# Syphilis in pregnancy and congenital syphilis notified in a public maternity hospital in Petrópolis – RJ

# Sífilis na gestação e congênita notificadas em um hospital maternidade pública de Petrópolis – RJ

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#### ABSTRACT

**Introduction:** Syphilis is a disease of high incidence in Brazil and when it occurs during pregnancy, it has important public health implications, as it is responsible for high rates of perinatal fetal mortality and morbidity. **Objective:** To verify the prevalence of gestational syphilis, the epidemiological profile of the pregnant woman and outcomes such as congenital syphilis. **Methods:** Descriptive and retrospective study of maternal and newborn data, obtained from the notification forms of SINAN, medical records, and delivery book of the HEAC maternity ward, from January 2017 to December 2019. **Results:** Four hundred and eighteen pregnant women with syphilis had a pregnancy outcome at HEAC. Seroprevalence for syphilis in pregnant women was 3.95% in 2017, 4.92% in 2018, and 4.73% in 2019. 204 (48.8%) women received adequate treatment before delivery. Among the outcomes, all were reported as congenital syphilis, with 45 (10.7%) having abortions or stillbirths and among live births, 58 (15.54%) were premature and 67 (17.9%) had some manifestation clinic. **Conclusion:** The number of pregnant women admitted to HEAC who were notified with gestational syphilis was higher than the average notification for these conditions found in Brazil in the years studied, but it was similar to the average found in the State of Rio de Janeiro. Over-reporting of congenital syphilis was identified, and newborns exposed to syphilis were included in this diagnosis, without criteria for congenital syphilis. Our reporting system proved to be fragile and unable to assess the real situation of congenital syphilis, in HEAC. **Keywords:** syphilis, congenital; prenatal care; infant, newborn; stillbirth; abortion.

#### RESUMO

Introdução: A sífilis é uma doença de alta incidência no Brasil e, quando ocorre durante a gravidez, tem implicações importantes na saúde pública, pois é responsável por altos índices mortalidade e morbidade fetal perinatal. **Objetivo:** Verificar a prevalência da sífilis gestacional, o perfil epidemiológico da gestante e os desfechos como a sífilis congênita. **Métodos:** Estudo descritivo e retrospectivo de dados maternos e de recém-nascidos (RNs) obtidos das fichas de notificação do Sistema de Informação de Agravos de Notificação (SINAN), dos prontuários e do livro de parto da maternidade do Hospital de Ensino Alcides Carneiro (HEAC), no período de janeiro de 2017 a dezembro de 2019. **Resultados:** Quatrocentas e dezoito gestantes com sífilis tiveram o desfecho da gravidez no HEAC. A soroprevalência para sífilis nas gestantes foi de 3,95% em 2017, 4,92% em 2018 e de 4,73% em 2019. Receberam tratamento adequado antes do parto 204 (48,8%) mulheres. Dentre os desfechos, todos foram notificados como sífilis congênita, sendo que 45 (10,7%) foram abortos ou natimortos e, entre os nascidos vivos, 58 (15,54%) foram prematuros e 67 (17,9%) apresentavam alguma manifestação clínica. **Conclusão:** O número de gestantes internadas no HEAC que foram notificadas com sífilis gestacional foi superior à média de notificação para esses agravos encontrada no Brasil nos anos estudados, porém foi similar à média encontrada no estado do Rio de Janeiro. Foi identificação se mostrou frágil e incapaz de avaliar a real situação da sífilis congênita no HEAC.

Palavras-chave: sífilis; sífilis congênita; cuidado pré-natal; recém-nascido; natimorto; aborto.

#### INTRODUCTION

The World Health Organization (WHO) estimates that syphilis infection affects one million pregnancies per year worldwide, leading to more than 300,000 fetal and neonatal deaths<sup>(1)</sup>.

In a systematic review published in the Bulletin of World Health Organization, a significantly higher rate of death or stillbirth, neonatal death, and prematurity or low birth weight was found among the children of women with syphilis, when compared to those of women without it<sup>(2)</sup>.

In 1986, in Brazil, congenital syphilis (CS) notification became compulsory. In 1995, Brazil became a signatory to Resolution CE116/14, of the Pan American Health Organization (PAHO)<sup>(3)</sup>, having made a commitment to eliminate the occurrence of CS by the year 2000. To achieve this objective, a disease control plan was developed based on improving prenatal care, aiming to speed up

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diagnosis and to provide timely treatment for cases of gestational syphilis<sup>(4,5)</sup>. The objective was not achieved by the scheduled date. In May 2016, the World Health Assembly adopted the 2016–2021 global health sector strategy for sexually transmitted diseases (STD). This strategy includes expanding evidence-based interventions and services to control STD and lessen their impact as a public health problem by 2030. The strategy defined goals for reducing the incidence of gonorrhea and syphilis in adults and recommended conducting a survey on STD global incidence until 2018<sup>(6)</sup>.

Compulsory notification of cases is an important surveillance measure, which allows for the greatest collection of data necessary to carry out epidemiological analyses and provides subsidies for planning control actions. Otherwise, underreporting makes it difficult to understand the magnitude of the problem, interfering with the ability to control diseases<sup>(7)</sup>, however, it is necessary for health surveillance services to inspect and investigate failures and errors in notifications.

In Brazil, in 2018, the Ministry of Health (MH) recorded an increase in notifications in the Notifiable Diseases Information System (*Sistema de Informações de Agravos de Notificação* – SINAN), with

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62,599 notified cases of syphilis in pregnancy (SP) (detection rate of 21.4/1,000 live births); 26,219 cases of CS (incidence rate of 9.0/1,000 live births); and 241 deaths from CS (mortality rate of 8.2/100,000 live births). Comparing 2018 to 2017, there is an increase of 25.7% in the detection rate in pregnant women and 5.2% in the incidence of CS. The MH also states that this result can be attributed "to the change in the criteria for defining cases for surveillance purposes, which made it more sensitive, while the less pronounced increase in CS can be attributed to the new more specific criterion"<sup>(8)</sup>.

The state of Rio de Janeiro has a higher detection rate of SP and CS than the rest of the country. 9,234 SP were reported (detection rate of 41.4/1,000 live births); 4,171 cases of CS (incidence rate of 18.7/1,000 live births); and 52 deaths from CS (mortality rate of 23.3/100,000 live births)<sup>(8)</sup>.

Congenital infection has been diagnosed in the range of 1 to 2% of women treated adequately during pregnancy, compared with 70 to 100% of untreated ones<sup>(1)</sup>.

Risk factors for CS involve maternal factors related mainly to few visits to prenatal care, undetermined duration of the disease in the mother, treatment in the third trimester, high non-treponemal test (NTT) at the time of diagnosis and the youngest gestational age of the fetus at the time of maternal diagnosis and treatment of syphilis<sup>(9)</sup>.

For the diagnosis of a child exposed to syphilis or with CS, a thorough evaluation is necessary right after delivery, when both the maternal history of syphilis and its treatment and follow-up during pregnancy, the child's clinical signs and symptoms (most of them, absent or unspecific) and complementary radiological and laboratory tests with the child's peripheral NTT compared to the mother's NTT test<sup>(8)</sup>.

# **OBJECTIVE**

To verify the prevalence of gestational syphilis, the epidemiological profile of the pregnant women, and the outcomes, such as CS.

#### **METHODS**

Retrospective, descriptive study, with collection of secondary data obtained from copies of the SINAN compulsory notification (CN) forms of SP and CS, from the archive of pregnant women admitted to the maternity ward of *Hospital de Ensino Alcides Carneiro* (HEAC), in the city of Petrópolis, Rio de Janeiro, from January 2017 to December 2019, and analysis of the delivery book and medical records of newborns (NB).

HEAC is the only public maternity hospital in the city, being a regional reference in maternal and child health and high risk maternity, serving 100% of users of the Unified Health System (*Sistema Unico de Saúde* – SUS).

For data collection, a semi-structured questionnaire was prepared with data from SINAN to SP and CS. Data on the pregnant-parturient women included: date of hospitalization and delivery; maternal age; social profile; obstetric profile; number of prenatal consultations; result of non-treponemic (venereal disease research laboratory – VDRL) and treponemic tests; treatment schedule and start date; performance or not of treatment; and scheme prescribed to the partner. NB data included: birth weight; gestational age; and screening of the diagnosis-treatment for CS.

EpiData<sup>®</sup> software was used for data collection and tabulation, and Epidata Analysis<sup>®</sup> was used for statistical assessment and preparation of tables and graphics.

The study included pregnant patients admitted to HEAC and diagnosed with syphilis, through positive serological test, detected during prenatal care or during hospitalization for childbirth or other complications, and who carried out their outcomes in HEAC. Pregnant women who did not have a pregnancy outcome documented in HEAC were excluded, despite having a positive VDRL test on admission.

#### RESULTS

In HEAC, between the years 2017 and 2019, notifications of 418 cases of SP and CS were evaluated, including stillbirths and abortions.

All pregnant women notified with SP during hospitalization and prenatal care had their conceptuses notified with CS and the incidence rate of CS was then equal to the detection rate of SP (Table 1).

The mean age of the pregnant women was 23.9 years, with a minimum age of 14 and a maximum of 43 years. Regarding race, it was found that 26.6% were classified as white and 65.3% as non-white. As for education, 40.4% had incomplete or complete elementary school. Regarding occupation, 49.3% reported staying home and 38.0% worked outside the home at the time of notification.

It was observed that 89.5% of the patients lived in Petrópolis and 9.2%, in neighboring municipalities.

Prenatal care was performed by 89.9% of pregnant women, with 50.7% starting prenatal care in the first trimester, 70.6% having performed more than 6 consultations. More than half of pregnant women (61.9%) were tested 2 or more times for syphilis during prenatal care. The diagnosis of syphilis was made in prenatal care in 72% of pregnant women, and screening for syphilis during prenatal care was negative in 14.4% patients, who made the diagnosis only during hospitalization for childbirth or abortion, when the test results were positive.

**Figure 1** shows NTT titers during hospitalization, when 35.5% had low titers, 1:1 or 1:2. It was found that two pregnant women presented non-reactor VDRL at the time of hospitalization, but had positive prenatal titers (1:16 and 1:4), although they reported having undergone adequate treatment, but without proof, and their conceptuses presented at birth titer of 1:2 in peripheral blood.

Table 1 – Number of syphilis in pregnancy and congenital syphilis in the maternity ward of Hospital de Ensino Alcides Carneiro, Petrópolis, RJ, between January 2017 and December 2019.

Year	Total of births at HAEC	Number of cases of syphilis in pregnancy and congenital syphilis	Percentage	Total livebirths at HEAC	In 1,000 livebirths
2017	3,158	125	3.95	3,120	40.06
2018	3,043	150	4.92	3,019	49.68
2019	3,020	143	4.73	2,985	47.90

HEAC: Hospital de Ensino Alcides Carneiro.

About 23.4% of pregnant women underwent a treponemic test (TT) upon admission. The vast majority of pregnant women did not show signs or symptoms of syphilis on admission. Only four (0.95%) had any sign described (ulcerated lesions in the genital region) in the SINAN notification or in the medical record.

As for the treatment, 72.0% did it before hospitalization, however the complete treatment with benzathine penicillin was performed in 48.8% of the parturients and considered inadequate or not performed in 51% of them (**Table 2**).

It was observed that the sexual partner was not treated in 336 (80.4%) cases.

Regarding the outcome of pregnancy, among the total of 45 stillbirths (10.8%), 23 were stillborn and 22, abortions.

58 (15.54%) NB with less than 37 weeks of gestation were observed. Among live births, 43 (11.62%) weighed less than 2,500g at birth, in three cases this information was not found in the researched documents (**Figure 2**). In this study, we found a prevalence of 15.55% of prematurity among live births.

**Table 3** shows that 68.8% of pregnancies that evolved with abortions (n=22)/stillbirth (n=23) did not have prenatal care.

It was found that 67 (17.96%) NB were symptomatic, with jaundice being the most frequent sign, with 54 (80.59%) cases. Skin lesions described as maculopapular and vesicular rash were found only in five (7.47%) of the symptomatic (**Table 4**). A case of Parrot's pseudoparalysis has been reported. Only four NB had an altered long bone radiography and 255 (68.36%) did not undergo the examination (**Table 5**).

The serology collected from the peripheral blood of NB for syphilis was performed with NTT (VDRL), which was positive in 353 of live births (94.64%), with titers ranging from 1:1 to 1:512 (**Table 6**).





**Table 2** – Frequency of treatment compliance of pregnant women with syphilis during prenatal care from 2017 to 2019 (n=418).

Pregnant women who underwent treatment for syphilis	n	%
Properly underwent treatment	204	48.8
Did not undergo treatment properly	158	37.7
Did not undergo treatment	56	13.3
Total	418	100.0



Figure 2 – Distribution of newborn weight of pregnant women with syphilis admitted to the *Hospital de Ensino Alcides Carneiro* between 2017 and 2019 (n=370).

**Table 3** – Prenatal evaluation of pregnant women with syphilis with a abortion/stillbirth outcome admitted to Hospital de Ensino Alcides Carneiro between 2017 and 2019 (n=45).

Prenatal care onset (n=45)	Abortion/stillbirth	
Frenatal Care Offset (11–45)	n	%
1 <sup>st</sup> trimester	3	6.66
2 <sup>nd</sup> trimester	10	22.22
3 <sup>rd</sup> trimester	1	2.22
Did not take prenatal care	31	68.88
Total	45	100.0
Number of consultations (n=45)	Abortion/stillbirth	
Number of consultations (1–45)	45	%
1 to 5	11	24.4
6 or more	3	6.66
Did not take prenatal care	31	68.88
Total	45	100.0

**Table 4** – Frequency of newborns of pregnant women with syphilis admitted to Hospital de Ensino Alcides Carneiro, symptomatic *versus* asymptomatic (n=373).

	n	%
Asymptomatic	306	82.03
Symptomatic	67	17.96
Total	373	100.0
Symptomatic cases (signs)	(n=67)	
	n	%
Jaundice	54	80.59
Hepatosplenomegaly	4	5.97
Periostitis	4	5.97
Skin lesions	5	7.47
Total	67	100.0

**Table 5 –** Frequency of radiological findings of long bones of newborns of pregnant women with syphilis admitted to *Hospital de Ensino Alcides Carneiro* between 2017 and 2019 (n=373).

	n	%
Altered radiography	4	1.072
Without changes	114	30.56
Not done or without information	255	68.36
Total	373	100.0

Among 155 successful analyses, 27 (17.41%) presented altered cerebrospinal fluid (CSF), 17 (10.96%) with reagent VDRL (**Table 7**), and 10 (6.45%) with proteinorachie above 150mg/dL. Among the samples analyzed, the presence of pleocytosis was not described.

One hundred and seventy-two NB with criteria for CS diagnosis (46.11%) were treated with crystalline penicillin G or procaine penicillin, at the dose recommended by the MH. Other therapeutic approaches were made after analyzing the cases and their framing in the diagnosis of NB exposed to syphilis, when the continuity of monitoring and treatment could not be guaranteed. Twenty-four NB (6.43%) did not have criteria for CS, according to pediatrics,

**Table 6 –** Distribution of the values of the titers of venereal disease research laboratory of peripheral blood of newborns of pregnant women with syphilis admitted to *Hospital de Ensino Alcides Carneiro* between 2017 and 2019 (n=373).

VDRL	n	%
1:1	121	32.43
1:2	90	24.12
1:4	71	19.03
1:8	37	9.91
1:16	17	4.55
1:32	6	1.60
1:64	7	1.87
1:128	3	0.80
1:512	1	0.26
Nonreactive	20	5.36
Total	373	100.0

VDRL: venereal disease research laboratory.

**Table 7** – Distribution regarding the titer of the venereal disease research laboratory of the CSF found in CSF puncture of newborns of pregnant women with syphilis admitted to *Hospital de Ensino Alcides Carneiro* between 2017 and 2019 (n=373).

VDRL CSF	n	%
1:1	8	2.14
1:2	5	1.34
1:4	3	0.80
1:64	1	0.26
Unsuccessful puncture	34	9.11
Nonreactive	138	36.99
Not performed	184	49.32
Total	373	100.0

VDRL: venereal disease research laboratory; CSF: cerebrospinal fluid.

and were discharged without treatment, with outpatient follow-up guidance. In two cases, there was no treatment because the mothers took the NB home at their own risk, having been notified to the Guardianship Council. Only two (0.53%) patients were treated with a drug other than penicillin (**Table 8**); these two patients did not undergo treatment for CS, but for suspected sepsis, as described by pediatrics in the medical records.

# DISCUSSION

It was found that the SP detection rate was above that found in other studies<sup>(10,11)</sup> and, according to the 2019 Epidemiological Bulletin, from the MH, above the Brazilian average, but closer to that found in the state of Rio de Janeiro<sup>(6)</sup>.

The incidence rate of CS per 1,000 live births was higher than that described in the 2019 Epidemiological Bulletin, from the MH<sup>(6)</sup>, in the respective years, both in comparison with data from Brazil and with data from the state of Rio de Janeiro. This can be explained by the criterion used by HEAC for notification of CS cases including cases of NB exposed to syphilis.

Most of the pregnant women notified with SP were non-white, with a mean age of 23 years, similar to data from Brazil<sup>(6)</sup> and other studies<sup>(5,12,13)</sup>.

Most had low education, whose data can be identified as a marker of poor access to health and adequate guidance regarding preventive care. Parker et al.<sup>(14)</sup>, in their work, discuss the importance of education as one of the most effective measures to prevent syphilis.

Prenatal care is very important for pregnant women with syphilis, due to the high probability of vertical transmission; therefore, they must be treated with special care. In this study, it was found that most of the pregnant women had adequate prenatal care and that most women were diagnosed with syphilis during the prenatal period. However, in some pregnant women, as in other studies<sup>(10,13,15)</sup>, this diagnosis was only made during hospitalization for childbirth. Further details of the data would be necessary to clarify whether this result would be due to the lack of adequate prenatal care, with a reduced number of consultations and tests, or if it was due to reinfection at a date closer to delivery. A study by Slutsker et al.<sup>(16)</sup> suggests that screening pregnant women in the third trimester effectively prevented most cases of CS.

Analyzing the results of the VDRL of pregnant women, several low titers were observed. It is known that in patients with syphilis properly treated, VDRL tends to be negative, although it may remain positive with low titers, which corresponds to the serological marking. Low titers may also be due to recent infection or late stages of

Table 8 – Frequency of treatments instituted for newborns of pregnant women with syphilis admitted to *Hospital de Ensino Alcides Carneiro* between 2017 and 2019 (n=373).

		n	%
	Crystalline Penicillin	171	45.84
Received treatment for congenital syphilis	Procaine Penicillin	1	0.26
	Total	172	46.11
	Crystalline Penicillin + Benzathine	57	15.28
	Benzathine Penicillin	116	31.09
Did not receive treatment for congenital syphilis	Ampicillin + Gentamycin	2	0.53
	No treatment	26	6.97
	Total	201	53.87

infection (late syphilis)<sup>(8)</sup>. Therefore, low titers in pregnant women should be analyzed carefully. Similar data were seen in the study by Cardoso et al.<sup>(13)</sup>, who suggested an unnecessary excess of treatment for pregnant women and children. In HEAC, in these cases, fetuses and their mothers were followed up in the pediatric sector, where TT IgM was requested for the parturient, in order to confirm or not the diagnosis.

It was observed that most pregnant women had not undergone the complete treatment recommended by the MH, similar data have been presented in other studies<sup>(13,17)</sup>. In most of the notifications, pregnant women did not present clinical manifestation of syphilis at diagnosis during prenatal or hospitalization, which is confirmed in the literature, which describes that most diagnoses occur in the late latent phase.

The number of uninvestigated and untreated partners concomitant with the pregnant women was high, as in several other studies<sup>(13,15)</sup>, which may suggest the possibility of reinfection of the treated pregnant women. The evaluation and treatment of sexual partners is crucial to stop the chain of transmission of infection. It is important to note that, despite the information collected in this study about sexual partners, the MH, since 2017, refers that the sexual partners of women with SP should be treated, but it does not add to the epidemiological criteria for diagnosing CS in NB<sup>(18)</sup>.

All NB in the study underwent analysis of non-treponemic laboratory examination (VDRL) of peripheral blood and only 20 presented as non-reactors.

According to the report of the National Commission for the Incorporation of Technologies in the Unified Health System (*Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde* – CONITEC), of August 20208, approximately 60 to 90% of NB with CS are asymptomatic at birth, which is in accordance with the results observed in this and in other studies<sup>(13,19)</sup>. Only the most severe cases are born with signs and symptoms, depending on the time of intrauterine infection and the treatment during pregnancy. It is known that two-thirds develop symptoms three to eight weeks after birth, so it is of great importance to keep the follow-up of these children in a specialized clinic. All NB in the present study received guidance for follow-up after hospital discharge.

The most common manifestation observed was jaundice, which may be due to hyperbilirubinemia secondary to syphilitic hepatitis and/or hemolysis, but there were not enough data to classify the jaundice as being actually caused by syphilis. Other manifestations described were skin changes, hepatosplenomegaly, periostitis, and osteochondritis, which are classically observed in the literature.

The most common radiographic abnormalities in untreated early CS are mainly affected by long bones. In this study, changes were observed in a few cases, but the radiographic study was not performed or there was no information about its performance in most NB.

According to the MH<sup>(8)</sup>, it is believed that neurosyphilis occurs in 60% of children with CS, based on the CSF changes found, such as VDRL reactivity, pleocytosis, and increased protein. Positive VDRL in CSF is the most important parameter, with 90% specificity and 54% sensitivity, being more common in children who are born symptomatic than in asymptomatic children. As in other studies<sup>(10,13)</sup>, CSF changes were positive in a few NB and the vast majority of them did not undergo the test.

Negative outcomes, such as abortion and stillbirth, were more frequent in pregnant women who did not undergo prenatal care and in pregnant women who did not receive treatment for syphilis. The MH (CONITEC), in 2020, states that 40% of pregnancies of women with untreated early syphilis would result in spontaneous abortion, with a higher risk in the first trimester<sup>(8)</sup>. The total number of SP with abortion and stillbirth as an outcome, found in our study, as well as underweight and prematurity, was similar to that found by other studies<sup>(11,19)</sup>. In the years 2017 and 2018, data from the Informatics Department of the Unified Health System (DATASUS) in Petrópolis show a mean percentage of premature infants in live births in this study (15.55%) shows an increase in the event in the group of NB exposed to syphilis during pregnancy.

The HEAC pediatric team approach was to not consider children without symptoms as CS, as well as those who had the lowest VDRL, equal to that of the mother or even a greater dilution and whose mothers were properly treated. These cases, despite having been notified by the maternity hospital at birth as CS, were subsequently reassessed by the team. In case of identifying the NB as "exposed to syphilis" rather than with CS, they were treated with benzathine penicillin, when there was no minimum guarantee about the continuity of the specific outpatient follow-up, to maintain the investigation, since these children should be followed up until there are 18 months of life. NB whose CS diagnosis was confirmed by the MH criteria were treated with crystalline penicillin.

The results presented lead to the observation that SP and CS continue to be an important public health problem in the city of Petrópolis, requiring greater investments to improve the quality of prenatal care and the NB. Another factor observed is the importance of training and updating professionals regarding the filling in of records and notifications, adapting them to the new guidelines of the MH, a fact confirmed by the meeting of fields in CN without filling in.

Further studies are needed, using the new diagnostic criteria for SP and CS proposed by the MH, so that the real panorama of syphilis in the city of Petrópolis can be visualized.

### **STRENGTHS OF THE STUDY**

The present study demonstrated that the rates of SP detection and CS incidence in Petrópolis are very high, requiring a more critical look at the health policies adopted in order to control these indexes. Flaws were also found in CN of SP, and CS, which need to be reviewed by the health surveillance sector.

This study was part of the final stage of the Professional Master's in Maternal and Child Health at *Universidade Federal Fluminense*, approved by a panel with professors and researchers at *Universidade Federal Fluminense* and *Universidade Federal do Rio de Janeiro*.

### LIMITATIONS

An important limitation of this work is the fact secondary data were analyzed, which may be subject to information filling and/or incompleteness flaws, and used CN data from HEAC's maternity ward, whose inclusion criteria for CS are different from those currently used by the MH.

# CONCLUSION

The number of cases of pregnant women admitted to HEAC who were notified with SP was higher than the average notification for these conditions found in Brazil in the years studied, but close to the average found in the state of Rio de Janeiro.

Most pregnant women with gestational syphilis were young adults with low education and non-white ethnicity.

Abortion and stillbirth cases were closely related to the absence of prenatal care.

The HEAC notification system proved to be fragile and unable to assess the real situation of CS, due to the inadequate data collection at admission.

#### Participation of each author

Bibliographic survey: LTV. Data collection: LTV, GVO, RVV. Tabulation of data in the software: LTV, GVO. Tables and graphics: LTV. Writing: LTV. Work orientation: ADMB, AJMOV. Work review: ADMB.

#### Approval by the Human Research Ethics Committee

Approved by the FASE/FMP/HEAC. CAAE 17995419.3.0000.5245.

#### **Conflict of interests**

The authors declare that there is no conflict of interests.

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The study was carried out with the authors' own resources.

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