Risk factors for stillbirth among pregnant women infected with syphilis from 2010–2016, Zhejiang Province, China

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Research article

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Abstract

Background: Syphilis infection is one of the most common maternal factors related to stillbirth. The study aims to determine the risk factors for stillbirth among pregnant women infected with syphilis. 

Methods: This was a retrospective study. Data on stillbirth and gestational syphilis were extracted from the PMTCT program database 2010–2016 in Zhejiang Province. A total of 8724 pregnancy women infected with syphilis were included. Multivariable logistic regression analysis was performed to assess the associations between gestational syphilis and stillbirth. 

Results: The stillbirth rate among pregnant women infected with syphilis was 1.74% (152/8724) in Zhejiang Province, China, from 2010–2016. Compared with live birth, stillbirth was significantly associated with lower maternal age, not being married, lower gravidity, previous history of syphilis, non-latent syphilis stage, and higher maternal serum titer for syphilis, inadequate treatment for syphilis, and later first antenatal care visit. With multivariable logistic regression analysis, non-latent syphilis (adjusted OR=2.03; 95% CI 1.17–3.53) and maternal titers over 1:4 (adjusted OR=1.78; 95% CI 1.25–2.53) were risk factors for stillbirth. Adequate treatment was the only protective factor for stillbirth (adjusted OR=0.16; 95% CI 0.10–0.25). 

Conclusions: Adequate treatment is effective in reducing the incidence of stillbirths among pregnant women infected with syphilis, and this is particularly important in women diagnosed with high RPR titer (under 1:4). 

Keywords: risk factors, syphilis, stillbirth, pregnant, syphilis stage, RPR

Background

Although, the total number of stillbirths has decreased greatly worldwide, from 4.0 million (95% CI 3.1–5.2) in 1990 to 2.1 million (95% CI 1.8–2.5) in 2015[1]. Stillbirth rates vary widely across geographic areas, ranging from 1.2 per 1000 births (95% CI 1.0–1.5) in Iceland to 56.3 per 1000 births (95% CI 32.3–98.2) in South Sudan in 2015 globally, and from 3.4 per 1000 births (95% CI 2.6–4.5) in Thailand to 27.6 per 1000 births (95% CI 23.1–32.8) in Pakistan in south and southeast Asia[1]. Since stillbirth is both a tragedy and an emergency, women were more likely to suffer from psychological distress and a high risk of recurrence than those women without a history of fetal loss[2-4,5]. In this way, stillbirths place a huge burden on both the family and society.

Syphilis remains the most common congenital infection worldwide and has tremendous consequences for the mother and her developing fetus if left untreated. This infection can occur at any stage of maternal syphilis and during any trimester[6]. The economic and reproductive costs are enormous, as 25% of pregnancies may result in stillbirth, miscarriage, preterm birth or other adverse pregnancy outcomes[7,8]. In 2012, an estimated 930,000 syphilis infections in pregnant women caused 143,000 early fetal deaths and stillbirths around the world[9]. The wide adoption of syphilis screening and effective treatment has rendered gestational syphilis entirely preventable[10-12]. However, there are many cases in which there is no sufficient intervention in gestational syphilis, especially in low-income and middle-income countries[13,14].
In China, both stillbirth and syphilis place a large burden on maternal and infant health. The latest data showed the average stillbirth rate in China to be 8.8 per 1000 births (95% CI 8.8–8.9) from 2012–2014, and the total number of stillbirths ranked in the top fifth of the world in 2015[15,16]. Syphilis affects a large number of pregnant women in China. In 2013, 15,884 pregnant women diagnosed with syphilis delivered children in China, and of which 14.0% suffered from serious adverse pregnancy outcomes including preterm delivery/low birth weight, or congenital syphilis in newborns or even stillbirth/neonatal death[8,17]. In 2011, the Chinese government initiated a national program for preventing mother-to-child syphilis transmission(PMTCT). In this program, all pregnant women are recommended to received syphilis screening, and appropriate treatment is provided to all infected women. Zhejiang Province is located on China's east coast, where the prevalence of syphilis among pregnant women was 0.3% according to the latest report[11]. There is a need to focus on the associations between stillbirth and gestational syphilis. The purpose of this study was to determine the risk factors for stillbirth among women infected with syphilis during pregnancy in Zhejiang Province. This will provide a significant reference for health care efforts.

Methods

This was a retrospective study based on data from the PMTCT program in Zhejiang Province. All pregnant women infected with syphilis and delivered babies from 2010–2016 were included, regardless of their birth outcomes. Stillbirth was defined as fetal death occurred at 28 weeks of gestation or more or death at delivery. Cases of birthweight ≥1000 g were included when the information on gestational weeks was missing. A questionnaire was used to collect all information, including maternal sociodemographic characteristics, utilization of PMTCT and antenatal care services, pregnancy outcomes, and other factors. We also extracted data from medical registries in hospitals and records in antenatal care systems. Multiple births were excluded because they involve a higher risk of adverse pregnancy outcomes. All information was collected via the network reporting system. Medical staff in hospitals were responsible for data collection. Quality control was performed by researchers from a women’s hospital of Zhejiang University that serves as a center for the PMTCT program. The study was approved by the ethics committee of this women’s hospital (number: 2016-0005). All information was kept confidential.

Syphilis PMTCT

In Zhejiang Province, syphilis testing and counseling are routinely offered to all pregnant women at their first antenatal care visit. Both positive results in the toluidine red unheated serum test (TRUST)/syphilis rapid plasma reagin (RPR) and treponema pallidum particle agglutination (TPPA)/pallidum particle agglutination (TPHA) tests indicate gestational syphilis. Women at high risk for syphilis are recommended to undergo more frequent screening. Before delivery, all women positive for syphilis were offered maternal serum testing again. Women with two courses of penicillin injections and at least 2 weeks off between the two courses were categorized into the adequate treatment group (2.4 million units of benzathine penicillin via weekly injections for 3 weeks or 0.8 million units of procaine penicillin by
daily injection for 15 days per treatment course). Erythromycin and ceftriaxone replacement therapy was recommended for women who were allergic to penicillin. The follow-up and healthcare services for mothers and their infants were performed by local women's and children's hospitals.

**Statistical analysis**

Data were analyzed using SPSS software V.16.0 for Windows. Categorical variables were presented as numbers and frequencies. The demographic characteristics of these infected women were described. The chi-square test was used to compare the prevalence of specific characteristics in women who did or did not suffer from stillbirths. The odds ratios (OR) and 95% confidence intervals (CI) of the factors for stillbirth were estimated using a multivariable logistic regression model. *P* values under 0.05 were considered to be indicative of significant differences. All tests were two-tailed. Women with one or more pregnancies during the study period were counted per pregnancy. Only women who were treated with two courses of penicillin injections were considered adequately treated. Maternal demographic characteristics, syphilis conditions, utilization of PMTCT, and antenatal care services are considered as factors related to stillbirth.

**Results**

**General characteristics**

During the study period, 8724 women were diagnosed with syphilis at some point during pregnancy. The stillbirth incidence among pregnant women infected with syphilis was 17.4 per 1000 births (152/8724). All stillbirth cases did not have congenital syphilis screening. The proportion of maternal age, marital status, gravidity, previous syphilis, syphilis stage, and maternal serum titer for syphilis testing, treatment, adequate treatment, and the time of the first antenatal care visit differed significantly between women with stillbirths and women without stillbirths (Table 1). Compared with live birth, stillbirth was significantly associated with lower maternal age, not being married, lower gravidity, previous history of syphilis, non-latent syphilis stage, and higher maternal serum titer for syphilis, inadequate treatment for syphilis, and later first antenatal care visit.

Table 1 Comparison of maternal socio-demographic characteristics and syphilis condition between women with stillbirths and women without stillbirths
| Variables                      | Category | Stillbirth (n=152) | Without stillbirth (n=8572) | P     |
|-------------------------------|----------|-------------------|-----------------------------|-------|
|                               |          | n | %    | n  | %    |       |
| Maternal age                  | <20      | 17 | 11.18 | 294 | 3.43 | 36.94 | <0.0001|
|                               | 20–24    | 46 | 30.26 | 1959 | 22.85 |
|                               | 25–29    | 45 | 29.61 | 3047 | 35.55 |
|                               | 30–34    | 19 | 12.50 | 1925 | 22.46 |
|                               | ≥35      | 25 | 16.45 | 1347 | 15.71 |
| Employ                        | Farmer   | 49 | 32.24 | 2891 | 33.73 | 1.28  | 0.735  |
|                               | Business | 12 | 7.89  | 598  | 6.98  |
|                               | Unemployed | 63 | 41.45 | 3753 | 43.78 |
|                               | Unknown  | 28 | 18.42 | 1330 | 15.52 |
| Education                     | Primary  | 29 | 19.08 | 1288 | 15.03 | 5.65  | 0.130  |
|                               | Middle   | 116| 76.32 | 6461 | 75.37 |
|                               | College  | 6  | 3.95  | 745  | 8.69  |
|                               | Unknown  | 1  | 0.66  | 78   | 0.91  |
| Married                       |          | 117| 76.97 | 7845 | 91.52 | 39.64 | <0.001 |
| Unmarried                     |          | 35 | 23.03 | 727  | 8.48  |
| Gravidity                     | 1        | 43 | 28.29 | 1594 | 18.60 | 9.21  | 0.002  |
|                               | ≥2       | 109| 71.71 | 6978 | 81.40 |
| Parity                        | 0        | 70 | 46.05 | 3827 | 44.65 | 0.12  | 0.729  |
|                               | ≥1       | 82 | 53.95 | 4745 | 55.35 |
| Minority                      |          | 10 | 6.58  | 541  | 6.31  | 0.02  | 0.893  |
| Previous syphilis             |          | 25 | 16.45 | 3264 | 38.08 | 29.75 | <0.001 |
| Previous fetal loss           |          | 11 | 7.24  | 822  | 9.59  | 0.96  | 0.328  |
| Syphilis stage                | Latent   | 118| 77.63 | 7068 | 82.45 | 21.57 | <0.001 |
|                               | Primary  | 16 | 10.53 | 326  | 3.80  |
|                               | Secondary | 3  | 1.97  | 67   | 0.78  |
|                               | Tertiary | 0  | 0     | 17   | 0.20  |
|                               | Unclear  | 15 | 9.87  | 1094 | 12.76 |
| Titer for TRUST/RPR > 1:4     |          | 59 | 38.82 | 1820 | 21.23 | 27.33 | <0.001 |
| before delivery               | Treated  | 76 | 50.00 | 7296 | 85.11 | 140.62| <0.001 |
| Adequately treated            |          | 26 | 17.11 | 5310 | 61.95 | 126.423 | <0.001 |
| First antenatal care visit    | ≤12      | 42 | 27.63 | 4087 | 47.68 | 69.92 | <0.001 |
|                               | 13-27    | 47 | 30.92 | 3082 | 35.95 |
|                               | ≥28      | 51 | 33.55 | 1111 | 12.96 |
|                               | Unclear  | 12 | 7.89  | 292  | 3.41  |

Note: Missing information was not included.
Factors associated with stillbirth

With multivariable logistic regression analysis, primary or secondary syphilis (adjusted OR=2.03; 95% CI 1.17–3.53) and maternal titers over 1:4 (adjusted OR=1.78; 95% CI 1.25–2.53) were risk factors for stillbirth when we adjusted the influence of maternal age, marriage, gravidity, previous syphilis, syphilis treatment, and first ANC. Adequate treatment was the only protective factor for stillbirth (adjusted OR=0.16; 95% CI 0.10–0.25) (Table 2).

Table 2 Multivariable logistic regression analysis on associations between gestational syphilis and stillbirth

| Variable                      | Crude OR and 95% CI | Adjusted OR and 95% CI | P value |
|-------------------------------|---------------------|------------------------|---------|
| Syphilis stage                |                     |                        |         |
| Latent                        | Ref                 | Ref                    | 0.043   |
| Primary or secondary          | 2.94 (1.72–5.01)    | 2.03 (1.17–3.53)       |         |
| Maternal titer > 1:4          | 2.35 (1.69–3.28)    | 1.78 (1.25–2.53)       | 0.001   |
| Completely treated            | 0.13 (0.08–0.19)    | 0.16 (0.10–0.25)       | <0.001  |

Note: Missing information was not included.

Discussion

In this study, the rate of stillbirth among pregnant women infected with syphilis was 17.42 per 1000 births. The figure was not only slightly higher than the global average level (14.9 per 1000 live births) in 2015 but also even double China’s national average (8.8 per 1000 births) from 2012–2014[1,15,18]. The global estimation of the rate of stillbirth was based on data from 195 countries, territories and selected subnational geographies from 1980–2015. These definitions of stillbirth include fetal death during 20–28 weeks of gestation, with the fetus weighing at least 500–1000 g[1]. Our national data were from 441 hospitals in 326 urban districts and rural counties[15]. Regional disparities in socio-economic background, inclusion criteria, and health care services might lead to the prevalence differences in different studies. The above comparison was performed between women infected with syphilis and the general population.

Syphilis infection is one of the most common maternal factors related to stillbirth, particularly in low-income and middle-income countries, not only because it is not rare[19], but also because of the low detection rate of syphilis during pregnancy[20]. Focusing on syphilis produced an 80% reduction in stillbirths, which performs better than strategies to prevent malaria, HIV, and bacterial vaginosis infections in pregnant women in developing countries[21]. Previous studies showed that the odds ratio of stillbirth among women infected with syphilis ranges from 1.88 to 6.87, which is higher than that among women without syphilis infection, based on data from both developed and developing countries[22,23]. The
findings confirmed the conclusion that efforts to combat stillbirth among women infected with syphilis must be strengthened.

In our study, higher maternal serum titers, primary or secondary syphilis stage, and lack of adequate therapy during pregnancy were independent risk factors for stillbirth. The results were consistent with large numbers of other reports[12,17,19,21,22-25]. Although in most studies, higher maternal titers were defined as serum titers over 1:8, which were more commonly regarded as risk factors for adverse pregnancy outcomes[19,26], we used a maternal titer threshold of 1:4, and this still greatly increased the occurrence of stillbirth. In our province, maternal titers were checked monthly to keep them under 1:4 or to achieve a 4-fold reduction by delivery. If not, these women were considered as having suffered from either treatment failure or reinfection and suggested to be retreated. Titer decline varied with maternal disease and treatment. As previously reported, titers usually were higher and declined rapidly in primary and secondary syphilis[10,27]. Accordingly, results showed that women who suffered from stillbirth had a larger proportion of primary and secondary syphilis.

The pregnancy outcomes could be greatly improved with adequate treatment. A large-scale meta-analysis indicated that the rate of stillbirths and fetal loss is 26.4% for untreated maternal syphilis and 21.3% for treated until the third trimester, whereas it dropped to 3.7% for non-syphilitic mothers[24]. Unfortunately, in this study, not all infected women received adequate therapy. The rate of adequate treatment was only 61.95% in women infected with syphilis who gave birth to live children. The corresponding data was only 17.11% in women who had stillbirths. This phenomenon reflected the current barriers to gestational syphilis prevention or prenatal care in developing countries. At the national level, only 79.1% of infected women received antenatal care at or before 37 gestational weeks, and 55.4% of women who experienced stillbirth received no or late treatment[16]. In India, women who reported at least 1 antenatal care visit accounted for 55.9% of the total women with stillbirths, and only 6.1% of these women underwent syphilis screening[28].

Screening and diagnosis are the first steps to prevent the transmission of syphilis from pregnant women to the developing fetus[29,30]. Dual point-of-care tests are available in our province and are cost-effective. When seropositive pregnant women were identified, gestational care with syphilis therapy was offered as a protective factor for combating adverse pregnancy outcomes. In our province, a large proportion of women infected with syphilis are unemployed and poorly educated, which might limit their adoption of PMTCT and antenatal care services. This is similar to previous reports in other areas[12]. Women with low socioeconomic status should be given more attention. In the United States, syphilis screening has even been advocated among asymptomatic, non-pregnant adults and adolescents[31]. In this way, it is necessary to promote health among all reproductive-age women.

This study has three main limitations that need to be taken into account. First, only pregnant women infected with syphilis and delivered babies from 2010–2016 were eligible for inclusion. Control group information of negative gestational syphilis tests was not collected. Hence, we could not compare the incidence of stillbirth in women infected with syphilis and women without syphilis infection in our study.
Second, the causes of stillbirth could be classified into fetal, placental, external, and undetermined. Many potential risk factors associated with stillbirths are modifiable and usually coexist, such as maternal demographic factors, maternal age, environment, nutrition, non-communicable diseases, antenatal care, obstetric complications, and birth information. These issues should be addressed concurrently with interventions related to syphilitic infection. Third, we did not consider congenital syphilis related influence as all stillbirths caused did not receive syphilis screening. Even so, this was a large-scale multi-center study in a high-prevalence area. Stillbirth attributable to maternal syphilis has been poorly tracked and investigated in China. Our results should be valuable for further prevention efforts.

Conclusions

Maternal syphilis is strongly associated with pregnancy outcomes. To prevent mother to child transmission of syphilis is a public health issue for the high incidence of pregnancy syphilis and the negative influence on pregnancy outcomes. Early identification should be strengthened to improve pregnancy outcomes. Adequate treatment is effective in reducing the incidence of stillbirths among pregnant women infected with syphilis, and this is particularly important in women diagnosed with high RPR titer (under 1:4).

Abbreviations

PMTCT: the national program for preventing mother-to-child syphilis transmission; TRUST: toluidine red unheated serum test; RPR: syphilis rapid plasma reagin; TPPA: treponema pallidum particle agglutination; TPHA: treponema pallidum particle agglutination

Declarations

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Authors’ contributors

C-C-D and S-S-L collaborated in collecting data. C-C-D designed the methodology and drafted the manuscript. X-HZ contributed to data cleaning and statistical analyses. L-Q-Q interpreted the study data and revised the paper. J X was responsible for the whole program, including study design, data acquisition, and quality control. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets analyzed during the current study are included in this published article. Further information is available from the corresponding author on reasonable request

**Ethics approval and consent to participate**

Ethical approval was obtained from the Women's Hospital School of Medicine Zhejiang University (2016-0005)

**Consent for publication**

not applicable

**Competing interests**

The authors declare that they have no competing interest

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