

Subsequent pregnancies in women with previous gestational syphilis

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Abstract *This study included data on syphilis-positive pregnant women seen for delivery or miscarriage, between 1997 and 2004, in Sao Lucas Hospital, Porto Alegre, RS. Their subsequent obstetric outcomes were studied, until December 2011, to see if the disease recurred. From 450 pregnant women with positive syphilis serology, seen from 1997 to 2004, 166 had at least one more obstetric attendance until December 2011, with 266 new obstetric outcomes. Congenital syphilis (CS) was demonstrated in 81.9% of the initial pregnancies and in 68.4% of the subsequent ones. The main causes of CS in subsequent pregnancies were a negative VDRL that turned positive at delivery, and undocumented treatment. VDRL titers were higher than 1:4 in 50.4% of the initial and 13.3% of the subsequent pregnancies ($p < 0.01$). Perinatal mortality rate was 119/1000 in initial and 41/1000 in subsequent pregnancies ($p < 0.01$). CS recurrence was frequent in subsequent pregnancies of women who tested positive for syphilis in a preceding pregnancy. No or inadequate prenatal care was the main risk factor for CS, both in initial and in subsequent pregnancies. These data suggest that non-infected neonates could have been defined as CS cases because of insufficient information about the mother's history.*

Key words *Congenital syphilis, Prenatal care, Pregnancy*

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Introduction

Congenital syphilis (CS) is still an important cause of fetal losses, neonatal deaths, prematurity and severe health problems in surviving children¹⁻⁶. Disease control faces several barriers of demographic, socio-economical and behavioral order and reflects the quality of health care⁷⁻⁹. In Brazil, public health measures have not yet managed to bring syphilis under control. A brief literature review reveals that CS is still a serious problem in all regions of the country^{3,10-14}.

Diagnosis of CS in asymptomatic newborn infants is complicated by the presence of maternal antibodies and by the impossibility of culturing *Treponema pallidum*^{15,16}. For this reason, information about maternal history – primarily designed for epidemiological surveillance – is used for CS case definition. This information also guides clinical management of the neonate¹⁷⁻²⁰. These highly sensitive criteria mistakenly classifies some non-infected neonates as infected. Notwithstanding, since the chance of an inadequately treated mother with syphilis transmit the infection to the fetus is between 40% to 100%, all newborn infants identified as potentially CS cases must be submitted to many diagnostic procedures. These include lumbar puncture, radiological exams and, in some cases, hospitalization for at least 10 days of antibiotic treatment^{17,18}.

The newborn of a mother who had syphilis is not considered a CS case, if maternal treatment during the current or a previous pregnancy was adequate and properly documented with appropriate diagnostic tests. When these conditions are not fulfilled, the infant will be investigated and treated and the mother will start treatment during the maternity stay.

It is not unusual for subsequent pregnancies of a woman with a history of syphilis to result in new CS cases. This fact motivated this study, which was conducted in a teaching hospital of the south region of Brazil. Its objectives included to evaluate CS frequency and its recurrence in subsequent pregnancies, to identify the criteria that defined these cases and to look at their perinatal outcomes.

Methods

This study was conducted in the public sector (SUS) of São Lucas Hospital (SLH) maternity ward. SLH is a teaching hospital that belongs to the Pontificia Universidade Católica do Rio

Grande do Sul (PUCRS), located in Porto Alegre, the capital of Rio Grande do Sul state. The SLH is a referring hospital for the East and Lomba do Pinheiro/Partenon regions in Porto Alegre. The population of this area is approximately 250,000 people. SLH also receives many referrals from the nearby city of Viamao.

Women from these regions are sent for or spontaneously seek obstetric care at SLH for labor or pregnancy complications that require urgent care. In Porto Alegre, routine prenatal assistance includes testing for syphilis with *Venereal Disease Research Laboratory* (VDRL) at the first consultation, at the beginning of the third trimester and at hospital admittance, for a total of three tests. In SLH, VDRL is realized in all women admitted for obstetric care (childbirth, stillbirth or miscarriage). Test results between 1:1 and 1:8 are subsequently confirmed by the treponemic method *Fluorescent Treponemal Antibody – Absorption* (FTA-ABS). If this test is positive, even low VDRL titers do not exempt the newborn from being investigated and treated according to applicable guidelines¹⁷⁻²⁰.

This study included women with at least two obstetric outcomes at SLH (miscarriage, vaginal delivery or cesarean section), with the first one positive for syphilis. Patients were identified using a database created for a previous study, which prospectively included all patients with positive syphilis serum tests, who were attended in the SUS sector of the SLH between May 1997 and December 2004³. During the year of 2012 a retrospective review of these patients medical records was done, investigating the occurrence of posterior obstetric care of the same patients, since the beginning of the inclusion period until December 2011. The initial pregnancy included in the recruitment period (1997-2004), was considered as “initial”, even if the patient may have had previous pregnancies. The pregnancies were classified as “subsequent” from the second one included in the study. The main investigated outcome was CS presence or absence, defined according to CDC¹⁷ and the Brazilian Ministry of Health (BMH)^{18,19} guidelines. These are also consistent with Pan American Health Organization definitions²⁰. Delivery or miscarriage of twins were considered as only one outcome. Posterior outcomes in which it was not possible to confirm or exclude CS were removed from the study.

Initial or subsequent pregnancies defined as CS cases according to these standards were classified in this study as “with CS”. Pregnancies in which the women had undergone documented

treatment with adequate doses of penicillin more than 30 days before delivery, with their sexual partner treated concurrently and with VDRL titers at least four times lower than before treatment, were defined as “without CS”. Subsequent outcomes in patients with negative syphilis tests were also considered as “without CS”.

We investigated the following maternal characteristics: number of pregnancies, prenatal care, VDRL results at pregnancy and at hospital admittance, and syphilis treatment. Prenatal care with less than two visits was defined as absent. Besides CS status and pregnancy outcome – live-birth, stillbirth or miscarriage – we also compiled data on newborn and stillbirth characteristics – weight, gestational age, and clinical, laboratorial and radiological indicators relevant to CS.

According to the SLH routine, all puerperal women without documented treatment as well as those with treatment considered inadequate, received at least 2,400,000 IU of benzathine penicillin G before discharge from the hospital. They also received a prescription to complete the treatment as outpatients, according to the Ministry of Health guidelines. Two additional doses were required with a week interval between them if syphilis was diagnosed more than a year ago or its duration was unknown^{18,19}. The same recommendation was given to sexual partners. The SLH outpatient unit conducted the first puerperal follow-up review, and after that they were sent for follow-up reviews at the basic health units. All gestational and CS cases at SLH are reported following Health Ministry rules issued respectively in 1986 and 2005. Besides this compulsory report, the Obstetrics Service routine includes telephone contacts between the hospital team and the basic health unit to which the patient is referred. These calls remind women of the need to make appointments and alert health workers to the need of syphilis treatment surveillance for the woman, her child and her partner. All cases are followed by the Congenital Syphilis Committee of Porto Alegre’s Health Secretary.

Data were compiled and analyzed with Epi Info 3.4 software. Chi-square or Fisher’s exact tests were used to indicate association and to compare proportions, and the Mann-Whitney-Wilcoxon test was used to compare medians. In some cases the odds ratio was used to measure the strength of association. A 5% level was accepted in the analysis as indicating significant association.

This study fulfilled all ethical principles contained in the Declaration of Helsinki (1964, re-

newed in 1975, 1983, 1989, 1996, 2000 and 2008) of the World Medical Association, as well as those in Resolution 466, dated December 2012²¹, of Brazil’s Health National Council. The study was approved by the PUC/RS Committee on Research Ethics; no consent forms were required, given the research’s retrospective nature.

Results

Between May 1997 and December 2004, 450 women were identified with a positive syphilis test as well as at least one obstetric outcome attended in the SLH public sector. Of these, 166 had one or more subsequent outcomes in this hospital, between October 1998 and December 2011, and were included in the study. In total, 438 obstetric outcomes were included: 166 initial ones and 272 subsequent ones. Of the subsequent cases, six (five miscarriages and one live newborn) were excluded because the mother did not have syphilis tests. This left 266 subsequent outcomes in the study (Figure 1).

On the occasion of the first included outcome, 41 (24.7%) of these 166 patients were primiparas, while 70 (42.1%) had one or two previous pregnancies, 32 (19.3%) had three or four previous pregnancies and 17 (10.3%) had five or more previous pregnancies (six patients did not inform obstetric history).

Considering the 166 initial outcomes, 30 (18.1%) corresponded to women “without CS”, and 136 (81.9%) corresponded to CS cases, including 15 (11%) stillbirths and 10 (7.4%) miscarriages (Figure 1 and Table 1).

Within 111 neonates with CS among the initial deliveries, 80 (72.0%) had conclusive laboratorial/ X ray results. Of these, 25 (31.2%) had an abnormal physical examination and/or altered laboratorial/X ray results, and 55 (68.8%) were asymptomatic (Table 1). For 31 neonates, physical examination was normal, but investigation was inconclusive.

In 266 subsequent pregnancies, 58 women had negative syphilis serology (hence without maternal syphilis) and 26 had positive serology, but with syphilis treatment considered adequate. So 84 (31.6%) of the subsequent pregnancies were classified as without CS. They included two miscarriages. Mothers with positive serology and absent or inadequate treatment represented 182 (68.4%) outcomes with CS; of these, 163 (89.6%) were live births, seven (3.8%) were stillbirths and 12 (6.6%) were miscarriages. (Figure 1 and Table 1).

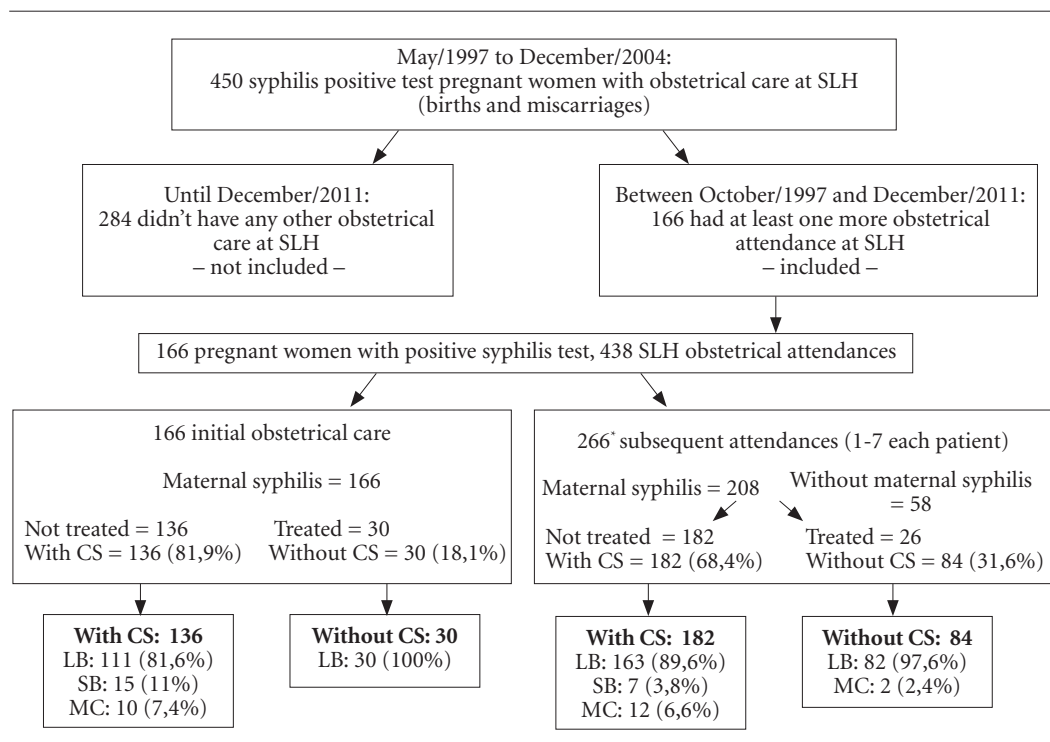


Figure 1. Structure of the study groups according to outcomes and pregnancy order.

* It was not possible to define or exclude congenital syphilis in six cases (1 live birth and 5 miscarriages).
SLH: São Lucas Hospital; CS: congenital syphilis; LB: live births; SB: stillbirths; MC: miscarriages

Table 1. Comparison between adverse outcomes frequency in initial and subsequent pregnancies, only among 318 pregnancies with congenital syphilis. São Lucas Hospital, Porto Alegre, RS, Brazil, 1997-2011.

Adverse outcomes	Initial pregnancy with congenital syphilis N = 136		Subsequent pregnancies with congenital syphilis N = 182		p**
	N	(%)	N	(%)	
Symptomatic newborns*	25/80 [†]	(31.2)	26/108 [†]	(24.1)	0.27
Gestational age < 37 weeks	34/130 [‡]	(26.2)	36/179 [‡]	(20.1)	0.19
Gestational age < 34 weeks	25/130 [‡]	(19.2)	19/179 [‡]	(10.6)	0.04
Miscarriages	10/136 [§]	(7.4)	12/182 [§]	(6.6)	0.74
Stillbirths	15/136 [§]	(11)	7/182 [§]	(3.8)	0.01
Perinatal mortality rate	119/1000	-	41/1000	-	0.01

* Abnormalities at physical examination and/or laboratory/radiological investigation. [†] Denominator related only to cases with conclusive investigation. [‡] Denominator related to live births and stillbirths, excluding cases with unknown gestational age.

[§] Denominator related to all pregnancies with congenital syphilis (miscarriages included). ^{||} (stillbirths with CS / live births with CS + stillbirths with CS) x 1000. ** Pearson's chi-square test.

Among 163 newborn infants with CS in the subsequent vaginal births/cesarean sections, in 108 cases (66.2%) the investigation was conclu-

sive, with 26 (24.1%) having abnormal physical examination and/or clinical, laboratorial or radiological alterations indicative of CS; and 82

(75.9%) were asymptomatic. In 55 cases, the physical examination was normal, but the investigation was inconclusive.

As shown in Figure 1, of the initial 166 cases included in the study, 155 (92.2%) fulfilled the CS case definition criteria. Considering all 438 pregnancies studied, there were 318 outcomes with CS, with significantly fewer cases in the 266 subsequent pregnancies ($n = 182/68.4\%$) than in the 166 initial ones ($n = 136/81.9\%$) ($p = 0.002$). Counting the number of patients ($n = 166$) and not the number of outcomes, the proportion of patients with CS in the subsequent pregnancies ($n = 119/71.6\%$) was also significantly smaller than that found for the initial pregnancies ($p = 0.02$).

The frequency of newborn infants with clinical abnormalities, as well as the frequency of miscarriages, did not differ significantly between initial and subsequent pregnancies with CS. The prevalence of premature deliveries (gestational age below 37 weeks) also did not differ between the groups with CS and without CS, and there was no difference in the frequency of premature deliveries between initial and subsequent pregnancies. However, gestational age below 34 weeks was more frequent in CS cases than in those without CS, and considering only CS cases, this condition was more frequent in the initial pregnancies (Table 1).

The perinatal mortality rate was 53/1000 considering all deliveries with CS, excluding miscarriages. Twenty patients had twenty stillbirths and one patient had three stillbirths, within these a twin pregnancy. According to methodology, twins counted as just one outcome, so 22 stillbirths were considered. The perinatal mortality rate was greater in the initial pregnancies than in the subsequent ones (Table 1).

Miscarriages excluded, the median birth weight of neonates with CS was 3.025g. This was significantly lower ($p < 0.01$) than the median birth weight of neonates without CS (3.220g). Considering only the cases with CS, the birth weights of neonates in the initial pregnancies (median 2.942g) were also significantly lower ($p < 0.01$) in comparison to the birth weights among subsequent pregnancies (median 3.110g).

In terms of prenatal care, we consider that it was absent when the mother had less than two visits prior to delivery. In the initial pregnancies, prenatal care was much more frequently absent in the cases with CS (30.5%) than in those without CS, which all had prenatal care. For subsequent pregnancies, prenatal care was absent in 30% of

those with CS and in 19% of those without CS. When we compare initial and subsequent pregnancies but consider only CS cases, the absence of prenatal care was similar (Table 2).

Analyzing the reasons for absent or inadequate treatment in 318 pregnancies classified as with CS, subsequent pregnancies had less occurrence of treatment prescribed with inadequate penicillin doses or with other antibiotics. The subsequent cases also had a lower proportion of mothers who did not make the required tests. However, the proportion of cases with a VDRL that was negative during pregnancy but positive at delivery was higher in subsequent pregnancies (Table 3).

In 136 initial pregnancies with CS, only 24 (17.7%) patients had some previous treatment. In 182 subsequent pregnancies with CS, one had no information and 178/181 (98.9%) had a history of previous treatment. For 141 of these cases (77.9%), previous treatment was undocumented, but eventually coexisted with other causes for CS case definition. In this same group, 28 pregnant women despite adequate and documented treatment had concepts classified as CS cases (Table 4).

For 313 out of 318 cases with CS, the VDRL record was known at the time of delivery or miscarriage. Considering all pregnancies with CS, including initial and subsequent ones, there was a higher frequency of maternal VDRL titers equal to or above 1:8 in those with adverse outcomes. Here an adverse outcome includes symptomatic newborn infants, preterm babies with 34 or fewer weeks of gestation, stillbirths and miscarriages. Our databank included 100 obstetric events with at least one of these adverse outcomes; of these, 43 (43.0%) had VDRL titers equal to or greater than 1:8. In contrast, only 48/213 (22.5%) obstetric events that did not have any adverse outcomes had titers $\geq 1:8$ (OR 2.5; 95% CI 1.5-4.3). Excluding miscarriages and including live births and stillbirths, VDRL titers $\geq 1:8$ were more frequent in the stillbirth mothers: 15/20 (75%). In comparison, such high levels occurred in only 71/273 (26%) mothers without adverse outcomes (OR 8.4; 95% CI 2.9-24.2).

Considering the group with CS, there was less mothers with high VDRL titers in the subsequent than in the initial pregnancies. In 133 initial pregnancies 67 (50.4%) had VDRL titers between 1:8 and 1:128, while 66 (49.6%) had titers up to 1:4. Among 180 subsequent ones, there were 24 (13.3%) mothers with titers between 1:8 and 1:128, while 156 (86.7%) had titers up to 1:4 ($p < 0.001$).

Table 2. Prenatal care in initial and subsequent pregnancies. São Lucas Hospital, Porto Alegre, RS, Brazil, 1997-2011.

Prenatal care (cases with information)	Initial pregnancy N = 166		Subsequent pregnancies N = 266*	
	With CS N = 128	Without CS N = 30	With CS N = 180	Without CS N = 84
	Absent†	39 (30.5%)	0 (0%)	54 (30%)
Present	89 (69.5%)	30 (100%)	126 (70%)	68 (81%)
	OR 26.92 (95% CI 1.66-435.89)		OR 1.82 (95% CI 0.97-3.42)	

* Six cases with undetermined diagnosis were excluded. † Prenatal care is considered absent when less than 2 visits. OR: odds ratio; CI: confidence interval.

Table 3. Comparison of causes that determined no or inadequate syphilis treatment, between initial and subsequent pregnancies with congenital syphilis. The sample includes 155 women who had 318 obstetrical outcomes with congenital syphilis case definition, of which 274 were live newborns, 22 were stillbirths and 22 were miscarriages. Porto Alegre, RS, Brazil, 1997-2011.

Main cause of absent or inadequate treatment of the pregnant woman	Initial pregnancy		Subsequent pregnancies		p*
	N	(%)	N	(%)	
	Adequate treatment, but without expected VDRL titer decrease or with VDRL titer increase	4	(2.9%)	11	
Penicillin dose improperly prescribed	7	(5.1%)	2	(1.1)	0.04
Pregnant woman has not done the requested exam	11	(8.1%)	5	(2.7)	0.03
Pregnant woman did not take the prescribed treatment	3	(2.2%)	5	(2.7)	1.00
Misinterpretation of serological tests resulting in absence of treatment	8	(5.9%)	9	(4.9)	0.71
No documented treatment	10	(7.4%)	24	(13.2)	0.09
Treatment with a nonpenicillin G regimen	5	(3.7%)	-	-	-
Sexual partner was not treated †	-	-	3	(1.6)	-
Absent prenatal care	43	(31.6%)	55	(30.2)	0.78
Penicillin treatment less than 4 weeks before delivery	6	(4.4%)	4	(2.2)	0.33
Pregnant woman did not complete the prescribed penicillin treatment	13	(9.6)	15	(8.2)	0.62
Negative VDRL during pregnancy, but positive at delivery	21	(15.4)	47	(25.8)	0.02
Unknown or other causes	5	(3.6)	2	(1)	0.14
Total	136	(100.0)	182	(100.0)	

* Pearson's chi-square test or Fisher's exact test. † The absence of sexual partner's treatment was included as a criteria for congenital syphilis case definition only in 2004.

VDRL: Venereal Disease Research Laboratory

Considering only the 68 cases with a VDRL that was negative during pregnancy and positive at delivery, this group's titers were lower in general, and VDRL titers were lower in the subsequent pregnancies when compared to the initial ones. In 21 initial pregnancies where the VDRL turned positive between pregnancy and labor, there were eight (38.1%) patients with titers between 1:8 and 1:32, and 13 (61.9%) with titers up to 1:4. In 47 subsequent pregnancies with the same situa-

tion, there were two (4.3%) patients with titers of 1:8 and 45 (95.7%) with titers up to 1:4 ($p < 0.001$).

Discussion

This study shows two faces of the problem that have been the maintenance of high prevalence of CS in practically all over the world. It reveals nu-

Table 4. Treatment before pregnancy in congenital syphilis cases, comparing initial and subsequent pregnancies, and congenital syphilis definition criteria in cases with previous adequate and documented treatment. Porto Alegre, RS, Brazil, 1997-2011.

Treatment before pregnancy	Initial pregnancy	Subsequent pregnancies
	N (%)	N (%)
Absent	112 (82.3)	3 (1.7)
Not documented	17 (12.5)	141 (77.9)
Incomplete or inadequate	5 (3.7)	9 (5.0)
Documented and adequate	2 (1.5%)	28 (15.5)
VDRL was negative during pregnancy and positive at birth	-	11
VDRL titer did not decrease or increased after treatment	-	7
Absent prenatal care	2	6
No VDRL information after treatment	-	4
	136 (100%)	181* (100%)

* 1 case without information on previous treatment.

merous cases of syphilis persistence or recurrence in succeeding pregnancies of a same woman, with high risk of *T. pallidum* transmission, and shows its adverse outcomes, like fetal death, prematurity and newborn disease. On the other hand, some of the results presented here indicate an increase, in subsequent pregnancies, of difficulty in identifying a maternal active infection and in distinguish infected from non-infected neonates. In posterior pregnancies, the residual positivity of serum tests increases diagnostic challenges, a fact that is aggravated by the lack of reliable previous medical records and deficiencies in the follow-up of women that had previously treated syphilis. Additional, failure in prenatal care appears as the greatest risk factor for CS, aggravated in subsequent pregnancies.

Although there was less occurrence of CS in subsequent pregnancies, almost 70% of them resulted in concepts defined as CS cases. It would be expected a much lower frequency, once after having an obstetric outcome with CS, the pregnant woman should have received a complete treatment and guidance about how to avoid reinfection. Besides that, it is thought that the occurrence of CS in a concept stimulates the woman to take a better care in the next pregnancy, looking for and realizing a complete prenatal care, because she is better informed and/or more worried about her pregnancy outcome. Although this situation could have happened with some women, the high number of CS in succeeding pregnancies, including those initially appropriately treated, indicates the opposite: more than half of patients that in initial pregnancy had prenatal care and an adequate treatment had at

least one more outcome with CS in subsequent pregnancies.

Syphilis recurrence in succeeding pregnancies had already got attention from other researchers: a study conducted in New York, United States, reviewed medical charts of 46 women with treponemal and non-treponemal positive tests and that had at least two consecutive births in same institution within five years. Forty percent of patients that had a CS associated outcome had another concept with CS in a subsequent pregnancy. The great risk factor was the use of cocaine²². In another survey, realized in Pará state, Brazil, the researchers studied serological and epidemiological aspects of women already submitted to syphilis treatment in a previous puerperium, and found evidence of reinfection in 66.7% of patients²³.

In the present study, the high frequency of syphilis recurrence, highlighted by raising VDRL titers, and the occurrence of fetal loss and newborn infants with clinical/laboratorial abnormalities due to CS, made it clear that reinfection or persistence of maternal syphilis happened in many cases, with consequent mother-to-child transmission of *T. pallidum*. However, some results suggest that, in comparison to initial pregnancies, in subsequent ones there was a higher proportion of not infected concepts, among those defined as CS cases. Features that were more frequent in outcomes related to CS than in those without CS, like gestational age under 34 weeks, perinatal mortality, lower birth weight and higher maternal VDRL titers, were also more frequent in the initial than in the subsequent pregnancies, when we analyzed only the group of

patients whose concepts met the criteria for CS case definition.

The high perinatal mortality rate found among CS cases confirm data already existent about syphilis in pregnancy²⁴⁻²⁷. In comparison to the perinatal mortality rate of Brazil's South Region, which was 9.2/1.000 in 2006, the perinatal mortality in this sample was six times higher and, among the initial pregnancies, it was 13 times higher. It is worth noting that this perinatal mortality rate refers to the 155 neonates whose mothers had repeated obstetric care in SLH, not included all CS cases occurred in SLH during the study period.

The frequency of clinical abnormalities was 31.2% in newborn infants with CS from initial pregnancies and 24.1% in newborn infants with CS from the subsequent ones, and that was not statistically different between the two groups. Given the other results of this study, we would expect that the proportion of symptomatic neonates would be lower in the subsequent pregnancies. The great proportion of cases with inconclusive investigation, in both groups, might have contributed to a non-statistical significance in this aspect. On the other hand, the presence of a relevant number of cases with clinical abnormalities shows unequivocally that, although not in majority, syphilis severely affected the concepts in subsequent pregnancies.

When analyzing the reasons for absence or inadequacy of maternal treatment in CS cases, we verified that in the subsequent pregnancies there were less cases of treatment prescribed with inadequate penicillin doses or with a nonpenicillin G regimen, which could mean better public policies targeted to qualification of pre-natal assistance through diagnostic routines and more standardized treatment. In Rio de Janeiro, a research that analyzed prenatal care professionals knowledge, practices and attitude towards syphilis, noticed a discrete positive effect of the greater access to technical protocols and training in the improving of gestational syphilis management²⁸. However, unfortunately there is still a relevant lack of knowledge by the professionals about mother-to-child transmission of syphilis^{4,29-32}. On the other hand, there was a lower proportion of pregnant women that did not made the requested tests in the subsequent pregnancies, which probably reflects the fact that some of the studied patients had been more concerned after a CS outcome.

Among the CS case definition causes, one of the most frequent was the positive VDRL titer at delivery that was negative during pregnancy.

This reason was much more frequent in subsequent pregnancies than in initial ones. The majority of these tests had low titers ($VDRL \leq 1:2$), which can be a result of three situations: a) a very recent infection, acquired during pregnancy; b) serofast patients with low VDRL titers, which can be negative in one laboratory and positive in another one; c) biologic false-positive VDRL, which is impossible to determine, once the treponemal test tends to be positive because of the previous syphilis³³.

It is known that the non-treponemal tests have the advantage to be low cost and high sensitivity (especially in the initial stages); however, a misinterpretation by inexperienced laboratory technicians is possible, since the result interpretation is subjective¹⁵. Therefore, it can happen that very low residual titers are interpreted as negative during pregnancy and, when tested at the hospital laboratory, presents as positive. Another difficulty happens in the case of positive serology during pregnancy in women that were previously treated. While in the evolution of the treated syphilis the non-treponemal test evolves to negatization, some patients remain with low titers for all life (in VDRL, up to 1:2); they are called serofasts, or patients with residual immune memory.

Patients with recurrent infections have a trend to show basal serum titers that increase with each subsequent infection²². Yet the treponemal tests remains positive in most treated patients, they can become negative in about 25%, especially among those treated in the initial stages³³. In the pregnant woman assessment, frequently it is difficult to state if a low non-treponemal test corresponds to a serofast or if this patient was infected again. The way to distinguish these two possibilities is a rigorous follow-up of the pregnant woman, with a monthly non-treponemal test during prenatal care. Thus, if the titer remains low, the woman can be considered as not having active syphilis, and her concept without CS^{18,19}. The frequencies of high or low maternal VDRL titers were assessed in this study with the aim of having one more instrument to investigate if there were more non-infected newborn infants among those who met the CS case definition in the subsequent pregnancies when compared with the initial ones. The remarkable preponderance of low VDRL titers in the subsequent pregnancies that resulted in cases defined as CS suggests that a great proportion of these may be due not to recontamination, but to residual titers.

On the other hand, although high VDRL titers were more frequent among pregnancies

with CS, and even more in those with adverse effects, it is important to note that a low titer does preclude active syphilis in the pregnant woman and, therefore, of CS in the concept. An expressive proportion of pregnant women with low VDRL titers had concepts with adverse effects: 57% considering all adverse outcomes and 25% considering only stillbirths. In a study conducted in this same population, some neonates from mothers with low non-treponemal titers had a negative VDRL at birth that turned positive in a few days, indicating a recent maternal infection, with placental transmission in the last weeks of pregnancy³.

The presence of CS is a marker of public health system failure and, especially, of prenatal care. It is known that the possibility of a newborn to be considered as a CS case is directly related to prenatal care availability, utilization and quality^{5,7,9,13-15,30,34-36}, and this fact is confirmed in this study. Unfortunately we did not have complete records about the time of prenatal care beginning, so we could not analyze this data. Many pregnant women start prenatal care too late, when there is no time to diagnose and treat syphilis in order to prevent CS. A systematic review demonstrated that pregnant women that start prenatal care within the first two trimesters have a much higher chance of receiving an effective intervention to avoid CS³⁶. A good prenatal care is important not only because it is the best opportunity to treat syphilis during pregnancy, but also because it allows to follow a woman who had an adequate treatment for syphilis before pregnancy and has a persistent low titer non-treponemal test, as noted above.

This study identified that lack of a previous treatment documentation was one of the main causes of CS case definition. This cause was very frequent in the initial pregnancies as well as in the subsequent ones, with a trend to increase in the last ones. Some case definition criteria, as undocumented treatment, or lack of information on partner's treatment, could be much less frequent in the presence of an effective system of documentation available to the obstetric center/maternity team. In Detroit, United States, where notified CS rate is very high, a study identified that this rate may have been overestimated because of deficiencies in the maternal background information system³⁷.

This study shows the importance of the "Prenatal Care Card", a national document, which should be prized and must follow the woman along life. All treatments received during and

between pregnancies should be recorded in this document, which contain an area, as in the child's vaccination card, in which the penicillin doses are specified. Every applied injection must be stamped, in order to really document the treatment accomplishment. The partner's treatment also should be registered in the same place. It is important that the health professional fills carefully all the card areas and encourages patients to keep the document, that should be used in all pregnancies.

It is known that partner's treatment implies in great difficulties to be accomplished, even with all the care, as that taken by the hospital where this study was conducted. Partners often do not come to appointments and refuse to do tests and treatment. One of the few studies that approached specifically this subject showed that among women who had syphilis before or during pregnancy, 86.2% reported the diagnosis to the partner and, within these, only 56% partners received at least one penicillin dose³⁸. This factor can contribute in a relevant way for the recurrence of CS.

The main limitation of this study consists in not include the obstetric events occurred outside of SLH. One fact that mitigates this bias is the regionalization system of health assistance in Porto Alegre, in which there is a great chance of a person that lives in the same region will look for the same hospital for assistance. We did not evaluate patients who have moved or who have searched for other hospitals for different reasons, but this bias does not compromise the importance in showing what happened with the subsequent pregnancies of the patients studied. Additionally, we believe in the external validity of this study because the follow-up of those pregnant women reflects what can happen with the majority of women in similar populations, even in different regions.

Another limitation was the retrospective nature of the second part of the study. Although data of patients included in the recruitment period (1997-2004) have been collected prospectively, data up to the end of 2011 were retrospectively obtained from medical records, therefore some data were not found, like illicit drugs use, alcohol abuse and income.

Notwithstanding its limitations, the study demonstrated that CS recurrence was frequent in successive pregnancies of a same patient. Adverse outcomes like fetal deaths, prematurity and disease in the newborn infants from subsequent pregnancies were common, although to a lesser

frequency and severity than in initial pregnancies. Absent or inadequate prenatal care was the main risk factor for CS, both in initial and subsequent pregnancies.

The data suggest that in subsequent pregnancies more neonates could have been defined as CS cases because of lack of information on the mother's previous history and prenatal care inadequacy. It is essential that CS guidelines be strictly observed, to prevent an infected neonate to be discharged from hospital without treatment. However, efforts should be done to spare a non-infected neonate from a complete investigation and unnecessary treatment, as long as the procedure is safe. This condition requires

a strictly follow-up of women that already had syphilis. Many pregnant women in this study did not look for prenatal care or did not make it properly. Pregnant and puerperal women in this situation should be actively searched and followed by the health system, to verify the evolution of their serum tests and to provide guidance about prevention. These patients must be submitted to monthly syphilis tests to document the maintenance of non-treponemal low titers or to disclose recontamination. It is important that information about test results and treatment be registered in a very explicit way so it can be used in diagnosis and management of CS in subsequent pregnancies.

Collaborations

MG Hebmuller and EG Lago participated on the project design, data acquisition and analysis, article editing, critical review and final version approval. HH Fiori participated on the project design, critical review and final version approval.

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