Pregnancy syphilis epidemic trends, clinical features, APOs risk factors, pregnancy-induced hypertension epidemics and related factors, in Northeast China Jilin Maternity Hospital 2013-2017

CURRENT STATUS: POSTED

Fangfang Hu
Jilin University School of Public Health

Huixin Yang
Jilin University School of Public Health

Lixin Sun
Changchun maternity Hospital

Jingjing Luo
Jilin University School of Public Health

Siwen Zhang
Jilin University School of Public Health

Taijun Wang
Jilin University School of Public Health

Xiangyi Zhang
Jilin University School of Public Health

Qing Zhen
Jilin University School of Public Health

yanghuixin999@126.com Corresponding Author
ORCID: https://orcid.org/0000-0002-7319-1579

DOI: 10.21203/rs.2.9191/v1

SUBJECT AREAS
Internal Medicine Specialties

KEYWORDS
Maternal syphilis; APOs; Treatment during pregnancy; Maternity hospital; Pregnancy-induced hypertension
Abstract
Background. It is of great public health significance to monitor the global meiosis mother-to-child transmission plan proposed by WHO and monitor the prevalence of maternal syphilis and the factors affecting mother-to-child transmission. Methods. We collected 271 medical records of prenatally diagnosed (from 87286 pregnant women) of syphilis among pregnant women a maternity hospital in Jilin Province China from 2013 to 2017. The chi-square test and Logistic multiple regression analysis were used to describe the clinical characteristics of pregnant women with syphilis and the related factors of adverse pregnancy outcome. Results. The average prevalence of maternal syphilis is 0.31% (95%CI: 0.27%-0.35%). The mean age of 271 pregnant women with syphilis is 27.62±5.4 years old. The maternal syphilis prevalence of absence of paid occupation is 73.8%; rural population accounts for 43.6%. Maternal women with a history of abortion accounted for 43.1%, of which 53.1% had abortion ≥2; The average rate of treatment in pregnancy is 25.5% (95%CI: 25.4%-25.6%). The prevalence rate of APOs are 43.9% (95%CI: 38.1%-49.9%), declined in five years (P<0.05). APOs was significantly higher in women at 30-34 age group than that in 0-24 age group (OR= 2.916, 95%CI: 1.298-6.549) and higher in Un-treatment in pregnancy than that in receive treatment (OR=2.469, 95%CI:1.225-4.975). PROM occurrence (OR=2.702, 95%CI:1.219-5.988); CRP elevation (≥10 mg/L) and RPR high titer (≥1:8) are related to the occurrence of APOs. Abortion, prematurity and low birth weight are associated with no treatment during pregnancy (P<0.05). Comparison of 42 cases of pregnancy-induced hypertension and non-pregnancy-induced hypertension, Dysmenorrhea (OR= 3.654, 95%CI:1.812-7.369) and elevated urine protein (OR= 2.259, 95%CI:1.161-4.394) are the influencing factors of maternal syphilis complicated with pregnancy-induced hypertension.
Conclusions. The prevalence of maternal syphilis in northern China is lower than that of 10 years ago, but the decline is still lower than that in the economically developed regions of the south. The rate of non-treatment of syphilis during pregnancy is high, and should be alert to the rebound of maternal syphilis.

Introduction
Maternal syphilis is an important public health problem in Perinatal health. In 2007, WHO proposed to
eliminate mother-to-child transmission (MTCT) of syphilis as a public health problem[1], and in 2016, it indicated about 2 million new cases of syphilis among pregnant women and 60% of which will be transmitted by MTCT worldwide each year[2]. The world trend of syphilis and maternal syphilis is that most occur in sub-Saharan Africa (SSA) and lower in developed countries such as the United States and Europe[3, 4]. Since the 1990s, the incidence of maternal syphilis has been increasing in China[5], China’s government officially launched a national program in 2010, specifically and directly aimed at controlling syphilis through expanding active screening for syphilis followed by treatment of infected patients in high-risk groups and pregnant women[6]. Free HIV, syphilis, and HBV tests are provided to all pregnant women. In 2013, the syphilis testing coverage in pregnant women was 96.40% in china[7]. The prevalence of maternal syphilis varies from region to region in China, the incidence of syphilis or maternal syphilis in northern China is lower than in the economically developed southern region. According to research conducted by data from various provinces, the prevalence of maternal syphilis in Beijing from 2013 to 2014 was 0.11%-0.14%[8], in Shanghai decreased from 0.38% to 0.10% in 2005-2015[9]. Some studies of maternal syphilis in maternity hospital shows that the prevalence in Shenzhen was from 0.49% to 0.12% in 2005-2017[10]. There are few studies on the prevalence of maternal syphilis in northeastern China, and there have been reports that Liaoning Province was 0.10% in 2010[11].

Syphilis in pregnancy can induce adverse pregnancy outcomes (APOs), including stillbirth, preterm birth, low birth weight, neonatal death and congenital infection among infants[12]. A high proportion of Syphilis in pregnancy are untreated or inadequately treated and the risk of APOs is 4.5 times that of undiagnosed pregnant women[13, 14]. Domestic research shows large proportions of women are not detected and treated at an early pregnancy stage, and the treatment rate varied from 69.8% to 96.8% and remained 83.6% in China 2015[5, 9].

In addition, other pregnancy-specific diseases can have a major impact on pregnant women and babies. Pregnancy hypertension affects 10% of pregnancies and is the second direct cause of maternal death worldwide[15, 16] and will have a greater impact on pregnant women and fetuses. The adverse perinatal outcomes associated with hypertensive disorders and Gestational diabetes are
generally referable to stillbirth, miscarriage, fetal growth restriction, placental insufficiency, and premature birth related complications[17-19]. Studies have shown that the difference in the prevalence of pregnancy induced hypertension in HIV positive and negative pregnant women (\( p=0.06 \)) approached significance[20].

The WHO and China have put forward the goal of eradicating mother-to-child transmission of syphilis, and have made various efforts to achieve effective control in some areas. However, pregnancy syphilis is different in different parts of the world, and the control effect is affected by many factors and China’s goal of eliminating mother-to-child transmission is rarely compared and reported in various regions. This study included all pregnant syphilis and newborns admitted to a maternity hospital in Jilin, China for 13-17 years. Case data, analysis of its prevalence, clinical characteristics and main factors affecting APOs, to explore the maternal and child health hazards of pregnancy-specific diseases, and to explore the prevalence of pregnancy-induced diseases in pregnancy-induced syphilis and related factors for protection Maternal and child health and the completion of the final elimination of syphilis mother-to-child transmission goals provide research basis.

Methods
Clinical Data Collection and Patient Selection
From 2013 to 2017, a total of 87,286 women were admitted to a maternity hospital in Changchun, China. The number of women admitted each year is 16,134, 20,244, 12,595, 20,545, and 17768. The syphilis, HIV, and hepatitis B tests in this hospital are 100% covered. A total of 271 cases of maternal medical records diagnosed as syphilis all will be included in the study, among them, there are 230 cases of pregnant women with live births. Diagnostic criteria for pregnancy syphilis[21]: ①pregnant woman or spouse has a history of syphilis infection, ②treponema pallidum particle agglutination (TPPA) and rapid plasma regain (RPR) are positive, ③have clinical symptoms of syphilis And signs. The diagnostic criteria for neonatal syphilis infection are positive for serological tests of mother and newborn syphilis. Adverse pregnancy outcomes (APOs) of syphilis were defined as abortions or stillbirth and, in live-born infants, premature birth, low birth weight and neonatal asphyxia (1minute APGAR scores ≤ 7).
The comorbidities studied in this study included anemia, hepatitis B, pregnancy with hypertension, pregnancy with diabetes, and pregnancy with intrahepatic cholestasis. To investigate the association between syphilis in pregnancy and maternal syphilis complicated with pregnancy-induced hypertension, we conducted an unmatched case-control study. Cases were syphilis among pregnant women diagnosed with any type of pregnancy-induced hypertension before discharge. 42 pregnant women with pregnancy-induced hypertension were classified as the pregnancy-induced hypertension group (PIH), and the rest were assigned to the non-pregnancy-induced hypertension group (NPIH).

Statistical Analysis
We calculated the crude incidence of maternal syphilis and its 95% confidence interval (CI). We performed the bivariate analyses between the potential risk factors and the outcome and estimated the odds ratios (OR) and respective 95% confidence intervals (95%CI). The variables that presented p-value ≤0.05 were included in the multivariate analysis model. We used multivariate logistic regression models to assess relevant factors with APOs in patients with maternal syphilis and P values <0.5 were regarded as statistically significant. Statistical analysis was done using SPSS for Windows (version 23.0).

Result
Prevalence and Clinical features in 271 pregnancy syphilis from 2013 to 2017

Screening for syphilis in 87,286 pregnant women, 271 were diagnosed as syphilis seropositive by prenatal diagnosis, and giving a prevalence of 0.31% (95%CI: 0.27%-0.35%). The figure 1 shows the prevalence trend of pregnancy syphilis in 2013-2017 and the prevalence χ2 trend test was not statistically significant (P>0.05) (Table 1).

The average age of the 271 pregnant women with syphilis is 27.0±5.4 years old, age range is 19-43 years old. Table 2 shows the demo- graphic characteristics of these infected pregnant women, the prevalence of absence of paid occupation is 73.8%, the urban population accounts for 43.9%, the town population is 12.5%, and the rural accounts for 43.6%. Regarding the Past history of pregnant women with syphilis, which have the history of Abortion is 53.1%, and the number of abortions ≥2 times accounted for 46.5%. The average pregnancy treatment rate for five years is 25.5%-74.5% did
not receive anti-syphilis treatment during pregnancy. In addition, serological testing of neonates found that 45.8% (124/230) of the newborns were infected with syphilis in 2013-2017.

Figure 1. The number and trend of maternal syphilis in 2013-2017

Figure 2. Number and trends of APOs and treatment during pregnancy in 2013-2017

Table 1. Prevalence rate of maternal syphilis, APOs and treatment in 2013-2017

| Year | maternal syphilis (%) | APOs (%) | Receiving treatment during pregnancy (%) |
|------|-----------------------|----------|-----------------------------------------|
| 2013 | 3.5                   | 50.0     | 21.4                                    |
| 2014 | 2.6                   | 57.6     | 25.0                                    |
| 2015 | 3.4                   | 44.2     | 30.2                                    |
| 2016 | 3.2                   | 33.9     | 26.2                                    |
| 2017 | 3.1                   | 38.2     | 25.5                                    |
| Total| 3.1                   | 43.9     | 25.5                                    |

Note: *χ² trend

Table 2. Clinical characteristics of 271 patients with pregnancy syphilis

| Hierarchical level/Characteristics | N=271 | %  |
|-----------------------------------|-------|----|
| General demographic indicators    |       |    |
| Age group                         |       |    |
| ≤24                               | 78    | 28.8 |
| 25-29                             | 110   | 40.6 |
| 30-34                             | 45    | 16.6 |
| ≥35                               | 38    | 14.0 |
| Occupation                        |       |    |
| Absence of paid occupation        | 200   | 73.8 |
| Public officials                  | 31    | 11.4 |
| Staff                             | 31    | 11.4 |
| Farmer                            | 9     | 3.4  |
| Place of residence                |       |    |
| City                              | 152   | 43.9 |
| Town                              | 34    | 12.5 |
| Rural                             | 85    | 43.6 |
|                  |        |        |
|------------------|--------|--------|
| Past history     |        |        |
| Abortions        |        |        |
| 0                | 127    | 46.9   |
| 1                | 77     | 28.4   |
| ≥2               | 67     | 24.7   |
| Dysmenorrhea     | 57     | 21.0   |
| Induction of labor| 17     | 6.3    |
| Treatment during pregnancy |        |        |
| Receiving treatment in pregnancy | 69     | 25.5   |
| Un-treatment in pregnancy        | 202   | 74.5   |
| APOs              | 119    | 43.9   |
| Neonatal syphilis infection       | 124   | 45.8   |
| Perinatal disease |        |        |
| PROM              | 41     | 15.1   |
| Placental abruption  | 2     | 0.4    |
| Umbilical cord winding | 75    | 27.7   |
| Comorbidities     |        |        |
| Gestational hypertension       | 42     | 15.5   |
| Gestational diabetes        | 13     | 4.8    |
| Intrahepatic cholestasis       | 1      | 0.4    |
| Anemia             | 80     | 29.5   |
| Hepatitis B        | 24     | 8.9    |

Prevalence and related factors of maternal APOs in pregnancy with syphilis from 2013 to 2017

In our study, APOs in 271 cases are 119(43.9%), and the prevalence was 33.85%-55.77% in 2013-2017 (Figure 2), the prevalence χ2 trend test was statistically significant (P<0.05) (Table 2).

In this study, 43.9% of patients developed APOs, And the risk of APOs occurring in different age groups is different (Crude OR=1.480), After adjustment, the APOs in the 30-34 age group were 2.421 times (95%CI:1.013-5.785) that of the ≤24-year-old age group. Treatment with anti-syphilis during pregnancy is a protective factor for APOs (Adjusted OR=0.405, 95%CI:0.201-0.816). APOs in high RPR group (≥1:8) was 4.64 times (95%CI:12.759-7.851) higher than that of low RPR group (<1:8) (Table 3).

Table 3. Analysis of associated factors for syphilis pregnant woman combined with APOs
| Hierarchical level/Characteristics | All Women | Women with APOs | %   | Crude OR | P       | Adjusted OR (95% CI) | P       |
|-----------------------------------|-----------|----------------|-----|----------|---------|----------------------|---------|
| **Total**                         | 271       | 119            | 43.9|          |         |                      |         |
| **General demographic indicators**|           |                |     |          |         |                      |         |
| **Age group**                     |           |                |     |          |         |                      |         |
| ≤24                               | 78        | 47             | 60.3| 1.480    | 0.003   | 1.485 (0.749-2.943)  | 0.258   |
| 25-29                             | 110       | 44             | 40.0| 1.485    | 0.258   | 1.485 (0.749-2.943)  | 0.258   |
| 30-34                             | 45        | 15             | 33.3| 2.421    | 0.047   | 2.421 (1.013-5.785)  | 0.047   |
| ≥35                               | 38        | 13             | 34.2| 2.039    | 0.148   | 2.039 (0.777-5.349)  | 0.148   |
| **Absence of paid occupation**    | 200       | 85             | 42.5| 0.804    | 0.432   |                      |         |
| **Non-urban population**          | 119       | 58             | 48.7| 0.890    | 0.659   |                      |         |
| **Past history**                  |           |                |     |          |         |                      |         |
| Dysmenorrhea                      | 57        | 21             | 36.8| 1.448    | 0.228   |                      |         |
| Abortion                          |           |                |     | 1.062    | 0.691   |                      |         |
| 0                                 | 127       | 59             | 46.5|          |         |                      |         |
| 1                                 | 77        | 30             | 39.0| 0.934    | 0.823   |                      |         |
| ≥2                                | 67        | 30             | 43.9| 1.270    | 0.480   |                      |         |
| Induction of labor                | 17        | 7              | 41.2| 0.888    | 0.815   |                      |         |
| Un-treatment in pregnancy         | 202       | 103            | 51.0| 3.446    | <0.001  | 2.469 (1.225-4.975)  | 0.011   |
| **Perinatal disease**             |           |                |     |          |         |                      |         |
| PROM                              | 41        | 24             | 58.5| 2.006    | 0.043   | 2.702 (1.219-5.988)  | 0.014   |
| Placental abruption               | 2         | 1              | 50.0| 1.280    | 0.862   |                      |         |
| Umbilical cord winding            | 75        | 26             | 36.7| 1.702    | 0.059   |                      |         |
| Laboratory                        |           |                |     |          |         |                      |         |
The incidence of most types of APOs (44.0% overall) decreased from 2013 to 2017 (Table 4). The incidence of stillbirth decreased from 17.9% in 2013 to 1.8% in 2015. The incidence of Abortion reached its highest value in 2014, but returned to the 2013 level in 2016; preterm birth and low birth weight declined overall, reaching a minimum in 2016 and a slight rebound in 2017; and neonatal asphyxia decreased from 19.5% in 2013 to 13.2% in 2015.

The rate of treatment of syphilis during pregnancy during 2013-2017 is 21.4%-30.2% (Figure 2). The prevalence χ2 trend test was not statistically significant (P>0.05) (Table 2). A total of 14 abortions in 119 APOS cases, none of which received anti-syphilis treatment. APOs were analyzed with or without anti-syphilis treatment, and the difference was statistically significant, and abortion, prematurity and low birth weight are associated with un-treatment (Table 5).

Table 4. Clinical characteristics of maternal APOS in pregnancy with syphilis
| Year | Total | AP | Stiff | Partial | Abortion | Total Pre | Low Birth | Veteran | N | % | CI | N | % | CI |
|------|-------|----|------|---------|----------|-----------|-----------|---------|---|---|----|---|---|----|
| 2013 | 56    | 28 | 50 .0 | 0.36 | 9       | 0.07 | 2 | 3.6 | 44 | 13 | .2  | 95 | .37 | 44 | .35 |
| 2014 | 52    | 29 | 55 .8 | 0.42 | 3       | 0.10 | 4 | 7.7 | 37 | 9  | .2  | 95 | .37 | 52 | .35 |
| 2015 | 43    | 19 | 44 .2 | 0.29 | 4       | 0.07 | - | -    | 40 | 9  | .2  | 95 | .37 | 43 | .35 |
| 2016 | 65    | 22 | 33 .8 | 0.22 | 3       | 0.06 | 4 | 7.7 | 56 | 5  | .2  | 95 | .37 | 65 | .35 |
| 2017 | 55    | 21 | 38 .2 | 0.25 | 4       | 0.07 | 1 | 1.8 | 53 | 9  | .2  | 95 | .37 | 55 | .35 |
| Total | 27    | 11 | 44 .0 | 0.38 | 1       | 0.06 | 0 | 1.8 | 23 | 5  | .2  | 95 | .37 | 27 | .35 |

Table 5. Effect of treatment of pregnancy women with syphilis on APOs
Prevalence and related factors of pregnancy syphilis complicated with pregnancy hypertension

This study analysis the pregnancy hypertension in maternal syphilis, and the average prevalence rate was 42 cases (15.5%) in 2013-2017. Table 6 shows the associated factors for syphilis pregnant woman combined with Pregnancy hypertension, with their confidence interval and $P$. The age composition of the PIH group showed that the $\leq 24$-year age group accounted for a maximum of 35.7%. Univariate analysis showed that the History of dysmenorrhea, and proteinuria levels were statistically significant ($P<0.05$) (Table 6).

Table 6. Analysis of associated factors for syphilis pregnant woman combined with HDP
| Hierarchical level/Characteristics | PIH n=42 | NPIH n=229 | P   | Crude OR | 95%CI  |
|-----------------------------------|----------|------------|-----|----------|--------|
| General demographic indicators    |          |            |     |          |        |
| Age group                         |          |            |     |          |        |
| ≤24                               | 15(35.7) | 63(27.5)   | 0.523 | 0.893    | 0.631-1.264 |
| 25-29                             | 14(33.3) | 96(41.9)   |      |          |        |
| 30-34                             | 6(14.3)  | 39(17.1)   |      |          |        |
| ≥35                               | 7(16.7)  | 31(13.5)   |      |          |        |
| Absence of paid occupation        |          |            |     |          |        |
| Non-urban population              |          |            |     |          |        |
| Past history                      |          |            |     |          |        |
| Dysmenorrhea                      |          |            |     |          |        |
| Abortion                          |          |            |     |          |        |
| Induction of labor                |          |            |     |          |        |
| Un-treatment in pregnancy         |          |            |     |          |        |
| Laboratory indicators             |          |            |     |          |        |
| Proteinuria Levels (g/24h)        |          |            |     |          |        |
| CRP (mg/L)                        |          |            |     |          |        |
| RPR                               |          |            |     |          |        |
| HDL (umol/L)                      |          |            |     |          |        |
| LDL (umol/L)                      |          |            |     |          |        |
| Triglyceride (umol/L)             |          |            |     |          |        |
| Total cholesterol (umol/L)        |          |            |     |          |        |
| Discussion                        |          |            |     |          |        |

The data for this study came from a maternity hospital in Changchun, northeast China. At present, most of the domestic research data on syphilis in pregnancy come from System of Prevention of Mother-to-Child Transmission of Syphilis Management, our study is based on clinical case data from maternity hospitals. In our study, only pregnant women with syphilis infection that delivered in 2013-2017 were eligible for inclusion. Hence, a total of 271 women were included in the analysis. We
analyzed demographic, clinical, syphilis-related characteristics and associated factors of maternal syphilis and APOs in these infected pregnant women in northeast China.

The study was conducted after the World Health Organization and China implemented the goal of eliminating mother-to-child transmission of syphilis. We identified that the prevalence of maternal syphilis in the studied region was 0.26%-0.35% from 2013 to 2017, and the average maternal syphilis is 0.31% (95%CI: 0.27%-0.35%), significantly lower than Jilin in 2010(0.58%)[22], Liaonin in 2015 (0.40%)[11]. According to relevant research in Shenzhen, the average prevalence of maternal syphilis is 0.37% in 2002-2010, after the implementation of the mother-to-child transmission elimination program, the prevalence rate fell to 0.18% in 2011-2017[10, 23]. Jilin Province is located in the northeastern part of China and belongs to an economically underdeveloped area. Research reports on syphilis or syphilis during pregnancy are less than in developed areas of China. From the prevalence of maternal syphilis in this study, the control effect of maternal syphilis in northeastern China is not as good as in the south. This reminds us that if we want to achieve the goal, we should not neglect the cold spot where syphilis or maternal syphilis prevalence is low. We must increase the implementation of policies. Otherwise, it will be difficult to completely eliminate the mother-to-child transmission of syphilis.

Among the subjects included in the study, the number of pregnant women under the age of 29 infected with syphilis was as high as 69.4%, and the proportion of syphilis ≤ 24 years old accounted for 28.8%. We note that the younger age in this study seems to be related to maternal syphilis, this may be related to the sexual activity period of the lower age group; this survey is more likely to be an influencing factor in rural and townships. The results were consistent with other similar studies conducted at home or abroad[24]. Therefore, for low-age people, we must pay close attention to it and give publicity and education. Pregnant women with risky sexual behavior or more than 2 abortions are recommended for pre-pregnancy screening and early treatment to avoid mother-to-child transmission. Women living in rural areas and women who are unemployed or housewives/farmers are often socially disadvantaged. In our study, we found that this less dominant population accounted for a large proportion of maternal syphilis cases. Former studies have shown
that active infection with Treponema pallidum (T.P) in women belonging to low socioeconomic level were disquieting. This is probably due to illiteracy and high proportion of unsafe sexual behavior[25]. Particular attention should be paid to promoting the use of pre-pregnancy syphilis screening and treatment adherence to these vulnerable groups.

Previous research confirmed the history of abortion is the risk factors of maternal syphilis[26]. In our study, half of all pregnant syphilis patients have a history of abortion, of which 53.1% are pregnant women with abortion ≥2 times. Which reminds us that pregnant women with habitual abortion should be forced to carry out syphilis screening before pregnancy. At the same time, we found that the risk of neonatal syphilis infection in this study region is very high (45.8%). According to reports, in 2012, global neonatal syphilis infection accounted for 11.0% (102,000/930,000) [27]. It is worth noting that the diagnostic criteria for neonatal syphilis infection in this article are positive for serological tests of maternal and neonatal syphilis, unlike the diagnosis of congenital syphilis (CS). At present, the world pays more attention to congenital syphilis and reports more widely, the incidence of congenital syphilis in china increased from 2.6 per 100,000 live births in 2000 to 69.9 in 2013, an increase of nearly 26 times[28, 29]. A four-pronged comprehensive syphilis control strategy consisting of increased prenatal screening coverage, increased treatment completion, earlier prenatal screening, and improved syphilis test characteristics have been shown to have a good effect on reducing CS[30]. The treatment during pregnancy is directly related to congenital syphilis and patients with maternal syphilis who do not receive treatment or have inadequate treatment during pregnancy may increase the risk of congenital syphilis[31, 32]. In our study, the untreated rate of maternal syphilis infection was significantly higher (74.5%) than other reports at home and abroad[5, 33]. The reason may be that the infection of syphilis is in an incubation period. As with HIV, women infected with syphilis might not exhibit any symptoms, indirectly leads to untreated or untimely and inadequate treatment during pregnancy, which is why screening during pregnancy is critical. Studies have shown that the prevalence of latent syphilis in Chinese maternal syphilis reached 67.6% in 2013[5]. Faced with such a high prevalence of latent syphilis, we should pay more attention to pre-pregnancy syphilis screening. Second, the hospital's prenatal screening coverage for maternal women can reach 100%,
this is an effective means to prevent mother-to-child transmission of syphilis. But in 2003 China officially cancelled the compulsory marriage check, which led to the lack of syphilis screening in the area before pregnancy. On the other hand, although the prevalence of maternal syphilis is not high, the treatment rate is low, the study found that the treatment of pregnant women during pregnancy was associated with a variety of adverse pregnancy outcomes such as Abortion, prematurity and low birth weight (p<0.05). This reminds us of the huge impact of no treatment during pregnancy on APOs in pregnant women.

The prevalence of APOs declined during 2013-2017 (chi-square trend test P<0.05), the reason may be that China has launched a comprehensive program to prevent mother-to-child transmission (iPMTCT). Studies have shown that serious adverse pregnancy outcomes such as abortion, stillbirth still have a certain prevalence rate of 15.1% (41/271), lower than the abortion and stillbirth rate of maternal syphilis in 2012, 15.4%[34]. This study also found that the risk of APOs in the 30-34 age group is higher than the ≤24 age group, which is not the same as some reports at home and abroad[35, 36], this may be related to the average age of the study population (27.0) is greater than other similar studies[37]. This study found that RPR high titers (≥1:8) in pregnant syphilis patients have a higher risk of developing APOs, which is the same as the findings of similar studies[38, 39]. At the same time, we noticed that the risk of APOs in maternal syphilis patients with elevated CRP was five times (p<0.05) higher than that of normal CRP pregnant women in us study. The latest study found that viral infections may cause an increase in CRP levels[40], which is similar to our results, reminding us that syphilis infection may also affect CRP expression.

In the research background, we pointed out that syphilis or certain viral infections can cause inflammation in the body, and the latest research shows that the chronic inflammation leads to many chronic diseases including cancer, cardiovascular diseases, etc[41]. Gestational hypertension has a certain prevalence in this study, the prevalence of maternal syphilis combined with pregnancy hypertension is 15.5%. But the incidence of pregnancy hypertension in the normal population (4.1%-19.4%)[16, 42, 43]. Studies have shown that maternal syphilis combined with pregnancy-induced hypertension has no significant association with age (p<0.05). It is well known that the risk of
developing pregnancy-induced hypertension in older women is significantly increased[44], which is clearly inconsistent with our findings, and this reminds us that in clinical practice, monitoring of patients with syphilis in the young age should be strengthened to prevent hypertension during pregnancy. We think this may be due to syphilis infection. Novikov Iu has found that syphilis can cause small blood vessel inflammation[45, 46]. And an excessive maternal innate immune response is sufficient to cause vascular inflammation and endothelial dysfunction, which contributes to the development of pregnancy hypertension during pregnancy[47-49]. Therefore, whether syphilis has the potential to cause pregnancy-induced hypertension and the relationship between viral infectious diseases and chronic diseases requires further research to confirm.

According to our knowledge, this is the first study on maternal syphilis epidemiology in northeast China based on hospital medical records. Using hospital clinical data to analyze the prevalence of maternal syphilis and adverse pregnancy outcomes, maternal syphilis treatment rates, adverse pregnancy outcomes, and apple influencing factors, we can see that the maternal syphilis picture in China is alarming. Integrated interventions on maternal syphilis still need to be further strengthened to promote maternal and children’s health. Government should commit more to investment in infrastructure of public health, health provider capacity building, and population education. In addition, more studies are needed to explore barriers and strategies to elimination of congenital syphilis in China.

LIMITATION

This study has several limitations. First, Treatment status, only the record of treatment during pregnancy, no data of early, middle and late treatment, and no record of treatment before pregnancy, so only the factors affecting the pregnancy outcome during pregnancy were analyzed. Second, only neonatal infection with syphilis cases rather than all congenital syphilis cases were included in our study and the newborns' RPR infection records in the adverse pregnancy outcomes, lack of follow-up CS data, some newborns have 4 times higher RPR than mothers. According to the diagnostic guidelines, CS can be directly diagnosed, but the conditions are not met. Follow-up diagnosis, lack of this information. There are also serious adverse outcomes in addition to abortion, stillbirth, newborns
with clinical manifestations may be transferred to hospital and lack of a complete record, so the CS situation was not analyzed. Third, there is no classification of pregnancy-induced hypertension in patients with endemic diseases, and there is no record of family history of hypertension. Syphilis can cause small vasculitis. Whether it is related to pregnancy-induced hypertension is still lack of case-control research evidence, but inflammation and various Related to chronic disease, associated with hypertension, this study only initially explored the relevant factors of pregnancy-induced hypertension in pregnant syphilis populations.

Declarations

Acknowledgements

The authors express their gratitude to Changchun Maternity Hospital, Changchun, Jilin, P.R.China for the support in publication of this article. Authors are thankful to Prof. Qing Zhen (Jilin University) for his guiding of this article.

Funding

This study does not have any external funding support.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions

HFF, YHX, SLX, ZQ conceived the study and involved in data collection. YHX, HFF, ZSW, WTJ, ZXY and involved in data analysis and critically reviewed the manuscript. HFF, YHX wrote the first draft of the manuscript. All authors reviewed and approved the final version of the manuscript.

Ethics approval and consent to participate

All subjects gave signed, informed consent to participate in the study, which was approved by the Institutional Review Board (IRB), School of Public Health, Jilin University.

Consent for publication

Not applicable in this section

Competing interests
The authors declare that they have no competing interests

References
1. Gomez GB, Kamb ML, Newman LM, Mark J, Broutet N, Hawkes SJ: Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis. *Bull World Health Organ* 2013, 91(3):217-226.

2. Organization WH: Advancing MDGs 4, 5 and 6: impact of Congenital syphilis elimination. *World Health Organization* 2016.

3. Padovani C, Oliveira RR, Peloso SM: Syphilis in during pregnancy: association of maternal and perinatal characteristics in a region of southern Brazil. *Rev Lat Am Enfermagem* 2018, 26:e3019.

4. McGettrick P, Ferguson W, Jackson V, Eogan M, Lawless M, Ciprike V, Varughese A, Coulter-Smith S, Lambert JS: Syphilis serology in pregnancy: an eight-year study (2005-2012) in a large teaching maternity hospital in Dublin, Ireland. *Int J STD AIDS* 2016, 27(3):226-230.

5. Dou L, Wang X, Fang W, Qian W, Qiao Y, Min S, Xi J, Jie Q, Li S, Wang AJBRI, : Epidemic Profile of Maternal Syphilis in China in 2013. 2016, 2016(6):1-8.

6. Chen XS, Yin YP, Wang QQ, Wang BX: Historical perspective of syphilis in the past 60 years in China: eliminated, forgotten, on the return. *Chinese Med J-Peking* 2013, 126(14):2774-2779.

7. Wang A-L, Qiao Y-P, Wang L-H: Integrated prevention of mother-to-child transmission for human immunode - ciency virus, syphilis and hepatitis B virus in China. *B World Health Organ* 2015, 93:52-56.

8. Zhang X, Yu Y, Yang H, Xu H, Vermund SH, Liu K: Surveillance of Maternal Syphilis in China: Pregnancy Outcomes and Determinants of Congenital Syphilis. *Med Sci Monit* 2018, 24:7727-7735.

9. Li Y, Zhu L, Du L, Qu L, Jiang W, Xu B: Effects on preventing mother-to-child transmission of syphilis and associated adverse pregnant outcomes: a longitudinal study from 2001 to 2015 in Shanghai, China. *BMC Infect Dis* 2017, 17(1):626.

10. : 2005—2017 2018, 18(9):896-898+918.

11. : 2011-2014 2015(6):43-44.

12. Fiumara NJ: Syphilis among mothers and children. *Annals of the New York Academy of Sciences*
10, 549(1):187-192.

13. Gomez GB, Kamb ML, Newman LM, Mark J, Broutet N, Hawkes SJ: Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis. *B World Health Organ* 2013, 91(3):217-226.

14. Hong FC, Wu XB, Yang F, Lan LN, Guan Y, Zhang CL, Feng TJ, Yang YZ, Yin YP, Yu WY et al: Risk of Congenital Syphilis (CS) Following Treatment of Maternal Syphilis: Results of a CS Control Program in China. *Clin Infect Dis* 2017, 65(4):588-594.

15. Abalos E, Cuesta C, Carroli G, Qureshi Z, Widmer M, Vogel JP, Souza JP, N WMSM: Pre- eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. *Bjog-an International Journal of Obstetrics and Gynaecology* 2014, 121:14-24.

16. L S, D C, A G, Ö T, AB M, J D, AM G, M T, L A: Global causes of maternal death: a WHO systematic analysis. *The Lancet Global Health* 2014, 2(6):e323-e333.

17. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC: Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. *Bmj-British Medical Journal* 2014, 348.

18. Lean SC, Derricott H, Jones RL, Heazell AEP: Advanced maternal age and adverse pregnancy outcomes: A systematic review and meta-analysis. *PLoS One* 2017, 12(10):e0186287.

19. Durnwald C: Gestational diabetes: Linking epidemiology, excessive gestational weight gain, adverse pregnancy outcomes, and future metabolic syndrome. *Semin Perinatol* 2015, 39(4):254-258.

20. Bodkin C, Klopper H, Langley G: A comparison of HIV positive and negative pregnant women at a public sector hospital in South Africa. *J Clin Nurs* 2006, 15(6):735-741.

21. Enders M, Hagedorn HJ: Syphilis in pregnancy. *Z Geburtshilfe Neonatol* 2002, 206(4):131-137.

22. X T: Sexually transmitted disease among pregnant women in Jilin Province. *China Pract Med* 2011, 32:255-256.

23. Hong FC, Yang YZ, Liu XL, Feng TJ, Liu JB, Zhang CL, Lan LN, Yao MZ, Zhou H: Reduction in mother-to-child transmission of syphilis for 10 years in Shenzhen, China. *Sex Transm Dis* 2014, 41(3):188-193.
24. Liao KJ, Zhang SK, Liu M, Wang QM, Liu J, Shen HP, Zhang YP: Seroepidemiology of Syphilis Infection among 2 Million Reproductive-age Women in Rural China: A Population-based, Cross-sectional Study. *Chinese Med J-Peking* 2017, 130(18):2198-2204.

25. Hussain Laghari A, Sultana V, Hussain Samoo A, Makhija P, Ara J, Hira: Prevalence and associated risk factors for syphilis in women with recurrent miscarriages. *Pak J Med Sci* 2014, 30(2):295-298.

26. Zhou H, Chen XS, Hong FC, Pan P, Yang F, Cai YM, Yin YP, Peeling RW, Mabey D: Risk factors for syphilis infection among pregnant women: results of a case-control study in Shenzhen, China. *Sex Transm Infect* 2007, 83(6):476-480.

27. Wijesooriya NS, Rochat RW, Kamb ML, Turlapati P, Temmerman M, Broutet N, Newman LM: Global burden of maternal and congenital syphilis in 2008 and 2012: a health systems modelling study. *Lancet Glob Health* 2016, 4(8):E525-E533.

28. Chen ZQ, Zhang GC, Gong XD, Lin C, Gao X, Liang GJ, Yue XL, Chen XS, Cohen MS: Syphilis in China: results of a national surveillance programme. *Lancet* 2007, 369(9556):132-138.

29. 2000-2013: 2014, 47(5):310-315.

30. Tan NX, Rydzak C, Yang LG, Vickerman P, Yang B, Peeling RW, Hawkes S, Chen XS, Tucker JD: Prioritizing congenital syphilis control in south China: a decision analytic model to inform policy implementation. *PLoS Med* 2013, 10(1):e1001375.

31. Hong FC, Wu XB, Yang F, Lan LN, Guan Y, Zhang CL, Feng TJ, Yang YZ, Yin YP, Yu WY et al: Risk of Congenital Syphilis (CS) Following Treatment of Maternal Syphilis: Results of a CS Control Program in China. *Clinical Infectious Diseases* 2017, 65(4):588-594.

32. Slutsker JS, Hennessy RR, Schillinger JA: Factors Contributing to Congenital Syphilis Cases - New York City, 2010-2016. *MMWR Morb Mortal Wkly Rep* 2018, 67(39):1088-1093.

33. Rowe CR, Newberry DM, Jnah AJ: Congenital Syphilis: A Discussion of Epidemiology, Diagnosis, Management, and Nurses' Role in Early Identification and Treatment. *Adv Neonatal Care* 2018, 18(6):438-445.

34. Wang Y, Wu M, Gong X, Zhao L, Zhao J, Zhu C, Gong C: Risk Factors for Congenital Syphilis Transmitted from Mother to Infant - Suzhou, China, 2011-2014. *MMWR Morb Mortal Wkly Rep* 2019,
35. Laopaiboon M, Lumbiganon P, Intarut N, Mori R, Ganchimeg T, Vogel JP, Souza JP, Gulmezoglu AM, Network WHOMSoMNHR: Advanced maternal age and pregnancy outcomes: a multicountry assessment. BJOG 2014, 121 Suppl 1:49-56.

36. Watson-Jones D, Changalucha J, Gumodoka B, Weiss H, Rusizoka M, Ndeki L, Whitehouse A, Balira R, Todd J, Ngeleja D et al: Syphilis in pregnancy in Tanzania. I. Impact of maternal syphilis on outcome of pregnancy. J Infect Dis 2002, 186(7):940-947.

37. Sakala J, Chizuni N, Nzala S: A study on usefulness of a set of known risk factors in predicting maternal syphilis infections in three districts of Western Province, Zambia. Pan Afr Med J 2016, 24:75.

38. Bhuiyan AR, Mitra AK, Ogungbe O, Kabir N: Association of HCV Infection with C-Reactive Protein: National Health and Nutrition Examination Survey (NHANES), 2009(-)2010. Diseases 2019, 7(1).

39. Kunnumakkara AB, Sailo BL, Banik K, Harsha C, Prasad S, Gupta SC, Bharti AC, Aggarwal BB: Chronic diseases, inflammation, and spices: how are they linked? J Transl Med 2018, 16(1):14.

40. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF: WHO analysis of causes of maternal death: a systematic review. Lancet 2006, 367(9516):1066-1074.

41. Umesawa M, Kobashi G: Epidemiology of hypertensive disorders in pregnancy: prevalence, risk factors, predictors and prognosis. Hypertension Research 2017, 40(3).

42. Liu X, Ruan Y, Liu Y, Zhang W: [Relationship between maternal age and hypertensive disorders in pregnancy]. Zhonghua Yi Xue Za Zhi 2015, 95(1):19.

43. Novikov Iu A, Novikov AI, Repina TV, Radul EV, Romanov AA: Changes in markers of systemic inflammatory response and functional state of the vascular wall in patients with early syphilis. Vestn Ross Akad Med Nauk 2010(5):21-24.

44. Byard RW: Syphilis-Cardiovascular Manifestations of the Great Imitator. J Forensic Sci 2018, 63(4):1312-1315.

45. Balasubbramanian D, Gelston CAL, Mitchell BM, Chatterjee P: Toll-Like Receptor Activation,
Vascular Endothelial Function, and Hypertensive Disorders of Pregnancy. *Pharmacological Research* 2017, 121:14.

48. Volpe L, Di Cianni G, Lencioni C, Cuccuru I, Benzi L, Del Prato S: Gestational diabetes, inflammation, and late vascular disease. *J Endocrinol Invest* 2007, 30(10):873-879.

49. Mrizak I: Inflammation and impaired endothelium-dependant vasodilatation in non obese women with gestational diabetes mellitus: preliminary results. *Lipids in Health Disease* 2013, 12(1):93-93.

Figures

![Figure 1](image1.png)

**Figure 1**

The number and trend of maternal syphilis in 2013-2017

![Figure 2](image2.png)

**Figure 2**

Number and trends of APOs and treatment during pregnancy in 2013-2017
