

## Syphilis and Miscarriage: A Study of 879,831 Pregnant Women in Brazil

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Received date: September 26, 2016; Accepted date: October 12, 2016; Published date: October 18, 2016

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### Abstract

**Objective:** Syphilis is a predominantly sexually transmitted infectious disease caused by the bacterium *Treponema pallidum*. It may seriously complicate pregnancy and result in miscarriage.

**Materials and Methods:** A retrospective, ecological study including 879,831 pregnant women who underwent prenatal screening from 2003 to 2016 was performed in the state of Goiás, located in the Central-West region of Brazil, with a population estimated at 6.7 million.

**Results:** The main finding was a much higher prevalence of syphilis among those who reported miscarriage (1.28%) compared to those who did not report miscarriage (0.71%) ( $p < 0.001$ ).

**Conclusion:** Participation in the study by pregnant women was very good. Of 1,308,411 pregnant women who were expected to participate, 879,831 were screened during this period, for a prevalence of 67.17%. Of 821,735 women selected for this study, 112,260 (13.66%) reported a miscarriage.

**Keywords:** Pregnant women; Prenatal screening test; Miscarriage; Disease surveillance; Dried blood spot on filter paper; Syphilis; Morbidity and mortality; Brazil

### Introduction

Syphilis is a predominantly sexually transmitted infectious disease caused by the bacterium *Treponema pallidum*. If untreated, the disease may progress to stages that compromise the skin and internal organs, such as the heart, liver, and central nervous system [1].

Congenital syphilis is due to hematogenous dissemination of *Treponema pallidum* from untreated or inadequately treated pregnant women to their fetus, via the placenta. Transmission may occur at any stage of pregnancy and at any stage of the disease; the probability of transmission is 50% to 100% in primary and secondary syphilis, 40% in early latent syphilis, and 10% in late latent syphilis. Direct transmission may occur in the birth canal. In cases of transmission of congenital syphilis, about 40% may end in miscarriage, stillbirth, and perinatal death [2].

The elimination of congenital syphilis is a priority for Latin America and the Caribbean. The document "Strategy and Action Plan for the Elimination of Mother-to-Child Transmission of HIV and Congenital Syphilis, 2010," reaffirms the commitment of countries in the Americas to eliminate vertical transmission of both diseases by 2015. This commitment is in line with the "Initiative for Elimination" goals set by the Pan American Health Organization (PAHO) and the United Nations Children's Fund (UNICEF), which are the reduction of vertical

HIV transmission rate to less than 2% and the incidence of congenital syphilis to less than 0.5 cases per 1,000 live births by 2015 [1].

The prevalence of syphilis in pregnant women is monitored by cross-sectional studies carried out both nationally and locally. The latest study was carried out in 2010-2011 with a sample of approximately 36,000 pregnant women distributed in the five Brazilian regions; the prevalence of syphilis in pregnant women was estimated at 0.85%. Women were screened with the venereal disease research laboratory (VDRL) test, and any positive titer was confirmed with the fluorescent treponemal antibody absorption (FTA-ABS) test. The regional prevalence found in this study was as follows: 1.05% (North), 1.14% (Northeast), 0.73% (Southeast), 0.48% (South), and 1.20% (Central-West) [3].

From 1998 to June 2014, 104,853 cases of congenital syphilis in children under one year of age were reported to the Notifiable Diseases Information System (SINAN), with 48,015 (45.8%) in the Southeast, 32,884 (31.4%) in the Northeast, 8,959 (8.5%) in the South, 8,856 (8.4%) in the North, and 6,139 (5.9%) in the Central-West region. In 2013, 13,705 cases of congenital syphilis in children under one year of age were reported, most of which (43.1%) were in the Southeast, followed by the Northeast (32.2%), South (11.4%), North (7.8%), and Central-West (5.5%) regions [2].

In 2013, 74.8% of mothers of children with congenital syphilis underwent at least one prenatal screening test, 18.5% did not undergo any prenatal screening test, and 6.7% had missing/no information. In the same year, among those who underwent prenatal screening, 58.7% were diagnosed with syphilis during prenatal care, 27.8% at delivery/

curettage, 9.4% after delivery, 0.5% were not diagnosed, and 3.6% had no information. Moreover, in the group of pregnant women diagnosed with syphilis during pregnancy, 12.5% were not treated, 5.3% were treated adequately, and 71.5% were treated inadequately. Among the partners of women who underwent prenatal care, 18.2% were treated, 60.4% were not treated, and 21.4% had missing/no information (Table ). From 2000 to 2013, the infant mortality rate (children under one year old) due to congenital syphilis was 1,241, with 536 (43.2%) in the Southeast (378 in the state of Rio de Janeiro, which represents 30.5% of Brazil), 422 (34.0%) in the Northeast, 126 (10.2%) in the North, 118 (9.5%) in the South, and 39 (3.1%) in the Central-West region [4,5].

Notification of syphilis in pregnancy as a sexually transmitted infection is compulsory due to its high prevalence rate and high rate of vertical transmission, ranging from 30 to 100% with inadequate or no treatment. All pregnant women clinically diagnosed with syphilis and/or non-treponemal serology reactive at any titer, whether performed prenatally or at birth or curettage, even in the absence of a positive treponemal test, are considered syphilis cases in pregnancy [6].

In the general population, about 12 million new cases of syphilis are diagnosed yearly in the world and at least half a million children are born with the congenital form of the disease. Moreover, mother-to-child syphilis causes another half a million stillbirths and miscarriages, and is a serious global public health problem, especially in developing countries [6].

Syphilis may seriously complicate pregnancy and result in miscarriage, stillbirth, nonimmune hydrops, intrauterine growth restriction and perinatal death, and serious sequelae in surviving infected children. Although the appropriate treatment of pregnant women often prevents such complications, the major obstacle has been the inability to identify infected women and get them to undergo treatment. Screening in the first quarter with nontreponemal tests such as rapid plasma reagin (RPR) or the VDRL test, together with confirmation of reactive individuals with treponemal tests, such as the FTA-ABS, is a cost-effective strategy. Those at risk should be tested again in the third quarter [7].

This study aimed to compare the prevalence of syphilis in pregnant women who reported miscarriages and to identify possible factors involved in the dynamics of disease progression.

## Materials and Methods

This is an ecological, retrospective study including 879,831 participants, a historical series of pregnant women screened by the Protection Program for Pregnant Women (PEPG) in the state of Goiás, from 2003 to 2016.

The PEPG was created by the Brazilian Institute for Research, Education, and Diagnostics (IPED), Medical Office of Health, after the Ministry of Health implemented the Program for Humanization of Prenatal Care and Birth (PHPN) in the state of Mato Grosso do Sul in 2002 and in Goiás in 2003, together with the Association of Parents and Friends of Exceptional Children (APAE) of those two states.

The PEPG performs 13 basic prenatal tests that aim to diagnose Chagas disease, hepatitis B, hepatitis C, HTLV infection, rubella, HIV infection, syphilis, and toxoplasmosis, among others. A dried blood spots on filter paper is used as a biologic material in screening tests, and is a logistically useful tool.

Blood samples from pregnant women were obtained by finger-stick with disposable lancets and collected on filter paper (S&S 903), and held at room temperature until dried. In the laboratory, the dried blood samples were eluted from the filter paper, and specific antibodies (IgG and IgM) were qualitatively tested with anti-*Treponema pallidum* by enzyme-linked immunosorbent assay (ELISA), according to the manufacturer's instructions (Mbiolog<sup>o</sup>, Brazil). The concentration of anti-*T. pallidum* is directly proportional to the intensity of color in the reaction [8].

Samples reactive in the ELISA test were confirmed by VDRL and FTA-ABS tests. The tests were carried out according to the manufacturer's instructions.

As the VDRL test may yield positive results in various diseases other than syphilis, such as lupus, liver disease, mononucleosis, leprosy, varicella, and rheumatoid arthritis, only titers >1:32 were deemed reliable for diagnosis. The test may also show false positive results in elderly people.

The VDRL test is usually positive between four and six weeks after infection. Titers usually begin to rise from one to two weeks after the appearance of a chancre.

## Data analyses

Initial data scrubbing was thoroughly carried out and simple frequencies were calculated to identify duplications and typos. Duplicate data and any inconsistency in completing the collection cards were discarded, accounting for 15.14%.

The variables included age, trimester of pregnancy at sample collection, number of reported miscarriages, and type of delivery. The age variable was organized into five groups: 1 ( $\leq 14$  years), 2 (15 to 19 years), 3 (20 to 29 years), 4 (30 to 39 years), and 5 ( $>40$ ). The distribution of the global prevalence of syphilis by municipality in the state of Goiás, Brazil, was also determined.

The data were organized in Excel<sup>®</sup> spreadsheets and descriptive measures were calculated using the Epi Info software (version 6.4) and Epi Info 2000 (version 3.2.2). A disease prevalence map was designed using Tab Win 32 software, available from the Ministry of Health of Brazil. The odds ratio was also calculated as a measure of association between reported miscarriages and diagnosis of syphilis. A confidence interval of 95% and alpha of 0.05 were determined in all analyses.

## Ethical Considerations

This study is a continuation of other projects carried out by the same author, namely, "Prevalence of screened diseases in the Program to Protect Pregnant Women in the state of Mato Grosso do Sul, Brazil, from 2004 to 2007," and "Syphilis in pregnancy: a study carried out with 879,831 pregnant women in Brazil," protocol No. 1046 "Letter of Approval" issued by the Ethics Committee for Research/CEP/UFMS.

## Location of the Study

The study was carried out using the PEPG data for the state of Goiás, a state government partnership with the Institute for Diagnostics and Research (IDP), maintained by APAE-Goiania, a nonprofit advocacy group, and philanthropic and public service entity.

## Results

The number of pregnant women expected to participate in the study was 1,308,411, calculated using a formula by EPSUS. (Qualification Program of Primary Health Care) From September 2003 to July 2016, 879,831 pregnant women were screened by the PEPG, an average of 67.17% during the period.

The PEPG in the state of Goiás, Brazil, screened 879,829 pregnant women; 821,785 (93.4%) were selected for the study after 58,044 (6.6%) were excluded due to inconsistent form completion. Of those in the study, 112,904 (13.7%) reported miscarriage.

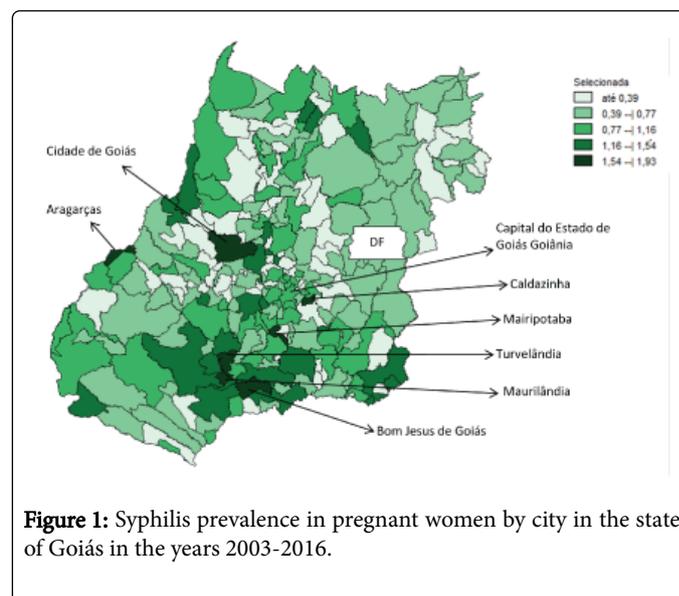
During the study, approximately 67% of pregnant women underwent prenatal screening tests and 6,501 cases were confirmed by serological tests in the state of Goiás. The prevalence rate was about 0.80%; 700,953 reported no miscarriage, 90,617 reported one miscarriage, 16,322 reported two miscarriages, 3,716 reported three miscarriages, and 1,605 reported four or more miscarriages.

Characteristics	Declared abortion				P <sup>4</sup>
	Yes	%	No	%	
Syphilis Age (in years)	1443	1.28	5061	0.71	<0.001
<14	262	0.23	8727	1.23	<0.001
15 a 19	11655	10.32	172373	24.32	<0.001
20 a 29	62975	55.78	393222	55.47	0.051
30 a 39	33738	29.88	122200	17.24	<0.001
≥ 40	3630	3.22	8517	1.20	<0.001
Cesaria					
None	12368	10.95	80684	11.38	<0.001
1	19462	17.24	80171	11.31	<0.001
≥ 2	7507	6.65	23944	3.38	<0.001
Not reported	73567	65.16	524082	73.93	<0.001
Trimester of pregnancy diagnosis of syphilis					
1°	66753	59.12	391567	55.24	<0.001
2°	28457	25.20	174795	24.66	<0.001
3°	4222	3.74	25330	3.57	0.004
Not reported	13472	11.93	117189	16.53	<0.001
Total	112904	100	708881	100	

**Table 1:** Characteristics of pregnant women attended by PPG<sup>1</sup>, referring to abortion statement, in the years from 2003<sup>2</sup> to 2016<sup>3</sup> in the state of Goiás - Brazil. Note: <sup>1</sup>Program to Protect Pregnant Women<sup>2</sup> from September 2003; <sup>3</sup>until July 2016; <sup>4</sup>Person of  $\chi^2$  test.

The overall prevalence of syphilis in pregnant women was 0.80% (95% CI, 0.77–0.81); when calculated for the 246 municipalities in the state of Goiás, Brazil, this indicator in some towns was zero, but was above 1.56% in seven towns: Aragarças, Cidade de Goiás, Caldeazinha,

Mairipotaba, Turvelândia, Maurilândia, and Bom Jesus de Goiás (Figure 1).



**Figure 1:** Syphilis prevalence in pregnant women by city in the state of Goiás in the years 2003-2016.

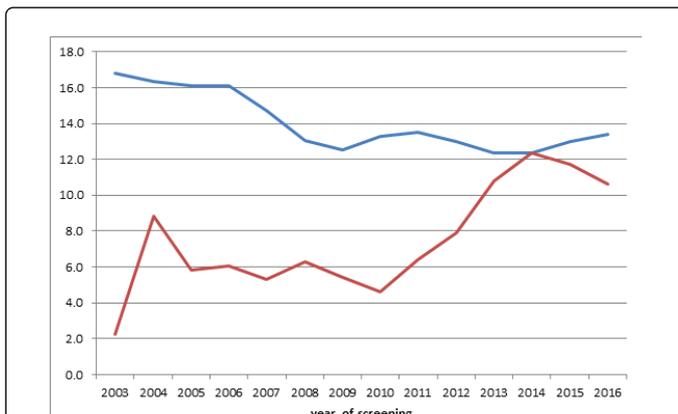
The reporting of miscarriages by pregnant women according to age was most common and statistically significant ( $p < 0.05$ ) in women  $\geq 30$  years of age. With respect to the type of delivery and the trimester of pregnancy, no pattern was found, although all differences were significant. The main finding, however, was a much higher prevalence of syphilis among pregnant women who reported miscarriages (1.28%), compared to those who did not report miscarriages (0.71%) ( $p < 0.001$ ) (Table 1).

Syphilis						
Abortion per year	Yes	%	No	%	OR <sup>2</sup>	IC 95%
2003 <sup>3</sup>	6	33.3	1340	16.7	2.48	0.93-6.63
2004	123	39	5764	16.1	3.33	2.65-4.18
2005	130	36	9922	16	2.96	2.38-3.67
2006	133	32.4	10901	16	2.51	2.03-3.09
2007	105	28.9	10005	14.6	2.32	1.85-2.92
2008	99	22.7	9048	13	1.96	1.56-2.46
2009	64	20.1	7373	12.5	1.76	1.33-2.31
2010	20	15.9	3603	13.2	1.24	0.76-1.99
2011	109	23.2	9836	13.4	1.95	1.57-2.41
2012	128	21.8	9587	12.9	1.88	1.54-2.29
2013	165	20.3	9255	12.3	1.81	1.52-2.16
2014	150	15.8	9428	12.3	1.34	1.12-1.60
2015	146	16	10107	12.9	1.28	1.07-1.53
2016 <sup>4</sup>	65	15.4	5292	13.4	1.18	0.91-1.54

**Table 2:** Association of abortions and diagnosis of syphilis in pregnant women screened by PPG<sup>1</sup> during the years 2003-2016 in the state of

Goiás-Brazil. Note: <sup>1</sup>Program to Protect Pregnant Women; <sup>2</sup>Odds Ratio; <sup>3</sup>From September 2003; <sup>4</sup>Until July 2016.

The prevalence of syphilis was also compared with the report of miscarriages per year, and a significant annual increase was observed, with the rate of women who reported miscarriage showing a downward trend (Figure 2). The odds ratio (OR) was statistically significant ( $p < 0.05$ ) between reported miscarriage and diagnosis of syphilis in almost all years. This association, however, decreased over time (Table 2).



**Figure 2:** The frequency of abortion statement, among pregnant women with confirmed syphilis in%, and the prevalence of syphilis in pregnant women screened by PPG<sup>1</sup> over the years 2003<sup>2</sup>-2016<sup>3</sup>, state of Goiás - Brazil. Note: <sup>1</sup>Program to Protect Pregnant <sup>2</sup>from September 2003; <sup>3</sup>until July 2016.

## Discussion

In Brazil, the Ministry of Health recommends that prenatal care be started immediately after the diagnosis of pregnancy. Pregnant women are instructed to have at least six appointments with a health service: one in the first trimester of pregnancy, two in the second trimester, and three in the third trimester. The screening tests for several diseases, including syphilis [9,10], are carried out at the first appointment, consequently leading to more diagnoses in the first trimester. According to Saab et al., syphilis is a major challenge to public health and is responsible for a large number of miscarriages [10,11].

The number of pregnant women who participated in this study was calculated according to the formula used by the EPSUS (Qualification Program of Primary Health Care), and slightly differs from the number of live births.

The goal of eliminating and controlling congenital syphilis by 2015, proposed both by the World Health Organization and the Ministry of Health of Brazil, is far from being achieved, and underreporting is a major obstacle [1,12].

According to the Epidemiological Bulletin published by the Ministry of Health, the prevalence of syphilis in pregnant women was estimated at 0.85% (positive reaction at any VDRL titer, confirmed by FTA-ABS). The regional prevalence found in this study was 1.05% (North), 1.14% (Northeast), 0.73% (Southeast), 0.48% (South), and 1.20% (Central-West) [3].

This study showed that the municipalities of Aragarças, Cidade de Goiás, Caldazinha, Mairipotaba, Turvelândia, Maurilândia, and Bom Jesus de Goiás, had the highest prevalence, above 1.56%.

Based on other studies, the chance of miscarriage increases with age; natural fertility and pregnancy rates decline, and the rate of intrauterine insemination also declines [13,14].

In women aged over 40 years, aneuploidy is common, miscarriage rates increase from two to three times, and implantation rates after in vitro fertilization decrease significantly [15-17].

The association between congenital syphilis and miscarriage was found in a study carried out by Carvalho, Isaiane da Silva e Brito, and Rosineide Santana [18].

This study showed that the prevalence of syphilis in pregnant women increased in the state of Goiás, although the association with miscarriage has decreased since the PEPG was implemented in this state. The data found in this study confirmed that syphilis does not only affect specific groups at risk, and that prevention should be of paramount importance for the general population [13].

The prevalence rates and incidence of congenital syphilis were higher than those reported by the World Health Organization, at one case per 1,000 live births [18].

## Conclusion

The PEPG is a program of utmost importance to the populations of large cities, small towns, indigenous people, and *quilombolas* in Brazil, since ethnic, epidemiologic, and individual differences are present not only between regions but also from state to state. The program investigates the prevalence of epidemiologic, clinical and laboratory aspects when infection is observed in the region, and directs public health services according to the percentage requiring coverage. This standardization aims to systematize data and information that can be used to help control and prevent new infections. In practice, the ongoing work developed by the PEPG has been extremely important.

## References

1. Arnaldo (2008) congenital syphilis and syphilis in pregnancy. *Rev Public Health* 42: 768-72.
2. Pereira GFM (2015) Epidemiological Bulletin of Syphilis – 2015, Brazil.
3. Pereira GFM (2012) Epidemiological Bulletin Syphilis-2012, Brazil.
4. Filho AMS (2012) Attention to low risk prenatal.
5. Magalhaes DMS, Kawaguchi IAL, Adriano DIAS, Calderon IMP (2013) Maternal and congenital syphilis: still a challenge. *Cad Saúde Pública* 29: 1109-1120.
6. Lima LHM, Gurgel MFC, Moreira-Silva SF (2006) Evaluation of congenital syphilis in the state of Espírito Santo. *DST j. bras. fri diseases. transm* 18: 113-116.
7. Genç M, Ledger WJ (2000) Syphilis in pregnancy. *Sex Transm Inf* 76: 73-79.
8. Mbiolog (2016) Principle Method Belo Horizonte.
9. Ministry of Health (2016) Prenatal - Women's Health Subcoordenação.
10. Saab F (2016) Syphilis prevalence in pregnant women who miscarried served by the maternity protection program - PPG Sergipe State, 2005 to 2007.
11. World Health Organization (2014) Global guidance on criteria and processes for validation: elimination of mother-to-child transmission (EMTCT) of HIV and syphilis, Geneva.

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12. Campos AL, Araújo MA, Melo SP, Gonçalves MLC (2010) Epidemiology of gestational syphilis in Fortaleza. *Cad Saude Publica* 26: 1747-1755.
  13. Magalhães DMS, Kawaguchi IAL, Dias A, Calderon IMP (2013) Maternal and congenital syphilis: still a challenge. *Cad Public Health* 29: 1109-1120.
  14. Abreu LG, Santana LF, Navarro PAAS, Reis RM, Ferriani RA, et al (2006) The pregnancy rate in women undergoing assisted reproductive techniques is less from 30 years. *Rev Bras Gynecol Obstet* 28: 32-37.
  15. van Rooij IA, Bancsi LF, Broekmans FJ, Looman CW, Habbema JD, et al. (2003) Women older than 40 years of age and those with elevated follicle-stimulating hormone levels differ in poor response rate and embryo quality in in vitro fertilization. *Fertil Steril* 79: 482-488.
  16. Toner JP, Flood JT (1993) Fertility after the age of 40. *Obstet Gynecol Clin North Am* 20: 261-272.
  17. Baird DT, Collins J, Egozcue J, Evers LH, Gianaroli L, et al. (2005) Fertility and ageing. *Hum Reprod Update* 11: 261-276.
  18. World Health Organization (1993) *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, ICD-10.*