Fetal Outcome in Pregnancy Infected Syphilis Treated with Penicillin G: A Systematic Review

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ABSTRACT

Background: Syphilis infection during pregnancy can cause congenital syphilis. Syphilis in pregnant women is treated with penicillin to prevent fetal infection and congenital syphilis. A systematic literature review is conducted to determine the efficacy of penicillin G by reviewing outcome parameters. **Methods:** A systematic literature review following the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines. **Results:** Through searches on PubMed, Science Direct, and Cochrane using keywords 'Antibiotics', 'Pregnancy', 'Syphilis', and 'Treatment', 230 articles were found. Twenty-five articles were duplicates, 135 articles did not meet the inclusion criteria, 75 articles were literature reviews, and 58 articles were not related to pregnant women, resulting in 6 journals that met the inclusion criteria. **Conclusion:** Penicillin G benzathine is the most common antibiotic used to treat syphilis in pregnancy. A total of 1,190 cases (26.26%) of congenital syphilis were found among 4,531 pregnant women infected with syphilis and receiving penicillin G benzathine therapy. The incidence of congenital syphilis was 2.4% in pregnant women who received therapy since the first trimester. The incidence of congenital syphilis increased 12 times if therapy was given in the second trimester and 33 times if given in the third trimester.

Keywords: Congenital syphilis, penicillin G, syphilis infection during pregnancy, syphilis treatment.

ABSTRAK

Latar belakang: Infeksi sifilis pada kehamilan dapat menyebabkan sifilis kongenital. Terapi *penicillin* bertujuan untuk mengatasi infeksi sifilis pada ibu hamil, agar janin tidak tertular dan tidak terjadi sifilis kongenital. Dilakukan tinjauan literatur sistematis untuk mengetahui khasiat *penicillin G* dengan meninjau parameter hasil. **Metode:** Tinjauan literatur sistematis mengikuti pedoman *preferred reporting items for systematic reviews and meta-analysis* (PRISMA). **Hasil:** Melalui pencarian data di PubMed, Science Direct, dan Cochrane menggunakan kata kunci 'Antibiotik' 'Hamil' 'Kehamilan' 'Sifilis' dan 'Tata laksana', didapatkan 230 artikel. Saat seleksi, terdapat 25 artikel duplikat, 135 artikel tidak memenuhi kriteria inklusi, tinjauan literatur 75 artikel, populasi bukan wanita hamil 58 artikel, sehingga didapatkan 6 jurnal yang memenuhi kriteria iklusi. **Simpulan**: *Penicillin G benzathine* adalah antibiotik yang paling umum digunakan untuk mengobati sifilis pada kehamilan. Sebanyak 1.190 kasus (26,26%) sifilis kongenital ditemukan di antara 4.531 wanita hamil yang terinfeksi sifilis dan menerima terapi *penicillin G benzathine*. Insiden sifilis kongenital didapatkan 2,4% pada ibu hamil yang mendapat terapi sejak trimester pertama. Kejadian sifilis kongenital meningkat 12 kali jika terapi diberikan pada trimester kedua dan 33 kali jika diberikan pada trimester ketiga. **Tigor Peniel Simanjuntak, Joshua Nathaniel Kuncoro. Luaran Janin pada Kehamilam Terinfeksi Sifilis yang Diterapi dengan *Penicillin G*: Tinjauan Sistematik.**

Kata Kunci: Kongenital sifilis, *penicillin G,* infeksi sifilis pada kehamilan, tata laksana sifilis.

INTRODUCTION

Congenital syphilis occurs when an untreated pregnant woman passes the infection to her unborn child, resulting in a significant global burden with approximately 6 million new cases annually.[1] In the United States, there was a notable 261% increase of congenital syphilis cases from 2013 to 2018.[2] Pregnant women have particular risks for syphilis transmission, including factors such as young age, unprotected sexual activity with multiple partners, low socioeconomic and educational status, substance abuse, and a history of previous sexually transmitted infections (STIs).[3] Syphilis is caused by *Treponema pallidum* and transmitted through sexual contact, creates a high risk to pregnant women. A not-appropriately-treated syphilis in pregnant woman has an up to 80% chance of transmitting the infection to the fetus.[4] *T. pallidum* can easily pass through the placenta, leading to fetal infection at any stage of pregnancy and causing congenital syphilis. The effects of congenital syphilis vary based on gestational age, the stage of maternal syphilis, and the effectiveness of treatment. Infants infected with congenital syphilis may experience severe complications such as cerebral palsy, hydrocephalus, sensorineural hearing loss, and musculoskeletal deformities.[4,5]

Combination of syphilis testing with timely penicillin treatment for *Treponema pallidum*-infected pregnant women have demonstrated efficacy in decreasing negative pregnancy

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outcomes. This intervention has also been deemed highly cost-efficient, even in regions with moderate or low rates of syphilis among expectant mothers.[6] According to WHO guidelines, the recommended first-line treatment is penicillin G benzathine at a dosage of 2.4 million units.[7,8]

Insufficient treatment and treatment commenced late in pregnancy continued to pose risks for stillbirth, preterm birth, low birth weight, and neonatal congenital syphilis. Each week of delayed treatment is correlated with a 2.82-fold rise in the likelihood of adverse pregnancy outcomes.[9] In cases of penicillin allergy, the recommended approach is penicillin desensitization, followed by treatment with penicillin G benzathine. As an alternative therapy, WHO recommends procaine penicillin at 1.2 million units or erythromycin at 500 mg four times a day.[10,11] Penicillin is the current first line of syphilis treatment.[12] This systematic review is on the side effects and the incidence of congenital syphilis after penicillin G treatment in pregnant women.

Search Strategy

The process described outlines a systematic approach to conducting a literature review on the topic of Fetal Outcome in Pregnancy Infected Syphilis Treated with Penicillin G, using three electronic search engines: PubMed, Science Direct, and Cochrane. The search strategy involved using a combination of keywords related to the topic of interest, including "Antibiotic", "Treatment", "Congenital Syphilis", "Pregnancy", and "Syphilis." These keywords were combined in different strings depending on the specific requirements of each electronic database. The search was limited to manuscripts written in the English language, and articles with unavailable full-text or irrelevant topics were omitted. This helps ensure that only relevant and accessible literature is included in the review.

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Study Selection

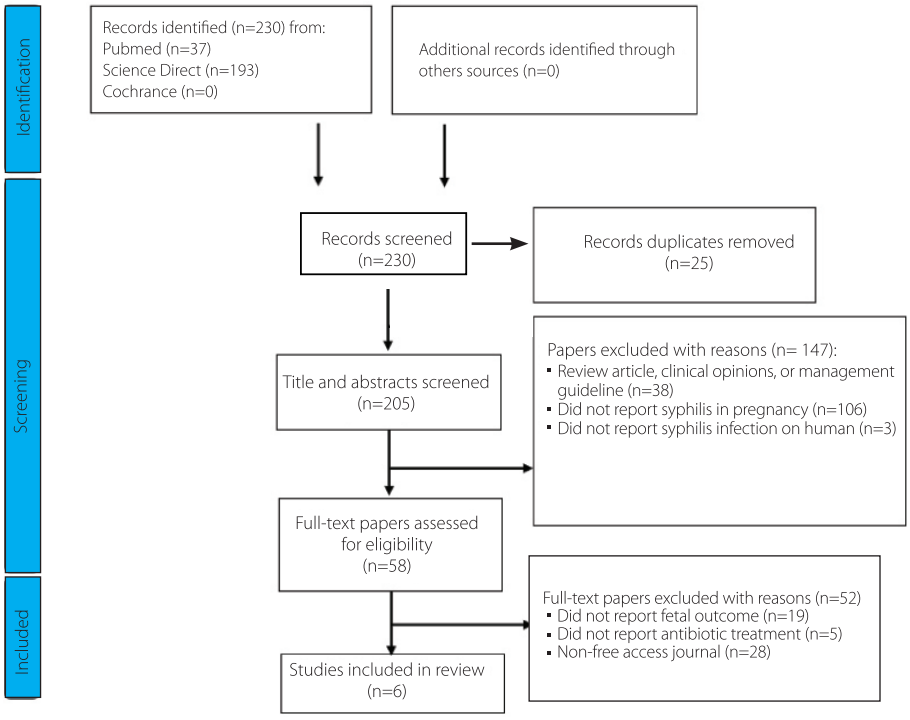
Articles were identified using "Antibiotic", "Pregnancy", "Congenital Syphilis", "Syphilis", "Treatment" as keywords on three electronic search engine; PubMed, Science Direct, and Cochrane.

The study selection process follows the criteria for inclusion and exclusion. The inclusion criteria were observational study, including case reports, case control studies, case series, and both prospective and retrospective cohort studies describing the type of antibiotic, dosage, and duration of treatment in pregnant women with syphilis, the time of diagnosis and the fetal outcome. Editorial articles, reviews, correspondences, and clinical opinions were excluded; dissertations, management guidelines, and *in vitro* studies were also excluded. Studies involving animal subjects were not considered for inclusion. Duplicates were removed using Zotero software.

Retrieved articles underwent initial screening based on their titles and abstracts to assess their relevance to the inclusion and exclusion criteria. The screening process was conducted by an investigator and supervised by a second investigator to ensure consistency and accuracy. Selected articles underwent a full-text assessment to confirm their suitability for this study; the same investigators who conducted the initial screening also performed the assessment of full texts and extraction of outcome and independent variables.

Data Extraction

An ad hoc electronic form of a Remote Desktop Protocol (RDP) file was prepared to collect qualitative variables from selected articles related to antibiotic treatment for pregnant women with syphilis. Since the data were retrieved from the results sections of the articles and did not involve direct interaction with human participants, local ethical approval is not necessary. The following variables related to the study were collected: 1) The first author; 2) Publication date; 3) The age of the mother; 4) Gestational age; 5) Severity of



Scheme. Algorithm of summarizing literature articles and selection process for reviewing of antibiotics therapy for pregnant women with syphilis infection.

syphilis; 6) The type of antibiotics; 7) Dose; 8) Duration administration; 9) Outcome.

Study Quality Assessment

This systematic review followed the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines.[13] The evaluation of case reports and case series use quality scale, such as the "methodological quality and synthesis of case-series and case-reports" scale, to ensure that included studies meet certain methodological standards.[13] This allows for a critical appraisal of the quality of evidence of the studies and facilitates the integration of their findings into the overall review.[11]

Result

Out of the initial 230 articles identified, 25 articles were identified as duplicates. After the initial screening, another 147 articles were excluded because the articles did not reported syphilis in pregnancy (n=106); did not report syphilis on human (n=3); review articles, clinical option, or management guideline (n=38) **(Scheme).** After full-text review on 58 articles, 52 were excluded: 19 articles did not report fetal outcome; 5 articles did not report antibiotic treatment; 28 are non-free access journals.

All 6 studies describing antibiotics treatment for syphilis infection used penicillin G benzathine. Penicillin G benzathine was used for the first-line therapy and other option for the alternative to penicillin were ceftriaxone and erythromycin. The dose of penicillin G benzathine given was a regimen of 2.4 MU single dose intramuscularly per week for three weeks.[11]

DISCUSSION

Syphilis is caused by *Treponema pallidum* and transmitted through sexual contact, creates a high risk to pregnant women with serious consequences if untreated, affecting various organ systems and leading to severe health issues. If syphilis in pregnancy is not appropriately treated, there is an up to 80% chance of transmitting the infection to the fetus.[4]

According to WHO guidelines, the recommended first-line treatment is penicillin benzathine at a dosage of 2.4 million units.[7,8] The efficacy of penicillin g benzathine treatment is high, reaching 98.2% in preventing congenital syphilis.[4] The World Health Organization (WHO) suggests that pregnant women with syphilis should receive a minimum of one dose of penicillin g benzathine (BPG) during the first trimester.[12]

A total of 4,531 cases of syphilis in pregnancy adequately treated with penicillin B from 6 studies was analyzed, and we found 1,190 (26,26%) cases of congenital syphilis. The high incidence may be related to late diagnosis and therapy initiated in the third trimester.[17]

In this analysis, pregnant women diagnosed with syphilis and treated during the first trimester had a congenital syphilis incidence of 2.4%. The incidence rose to 28% if diagnosed and treated in the second trimester, and reached 80% if diagnosed and treated in the third trimester.[2,5,14]

Qin, *et al*, noted a 2.82-fold rise in the risk of adverse pregnancy outcomes for every week of delayed treatment.[18] Wan, *et al*, noted that insufficient treatment and treatment commencement in the later stages of pregnancy continued to be associated with risks of stillbirth, preterm birth, low birth weight, and congenital syphilis.[9] Tsai S, *et al*, stated that early detection and immediate administration of appropriate penicillin treatment are essential for the effective management of syphilis during pregnancy.[19] It is crucial to prevent congenital syphilis

Table 1. Published studies of antibiotics treatment for syphilis in pregnancy.

Authors	Number of Samples	Publication Date	Type of Studies	Antibiotic	Dose	Monitoring Modalities	Outcome
Nakasuji, *et al.*[5]	8	Jul 2019	Case Report	Penicillin B	2,4 MU Single Dose	Seropositive	Congenital Syphilis (n=1)
Stafford, *et al.*[2]	43	Feb 2019	Research Article	Penicillin B	2,4 MU Single Dose	VDLR	Congenital Syphilis (n=12) Chorioamnionitis (n=5) IUFD (n=2) PPROM (n=6)
Anugulruengkitt, *et al.*[14]	69	Aug 2019	Research Article	Penicillin B	2,4 MU Single Dose	VDLR	Stillbirth (n=3) Low Birth Weight (n=15) Congenital Syphilis (n=26)
Lannoy, *et al.*[15]	3724	Oct 2022	Research Article	Penicillin B	2,4 MU Single Dose	VDLR	Congenital Syphilis (n=836)
Swayze, *et al.*[16]	607	May 2022	Research Article	Penicillin B	2,4 MU Single Dose	VDLR	Congenital Syphilis (n=302) Preterm Birth (n=57) IUFD (n=18)
Nishijima, *et al.*[17]	80	Jun 2020	Research Article	Penicillin B	2,4 MU Single Dose	RPR	Congenital Syphilis (n=13) Stillbirth (n=1) Misscariage (n=1)


Table 2. Incidence of congenital syphilis from pregnancy infected syphilis with adequate treatment penicillin G.

Authors	GA at Diagnosis	Total of Sample	Incidence of Congenital Syphilis	Percentage (%)
Nakasuji Y, *et al.*[5]	First Trimester	7	-	-
	Second Trimester	-	-	-
	Third Semester	1	1	100
Stafford I, *et al.*[2]	First Trimester	23	-	-
	Second Trimester	10	4	40
	Third Trimester	10	8	80
Anugulrusukitt, *et al.*[14]	First Trimester	11	1	9,09
	Second Trimester	22	5	22,7
	Third Trimester	25	20	80
Lannoy H, *et al.*[15]	First Trimester	1760		
	Second Trimester	847	836	24
	Third Trimester	1117		
Swayze E, *et al.*[16]	Did not report	607	302	49,8
Nishijima T, *et al.*[17]	Mean GA 13,8 week	80	15	18,75

and other adverse outcomes in pregnancy resulting from maternal syphilis.[19] This is aligned with our findings that the incidence of congenital syphilis is highest if diagnosed in the third semester, even if the mother was adequately treated with penicillin G.

CONCLUSION

Penicillin G benzathine is the most common antibiotic used to treat syphilis in pregnancy. A total of 1,190 cases (26.26%) of congenital syphilis were found among 4.531 pregnant women with syphilis and receiving penicillin g benzathine therapy. The incidence of congenital syphilis was 2.4% in pregnant women who received therapy since the first trimester. The incidence of congenital syphilis increased 12 times if therapy was given in the second trimester and 33 times if given in the third trimester.

LIMITATION

Our review did not use information from paid journals for lack of funding and articles published over the past 10 years, these limitations prevent a comprehensive understanding of the full range of potential adverse effects linked to antibiotic exposure during pregnancy.

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