

SYSTEMATIC REVIEW

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## Effectiveness of treating gestational syphilis in the last trimester on the incidence of congenital syphilis: a systematic review and meta-analysis

### Efectividad del tratamiento de la sífilis gestacional en el último trimestre sobre la incidencia de sífilis congénita: revisión sistemática y metanálisis

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#### ABSTRACT

**Objectives:** To evaluate the effectiveness and safety of treatment for gestational syphilis during the third trimester on maternal and perinatal outcomes, according to the timing of administration relative to delivery, and assess the certainty of the body of evidence.

**Materials and methods:** This systematic review included randomized controlled trials, quasi-experimental studies, cohort studies, and case series involving women diagnosed with GS at 28 weeks' gestation or later, treated with penicillin or other antibiotics. Search was done in 2023 and updated on June 2025. Two researchers selected studies and extracted data. We assessed the incidence of Congenital Syphilis and maternal treatment failure. Outcomes are presented by maternal and perinatal endpoints and treatment regimen.

**Results:** No randomized controlled trials were identified. Ten cohort studies comprising 5438 women with GS and three case series of Congenital Syphilis were included. Benzathine penicillin G administered during the third trimester might be associated with a cumulative incidence of Congenital Syphilis of 8% (95% CI: 2–13%). The effectiveness of treatment administered 4 weeks before delivery remains uncertain. Aminopenicillins were possibly associated with a 43% incidence of Congenital Syphilis. Safety data were limited. Case series of foetuses with hidrops fetalis associated with gestational syphilis to mothers treated with a 10-day course of intravenous aqueous crystalline penicillin G showed seven newborns with complete response, suggesting prevention of Congenital Syphilis.

**Conclusion:** Treatment of GS with benzathine penicillin G during the third trimester is beneficial in reducing the risk of Congenital Syphilis. However, as its effectiveness is uncertain when administered fewer than 30 days before delivery, neonates born within this timeframe should continue to be managed in accordance with current guidelines for possible Congenital Syphilis. Aminopenicillins may be associated with a high rate of treatment failure. Alternative strategies to treat the fetus during the final four weeks of pregnancy are needed to reduce the risk of Congenital Syphilis.

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**Keywords:** Syphilis; congenital syphilis; treponema pallidum; pregnant women; penicillins; macrolides; ampicillin; therapeutics.

## RESUMEN

**Objetivos:** evaluar la efectividad y seguridad del tratamiento de la sífilis gestacional durante el tercer trimestre en los desenlaces maternos y perinatales, según el momento de administración con relación al parto, y evaluar la certeza del cuerpo de evidencia.

**Materiales y métodos:** esta revisión sistemática incluyó ensayos clínicos aleatorizados, estudios cuasiexperimentales, estudios de cohorte y series de casos que involucraron mujeres diagnosticadas con sífilis gestacional a las 28 semanas de gestación o más, tratadas con penicilina u otros antibióticos. La búsqueda se realizó en 2023 y se actualizó en junio de 2025. Dos investigadores seleccionaron los estudios y extrajeron los datos. Se evaluó la incidencia de sífilis congénita y el fracaso del tratamiento materno. Los desenlaces se presentan por puntos finales maternos y perinatales y por esquema terapéutico.

**Resultados:** no se identificaron ensayos clínicos aleatorizados. Se incluyeron diez estudios de cohorte que comprendieron 5.438 mujeres con sífilis gestacional y tres series de casos de sífilis congénita. La penicilina G benzatínica administrada durante el tercer trimestre podría estar asociada con una incidencia acumulada de sífilis congénita del 8 % (IC 95 %: 2–13 %). La efectividad del tratamiento administrado 8 o 4 semanas antes del parto sigue siendo incierta. Las aminopenicilinas posiblemente se asociaron con una incidencia del 43 % de sífilis congénita. Los datos de seguridad fueron limitados. Las series de casos de fetos con hidropesía fetal asociada con sífilis gestacional en madres tratadas con un esquema de 10 días de penicilina G acuosa cristalina intravenosa mostraron siete recién nacidos con respuesta completa, lo que sugiere prevención de sífilis congénita.

**Conclusión:** el tratamiento de la sífilis gestacional con penicilina G benzatínica durante el tercer trimestre es beneficioso para reducir el riesgo de sífilis congénita. Sin embargo, dado que su efectividad es incierta cuando se administra con

menos de 30 días antes del parto, los neonatos nacidos dentro de este periodo deben continuar siendo manejados de acuerdo con las guías actuales para posible sífilis congénita. Las aminopenicilinas pueden estar asociadas con una alta tasa de fracaso terapéutico. Se necesitan estrategias alternativas para tratar al feto durante las últimas cuatro semanas de gestación con el fin de reducir el riesgo de sífilis congénita.

**Palabras clave:** sífilis; sífilis congénita; treponema pallidum; mujeres embarazadas; penicilinas; macrólidos; ampicilina; terapéutica.

## INTRODUCTION

Syphilis is an infection caused by the bacterium *Treponema pallidum* (TP), transmitted through sexual contact, transplacental passage, or blood transfusion (1). Its incidence has increased globally, particularly in Latin America and Africa (2). Gestational syphilis (GS) refers to infection acquired during pregnancy or the presence of an untreated preexisting infection in a pregnant woman. TP can cross the placenta from the end of the first trimester onwards (3). Vertical transmission may be asymptomatic or result in adverse outcomes including intrauterine death, preterm birth, or neonatal sepsis (4). Infants infected in utero are diagnosed with congenital syphilis (CS). Timely diagnosis and treatment of gestational syphilis can prevent or cure CS (5). Failures in prevention are often associated with lack of access to, or nonattendance at, antenatal care (6).

Penicillin remains the standard treatment for syphilis, GS, and CS (4). Given that TP divides approximately every 30 hours (7), effective bactericidal activity in early syphilis requires penicillin concentrations to remain above 0.03 IU/mL (18 ng/mL) for 7–10 days without interruption exceeding 24 hours (8). In late syphilis, due to slower bacterial replication, a longer duration of treatment is necessary to maintain adequate therapeutic levels (8).

The generic name of the antibiotic is benzylpenicillin or penicillin G. It is available as

an aqueous solution for parenteral use specifically, aqueous crystalline penicillin G. This formulation has a rapid onset and a short half-life (30–60 minutes), necessitating frequent intravenous administration. It crosses the blood–brain barrier in the presence of inflammation and achieves effective transplacental passage (9), making it the treatment of choice for neurosyphilis and CS (4). Depot formulations such as procaine penicillin and benzathine penicillin G are also available. Procaine penicillin comprises penicillin and procaine in equimolar concentrations, resulting in slower absorption when administered intramuscularly every 8–12 hours (10). Benzathine penicillin G, formed by combining penicillin G with diphenylethylenediamine, has a half-life of approximately seven days and is also administered intramuscularly (8). Benzathine penicillin G is indicated for the treatment of early syphilis (single dose) and late syphilis (three weekly doses) (4), based on its pharmacokinetic requiring fewer doses. Although aqueous crystal-line penicillin G has been used to treat gestational syphilis since 1949 (11), current practice typically involves the use of benzathine penicillin G in the same regimen as for non-pregnant women (4).

Alexander et al. reported that a single dose of 2.4 million units of benzathine penicillin G administered to pregnant women with syphilis cured 98% of CS cases (12). Notably, four of the six CS cases occurred in neonates born within two weeks of maternal treatment. These findings appear to support current guideline recommendations which consider neonates born to mothers treated less than 30 days prior to delivery as possibly infected and in need of additional treatment (4,13,14).

Given that a substantial proportion of women are diagnosed with syphilis during the third trimester (15,16), and that partner treatment is often inadequate resulting in a heightened risk of maternal reinfection later in pregnancy (17,18) it is essential to appraise the evidence supporting the classification of treatment as

inadequate if administered within 30 days of delivery. This recommendation leads to neonates undergoing a 10–14 day course of intravenous aqueous crystalline penicillin G (4), which may increase the risk of adverse events associated with intravenous therapy and prolonged hospital stays, particularly among preterm neonates (19). Likewise, it is relevant to answer the question about the risk of congenital syphilis occurring within the last twelve weeks, and more specifically within the final four weeks of pregnancy, among women who receive standard treatment with benzathine penicillin G or alternative regimens.

This systematic review therefore aims to assess the effectiveness and safety of treatment for gestational syphilis during the third trimester on maternal and perinatal outcomes, with specific reference to the timing of administration relative to delivery and the certainty of the available evidence.

## METHODS

### Design

**Systematic Review.** The protocol was the degree work to obtain the title of specialist in Obstetrics and Gynecology at the National University of Colombia (see the registered document at the university in November, 2023 Supplementary Appendix 1). This manuscript follows the recommendations of the PRISMA statements to report Systematic Reviews.

### Eligibility Criteria

This systematic review included randomized controlled trials, quasi-experimental studies, cohort studies, and case series available in full text. Eligible studies involved women with a confirmed diagnosis of gestational syphilis or women with suspected or confirmed reinfection, previously untreated, at 28 weeks' gestation or beyond, who received antibiotic treatment with penicillin or other antibiotics ( $\beta$ -lactams or macrolides) with or without a comparison group. We excluded studies that did not report data specific to this gestational

age group. Studies published in Spanish, English and Portuguese, between 1999 and 2025 were searched, based on the adoption of the term “inadequately treated” in the 2005 CDC guidelines, which referred to treatment administered fewer than four weeks before delivery (20).

### Search strategy and databases

Searches were conducted by a specialist of the former STI Cochrane Group, in MEDLINE, EMBASE, and CENTRAL (see Supplementary Appendix 2), The strategy combined controlled vocabulary and freetext terms for “Syphilis”, “Pregnancy”, “Penicillins”, “Cephalosporines”, and related concepts. Syntax was refined using field codes, proximity operators and Boolean operators. Additionally, a snowballing technique was used to identify further relevant references. The initial search was performed in December 2023 and updated in June 2025. References were managed and de-duplicated using EndNote®.

### Screening and data extraction.

Two of three reviewers (AG, VM, and MTV) independently screened titles, abstracts, and full texts, and extracted data. Discrepancies were resolved by a fourth reviewer (HG). We used Rayyan software (21) to facilitate the screening process. Full texts of potentially eligible studies were reviewed to confirm inclusion and rule out exclusion criteria. Extracted data included study characteristics (design, sample size calculation, funding), population characteristics (trimester at diagnosis, gestational syphilis confirmation method, infection stage), treatment details (type of antibiotic, number treated, definitions of adequate/inadequate or complete/incomplete treatment, timing of administration relative to delivery), and outcomes.

### Risk of bias assessment.

We consider to use the ROB II tool (22) for RCTs and the ROBINS-I tool (23) for quasi-experimental and controlled cohort studies. Uncontrolled cohort studies were assessed using

a tool, developed by our team, to assess the risk of bias in series of subjects exposed to an intervention (see Supplementary Appendix 3). Case series were evaluated using the Joanna Briggs Institute checklist (24).

### Outcomes measured

Incidence of Congenital Syphilis, poor fetal outcomes, and maternal treatment failure (i.e., no serological titre decline post-treatment). Safety outcomes included systemic allergic reactions and Jarisch–Herxheimer reactions.

### Data synthesis and statistical analysis.

Effects of treatment are presented as CS incidence of by study type, outcome, and antibiotic used. Subgroup analyses were conducted based on time from treatment to delivery and treatment adequacy. The mother was the unit of analysis for treatment, and the foetus or neonate for outcomes. Incidence of Congenital Syphilis was pooled using meta-analysis of cumulative incidences, applying the direct method with a random-effects model (25). Where heterogeneity was high, we reported the range of estimates. Heterogeneity was assessed visually and using the  $I^2$  statistic.

**Certainty of evidence.** The certainty of the evidence was evaluated using the GRADE approach, considering risk of bias, inconsistency, directness, imprecision, and other factors. For observational studies, upgrading was considered when large effect sizes, dose–response relationships, or bias toward the null with consistent effect direction were present (26).

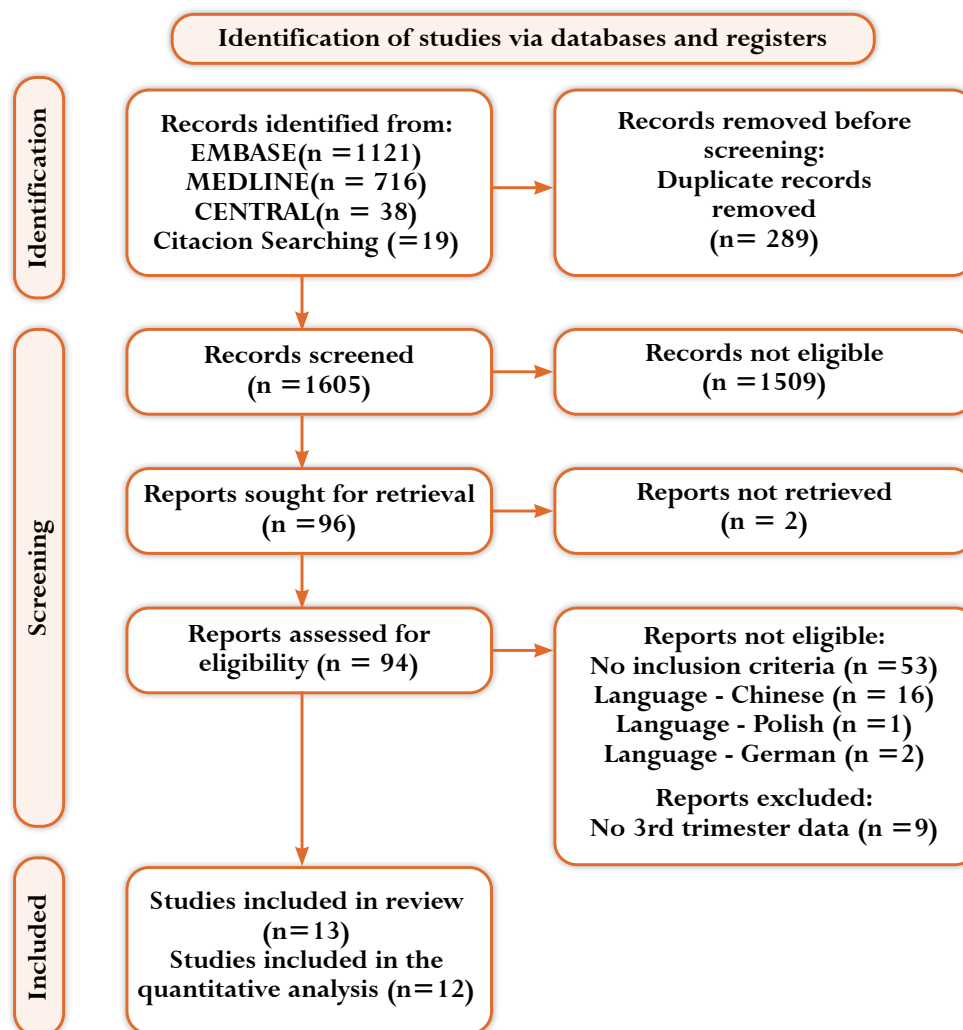
## RESULTS

### Screening and selection of studies

A total of 1,894 records were identified, of which 289 were excluded as duplicates. The remaining 1,605 titles and abstracts were screened for eligibility. Ninety-six articles were assessed in full text; of these, 53 did not meet the inclusion criteria, 19 were excluded due to language restrictions (Chinese:  $n=16$ ; German:  $n=2$ ; Polish:  $n=1$ ), nine did not report data specific to women in the

third trimester, and two were unavailable (see Supplementary Appendix 4). Thirteen studies were

ultimately included: ten cohort studies (12,27-35) and three case series (36-38) (Figure 1).



**Figure 1.** Flowchart of studies.

**Source:** Authors.

### Study characteristics

Eight of the ten cohort studies were retrospective, four were from China (27,28,32,34), and one each from the United States (12), Japan (30), Thailand (29), and Tanzania (33). Three of the ten were cohorts with control group (not treated) (28,32,34). Data sources included hospital records (12,29,30,33), administrative databases or information systems (27,28,32,34), and public health program records (31,35). The case series were conducted in the United States (36), Colombia (37), and Thailand (38). None of the included studies received industry funding.

The cohort studies collectively included 5,438 pregnant women diagnosed with syphilis in the third trimester, along with their respective fetuses. Diagnosis of maternal syphilis was based on a positive non-treponemal test confirmed by a treponemal test, with one study using the reverse algorithm (29). The stage of maternal syphilis at diagnosis was not reported in three studies (28,33,34) (Table 1). All studies diagnosed congenital syphilis neonatally, using between two and five clinical and paraclinical criteria. (Table 2).

**Table 1.**  
**Baseline characteristics of women with gestational syphilis who have received treatment in the last trimester of pregnancy.**

Author	Country	Year of the study	Type of study	Population third quarter	Diagnosis	Syphilis stage	Time between treatment and delivery
Alexander, J. et al (12) 1999	United States	1987 -1989	Retrospective cohort based on hospital population	77	VDRL o RPR/ Treponemal	Primary Secondary Early latent, late	< 12 w†
Dou et al (27) 2016	China	2013	Retrospective cohort based on administrative data	1966	Positive Treponemal and not treponemal test	Primary, Secondary, Early or late latent	< 12 w
Hong, F. et al (28) 2017	China	2003- 2014	Retrospective cohort Based on administrative data	551	TRUST / TPPA	Uninformed	<12 w‡
Lueng-mettakul et al (29) 2025	Thailand	2015-2021	Retrospective cohort based on hospital population	104	RPR/TPHA before 2017 Inverse algorithm after 2017	Primary, Secondary, Early or late latent	< 12 w
Nishijima, T. et al (30) 2020	Japan	2010- 2018	Retrospective cohort based on hospital population	14	RPR	Primary Secondary Early latent, late latent and unknown duration	< 8 w
Qin JB, et al (31) 2013	China	2007 - 2012	Prospective cohort (Public health program)	143	TRUST / TPPA	Early, latent, late	<10 w
Wan et.al. (32) 2020	China	2013-2019	Retrospective cohort based on information system	1234	RPR or TRUST / TPPA or ELISA	Primary, secondary, tertiary or latent.	
Watson-Jones, D. et al (33) 2002	Tanzania	1997-1999	Retrospective cohort based on hospital population	99	RPR/ Treponemal	Uninformed	< 12 w‡
Zhang X et al (34) 2016	China	2013-2014	Retrospective cohort based on administrative data	737	TRUST - RPR/ TPHA	Uninformed	< 12 w*
Zhu et al (35) 2010	China	2002-2006	Prospective cohort (Public health program)	630	RPR/ TPHA	Primary, Secondary, Early and late Latent,	< 12 w*

Camacho et al (36) 2021	Colombia	2016-2020	Case series	4 new-borns	Quantitative VDRL and hidrops fetalis	NA	> 28 weeks (3 cases)
Sheffield J, et al. (37) 2002	United States	1992 -1998	Case series	43 new-borns	Quantitative VDRL -RPR	NA	> 37 weeks (65%)
Yanase et al. (38) 2025	Thailand	2024-2025	Case series	5 new-borns	Quantitative VDRL/placenta (1 case) Hidrops fetalis	NA	> 26 weeks (4 cases) > 28 weeks (1 case)

Rapid plasma reagin (RPR), Treponema pallidum hemagglutination (TPHA), Treponema pallidum particle agglutination (TPPA), Tolidine red unheated serum test (TRUST)

\* Pregnant women over 28 weeks of age were included

† The mean gestational age at the time of syphilis treatment and at the time of delivery was 32.75 + 6.73 and 38.60 + 1.57 weeks respectively.

‡ Pregnant women over 30 weeks of age were included

§ Pregnant women over 32 weeks of age were included

Venereal Disease Research Laboratory (VDRL)

\*\* The number of patients who received Penicillin at third trimester

Source: Authors.

### Risk of bias assessment

All cohort studies were assessed as having a very high risk of bias (two or more domains rated as high risk) (Figure 2 and Supplementary

Appendix 5). None of the studies reported a sample size calculation. The case series scored 6/10 (37), 7/10 (36), and 9/10 (38) on the Joanna Briggs Institute checklist (Supplementary Appendix 5).

Study	Selection risk of bias	Detection and performance risk of bias	Missed data risk of bias	Confusion risk of bias	Risk of bias	Other problems
Alexander, J. et al. (12) 1999	Low	High	Unclear	High	Very High	Weak methodology for causal inference
Dou et al (27) 2016	Low	High	Unclear	High	Very High	Weak methodology for causal inference
Hong, F. et al (28) 2017	High	Low	High	High	Very High	Weak methodology for causal inference
Luengmettakul et al (29) 2025	High	High	Low	High	Very High	Weak methodology for causal inference
Nishijima, T. et al (30) 2020	High	Low	Low	High	Very High	Weak methodology for causal inference
Qin JB, et al (31) (2013)	High	High	High	High	Very High	Weak methodology for causal inference
Wan Z et al (32) 2020	Low	High	Low	High	Very high	Weak methodology for causal inference
Watson-Jones D. et al 2002 (21)	High	Low	High	High	Very High	Weak methodology for causal inference
Zhang X et al (34) 2016	Unclear	High	Low	High	Very High	Weak methodology for causal inference
Zhu et al (23)	Unclear	High	Low	High	Very High	Weak methodology for causal inference

**Figure 2.** Risk of bias in cohorts without control assessing use of antibiotics gestational syphilis in the last trimester of pregnancy.

Source: Authors.

## Effect of treatment in cohort studies

### 1. Congenital syphilis

1.1. Seven studies (12,27,28,31,32,34,35) assessed the use of penicillin in 5,155 fetuses exposed to gestational syphilis during the third trimester. The pooled incidence of congenital syphilis might be 8% (95% CI: 5–11%;  $I^2 = 97.2\%$ ). Certainty of evidence: low (very high risk of bias; heterogeneity and upgraded one level due to magnitude of effect) (Figure 3A). Higher heterogeneity was observed

in studies mixing in one group incomplete and not treated women with GS treatment cohorts (31,35) (range: 3–28%; 2,739 patients). Two studies (12,31,35) assessed benzathine penicillin G in 159 fetuses treated within the last four weeks of gestation, with congenital syphilis incidence ranging from 6.5% to 23.4%. However, the actual effect is uncertain due to very low certainty of evidence (very high risk of bias; imprecision) (Table 2).

**Table 2.**  
Effectiveness and safety of antibiotics for treating gestational syphilis in the last trimester. Maternal and perinatal outcomes

Study	Type of treatment	Diagnosis of CS	CS incidence (95%CI)	Last 4 weeks (95%CI)	Maternal treatment failure (95%CI)	Adverse events incidence (95%CI)
Alexander, J. et al. (12) 1999	Benzathine penicillin G	1. Abnormal physical examination consistent with CS 2. NTT 4-fold higher than mother at delivery 3. Placenta with syphilis infection	4/77 - (5.2%) (1.4% to 12.8%) <sup>a</sup>	2/31 6.5% (0.8% to 21.4%)	1/77 1.3% CI (0.1 - 6.2) <sup>b</sup>	-
Dou et al (27) 2016	Benzathine penicillin G or procaine penicillin	1. Positive TT and NTT 4-fold higher than mother at delivery 2. IGM positive for Tp 3. To in dark-field microscopy	67/1966 – 3.4% (2.7% to 4.3%)	NR <sup>c</sup>	-	-
	Untreated + treated after 37 weeks		341/8795 – 3.97% (3.50-4.30)			
Hong, F. et al (28) 2017	Benzathine penicillin G or procaine penicillin	1. NTT 4-fold higher than mother at delivery 2 A four-fold or greater rise in NTT titre during the follow-up 3. A reactive 19S-IgM-TPPA 4 A reactive NTT that did not revert to nonreactive by end of 18 months' follow-up	11/551 – 2.15% (1.1% to 3.8%)	-	-	-
	No treated		141/1153 - 12.23% (10.4% to 14.3%)			
Lueng-mettakul et al (29) 2025	Benzathine penicillin G	1. Abnormal physical examination consistent with CS 2. NTT 4-fold higher than mother at delivery 3. Placenta with syphilis infection	NR <sup>h</sup>	NR <sup>h</sup>	-	-
Nishijima, T. et al (30) 2020	Aminopenicillins	1. Serum NTT titer >4-fold that of the mother's 2. (FTA-ABS) test result positive for serum IgM 3. Lesion tissue or body fluid samples positive by PCR 4 lesion or fluid samples positive for T. p on dark field microscopy 5. Abnormal physical examination consistent with CS	6/14 – 42.9% (19.6% to 68.9%) <sup>f</sup>	-	2/14 14.3% (1.8% to 42.8%)	3/14 21.4% (4.7 % to 50.8%)

Qin JB, et al (31) (2014)	Benzathine penicillin G	1. A positive dark-field or fluorescent antibody test of body fluid 2. Abnormal physical examination consistent with CS and NTT 4-fold higher than mother at delivery 3. FTA-ABS 19S IgM test 4. A reactive NTT test 18 months after birth	26/143 – 18.2% <sup>d</sup> (12.2% to 25.5%)	30/128 – 23.4% (16.4% to 31.7%)	-	-
Wan Z et al (32) 2020	Penicillin, not specified	1. Positive TT and Non TT 4-fold higher than mother at delivery	34/1234 – 2.8% (1.9% to 3.8%)	-	-	-
	No treated	2. IGM positive for Tp 3. To in dark-field microscopy	30/1364 – 2.2% (1.5% to 3.1%)	-	-	-
Watson-Jones, D. et al (33) 2002	Benzathine penicillin G	-	-	-	-	-
Zhang X et al (34) 2016	Benzathine penicillin G or procaine penicillin	1. Serum NTT titer >4-fold that of the mother's 2. Abnormal physical examination consistent with CS 3. positive Non TT tests lasting until 18 months after birth	19/737 – 2.6% (1.6% to 4%)	-	-	-
	No treated	4. Infants with positive IgM 5. Treatment to mother less than 30 days to delivery	28/745 -3.8% (2.5% to 5.4%)	-	-	-
Zhu et al (35) (2010)	Benzathine penicillin G (2 dose for early- 3 dose for late)	1. Congenital syphilis is syphilis in an infant whose mother has transmitted the infection vertically to the fetus	175/630 -27.8% (24.3% to 31.5%) <sup>d</sup>	-	-	-

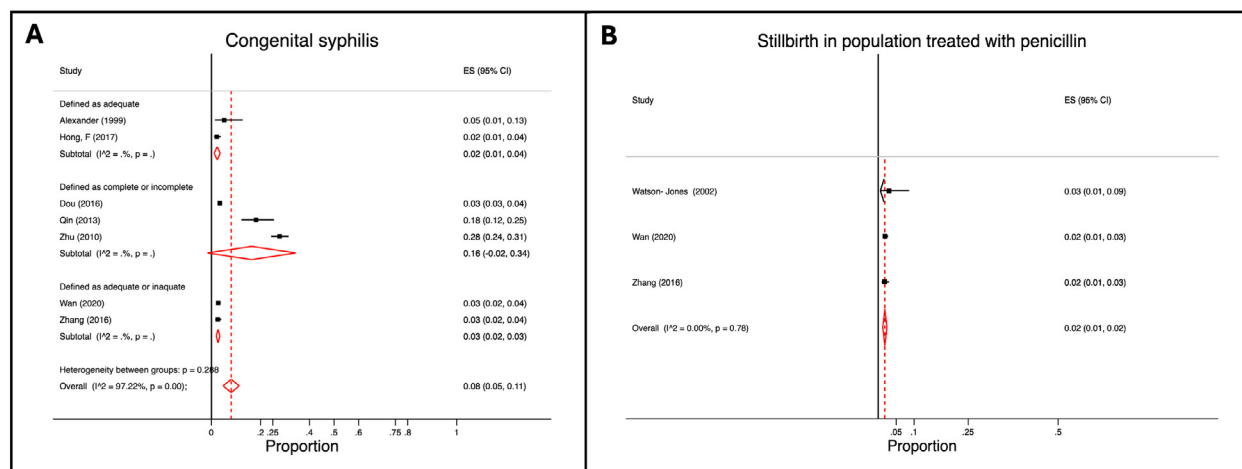
95%CI: 95%Confidence Interval

The 95% confidence interval was estimated by the authors of the SR as it is not contained in the manuscripts of the included studies.

CS: Congenital syphilis TT : treponemal Tests. NTT No treponemal test

- Women from 30 – 42 weeks of GA were included. However, women from 26 – 30 of GA were also included. Taking into account this group CS cumulative incidence was 3.7%. 4/6 cases were treated in the last 2 weeks of pregnancy
- One woman was HIV infected
- Prematurity by Ultrasound or LMP. Dubovitz was also performed. With this test prematurity incidence was 5.8%. Poor pregnancy outcomes were 28,5% in high- titer active syphilis and 18,1 for low-titer active syphilis
- Data were not adjusted by complete or incomplete treatment (25%)
- The denominator combines treated and untreated women for GS
- Women initiating treatment < 60 days before delivery were analysed. Women treated > 60 days CS cumulative incidence was 14%
- NR: Data published not reported because the proportions included untreated women.
- The authors combined untreated women with those treated fewer than 30 days before delivery, as well as women who received an incomplete treatment regimen prior to delivery. Among women treated after 28 weeks' gestation, the study reported a congenital syphilis incidence of 23 out of 104 cases; however, the cumulative incidence of congenital syphilis is not reported consistently throughout the publication.

**Source:** Authors.



**Figure 3.** Incidence of CS and Stillbirths in women with GS treated with penicillin in the third trimester of pregnancy (A. Congenital Syphilis n= 5298; B. Stillbirth n= 2070).  
**Source:** Authors.

1.2. One cohort (30) evaluated the use of aminopenicillins in 14 fetuses exposed to syphilis eight weeks prior to delivery. The incidence of congenital syphilis could be 42.9% (95% CI: 19–69%). Certainty of evidence: low (high risk of bias; imprecision; and upgrade because substantial magnitude of treatment failure).

1.3. Three studies (28,32,34) reported the incidence of congenital syphilis in 3,262 pregnant women who did not receive any treatment. Incidence ranged from 2% to 12.2%, but the effect remains uncertain due to very low certainty of evidence (very high risk of bias; imprecision) (see Supplementary Appendix 6 Figure S1). One study (27) reported a cohort of 8,795 women with gestational syphilis, which included both untreated women and those who received treatment less than 30 days before delivery; the reported incidence of congenital syphilis was 3.97%.

## 2. Maternal treatment failure

One cohort (12) evaluated treatment failure in 77 women treated with benzathine penicillin G according to syphilis stage. Incidence was 1.3% (95% CI: 0.03–7%), but incidence of failure may be higher or lower because certainty of evidence: very low (high risk of bias; heterogeneity; imprecision). Another study (30) assessed 14 pregnant women treated with amoxicillin or ampicillin for 30–78

days; failure rate was 14.3% (95% CI: 1.8–42.8%). Certainty of evidence: low (high risk of bias; imprecision; upgraded due to frequency of failures).

## Secondary Outcomes

### 3. Stillbirth due to gestational syphilis

3.1. Three studies (32-34) reported on stillbirth in pregnant women treated with penicillin. The pooled incidence was 2% (95% CI: 1–2%; 2,070 patients) (Figure 3B).

3.2. In the study by Nishijima et al. (30), stillbirth occurred in one of 14 women treated with aminopenicillins (7%; 95% CI: 0.2–33.9%) (Table 2).

3.3. Two studies (32,34) reported stillbirths among 2,109 untreated women. Incidence ranged from 1.8% to 3.1%. Nevertheless, the effect of antibiotics in stillbirth is uncertain because certainty of evidence is very low because (very high risk of bias; heterogeneity; imprecision).

### 4. Prematurity

4.1. Three studies (32-34) reported preterm birth in 2,075 women treated with penicillin. Incidence ranged from 12.2% to 14.6%, with substantial heterogeneity (I<sup>2</sup> = 81.83%) (Supplementary Appendix 6 Figure S2).

4.2. Watson-Jones et al. (33) additionally assessed prematurity using the Dubowitz score in 69 women, reporting a 5.7% incidence (95% CI: 1.6–14.2%) (Table 2).

4.3. Two studies (32,34) reported preterm birth in untreated women; incidence ranged from 10.5% to 14% (2,109 participants) (Table 2).

Though prematurity incidence might be higher or lower because certainty of evidence was qualified very low (very high risk of bias; heterogeneity; imprecision).

## 5. Safety

5.1. None of the included studies assessed serious adverse events.

5.2. One cohort (30) evaluated non-serious adverse events in 14 women treated with aminopenicillins. Mild adverse events occurred in 21.4% (95% CI: 4.7–50.8%). However, the estimation is uncertain due to very low evidence (very high risk of bias; imprecision) (Table 2).

### Effect of treatment in case series

Three case series were included. In one study (37), 43 neonates with confirmed congenital syphilis were reported. Among them, 32 mothers (74%) had received benzathine penicillin G during the third trimester; 28 were treated less than 30 days before delivery. Of these, 68% (19/28) delivered within 10 days of treatment, and 50% of deliveries were preterm.

A second case series (36) described four cases of congenital syphilis with hydrops fetalis. Two women were diagnosed with GS at 26 and 29 weeks of gestation and treated with intravenous aqueous crystalline penicillin G (5 million units every 4 hours for 14 days). Hydrops resolved in both foetuses. At delivery, maternal VDRL titres declined (from 1:64 to 1:2 at 37 weeks and from 1:32 to negative at 36 weeks). Neither neonate had clinical or radiological signs of congenital syphilis; VDRL titres were 1:8 and negative, respectively. Both infants received a prophylactic intramuscular dose of aqueous crystalline penicillin G (50,000 units). No follow-up data at six months were available.

The third case series (38) reported five cases of congenital syphilis with hydrops fetalis. Four were diagnosed at 26 weeks' gestation, and one beyond 28 weeks. Two women received intravenous

aqueous crystalline penicillin G; both neonates responded favorably. Of the three women who received intramuscular benzathine penicillin G, two delivered neonates with congenital syphilis and one neonate responded to treatment. The certainty of evidence was very low (very high risk of bias; imprecision), rendering the actual effect uncertain.

## DISCUSSION

This systematic review on the effects of benzathine penicillin G for the treatment of gestational syphilis in the third trimester informs absolute incidence of congenital syphilis might be of 8%. However, substantial heterogeneity was observed, which may in part be explained by the inclusion of studies that combined adequately and inadequately treated cases or complete and incomplete treatment regimens (see Supplementary Material Appendix 6). Furthermore, the use of aminopenicillins appears to be associated with a higher incidence of treatment failure (14%) and a notably elevated incidence of congenital syphilis (43%). The effectiveness of benzathine penicillin G administered four weeks before delivery in preventing congenital syphilis remains uncertain. In addition, safety data on its use during the third trimester are limited.

Amplitude of the search and applicability of the evidence. We conducted a comprehensive search across three major databases and supplemented it with snowballing. A limitation of our approach was the inclusion of only three languages. Our findings support current guideline recommendations regarding the benefit of benzathine penicillin G for managing gestational syphilis and preventing congenital syphilis in the third trimester. The available evidence neither confirms nor refutes the adequacy of benzathine penicillin G when administered within 30 days of delivery.

Comparability of results. We identified three systematic reviews (SRs) evaluating the effects of benzathine penicillin G in gestational syphilis during the third trimester (38–40). Qin et al. (40) conducted a review comparing perinatal outcomes in women with gestational syphilis versus those

without syphilis. This SR was rated as low quality (AMSTAR 2: 6/16). In a subgroup analysis of 19 studies involving treatment after 28 weeks' gestation, the pooled incidence of congenital syphilis was 40.6% (95% CI: 31.3–50.7), notably higher than our estimate. This discrepancy may be explained by the predominance of Chinese studies (17/19), which may differ in diagnostic thresholds and treatment standards. It was also unclear whether cases of possible congenital syphilis were misclassified as confirmed, potentially introducing detection bias. Three studies included in our review (31,33,35) were also included in theirs. Another SR by Pascoal et al. (39) investigated risk factors for congenital syphilis (AMSTAR 2: 7/16). While it included eight cohort studies, it did not report congenital syphilis incidence among infants born to women diagnosed and treated after 28 weeks. One of its included studies overlapped with ours (28).

The use of intravenous aqueous crystalline penicillin G during the third trimester was addressed in a review of case series by Yanase et al. (38), which included the study by Camacho et al. (36). That review reported nine cases of hydrops fetalis in foetuses of mothers treated with intravenous aqueous crystalline penicillin G. Six had a complete response, two partial responses, and one resulted in intrauterine death. Five of the complete responses occurred in foetuses diagnosed at or beyond 28 weeks. In contrast, of nine foetuses treated with intramuscular benzathine penicillin G, only two had complete responses, four partial, and three had no response two of whom died in utero. The authors hypothesised that intravenous aqueous crystalline penicillin G may offer advantages in cases involving systemic infection. Although based on low-certainty evidence from case series, this observation raises a plausible hypothesis: that intravenous penicillin G could be beneficial in treating foetuses infected with *T. pallidum* late in gestation. Therefore, the safety and efficacy of maternal intravenous aqueous crystalline penicillin G during the third trimester require further evaluation.

Limitations. A potential limitation of this review is selection bias from excluding studies published before 1999. However, studies from earlier decades often lacked clear definitions of “possible syphilis”, a term formally introduced in 2005 (4). We did not assess publication bias. Additionally, reporting of safety outcomes across treatment alternatives was limited.

Implications for clinical practice. Until more robust evidence becomes available, pregnant women diagnosed with gestational syphilis before 37 weeks' gestation should receive at least one intramuscular dose of benzathine penicillin G. If delivery occurs within 30 days of treatment, the neonate should be managed in accordance with current guidelines for “possible congenital syphilis”, including a 10-day course of intravenous aqueous crystalline penicillin G (4,13,14).

Implications for research Although only case series suggest that maternal intravenous aqueous crystalline penicillin G may prevent congenital syphilis in foetuses infected in utero prior to maternal treatment, these findings point to a potential therapeutic window during the final four weeks of pregnancy. This is supported by the following considerations:

- a) Between 2.5% and 27% of neonates with congenital syphilis may have central nervous system (CNS) involvement (41-43).
- b) The only effective treatment for neurosyphilis is aqueous crystalline penicillin G (4), which crosses the inflamed blood–brain barrier more effectively than benzathine penicillin G (44,45).
- c) This is biologically plausible, given that aqueous crystalline penicillin G crosses the placenta and achieves foetal concentrations equivalent to maternal levels (46).
- d) Current guidelines recommend hospitalization and invasive therapy for neonates with “possible congenital syphilis”, increasing the theoretical risk of healthcare-associated infections (47). This risk could potentially be mitigated by administering intravenous aqueous crystalline

penicillin G to the mother for 10 days before delivery, thereby achieving therapeutic foetal levels. Therefore, randomized controlled trials are needed to compare the maternal and neonatal outcomes of intravenous aqueous crystalline penicillin G versus benzathine penicillin G when administered up to eight weeks before delivery

## CONCLUSION

Treatment of gestational syphilis with benzathine penicillin G during the third trimester is effective in reducing the risk of congenital syphilis. However, as its efficacy remains uncertain when administered fewer than 30 days before delivery, neonates born within this period should continue to be managed according to current guidelines for possible congenital syphilis. Aminopenicillins appear to be associated with a high rate of treatment failure. Alternative strategies to treat the foetus during the final four weeks of pregnancy are needed to reduce the risk of congenital syphilis.

### Ethical issues

The project was approved by the Medical School Ethical Committee at the Universidad Nacional de Colombia. Minute number 001 of 2023

### Differences between protocol and review:

- We changed the inclusion of studies by type of treatment from those that compare antibiotic treatment with any type of penicillin and alternative treatments by inclusion of studies that used any penicillin or other antibiotics ( $\beta$ -lactams or macrolides) with or without a comparison group. Based on the fact we found some cohorts without control group that evaluate the congenital syphilis incidence. We included studies published in Portuguese.
- We prioritized first perinatal outcomes over maternal outcomes.
- Cohorts were not evaluated by using the Newcastle – Ottawa tool. The assessment bias for a series of exposure to intervention without

a control group was done with a tool included in supplementary material designed by our group.

- Since current guidelines for the management of gestational and congenital syphilis recommend considering as “infected” all neonates born with less than 4 weeks of treatment, the more important effect measure is the actual cumulative incidence of congenital syphilis in those neonates whom receive any antibiotic treatment, taking into consideration the time between treatment and the delivery. Likewise, this approach allow us to estimate the antibiotic effect in the newborn, in cohorts with or without control group. Therefore, it is more appropriate to use the pooled estimate of incidence or absolute risk of congenital syphilis as the primary outcome measure.

We did not estimate Relative Risk or Odds ratio because this approach is appropriate when the a priori hypothesis assumes no difference between two options, such as comparing treatment versus no treatment. Therefore, in this context, the use of relative risk or risk difference may not be informative.

### Author contribution

AMGT and LVMC contributed to protocol development, initial search, study selection, data extraction, and the writing and review of the final manuscript.

MTVO contributed to the updated search, study selection, data extraction, analysis, and the writing and review of the final manuscript.

HGGD contributed to protocol development, initial search, study selection, data extraction, analysis, and the writing and review of the final manuscript.

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## **COMPETING INTEREST STATEMENT**

AMTM, LVMC, and MTVO declared that they have no conflicts of interest.

HGGD declared a potential conflict of interest due to his position as Editor-in-Chief of the Colombian Journal of Obstetrics and Gynecology. He states that the manuscript was evaluated by three independent peer reviewers and that the journal's standard editorial process was fully followed. The reviewers' reports are available for inspection if required.

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