

Syphilis during Pregnancy: A Study of 879,831 Pregnant Women in Brazil

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Received date: September 04, 2016; Accepted date: September 29, 2016; Published date: October 04, 2016

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Abstract

Background: The World Health Organization (WHO) estimates that approximately 350 million new cases of curable sexually transmitted disease (STD) are reported annually in individuals aged 15 to 49 years. Furthermore, the WHO estimates that syphilis during pregnancy causes more than 300,000 fetal and newborn deaths annually and increases the risk of premature death for approximately 215,000 children. In Brazil, more than 100,000 cases were reported during pregnancy between 2005 and 2014. In 2013 alone, approximately 14,000 cases of syphilis in children younger than one year were reported. The present study evaluated the prevalence of syphilis in pregnant women and identified factors involved in the dynamics of disease maintenance.

Material and Methods: This retrospective ecological study included 879,831 pregnant women who underwent prenatal examinations between 2003 and 2016 in the state of Goiás, located in the midwestern region of Brazil with an estimated population of 6.7 million inhabitants.

Results: Approximately 67% of the pregnant women in the state of Goiás underwent prenatal screening tests during the study period. The study included 821,785 (93.4%) women: 58,046 (6.6%) were excluded owing to data inconsistencies. Overall, 12,933 women tested positive for syphilis immunoglobulin M and G (IgM, IgG) via recombinant enzyme-linked immunosorbent assay screening; 6,501 cases were confirmed venereal disease research laboratory and fluorescent treponemal antibody absorption tests. The mean prevalence of syphilis in the study period was approximately 0.80%, ranging from a minimum and maximum of 0.22% (95% confidence interval [CI] 0.14-0.35) and 1.24% (95% CI 1.15-1.30) in 2013 and 2015, respectively.

Conclusions: The rate of detection of syphilis cases in pregnant women in Brazil has increased in recent years. The severity of the current situation requires intensification of preventive actions to decrease morbidity and mortality in pregnant women with syphilis and, consequently, to avoid transmission to newborns. In this study, the mother's age at pregnancy and the reported number of spontaneous abortions strongly influenced the observed prevalence.

Keywords: Pregnancy; Pregnant women; Prenatal; Gestation; Dried blood spots; Filter paper; Syphilis; Morbidity; Mortality; Brazil

Introduction

In June 2016, the World Health Organization (WHO) [1] released a document that described the status of sexually transmitted diseases (STDs) worldwide, especially in the context of a resolution from the General Assembly of the United Nations, which approved the 2030 Agenda for Sustainable Development [2]. The WHO document presented current estimates of the prevalence of STDs and proposed a global strategy for confronting the physical, psychological, and social barriers for people suffering from these infections [3]. The morbidity and mortality associated with STDs are a major public health problem. The WHO has estimated that 350 million new cases of curable STDs occur annually in individuals aged 15 to 49 years, especially Chlamydia trachomatis infection (131 million), *Neisseria gonorrhoeae* infection (78 million), syphilis (6 million), and *Trichomonas vaginalis* infection (142 million) [1]. Furthermore, particular attention should be paid to viral STDs, whose prevalence is high; more than 400 million people are

estimated to be infected with *herpes simplex* virus type 2, and approximately 290 million women are infected with human papillomavirus [3]. Syphilis is a systemic infectious disease with chronic evolution; the infection is caused by the hematogenous dissemination of *Treponema pallidum*, a sexually and perinatally transmitted spirochete. Infection may result in acquired and congenital forms of the disease [4]. This disease has remained a serious public health problem for more than a century after the first description of *T. pallidum* by Fritz Richard Schaudinn and Paul Erich Hoffmann and the development of a serological test for its diagnosis proposed by August Paul Von Wassermann [5]. Recent estimates indicate a decrease in the number of cases of syphilis during pregnancy between 2008 and 2012, representing progress towards the elimination of the vertical transmission of *T. pallidum*. The 40% reduction was most prevalent in Asia, particularly India. Despite these advances, 1 million new cases of syphilis during pregnancy are reported annually, with more than 300,000 fetal and neonatal deaths [3,6]. In addition to causing fetal and neonatal deaths, the vertical transmission of *T. pallidum* worldwide may lead to low birth weight, neonatal diseases, and latent infection, which may result in late sequelae [7].

In developing countries, syphilis and its congenital form remain significant public health problems that affect 10%–15% of pregnant women [8]. Globally, Africa has the highest incidence of the disease, accounting for 63% of cases reported annually in pregnant women [9]. In 2010, the WHO reported an estimated 11 million new cases of syphilis per year worldwide, including 2.4 million in Latin America and the Caribbean [10]. In 2012, an estimated 930,000 maternal syphilis cases were associated with 350,000 adverse pregnancy outcomes, including 143,000 early fetal deaths and stillbirths, 62,000 neonatal deaths, 44,000 premature or low-weight births, and 102,000 infants infected worldwide. Nearly 80% (274,000) of the adverse outcomes occurred in women who had received prenatal care at least once. Comparing the 2008 and 2012 estimates revealed that the incidence of maternal syphilis had decreased by 38%, from 1,488,394 cases in 2008 to 927,936 cases in 2012; similarly, the incidence of congenital syphilis had decreased by 39%, from 576,784 to 350,915 cases. India accounted for 65% of this reduction [9]. Analyses excluding data from India showed an 18% decrease in maternal and congenital syphilis cases worldwide. Syphilis during pregnancy has shown to affect 1% or more of fetuses in over 55 countries, eventually causing fetal death, prematurity, low birth weight, neonatal disease, and infections in newborns. These adverse results can be avoided by simple and inexpensive tests and penicillin-based treatments [11]. Between 2005 and 2014, 100,000 cases of syphilis during pregnancy were reported in Brazil, with a constant increase in the rate of detection in this period. In 2013, there were approximately 21,000 reported cases, with a detection rate during pregnancy of 7.4 cases per 1,000 live births [12]. In the state of Goiás, notification started in January 2007, with the introduction of an epidemiological investigation sheet (ficha de investigação epidemiológica-FIE) specific for this disease [13]. The present study evaluated the prevalence of syphilis in pregnant women and identified factors potentially involved in the dynamics of disease maintenance in this population.

Materials and Methods

This ecological and retrospective study included a historical series of 879,831 pregnant women screened by the Pregnant Women Protection Program (Programa de Proteção à Gestante-PPG) in the state of Goiás between 2003 and 2016. The PPG was created following the Ministry of Health implementation of the Program for Prenatal and Birth Humanization (Programa de Humanização do Pré-Natal e Nascimento-PHPN) in the state of Mato Grosso do Sul in 2002, and in the State of Goiás in 2003, in partnership with the Association of Parents and Friends of the Intellectually Disabled (Associação dos Pais e Amigos dos Excepcionais-APAE) of both states, via the Institute for Research, Education, and Diagnosis (Instituto de Pesquisas, Ensino e Diagnósticos-IPED) and municipal and state health offices. The PPG performs 13 basic examinations during the prenatal period. It diagnoses, among other pathologies, Chagas disease (American trypanosomiasis), hepatitis B, hepatitis C, human T-lymphotropic virus infection, rubella, human immunodeficiency virus (HIV) infection, syphilis, and toxoplasmosis. The screening examinations are performed using dried blood spots stored on filter paper, a technique validated by Gómez et al. [14].

Blood samples from pregnant women were obtained via digital puncture using disposable lancets, collected on filter paper (S and S 903), and dried at room temperature. In the laboratory, the dried blood samples were eluted from the filter paper, and a qualitative determination of specific anti-*Treponema pallidum* antibodies (IgG

and IgM) was performed using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Mbiolog[®], Brazil), following the manufacturer's instructions. The technique was performed according to the manufacturer's instructions. The concentration of anti-*Treponema pallidum* antibodies is directly proportional to the color intensity of the reaction. Positive filter paper samples were re-tested using serum via the venereal disease research laboratory (VDRL) and fluorescent treponemal antibody absorption (FTA-ABS) tests, according to manufacturer instructions [15]. Considering that the VDRL test results may indicate positivity for diseases other than syphilis, including lupus, liver disease, mononucleosis, leprosy, varicella, and rheumatoid arthritis, we only considered values higher than 1/32 as reliable for syphilis diagnosis. The test may also result in false-positive findings in older adults. The VDRL test is usually performed 4–6 weeks after infection. In general, antibody titers begin to increase 1–2 weeks after the development of a hard chancre. Although our results may contain limitations inherent to all studies involving data collected retrospectively, including ecological studies, we believe the sample size (over 800,000 pregnant women were included in the study) significantly reduced the effect of the potential data inconsistencies.

Ethical considerations

This study is a continuation of the “Prevalence of screened diseases in the Pregnant Women Protection Program of the State of Mato Grosso do Sul between 2004 and 2007” project and was approved by the Research Ethics Committee of CEP/UFMS (Protocol No. 1046).

Study location

The study was conducted using data from the PPG of the state of Goiás, a partnership between the state government, and the Institute of Diagnosis and Prevention/APAE from Goiânia, Goiás; the latter is a non-profit, rights-defending, and philanthropist public organization.

Theory/calculations

Initially, a thorough database cleaning was performed, and simple frequencies were calculated to identify duplications and typos. Duplicated records (6.6%) were discarded, and inconsistencies in the filling of the collection cards were addressed. The selected variables included patient age, pregnancy trimester at the time of examination, number of reports of spontaneous abortions, type of birth, and number of previous pregnancies. Subjects were divided into five age groups: 1 (9–14 years of age), 2 (15–19 years of age), 3 (20–29 years of age), 4 (30–39 years of age), and 5 (40 years of age or older). Data were organized using Excel[™] spreadsheets, and the descriptive measurements were calculated using EpiInfo software version 6.4, Epi Info 2000 version 3.2.2v, and ArcView GIS version 3.3. Coverage probability was calculated using the general expected rate for pregnant women at a confidence interval (CI) of 95%. Prevalence was defined using the information provided by the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística-IBGE) [16], assuming a population of 6,707,681 inhabitants in the state of Goiás, 3,357,153 (50.05%) of which were women. The estimated pregnancy rate in the state of Goiás was 67.33 pregnant women per 1,000 fertile women. Thus, the estimated number of pregnant women in 2016 was 95,935, and the expected population of pregnant women between September 2003 and July 2016 was 1,308,411 individuals, 879,831 of whom were screened (67.17%).

Results

| Year | Born alive | Fetal morbidity | Induced abortions | Women population aged between 15 to 44 years of age | Expected pregnant for the period | pregnant screened by PPG | Coverage PPG |
|-------------------|--------------------|-------------------|-------------------|---|----------------------------------|--------------------------|--------------------|
| 2003 ^a | 92081 | 1471 ^a | 581 ^a | 1222611 | 94128 ^a | 7703 ^a | 8,18% ^a |
| 2004 | 91231 | 1469 | 603 | 1243539 | 93377 | 36145 | 38,70% |
| 2005 | 91556 | 1366 | 596 | 1283962 | 93510 | 62059 | 66,36% |
| 2006 | 87483 | 1282 | 608 | 1298340 | 89364 | 69248 | 77,49% |
| 2007 | 85159 | 1203 | 585 | 1300387 | 86943 | 68396 | 78,67% |
| 2008 | 87462 | 1215 | 645 | 1312938 | 92588 | 70019 | 75,65% |
| 2009 | 87485 | 1163 | 650 | 1329534 | 89291 | 70433 | 78,88% |
| 2010 | 87476 | 1115 | 651 | 1335935 | 89,24 | 72521 | 81,26% |
| 2011 | 89742 | 1254 | 716 | 1348402 | 91704 | 73136 | 79,75% |
| 2012 | 93274 | 1343 | 726 | 1354631 | 95338 | 75171 | 78,85% |
| 2013 | 94822 | 1314 | 777 | 1485876 | 96909 | 75857 | 78,27% |
| 2014 | 99798 | 1282 | 796 | 1583476 | 101865 | 77732 | 76,30% |
| 2015 | 99542 | 1226 | 775 | 1637325 | 101530 | 77182 | 76,01% |
| 2016 | 95329 ^b | 293 ^c | 322 ^c | 1695865 ^b | 95935 | 44229 ^d | 46,10% |
| TOTAL | 1.282.440 | 16.996 | 9.031 | 19.432.821 | 1.308.411 | 879.831 | 67,17% |

^aData from September to December 2003; ^bEstimate for the year; ^cData for from January to May 2016; ^dData for from January to July 2016

Table 1: Coverage Protection Program for Pregnant Women (PPG) compared to the number of pregnant expected for the period in the state of Goiás 2003-2016.

In Goiás, the PPG began its activities in September of 2003, with an initial coverage of 8.18%, based on the total number of pregnant women expected for that year. Between September 2003 and July 2016, 879,831 pregnant women were screened by the program, which corresponds to an average of 67.17% coverage for the period (Table 1). However, because of inconsistencies in data filling, 58,046 (6.6%) women were excluded from the analysis; therefore, a total of 821,785 (93.4%) women were included in the present study (Figure 1). The numbers of live-born infants, fetal deaths, and abortions are presented in Table 1. Among the screened filter paper samples, 12,933 (1.57%) demonstrated positive results on the ELISA. Of these, 6,504 (0.8%) cases were confirmed via the VDRL and FTA-ABS tests (Figure 2). The diagnosis was confirmed in the first trimester in approximately 50% of pregnant women.

The percentages of syphilis cases diagnosed in the first, second, and third trimesters were 49.71%, 30.55%, and 4.49%, respectively. The gestational trimester was undefined at diagnosis in 15.14% of cases. The frequency of syphilis was significantly higher in pregnant women aged 30 years or older, and in those who reported previous abortions ($p < 0.001$) (Table 2).

The average prevalence of syphilis in pregnant women during the study period was 0.80% (95% CI: 0.77-0.81); this prevalence varied between 0.22% (95% CI: 0.14-0.35) in 2003 and 1.24% (95% CI: 1.15-1.30) in 2015. However, after 2010, there was a strongly increasing trend in the frequency of syphilis cases during pregnancy (Figure 3).

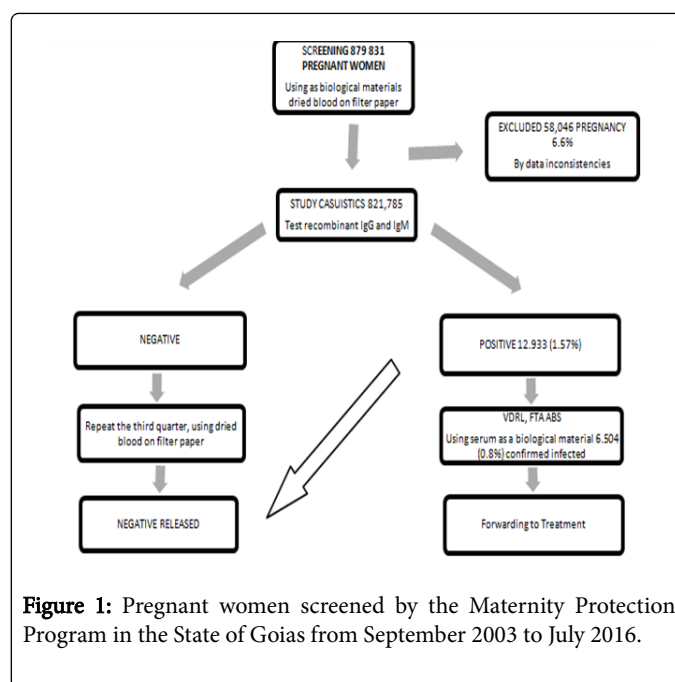
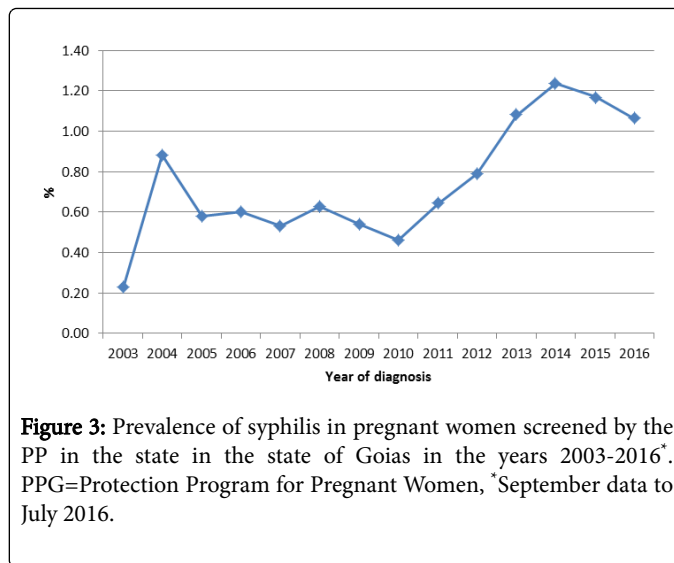
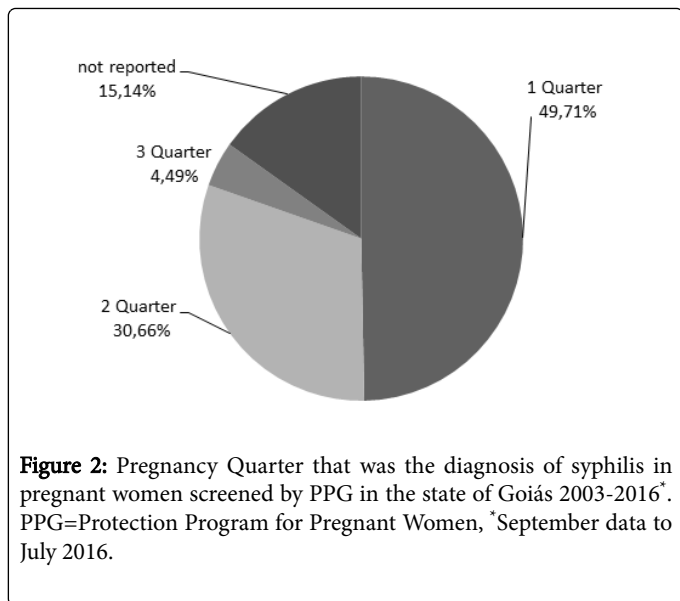


Figure 1: Pregnant women screened by the Maternity Protection Program in the State of Goiás from September 2003 to July 2016.



| Characteristics | Positive | | Negative | | p ^c |
|-----------------------------|----------|-------|----------|-------|----------------|
| | N | % | N | % | |
| Age (in years) ^a | | | | | |
| <14 | 43 | 0.66 | 8946 | 1.10 | <0.001 |
| 15-19 | 1201 | 18.54 | 182827 | 22.55 | <0.001 |
| 20-29 | 3552 | 54.83 | 452645 | 55.83 | 0.105 |
| 30-39 | 1511 | 23.33 | 154427 | 19.05 | <0.001 |
| ≥ 40 | 171 | 2.64 | 11976 | 1.48 | <0.001 |
| Abortions ^b | | | | | |
| None | 1623 | 24.95 | 190482 | 23.36 | 0.061 |
| 1 | 1067 | 16.41 | 89988 | 11.04 | <0.001 |
| 2 | 256 | 3.94 | 16166 | 1.98 | <0.001 |
| ≥ 3 | 120 | 1.85 | 5307 | 0.65 | <0.001 |
| Not reported | 3438 | 52.86 | 513338 | 62.96 | <0.001 |
| Cesárea ^c | | | | | |
| None | 1039 | 15.97 | 92013 | 11.29 | <0.001 |
| 1 | 845 | 12.99 | 98788 | 12.12 | 0.032 |
| ≥ 2 | 383 | 5.89 | 31068 | 3.81 | <0.001 |
| Not reported | 4237 | 65.14 | 593412 | 72.79 | <0.001 |
| Pregnancy (amount) | | | | | |
| 1 | 1649 | 25.35 | 310354 | 38.07 | <0.001 |
| 2 | 1659 | 25.51 | 234422 | 28.75 | <0.001 |
| ≥ 3 | 2823 | 43.40 | 220426 | 27.04 | <0.001 |

| | | | | | | |
|-----|--------------|-----|------|-------|------|--------|
| | Not reported | 373 | 5,73 | 50079 | 6.14 | 0.172 |
| HIV | | 73 | 1.12 | 1121 | 0.14 | <0.001 |

^aFrom September 2003; ^bBy July 2016; ^c χ^2 de Person; PPG=Protection Program for Pregnant Women; HIV=human immunodeficiency virus

Table 2: Characteristics of pregnant women screened by PPG, according to diagnosis of syphilis in the years 2003a to 2016b in the state of Goiás-Brazil.

Discussion

The last survey of the Ministry of Health on the prevalence of syphilis among pregnant women in Brazil was conducted in 2010–2011. That study included approximately 36,000 participants distributed across the five macro-regions of Brazil, with a disease prevalence estimated at 0.85%. VDRL tests showing a reaction at any titer were considered positive and were confirmed via FTA-ABS. The prevalences reported in the aforementioned study and in our work in Goiás were 1.20% [17] and 0.80%, respectively. Botelho et al. [18] observed a 2.69% prevalence in the state of Mato Grosso do Sul, also located in the midwestern region of the country. The rate observed in our study is similar to the average national rate [18].

The results obtained in the present study indicate a clear upward trend in the prevalence of syphilis in the study population. In the past 8 years, 3,507 cases of syphilis in pregnant women in Goiás were registered in the Disease Notification System (Sistema de Informação de Agravos de Notificação–SINAN), which represents an average of 438 notifications per year. The number of syphilis cases among pregnant women in the current study was higher than that registered in the Goiás monitoring system. Botelho reported that prenatal screening and child follow-up after birth could help decrease the disease prevalence and complications as well as maternal and child morbidity and mortality [19]. However, we must also consider congenital syphilis as a risk factor for the concomitant occurrence of infections with distinct etiology in these newborns. Recently, Cortese et al. published a review on early and late infections in newborns, which continue to lead to high morbidity and mortality in this age group [20].

The Ministry of Health of Brazil recommends that prenatal follow-up be initiated immediately after confirmation of pregnancy. Pregnant women are encouraged to undergo at least 6 examinations through healthcare services: 1, 2, and 3 in the first, second, and third trimesters of pregnancy, respectively. The first examination involves screening for various diseases, including syphilis [19,21], leading to a higher rate of diagnosis of diseases in the first trimester. Saab et al. considered syphilis to be one of the greatest public health challenges, which was responsible for a large number of abortions [21].

The United States Centers for Disease Control and Prevention (CDC) recommends that individuals diagnosed with an STD, especially HIV, syphilis, and gonorrhea, be assisted by healthcare services as early as possible. The recommendation is extended to the sexual partners of these patients, with the goal of interrupting disease transmission [22]. Pinto et al. reported that physicians and public health agents have observed a significant increase in the prevalence of syphilis in the last decade, an observation that has renewed interest in the subject [21,23] and helped to intensify actions aimed at improving the outcomes of these diseases.

The Ministry of Health in Brazil reported that the prevalence of syphilis increased from 2011 to 2015. Similarly, an increase in the incidence rate of congenital syphilis has also been observed, from 1.7 to 4.7 cases per 1,000 live-born infants in 2004 and 2013, respectively [23]. At the national level, the highest incidence of congenital syphilis in 2013 was observed in children born to mothers 20 to 29 years of age (50.2%). We observed different rates in Goiás, where the incidence was highest in pregnant women 30 to 39 years of age.

The incidence of HIV infection was 8 times higher in pregnant women with syphilis than in those without a confirmed diagnosis of infection ($p < 0.001$) (Table 2). These findings indicate that health authorities should develop actions targeting this population, which appears to be more vulnerable to STD infections.

Although the etiological agent and transmission methods of syphilis are known, and treatments have a high rate of cure, the disease incidence remains high. Future studies should elucidate the reasons for this high incidence, including failure in the application of protocols for disease surveillance, assistance, and prevention [5].

Conclusions

The current study conducted by the PPG reinforces the need for notification and surveillance of syphilis and underscores the essential role of monitoring vertical transmission. From 2011 to 2013, an upward trend in the number of cases of syphilis was observed among pregnant women in the state of Goiás; this increase was above 100%, and the detection rate reached 9.05 cases per 1,000 live-born infants [23]. Patients voluntarily visited the public health centers, which indicates strong program adherence (67.17%) among pregnant women during the study period.

Acknowledgements

Pregnant women, APAE (Association of Parents and Friends of Exceptional Goiânia), Municipal and State Departments of Goiás, Brazil.

Funding Source: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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