the adequacy of the maternal-child care line.

The currently available evidence does not address hospital CT for the community of puerperal women, nor those considered at risk. In short, all studies mentioned directly or indirectly care fragmentation, the fragility of the *continuum* of maternal care evidenced the lack of puerperal consultation and the inadequacy of the line of maternal and childcare. Another study points out that care actions are incipient, and that comprehensive care is expected in the RAS, it is fragile, also considering the lack of follow-up after hospital discharge.[21] Therefore, the CT process from the hospital to home is a challenging moment, as sometimes it is necessary for this care to be performed by the family members themselves.[22]

Study 1, conducted in Australia, found a gap in the postpartum period characterized by lack of information and psychosocial care. Still, women assisted in the public sector had better postpartum follow-up compared with the private sector. As for the guidance on reevaluation in health services, study 2, Sweden, made clear that the most sought service are the emergency sectors, denoting disarticulation with PHC. In terms of satisfaction perceived by women, there is greater satisfaction of those who opted for home birth, study 1, and who had a continuous follow-up in the prenatal, childbirth, and puerperium periods. Satisfaction was also perceived in women, study 2, who remained longer in hospital, that is, who had more direct and prolonged postpartum care.

For Barimani et al,[15] greater flexibility in hospital stay could improve the satisfaction of new mothers. However, understanding that satisfaction is related to more direct assistance in the postpartum period, it can be inferred that care continuity needs to be guaranteed in PHC, since it is responsible for coordination of care and longitudinal monitoring.[10] A systematic review study with meta-analysis showed a significant reduction of one and a half days in hospital stay in favor of patients who received CT intervention.[23]

Therefore, for the care continuity to occur, it is recommended that the maternity hospital report the discharge of the puerperal woman and the NB to the health unit of the PHC to which they are linked so that the appointments are scheduled, guaranteed the First Week of Integral Health (4). Regarding readiness for hospital discharge, the original study that validated the Readiness for Hospital Discharge Scale (RHDS) was published in 2006 and involved 356 participants, including 121 adult patients (medical-surgical), 122 postpartum mothers and 113 fathers of hospitalized children.[20] In Brazil, the instrument for adults was adapted transculturally in 2015;[24] however, the specific version of the puerperal women has not been validated so far. This version is only available in English, Chinese, Spanish, Turkish, and Polish.[25]

In study 3, from Turkey, the RHDS scale was applied for puerperal women, showing that 94.3% were ready for hospital discharge and 85.9% received guidance for discharge by doctors and nurses. The scale was also used in Poland, study 4, and data indicated that 96.5% of women reported being ready for discharge. The perception of women regarding readiness for hospital discharge is related to their participation in the discharge process. From this evaluation, it is possible to identify early mothers at risk of problems in the postdischarge period, especially those who need more care and monitoring, to prevent adverse results.[26]

Regarding readmissions and readmissions in the postpartum period, a study performed in Tunisia (North Africa) had as statistically significant risk factors for readmission cesarean section, emergency cesarean section, anemia, and thrombocytopenia.[27] A study conducted in Massachusetts, United States, confirms the finding of increased risk of readmissions after cesarean delivery. It also cites as main causes complications of the surgical wound and infections.[28]

Which sought to relate the causes of hospital readmissions associated with fragmentation of care in the postpartum period, also found complications of the wound and uterine infections as associated causes. It also related these findings to high hospital costs and long duration of hospitalizations. In addition to the causes of readmissions identified,

women may present an increased risk of certain morbidities in their subsequent pregnancies.[29] Another study that aimed to analyze puerperal complications identified a high prevalence of complications associated with the high rate of cesarean sections and invasive procedures in vaginal delivery.[30] Therefore, it is expected that, after hospital discharge, this care will be continuous, to provide comprehensive care, by the multidisciplinary team of primary healthcare.[21]

Concerning the continuing care from maternity to the community, the two studies that addressed this theme showed that the puerperal consultation occurred in 47% in Ethiopia (Africa) and 32.2% in Brazil. In this context, Brazilian studies have identified a low rate of adherence to puerperal consultation, ranging from 16.8 to 43.08%.[31,32]

The studies mentioned above consider adherence to puerperal consultation as, at least, the attendance to one consultation. Nevertheless, this scenario falls short of that recommended by the WHO,[33] which provides for a minimum of 3 postpartum consultations, thus distributed: one between 48 and 72 hours after delivery; another between 7 and 14 days, and the third, in the 6th week.

When the reasons for nonadherence are investigated, there are reasons for forgetfulness, complications with the NB, transportation difficulties, and distance between home and health unit.[34] As associated factors, it is found that puerperal consultation is related to lower income and schooling, as well as not being addressed/valued during prenatal consultations.[35]

In this regard, to investigate the orientation on the importance of puerperal consultations both during prenatal care and in the immediate postpartum period in the hospital, Vilela et al.[36] performed a study with 216 puerperal women, in a municipality of the state of Mato Grosso, Brazil. They found that 92.1% of the puerperal women did not receive prenatal care and only 5.6% were guided at the hospital. Thus, it shows the need for measures that promote the awareness of health professionals about the importance of guidance as well as the scheduling of puerperal consultation, effectively effecting the referral and counter-referral system.

Conclusion

The present study showed the scarcity of research related to continuity of care from the perspective of postpartum women, which unveils a knowledge gap, requiring greater emphasis and concern with this theme, to improve the care of this population. It was possible to identify weaknesses in the postpartum care, both in relation to the guidelines provided as to the care issues offered in the hospital and in primary health care. Cesarean section was identified as a risk factor for hospital readmission. The mothers' perceived satisfaction was related to a continuous follow-up in the pregnancy-puerperal cycle. However, the findings show discontinuity of care, given the frequency of nonadherence to puerperal consultation. Although readiness for discharge has identified adequate rates, there are few studies in this area, since the RHDS instrument for postpartum women is validated in few countries. Transition studies of postpartum care were not found, which requires proposing new studies.

Conflict of Interests

The authors have no conflict of interests to declare.

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FEBRASGO POSITION STATEMENT

Operative vaginal delivery

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

Key points

- When the correct technique is applied, forceps and vacuum extractors have low rates of complications.
- For the fetus with signs of hypoxia in the expulsive phase, operative vaginal delivery has the potential to reduce exposure to intrapartum factors that promote hypoxic-ischemic encephalopathy.
- Medium and/or rotational forceps are appropriate options in selected circumstances and require skill and experience.
- Even though forceps are more effective than vacuum extraction for operative vaginal delivery, they are more associated with severe perineal lacerations.
- Cephalohematoma is more likely to occur with increasing duration of vacuum extraction.
- Flexible vacuum cups have higher failure rates, but lower incidences of trauma to the newborn's scalp.

Recommendations

- Operative vaginal delivery is contraindicated if the fetal head is not engaged, delivery presentation is unknown, or if the fetus has suspected or diagnosed bone demineralization or bleeding disorders.
- Ultrasound evaluation prior to instrumentation of labor is recommended when there is doubt in the clinical assessment of delivery presentation.
- Routine episiotomy is not recommended in operative vaginal delivery because of poor healing and discomfort associated with mediolateral episiotomy, and the risk of injury to the anal sphincter and rectum with midline episiotomy. When individually indicated, it should be mediolateral and performed only after a successful traction test.
- In the prolonged pelvic period of fetuses estimated to weigh more than 4,500 grams, intrapartum cesarean section for prevention of shoulder dystocia is preferable to low operative vaginal delivery or outlet delivery. Similarly, operative vaginal delivery with the fetal head in the mid pelvis should be avoided in fetuses estimated to weigh more than 4,000 grams, and intrapartum cesarean section is indicated. In these situations, instrumental delivery should only be considered in the presence of experienced operators, through individual assessment of fetal position and size, history of previous deliveries and maternal habits.
- The attempt to use forceps must be interrupted if there is no progression of the cephalic pole after three tractions performed with correct grip by an experienced operator.
- Vacuum extraction should be avoided before 32 weeks and caution should be exercised between 32 and 36 weeks, as the lower safe limit for gestational age has not been established yet.
- Vacuum extraction should be stopped when there is no evidence of progressive descent of the fetal head or when the cup detaches on three occasions.
- Sequential use of vacuum extraction and forceps is associated with increased neonatal complications and should not be routinely performed. After a failed vacuum extraction attempt, the risks and benefits of a sequential attempt to use a forceps or cesarean section should be evaluated.
- Neonatologists must be informed about the technique used in operative vaginal delivery.

Background

Operative vaginal delivery is used to provide a safe birth via the vaginal route based on maternal and fetal indications. Its greater benefits are the prevention of a cesarean section and its associated morbidities, as well as neonatal complications arising from intrapartum hypoxia.[1]

Although the forceps has been presented as the resource with the greatest potential for saving lives in the history of medicine, its current replacement by cesarean section is a result of the lack of preparation of the new generation of obstetricians, the inability of professors to teach its practice and the growing medical judicialization of obstetrics. The forceps instrument currently holds stigma and social prejudice arising from maternal and neonatal trauma caused by misuse. Vacuum extractors are more contemporary instruments, and although less effective than forceps, they are easier to use and have advantages that have made them instruments of choice in several countries.[2]

In recent decades, an increase in the rates of cesarean sections performed in the second stage of labor has been observed with a concomitant reduction in operative vaginal delivery. Difficult fetal extraction in cesarean section is an event associated with failure or lack of attempt at operative vaginal delivery, potentially aggravating maternal and neonatal morbidity. Therefore, the acquisition of skills and competences related to the use of forceps and vacuum extractors has become essential in the current process of training obstetricians.[3]

What are the main indications and contraindications for operative vaginal delivery?

For the fetus with signs of hypoxia in the expulsive phase, operative vaginal delivery has the potential to reduce exposure to intrapartum factors that promote hypoxic-ischemic encephalopathy.[1] The main indications for operative vaginal delivery are signs of acute fetal hypoxia, maternal exhaustion, prolonged expulsive period, umbilical cord prolapse with complete cervical dilation, sudden death of the parturient, arrested labor, persistent asynclitism, rotational dystocia, third-degree deflected cephalic presentation (face) with variety of anterior chin position, resistance of the soft tissue, uterine inertia, poor abdominal press. The aim of forceps (or vacuum) called prophylactic (relief) is to reduce the effort and discomfort of the pelvic period. Operative delivery is useful in maternal conditions or complications that contraindicate expulsive effort (cardiopathies, severe respiratory diseases, stroke, aneurysm, esophageal varices, spinal cord trauma, myasthenia gravis, proliferative retinopathy, neuromuscular pathologies, etc.), in preventing the non-reassuring fetal status and in pelvic vaginal delivery when the head is stuck after failure of the initial maneuvers.[4,5]

Because it causes less maternal trauma than the forceps, the vacuum extractor is an excellent alternative for operative vaginal delivery, especially for outlet delivery. Its indications are similar to those of the forceps. However, as the vacuum extractor requires more time for fetal extraction, it should not be the preferred method in emergency situations. The main advantages of vacuum extraction include a reduction in application errors, greater ease of learning, the possibility of self-direction and autorotation, less use of force on the fetal head, less need for analgesia and episiotomy and the reduction of birth canal lacerations. Vacuum-extractors with flexible cups cause less severe trauma to the fetal scalp than those with rigid cups, and should be preferred in simple vaginal deliveries.[4,5]

Operative vaginal delivery is contraindicated if the fetal head is not engaged or the delivery presentation is unknown. The following are absolute contraindications to operative vaginal delivery: cephalopelvic disproportion, total or partial placenta previa and anomalous presentations such as transverse, second-degree deflected cephalic (forehead) and third-degree deflected cephalic (face) with a variety of posterior chin positions. It is also relatively contraindicated if the fetus has suspected or diagnosed bone demineralization (osteogenesis imperfecta) or bleeding disorders (hemophilia, Von Willebrand disease, alloimmune thrombocytopenia). Operative vaginal delivery in fetuses weighing more than 4,000 grams must be judicious when choosing either forceps or the vacuum extractor. With regard to fetuses with an estimated weight of less than 2,000 grams, forceps are the safest instrument and can be used in fetuses as small as 1,000 grams.[4,5]

In the prolonged pelvic period of fetuses estimated to weigh more than 4,500 grams, intrapartum cesarean section to prevent shoulder dystocia is preferable to low operative vaginal delivery or outlet delivery. Similarly, operative vaginal delivery with the fetal head in the mid pelvis (De Lee station 0 and + 1) should be avoided in fetuses weighing more than 4,000 grams, and intrapartum cesarean section is indicated. In these situations, instrumental delivery should only be considered in the presence of experienced operators, through individual assessment of fetal position and size, history of previous deliveries and maternal habits.[6]

Vacuum extraction is not risk free (cerebral and retinal hemorrhage), and is also contraindicated in prematurity (gestational age < 32 weeks). Between 32 and 36 weeks, the vacuum extractor must be used with great caution, as the lower safety limit for gestational age has not been established yet. As the fetal extraction time with the vacuum extractor is prolonged, the instrument should also not be used if there are signs of fetal hypoxia. Vacuum extractors are also not indicated for pelvic vaginal delivery (breech baby) nor for face pre-

sentation, and should be replaced by forceps in these situations. Contraindications to vacuum extraction, although relative, also include: previous collection of blood or trauma to the fetal scalp, fetal death, anomalies of the cephalic pole (anencephaly, hydrocephalus), macrosomia and negative test traction in a previous attempt to use forceps.[5,7]

What are the main instruments currently recommended for operative vaginal delivery?

Forceps and vacuum extractors are the main instruments recommended for extracting the fetus from the birth canal, performed by grasping and pulling the fetal cephalic pole. The choice of instrument is related to the operator's preference and experience, and to maternal and fetal conditions.[8,9]

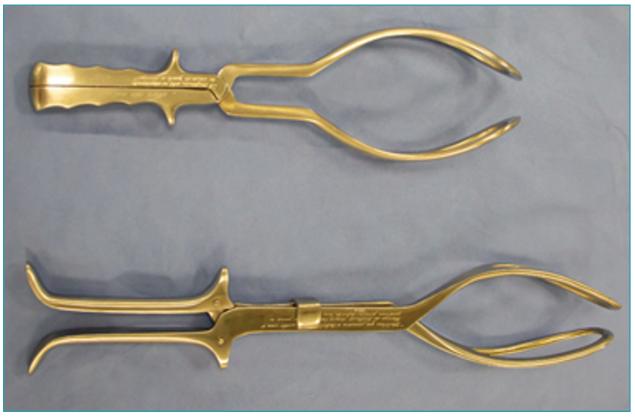
Forceps are instruments with two broad branches, each with four components: blade (seizes the cephalic pole), shank (or pedicle; located between the handle and the blade), joint and handle. The best known models nowadays are Simpson, Kielland, Piper and Marelli.[9]

Although forceps are more effective than vacuum extractors, they are more associated with severe perineal lacerations. Simpson's forceps are the most widespread worldwide. It features crossed branches, English (by fitting) fixed lock, handle with finger grips and fins (finger support) and fenestrated blades. The cephalic (adapts to the cephalic pole) and pelvic (adapts to the maternal pelvis) curvatures of the blades are prominent, and this specificity is advantageous for the grip and traction of the cephalic pole. It has three sizes, with shank lengths of 30, 33 and 35 cm.[4,5,9]

Kielland's forceps have crossed branches, but the articulation is performed by sliding, allowing the asymmetrical application of the blades in the vagina and the correction of asynclitism. It is 39cm long, handles are smooth with fin and identification buttons (knobs) on the front side. In the articulated instrument, the shanks are superimposed with the right above the left. Blades are fenestrated with smooth and rounded edges, and have very discreet cephalic and pelvic curvatures, which makes it an specific instrument for wide rotations (Figure 1).[9]

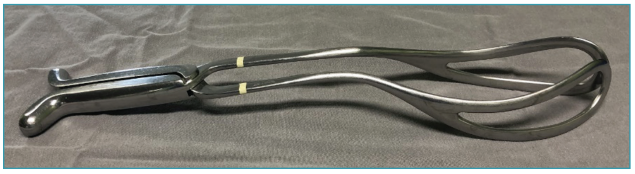
The Piper's forceps are specific instruments for extracting the head (breech baby) in pelvic delivery. It has long (44cm long) crossed branches, English lock and handle without finger grips and fins. Blades are fenestrated with very prominent cephalic and pelvic curvatures. A third curvature, the perineal, is present on the underside of the handles, close to the blades (Figure 2).[9]

Marelli's forceps are specific for fetal extraction in cesarean sections. It has crossed branches, English lock and smooth handle without fins. Its blades are fenestrated without a pelvic curvature ("bayonet" shaped blade), since fetal extractions with this instrument are performed through the abdomen (Figure 3).[5,9]



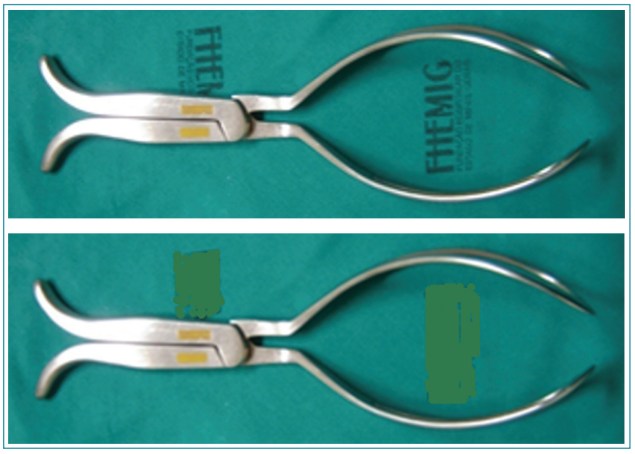
Source: photographic record by the authors.

Figure 1. Simpson (upper) and Kielland (lower) forceps



Source: photographic record by the authors.

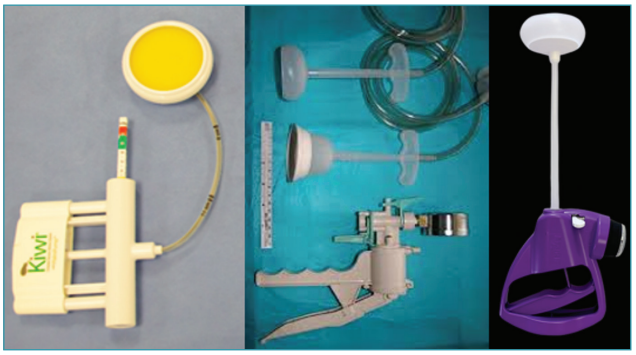
Figure 2. Piper's forceps



Source: photographic record by the authors.

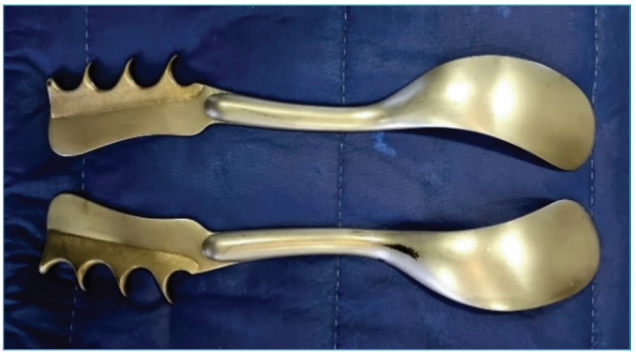
Figure 3. Marelli's forceps

Vacuum extractors are instruments that have a cup, a connecting tube and a suction pump. By means of negative pressure, the cup, applied to the scalp, pulls the fetal head. Cups can be rigid (made of metal), semi-rigid or flexible and have a bell or mushroom shape (Figure 4). Flexible bell vacuum extractors have higher failure rates, but lower incidences of trauma to the newborn's scalp.[8]



Sources: photographic records by the authors; https://www.panamedical.com.br/vacuo-extratores.

Figure 4. Kiwi Omni Cup® (left), Mityvac® (center) and Mystic II (right) vacuum extractors



Source: photographic record by the authors.

Figure 5. Thierry's spatulas

Spatulas and the Odon device are less widespread instruments. Spatulas are instruments with two independent and symmetrical branches that do not articulate. Each branch has a stem, handle and solid, wide blade. The branches act as independent levers and the fetal head is not pinched between the blades. The action of the spatulas is similar to that of the shoe presser, whose function is to help slide. Thierry, Velasco and Teissier spatulas are described.[10] Velasco's spatulas are smaller and straighter. Thierry's spatulas are larger and have a slight pelvic curvature at the upper edge of the blade (Figure 5). Compared to forceps and vacuum extractors, neonatal complication rates for spatulas appear to be similar or lower. Rates of severe perineal lacerations are also similar, but vaginal wall lacerations are more common.[11]

The Odon device is a film-type polyethylene instrument that creates an air envelope around the fetal head, allowing extraction by means of traction (Figure 6).[12,13] It has the potential to be safer and easier to apply than forceps and vacuum extractors. Currently, it is being used in multicenter experimental clinical trials, although not yet cleared by regulatory agencies for clinical practice. In a pilot observational study, the success rate at birth was close to 50% without severe maternal or neonatal adverse outcomes, but lower than those of the other instruments.[14]

How should operations in operative vaginal delivery be classified?

Classifications of operations in operative vaginal delivery are based on pelvic planes and delivery mechanisms. The application performed before the engagement of the cephalic pole ("high forceps") is contraindicated. The American College of Gynecology and Obstetrics (2015), endorsed by the Royal College of Obstetricians and Gynecologists (2020) has the most current classification (Chart 1).[4,5]

Chart 1. American College of Gynecology and Obstetrics Classification of Operative Vaginal Delivery (2015)[4]

Type	Findings
Outlet	The fetal scalp is visible at the vaginal introitus without separating the labia minora; the fetal skull has reached the pelvic floor and is near or occupying the perineum; the sagittal suture is in the antero-posterior (OA, OP) or oblique (LOA, ROA, LOP, LOP) diameter, with rotation not exceeding 45°.
Low	Cephalic apex in the De Lee plane + 2 or below, without reaching the pelvic floor. Two situations may occur: a) Rotation ≤ 45° (LOA, ROA, LOP, ROP); b) Rotation > 45° (include LOT and ROT).
Mid	The cephalic pole is engaged, but above De Lee's plane + 2; rotation can be ≤ 45° or > 45°.

OA: occiput anterior; OP: occiput posterior; LOA: left occiput anterior; ROA: right occiput anterior; LOP: left occiput posterior; ODP: occipito-right-posterior; LOT: left occiput transverse; ROT; right occiput transverse

Source: Adapted from Odon Device (2020)[12] and Silvestri (2013)[13].

Figure 6. Odon device

What are the prerequisites for performing an operative vaginal delivery?

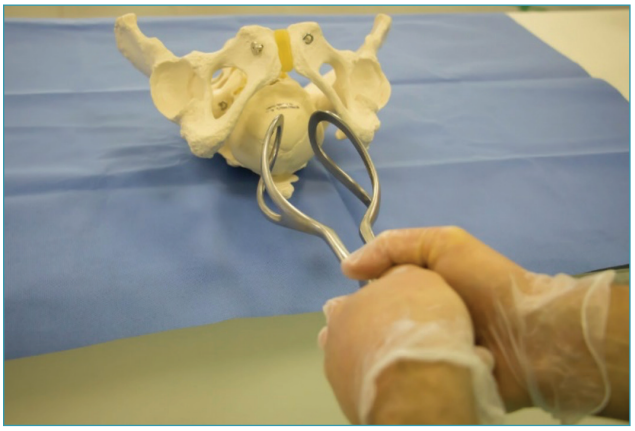
The main prerequisites for operative vaginal delivery include information and agreement on the benefits and risks of the procedure, adequate maternal pelvis, fetal weight estimate performed (clinical or ultrasound), engagement of the cephalic pole, complete cervical dilation and effacement, ruptured membranes, previous bladder emptying, knowledge of the presentation and variety of position, and satisfactory anesthesia (regional block in medium / rotational applications, pudendal or perineal blocks in low and outlet applications).[15]

What are the main operative times and technical details of forceps application?

The application of the forceps must be preceded by a urinary catheter and satisfactory maternal anesthesia. Low spinal anesthesia ("saddle") is preferred, especially in emergency situations and in mid and rotational forceps. It has the advantages of quick installation, providing anesthetic blockade of the sacral fibers and perineal relaxation without interfering in uterine contractility, abdominal press and quality of pushing. In situations where the parturient is already under analgesia by epidural block, with a catheter installed, the infusion of higher doses of anesthetics will be necessary and the time for achieving satisfactory analgesia will be longer.[16]

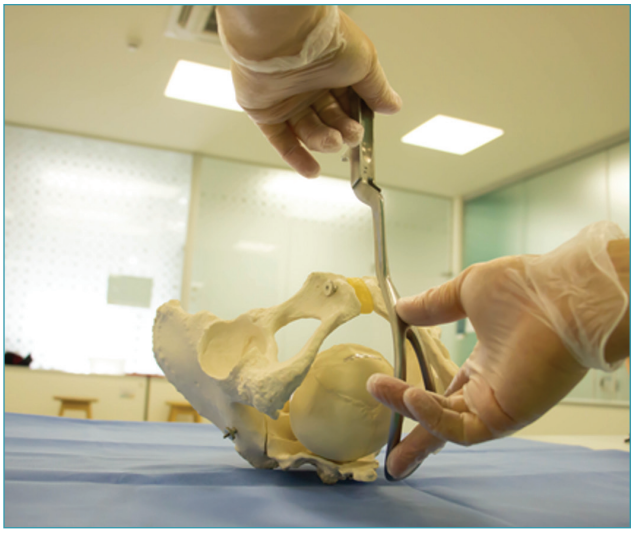
The operative times are sequentially: presentation of the instrument in front of the vulva, introduction and application, gripping of the cephalic pole, assessment of grip, traction test and definitive traction (with or without rotation).[4,5]

The first stage involves presenting the instrument to the vulva, simulating the way it will look after being applied to the fetal head (Figure 7). The grip includes the application (introduction and placement) and the actual grip. In the case of forceps, to apply the branches, movements of "lower introduction" are performed, always penetrating with the blades through the sacral voids (bilateral spaces between the sacrum and the hamstrings). In oblique varieties, the posterior branch must always be the first one to be applied. In transverse varieties (Kielland's forceps), the first branch to be inserted is optional, but the anterior branch is usually preferred. In the direct varieties (occiput posterior [OP] and occiput anterior [OA]), the left branch must be applied first in order to avoid the need to uncross the branches after applying the second (right branch) (Figures 8 and 9). In the rotated cephalic pole, the branch that will be applied to the anterior parietal is introduced through the triple spiral movement, which sequentially includes translation, lowering and torsion of the handle (Lachapelle's maneuver) (Figure 10). It is important to point out that manual rotation is an alternative for correcting the rotated cephalic pole (trans-



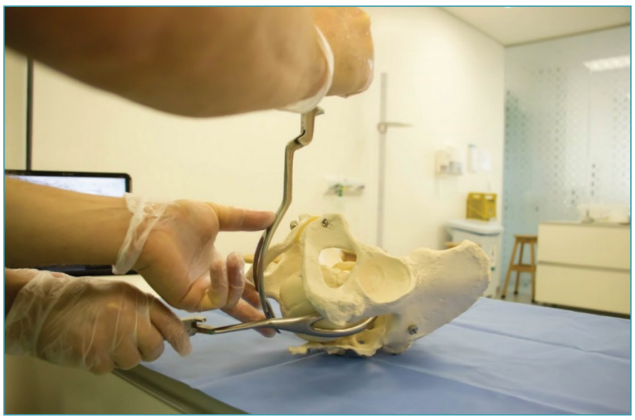
Source: photographic record by the authors.

Figure 7. Simpson's forceps presentation in the occiput posterior position



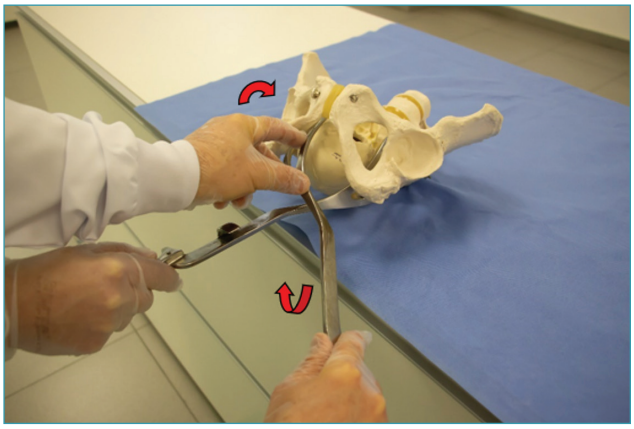
Source: photographic record by the authors.

Figure 8. Application of the left branch of Simpson's forceps in the occiput posterior position



Source: photographic record by the authors.

Figure 9. Application of the right branch of Simpson's forceps in the occiput posterior position

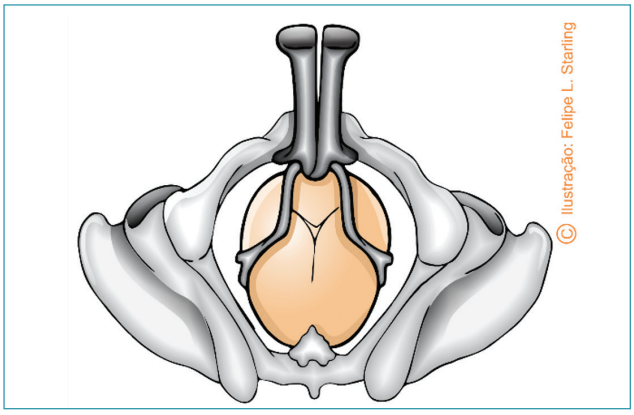


Source: photographic record by the authors.

Figure 10. Application of the right branch of Kielland's forceps with the La Chapelle spiral, in the left occiput anterior (LOA) position

verse and oblique position varieties). The cephalic pole is grasped with the tips of the fingers positioned on the parietal bones (thumb on one side and the other fingers on the other). During uterine contraction, the fetal head is slightly elevated, flexed and rotated, until it is positioned in a variety of OP positions.[4,5]

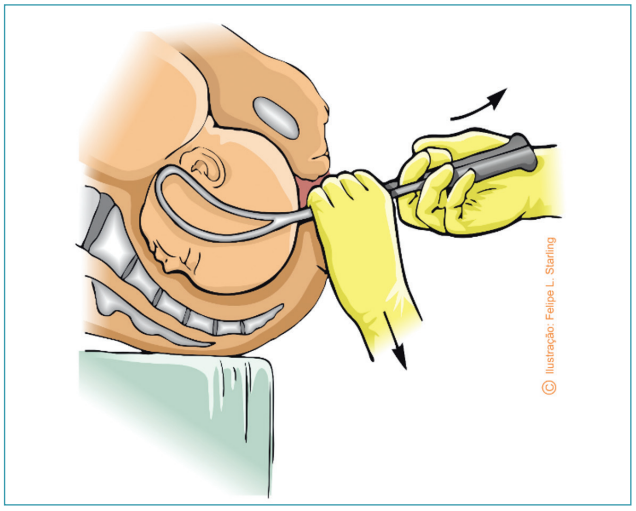
The biparietal-mentonian is the ideal grip. Three fundamental diagnostic criteria (Laufe's criteria) are used to check the correct grip: the small fontanel must be a transverse finger width from the plane of the handles ("in the center of the figure"); the sagittal suture must be placed perpendicularly and equidistant from the plane of the handles; the blade fenestrae should not be perceived by more than a finger pad between the grasped head and the forceps on either side (Figure 11). After checking the ideal grip, the branches must be moved towards the occiput.[4,5]



Source: Illustration by Felipe Lage Starling (authorized).

Figure 11. Fundamental diagnostic criteria for ideal grip (Laufe)

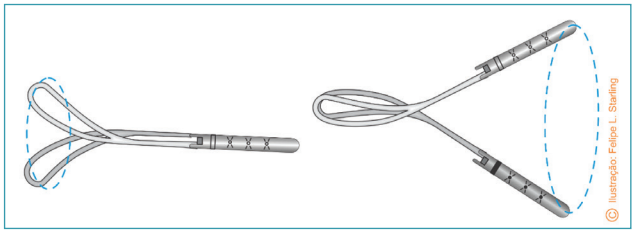
The traction must be simultaneous to the contractions and performed axially, that is, in the axis of the birth canal, perpendicularly to the presentation stop plane. The operator should be seated at an adequate height with the chest at the same level as the birth canal and the arms flexed just below the table. The force must be exerted only with the arms. To obtain axial traction, the dominant hand positioned on the handles exerts force directed at the operator's chest. Simultaneously, the other hand positioned on the rods applies downward force against the maternal perineum (Saxtorph-Pajot maneuver) by providing a 45° vector and effective axial traction (Figure 12).[4,5]



Source: Illustration by Felipe Lage Starling (authorized).

Figure 12. Axial traction (Saxtorph-Pajot maneuver) in the occiput posterior position

Rotation is performed in the oblique and transverse varieties simultaneously with traction. Rotation with Simpson's forceps should be performed with a wide movement of the handles in an arc (circumduction). With the Kielland's forceps, the movement of the handles is performed in a "key through the keyhole" movement and the rotation can be completed before traction (Figure 13). Note that Simpson's forceps are more suitable for small rotations. The Kielland's forceps should be the instrument of choice for rotations, especially when above 45°. Once rotation is completed and successful traction is confirmed (positive traction test),

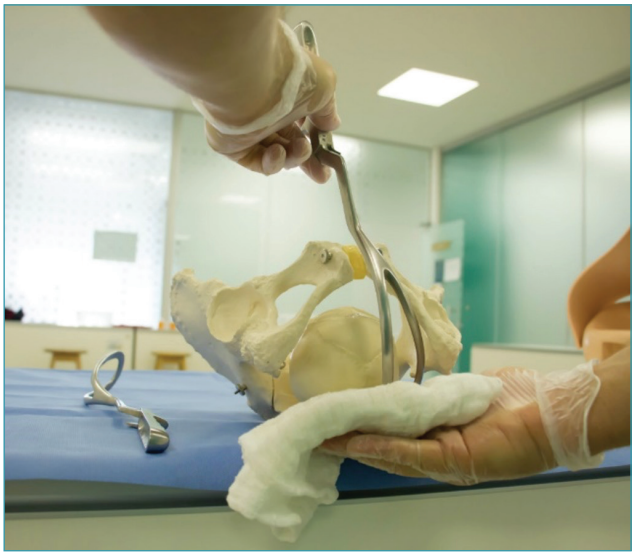


Source: Illustration by Felipe Lage Starling (authorized).

Figure 13. Key through the keyhole rotation with Kielland's forceps and wide circumduction movement of the handles with Simpson's forceps

with the cephalic pole with the occiput below the pubic symphysis, the need for episiotomy is assessed.[4,5]

The removal of forceps branches must precede the complete exit of the fetal head and must be performed as soon as the mandible is accessible. The branches are removed in reverse order of their application (Figure 14). Detachment of the cephalic pole is completed by the modified Ritgen maneuver. After the fetal extraction and delivery are completed, the birth canal is revised and if necessary, lacerations are repaired and/or episiorrhaphy is performed.[4,5] Despite the high effectiveness for resolution of the delivery, the attempt to use forceps should be interrupted if there is no progression of the cephalic pole after three tractions performed with correct grip by an experienced operator.[4,5]

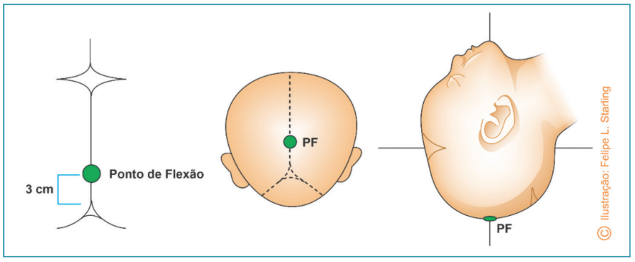


Source: photographic record by the authors.

Figure 14. Removal of Simpson's forceps branches in the occiput posterior position

What are the main operative times and technical details of applying the vacuum extractor?

Pudendal nerve block may be preferable to neuraxial anesthesia when choosing vacuum extraction. Local anesthetic infiltration is performed bilaterally below the sciatic spines. Unlike forceps blades, vacuum extractor cups do not come into significant contact with the vaginal walls and do not increase the diameter of the cephalic pole.[5,15] The vacuum extractor must be tested by the operator immediately before use by creating vacuum through compression of the cup on the palm of the hand. The instrument must be presented in front of the vulva, demonstrating how the cup will be applied to the fetal head.[17,18] The fetal scalp must be dried before the cup is applied. The cup will perform the action of gripping the cephalic pole, and must be introduced in the vulvar vestibule and applied over the sagittal suture, equidistant from the parietal bones with its center 3cm in front of the lambda (at the point of flexion). With the center of the cup positioned at the flexion point, its posterior edge will be 1cm (one finger) away from the lambda (Figure 15). The cup must not be inadvertently applied over the fontanels. The positioning of the cup is the same for any variety of position. In oblique position varieties (left occiput anterior [LOA], left occiput posterior [LOP], right occiput anterior [ROA], right occiput posterior [ROP]), the cup traction performed during the vacuum-extraction process promotes the descent of the cephalic pole with autorotation.[17,18]



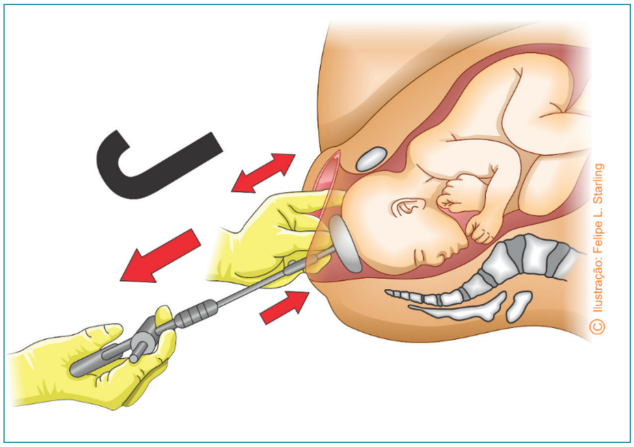
Source: Illustration by Felipe Lage Starling (authorized).

Figure 15. Fetal cephalic pole flexion point

A good grasp should be checked before traction, confirming the absence of maternal tissue between the cup and the fetal head. The manometer should be calibrated to a maximum of 500 mmHg (between 350 and 500 mmHg) during contractions with a reduction to 100 mmHg during uterine relaxation.[17,18] However, maintaining pressure between 350 and 500 mmHg between contractions with the aim to avoid discontinuing the descent and detachment of the cup does not seem to increase neonatal complications and has also been recommended.[19]

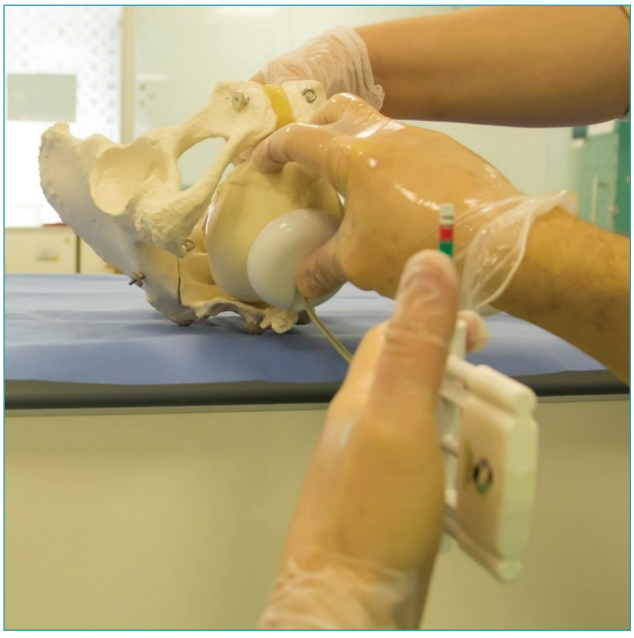
The operator, seated in front of the delivery table with the chest at the level of the birth canal, must pull perpendicularly to the cup plane until the occiput is positioned below the pubic symphysis. Traction performed during uterine contraction should follow the pelvic curvature (Pajot's manuver), keeping the traction shank always straight at a 90° angle with the cup. Thus, the pulling hand exerts a perpendicular force to the planes of the cup and the fetal cephalic pole, towards the operator's chest. Efficient traction is obtained by the imbalance between the hand that pulls and the hand that keeps the cup attached to the fetal cephalic pole, similar to a "tug of war". This force is opposite and slightly stronger than the force exerted by the hand that keeps the cup attached to the fetal cephalic pole. The cup is kept attached to the fetal cephalic pole by means of a force that is also perpendicular and exerted

in a superior direction, in the opposite direction to the traction force with a slightly weaker intensity than this, sufficient to prevent the cup from detaching during the entire action of traction. The superior steering force is exerted by the thumb positioned in the center of the cup. Simultaneously, index and middle fingers are positioned directly on the cephalic pole, thereby contributing to maintain the cup attached to the fetal scalp (Figures 16 and 17). The manometer must be observed throughout the traction process in order to detect the loss of vacuum, indicative of calibration correction.[17,18]



Larger red arrow: perpendicular pull force downwards
Smaller red arrow: perpendicular force maintaining the cup at the fetal cephalic pole (thumb finger) upwards
Double red arrow: maintenance of the cup attached to the scalp (index and middle fingers)
Black letter J: direction resulting from the traction in the shape of a J (Pajot's maneuver)
Source: Illustration by Felipe Lage Starling (authorized).

Figure 16. Vacuum extraction traction technique



Source: Photographic record by the authors.

Figure 17. Vacuum extraction traction technique

As soon as the occiput reaches the pubic symphysis, the suction pump and the connecting tube of the vacuum extractor are elevated and the need for episiotomy is assessed. After vulvar exteriorization of the fetal mandible, the cup is removed by pressing the pressure relief valve (vacuum). The extraction of the fetal cephalic pole is completed with the modified Ritgen maneuver.[17,18] Vacuum extraction is usually achieved with up to three pulls. Three additional gentle pulls are acceptable to complete the cephalic pole deflection. The vacuum extraction attempt should be stopped when there is no evidence of progressive descent of the fetal head, when the cup detaches on three occasions or when the traction time exceeds 20 minutes. During traction, the sudden detachment of the cup by loss of vacuum and vigorous movements must be avoided, as it leads to scalp lacerations. The sequential use of the vacuum extractor and the forceps is associated with increased neonatal complications and should not be routinely performed. Therefore, after a failed vacuum extraction attempt, the risks and benefits of a sequential attempt at forceps or a cesarean section must be carefully evaluated.[17,18]

What are the specific forceps techniques that require greater skill and competence by the operator?

Medium and/or rotational forceps are appropriate options in selected circumstances and require operator skill and experience.[4,5,20] The posterior oblique and transverse position varieties and the head stuck (breech baby) in pelvic delivery determine specific forceps application techniques.[9,20]

In forceps in posterior oblique varieties (ROP and LOP), there are three technical options related to the model, forceps availability, and operator skill and preference. Although rotation to OP requires more skill, it should be preferred whenever possible, avoiding detachment of the cephalic pole in OA. In all application possibilities, the posterior branch must be introduced first. Subsequently, the second (anterior) branch is introduced through the Lachapelle's maneuver.[9,20]

One option is to rotate 45° in the posterior direction for OA. In this situation, the branches of the forceps are applied with the pelvic curvature of the blades in an anterior direction. Although rotation is not wide, detachment of the cephalic pole occurs in the posterior variety (OA), which requires more vigorous traction and indicates Simpson's forceps as the preferred instrument. The rotation must be performed in a wide movement of circumduction of the handles.[9,20]

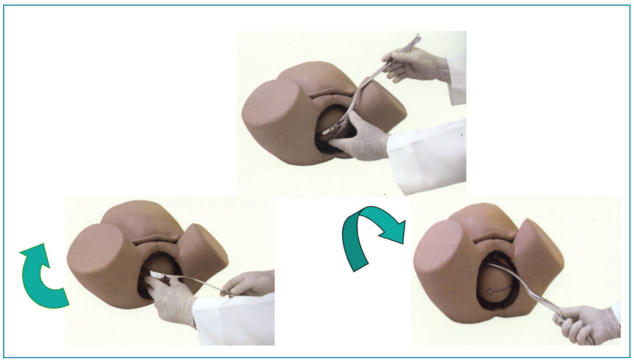
A second strategy for applications in posterior varieties, which has the advantage of avoiding detachment of the occiput against the perineal musculature, is to perform a wide 135° anterior rotation for the OP, followed by a single-grip extraction. This technique re-

quires operator experience and the use of a Kielland's forceps. Here, the slight pelvic curvature of this forceps allows the blades to be directed downwards at the time of application. Once the 135° of rotation is completed ("key through the keyhole"), the pelvic curvature of the forceps is positioned in the same direction as the maternal pelvic curvature and the cephalic detachment occurs in the OP variety, with no need for a second grip.[9,20]

A third technical option for the posterior varieties, which also has the advantage of cephalic detachment in the OP variety, is to perform the 135° rotation by means of Scanzoni's maneuver (double grasp) using a Simpson's forceps. The technique is useful when Kielland's forceps are not available and/or when there is an operator with dexterity and appreciation of the procedure. The first application is performed with the pelvic curvature of the forceps directed upwards, towards the fetal bregma. After a 135° rotation performed with a wide circumduction movement of the handles, the pelvic curvature of the forceps is directed downwards and the cephalic pole in the OP variety. As Simpson's forceps blades have a wide pelvic curvature, the instrument must be removed for a second application, and extraction of the cephalic pole with the pelvic curvature of the blades facing downwards is prohibited. The second grip follows the principles for application and detachment of the fully rotated cephalic pole.[9,20]

Among these three techniques in posterior presentations, the 135° rotation with Kielland's forceps in a single grip is undoubtedly the most advantageous as it promotes detachment in the OP variety, with a reduction in vaginal manipulation and use of force.[9,20]

Kielland's forceps are the most indicated for application in transverse varieties (right occiput transverse [ROT] and left occiput transverse [LOT]). The option of applying the anterior branch first is advantageous, as it requires a wide Lachapelle maneuver, which can be hampered when one chooses to apply the first branch posteriorly in the pelvis. As this displaces the cephalic pole anteriorly, insertion of the anterior branch by means of the triple spiral movement is made difficult. Thus, the first branch is applied anteriorly, through movements of translation, lowering and twisting of the handle (Lachapelle maneuver - itinerant technique) (Figure 18). The second branch is introduced later, directly. Asynclitism is often present in these position varieties, requiring its correction prior to assessment of the correct grip, rotation and traction. For this, one of the branches must penetrate more than the other in the birth canal, depending on the type of asynclitism (anterior or posterior). The correction for the synclitism position is performed by sliding the already articulated branches of the forceps. It is recommended to pull the branch that penetrated the most into the birth canal, avoiding to push the branch that penetrated the least



Source: Adapted from Benzecry (2006).[9]

Figure 18. Application of the right branch of Kielland's forceps to the anterior parietal bone by means of the Lachapelle maneuver (translation, lowering and torsion of the handle) in the left occiput transverse position

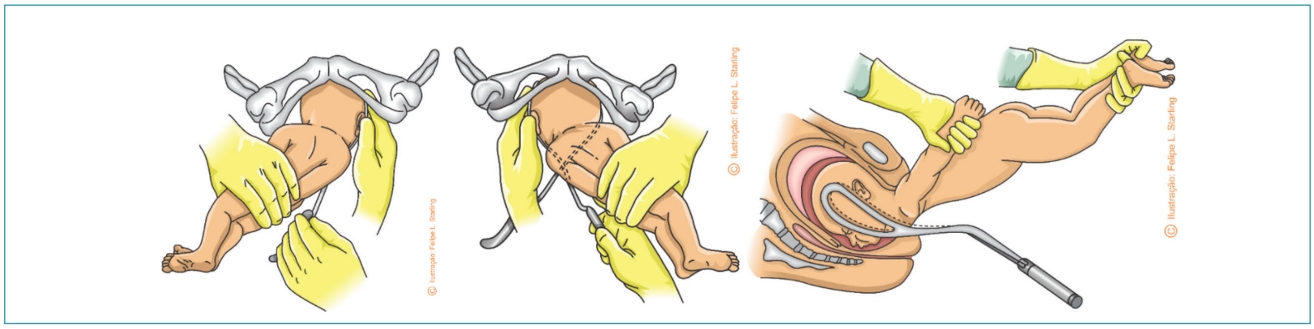
in order to avoid trauma to the upper portions of the birth canal. Correction of asynclitism is confirmed using Laufe's criteria, before performing rotation ("key through the keyhole") and traction.[9,20]

Because it has larger branches and ample perineal curvature, Piper's forceps are the most indicated for impaction of the head (breech baby) (Figure 2). In the technique, an assistant lifts the body of the fetus by the lower limbs or with a compress positioned under the fetal abdomen. Positioned horizontally, the left branch is introduced first, directly. Subsequently, the right branch is introduced in a similar way without greater difficulty in articulating with the left branch. When assessing the correct grip, the facial line must be equidistant from the articulated branches of the forceps, the finger must not penetrate through the fenestrae of the blades and the chin must be close to or at most 1.5cm from the plane of the shanks. In the previous varieties, the application is performed in OP with the branches introduced under the fetal body. Traction should be axial, following the curvature of the maternal pelvis until the suboccipital region is positioned under the pubic arch. The head is extracted by accentuating the flexion and subsequently moving the articulated instrument towards the maternal abdomen. The instrument must be disarticulated before complete extraction of the cephalic pole (Figure 19).[9]

In the later varieties, the branches are introduced over the fetal body and the application takes place in the OA. Traction is exerted forward, with the mandible and fetal neck resting on the superior border of the pubic symphysis. The fetal trunk is then elevated towards the maternal abdomen.[9]

How should the sequencing of instruments and handling be done in the face of failed attempts at operative vaginal delivery?

The sequential use of forceps and vacuum is associated with increased rates of cerebral, subdural, and subarach-



Source: Photographic record by the authors.

Figure 19. Application of Piper's forceps on the stuck head with the occiput positioned anteriorly (occiput posterior position)

noid hemorrhage in newborns, as well as facial nerve and brachial plexus injuries. Severe perineal lacerations are also more common.[21] The effectiveness in resolving operative vaginal delivery is greater with forceps than with vacuum extractors. Therefore, after a failed attempt at vacuum extraction, the risks of a subsequent attempt at forceps must be weighed against the risks of a cesarean section. In contrast, in situations where the forceps attempt fails, the attempt at vacuum extraction is contraindicated, and the subsequent cesarean section must be performed.[22] Before performing the cesarean section, it is recommended to de-impact the cephalic pole by means of maneuvers or other instruments (Coyne, Sellheim or Murless levers; C-Snorkel; fetal pillow).[23]

What is the role of ultrasound in operative vaginal delivery?

Ultrasonography can be used to confirm the diagnosis of the variety of position and height of the cephalic pole, helping to assess the probabilities of success and the risks of operative vaginal delivery. It has also been described in the objective monitoring of rotational applications. The parameters evaluated when determining the position and variety of position are the cerebellum, orbits and midline falx. Ultrasonographic measurements of head circumference, the distance between the perineum and the fetal skull, and the angle of progression are predictive of difficult operative vaginal deliveries. Studies reveal that ultrasound increases the diagnostic accuracy of positional variety with no differences in maternal or neonatal outcomes.[24] Therefore, there is still not enough evidence to recommend the routine use of abdominal or perineal ultrasound for assessment of the station, flexion and descent of the fetal head in the second stage of labor.[5]

What are the recommendations for episiotomy, antibiotic prophylaxis, and thromboprophylaxis in operative vaginal delivery?

Operative vaginal delivery is one of the indications for episiotomy, which must be selective. Current recommendations do not advocate routine episiotomy in operative vaginal delivery given the poor healing and discomfort associated with mediolateral episiotomy, and the risk of injury to the anal sphincter and rectum with median episiotomy.[4,25,26] However, in the context of instrumental delivery, episiotomy is presented as a risk modifying procedure, and not as a treatment for severe perineal lacerations. The search for the best scientific evidence regarding the effect of episiotomy on the risk of severe perineal lacerations in operative vaginal delivery, to be obtained through randomized clinical trials, is hampered by the challenge of composing dichotomized groups into 0% and 100% performance of the procedure, as well as in biases introduced by the heterogeneity of operators' skills and the difficulty in ensuring that an appropriate incision angle (between 40° and 60°) is always obtained in the intervention group. Therefore, the value of large observational studies remains, which demonstrate that mediolateral episiotomy can play an important role in preventing severe perineal lacerations during operative vaginal delivery.[27] Selecting parturients for undergoing or not an episiotomy during operative vaginal delivery requires operator experience and skill, especially when opting for posterior cephalic detachment (OA). The moment of the episiotomy should not precede the test of traction and the rotation maneuvers, avoiding the performance of the procedure in the event of a failed attempt at operative vaginal delivery. Therefore, after the descent of the presentation, with the occiput below the pubic symphysis, in the anterior detachment (OP), the elevation of the cephalic pole begins by means of the displacement of the articulated handles of the forceps towards the maternal abdomen and the evaluation of the need for episiotomy.[28,29] A single intravenous dose of antibiotics is recommended in operative vaginal delivery, as it significantly reduces the likelihood of infection and has few adverse events. Correct asepsis techniques and the use of personal protective equipment are also advised.[30] After operative vaginal delivery, puerperal women should be reassessed for the risk of venous thromboembolism and the need for thrombo-

prophylaxis. Risk factors, such as prolonged labor and immobility are frequently associated with instrumental delivery.[31]

What are the main maternal and neonatal complications of operative vaginal delivery?

When used in the correct technique, forceps and vacuum extractors have low rates of maternal and neonatal complications.[4,5,32] Maternal complications associated with the use of forceps are lacerations in the birth canal (uterine, cervical and/or vaginal), severe perineal lacerations (third and fourth degrees), prolonged episiotomy, bladder and/or urethral injuries, and hematomas.[33] Neonatal complications associated with forceps include subgaleal hemorrhages, abrasions, facial lacerations, ocular compressions, corneal abrasions, paralysis of the facial and/or hypoglossal nerves, cervical spine injury, skull fracture, and intracranial hemorrhage.[4,5,34,35] Third- and fourth-degree (severe) perineal lacerations are also maternal complications related to vacuum extraction, but in smaller proportions than instrumental delivery with forceps. The main neonatal complications in vacuum extraction occur because the traction is applied to the scalp. The main ones are scalp lacerations, cephalohematomas and intracranial, subgaleal and retinal hemorrhages. Cephalohematomas are more frequently associated with application errors (cups attached outside the flexion point) and failures in fetal extraction. They are more likely to occur with increasing duration of vacuum extractions.[36] Even though there is association between operative vaginal delivery and severe perineal lacerations, pelvic floor function and sexual function scores within one year of delivery do not appear to differ in relation to cesarean delivery.[37] Obstetricians should be trained to recognize and treat maternal complications. Neonatologists should be informed about the technique used in operative vaginal delivery in order to assess and observe potential associated neonatal complications.[4,5]

What should analgesia and urinary tract care be like after operative vaginal delivery?

Postpartum analgesia with non-steroidal anti-inflammatory drugs and paracetamol should be routinely performed after assisted birth with forceps or a vacuum extractor.[38] Postpartum women should be instructed about the risk of urinary retention present with the association between analgesia and operative vaginal delivery. They should be encouraged to empty their bladder in the postpartum period and have their urinary time and volume (including residual volume) monitored. Intermittent or even indwelling urinary catheterization may be necessary for 24 to 48 hours. In more lasting bladder dysfunctions, urological evaluation and clean intermittent self-catheterization may be necessary. Physical therapy can be offered as a strategy to reduce the risk of urinary retention within three months of delivery.[39]

Final considerations

In the evolution of childbirth care, forceps are the resource with the greatest potential to save lives. Although vacuum extractors are more recent, they are also effective devices for assisted birth and offer the advantage of simplifying the operative technique. With adequate knowledge and skill, the cost-effectiveness and safety of instrumental vaginal delivery are favorable and endorse current guideline recommendations for operative vaginal delivery. Despite the obvious advantages, the potential of operative vaginal delivery is currently limited both by ignorance and misuse. The progressive replacement of forceps and vacuum extractors by cesarean section motivated by the lack of preparation of the new generation of obstetricians seems to introduce a real possibility of the disappearance of these instruments from the medical practice of childbirth care. The emergence of new instruments that although less effective, require less technical skill from the operator seems to be a reflection of the current inabilities of obstetricians for operative vaginal delivery. Therefore, training in these important skills must be urgently reconsidered, before this art is lost forever.

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Manuscript

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

- **Original articles:** full prospective, experimental or retrospective works.
- **Case reports:** They are of interest if well documented from a clinical and laboratory point of view and should contain new or unexpected aspects in relation to cases already published. Authors should indicate this information in the referral letter. The text of **Introduction** and **Discussion** sections must be based on an up-to-date literature review.
- **Review articles:** Spontaneous contributions are accepted, including integrative, scoping, or systematic reviews with or without meta-analyses. Narrative reviews will only be accepted exceptionally, given the questionable scientific evidence they represent. The methods and procedures adopted to obtain data inserted in the text must be described and based on recent references, including the current year. As this is still subject to controversy, the review should discuss trends and lines of investigation in progress. In addition to the review text, the synthesis and conclusions must be presented.
- **Letters to the Editor:** Must address editorial matters or not, but present relevant information to readers. The letters may be summarized by the editorial board, always keeping the main points. In the case of criticism or comments on published works, the letter is sent to the authors of the cited article so their response can be published simultaneously. All data presented in the letter must be fully citable and cited in the supporting reference list (unpublished data should not be described in the letter).
- **Editorial:** By invitation of the editor only.

OBS. Manuscripts containing results of original clinical or experimental research have priority for publication

Manuscript structure

Title

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

Abstract

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

1. Abstract: for original articles

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

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

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

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

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

2. Abstract: for systematic review articles

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

Objective: State the main objective of the article.

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

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

Data collection: Summarize the conduct used in data extraction and how it was used.

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

Conclusions: State the main conclusions and their clinical utility.

3. Abstract: for integrative/scoping reviews

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

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

Keywords

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

Manuscript body

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

Introduction

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

Methods

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

method comprises the material and procedures adopted in the study in order to be able to answer the main question of investigation. The **Methods** section should be structured starting with the type of study design, to show if it is appropriate to achieve the research objective; the research setting (the place and time in which it was developed); the data collection; the intervention to be performed and evaluated (if any) and also the alternative intervention; the statistical methods used and the ethical aspects of research.

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

Randomized clinical trial:

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

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

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

Qualitative studies:

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Results

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

Discussion

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

Conclusion

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

References

In manuscripts submitted to the RBGO, authors must number references in order of entry in the work and use these numbers for citations in the text. An excessive number of references should be avoided, selecting the most relevant for each statement and giving preference to more recent works. Do not use citations of difficult to access, such as abstracts of works presented at conferences, theses or publications with restricted circulation (not indexed). Cite primary and conventional references (articles in scientific journals and textbooks). References such as "unpublished observations" and "personal communication" should not be used. Authors' publications (self-citation) should only be used if there is a clear need and they are related to the topic. In this case, include only original works published in regular journals (do not cite chapters or reviews) among the bibliographic references. The number of references should be limited to 35, except for review articles. Citations of references must be placed after the period in superscript, without space after the last word (sequential and numerical citations). Authors are responsible for the accuracy of data contained in the references. To format your references, check **Vancouver:** https://www.ncbi.nlm.nih.gov/books/NBK7256/.

Submission of manuscripts

Articles must be submitted electronically, according to instructions available on the website: http://mc04.manuscriptcentral.com/rbgo-scielo.

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