

Alternative Treatments for Syphilis During Pregnancy

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SYPHILIS IN PREGNANCY

Syphilis in pregnancy continues to be a problem worldwide. In the United States, the rate of congenital syphilis continues to rapidly rise with the highest number of cases reported in 2017 since 1997.¹ In fact, congenital syphilis is among the most common neonatal infections contributing to early infant mortality. There are more cases of congenital syphilis than perinatally acquired human immunodeficiency virus infection.²

If a pregnant woman is infected with syphilis and not properly treated, the fetus has up to an 80% likelihood of being infected.¹ Syphilis infection during pregnancy is associated with miscarriage, stillbirth, or neonatal death shortly after delivery in 30% of cases.³ If the fetus survives, the pregnancy may be complicated by preterm birth, low birth weight, and congenital syphilis.^{2,3} Early congenital syphilis is associated with bone deformities, rashes, jaundice, lethargy, and anemia.⁴ Later consequences of congenital syphilis include neurological impairment, sensorineural deafness, and blindness due to interstitial keratitis.⁴

The current standard of care for the treatment of syphilis acquired during pregnancy is benzathine penicillin G, as a single intramuscular injection of 2.4 million units.⁵ Benzathine penicillin G treatment is highly effective. The success of benzathine penicillin G treatment is as high as 98.2% in the prevention of congenital syphilis.⁶ In nonpregnant patients, doxycycline⁷ and ceftriaxone⁸ are accepted alternative treatments; however, benzathine penicillin G is the only recommended treatment for syphilis in pregnancy.⁵

In the case of penicillin allergy, the only treatment recommendation is penicillin desensitization followed by treatment with benzathine penicillin G.⁵ One third or more pregnant women may undergo allergic reactions during desensitization procedures⁹; therefore, the desensitization process requires close monitoring by experienced personnel.⁹ Another challenge for the treatment of syphilis during pregnancy is the access to benzathine penicillin G. There have been stockouts and shortages of benzathine penicillin G globally and multiple disruptions in manufacturing and the supply chain.^{10,11} Additionally, in many settings, it may be preferable to administer oral medications instead of injections. New and alternative treatments are urgently needed.

Therefore, to assess the current evidence for alternative treatments and describe the path forward, we reviewed published alternative treatments for pregnant women diagnosed with syphilis.

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REVIEW OF PRIOR EXPERIENCE WITH ALTERNATIVE TREATMENTS

We searched 3 databases: PubMed, Embase, and Scopus between the dates of January 1, 1970, and December 31, 2018. We examined cases of nonpenicillin treatments of syphilis in pregnant patients and excluded studies involving only penicillin.

We defined successful maternal treatment as both a 4-fold decline in maternal rapid plasma reagin (RPR) titer from the time of diagnosis compared with the time of delivery and the resolution of presenting clinical findings. Congenital syphilis prevention was defined as the absence of congenital syphilis.

We identified 6 publications between 1970 and 2018 that described alternative treatments for syphilis in a total of 21 pregnant patients (see Table 1). There were no publications reporting more than 15 cases or any randomized or comparative controlled trials that investigated alternative treatments for syphilis during pregnancy.

Amoxicillin

In a case series by Katanami et al.¹² in Japan, the authors reported 2 case patients treated with oral amoxicillin as an alternative to penicillin. Although, in Japan, benzathine penicillin G is the recommended treatment for syphilis in pregnancy, the authors report that benzathine penicillin G is not routinely available, and they typically use benzylpenicillin benzathine hydrate, amoxicillin, or ampicillin as alternatives.¹² In their case series, one mother at 13 weeks of gestation received oral amoxicillin 6 g and probenecid 1 g daily for a 14-day course.¹² The second case patient at 6 weeks of gestation received oral amoxicillin 1.5 g with probenecid 750 mg daily for treatment days 1 to 3, oral amoxicillin 3 g daily with probenecid 750 mg daily for treatment days 4 to 6, and intramuscular ceftriaxone 2 g daily for treatment days 7 to 14.¹² Case patient 1 had a decline in RPR titer from 1:16 to 1:4 6 months after treatment. Case patient 2 had a decline in RPR titer from 1:32 to 1:4 6 months after treatment. The newborns had no evidence of congenital syphilis.¹²

Cephalosporin Antibiotics

As reported above, one of the Katanami et al.¹² cases described the successful use of intramuscular ceftriaxone in conjunction with oral amoxicillin for the treatment of syphilis during pregnancy with the prevention of congenital syphilis. Zhou et al.¹³ reported 11 pregnant women with primary or secondary syphilis treated with intramuscular ceftriaxone. In 3 case patients with primary syphilis, each received a 7-day course of intramuscular ceftriaxone 250 mg, which was repeated at 28 weeks of gestation for 1 case patient. In 8 case patients with secondary syphilis, each received a 10-day course of intramuscular ceftriaxone 250 mg, which was repeated at 28 weeks of gestation in 7 case patients.¹³ Researchers reported that all case patients were successfully treated, and their newborns had no evidence of congenital syphilis.¹³

Macrolide and Azalide Antibiotics

Fenton and Light¹⁴ reported a case of a 32-week pregnant woman who was treated with oral erythromycin stearate 750 mg

TABLE 1. Alternative Options to Penicillin for Treatment of Syphilis During Pregnancy

Author	n	Antibiotic	Dosage	Route	Frequency	Population	Penicillin Allergy	Outcome	Adverse Reactions	Notes
Katanami et al.	2	Amoxicillin and probenecid, Ceftriaxone	*Variable doses	Oral (amox) IM (Ceftriaxone)	Daily for 14-day course	Pt 1: 13 weeks of gestation Pt 2: 6 weeks of gestation	Not reported	Maternal: decline in RPR titers Fetal: no evidence of congenital syphilis	Pt 2 developed hyperemesis gravidarum and unable to tolerate orals. Required change to Ceftriaxone	Pt 1: amoxicillin 6 g, probenecid 1 g Pt 2: amoxicillin 1.5 g and probenecid 750 mg for Days 1–3, amoxicillin 3 g and probenecid 750 mg for Days 4–6, Ceftriaxone 2 g IM for Days 8–14 7-day course for primary syphilis, 10-day course for secondary syphilis. Repeated at 28 weeks of gestation (8/11 patients repeated for 7 or 10 days depending on stage)
Zhou et al.	11	Ceftriaxone	250 mg	IM	Daily *Variable courses	4–18 weeks of gestation	All patients	Maternal: decline in RPR (>4 fold decline) and symptoms Fetal: no evidence of congenital syphilis	3 patients with Jarisch-Herxheimer reaction. No fetal distress	
Fenton and Light	1	Erythromycin	750 mg	Oral	Four times daily for 12-day course	32 weeks of gestation	Yes	Maternal: RPR decline (>4 fold decline) Fetal: congenital syphilis at birth		
Hashisaki et al.	1	Erythromycin	500–800 mg	Oral	Four times daily for 15-day course × 2	26 weeks of gestation	Yes	Maternal: Failed treatment. Required penicillin desensitization Fetal: evidence of congenital syphilis, may have been treated in utero with penicillin		First course: erythromycin ethylsuccinate 800 mg Second course: erythromycin stearate 500 mg
Zhou et al.	5	Azithromycin	1 g	Oral	Daily *Variable courses	16–28 weeks of gestation	All patients	Maternal: successful treatment Fetal: all 5 infants with congenital syphilis		1–10 day course 3/5 patients received second course at 32 weeks of gestation
Mascola et al.	1	Tetracycline	500 mg	Oral	Four times daily for a 2 week course	8 th month gestation	Not reported	Maternal: Failed treatment. Required Penicillin. Fetal: At 10 weeks diagnosed with congenital syphilis (1:128)		

*Variable courses: refers to the notes in the final column of the table and has further clarifications on treatment course. All antibiotics are US Food and Drug Administration Category B in pregnancy, with the exception of tetracycline, which is Category D in pregnancy. Pt, patient.

4 times daily for 12 days. She had at least a 4-fold decline in RPR titer; however, the newborn had evidence of secondary syphilis at 11 weeks of life.¹⁴ In another case report by Hashisaki and Wertzberger,¹⁵ researchers reported a pregnant woman at 26 weeks of gestation with a syphilis chancre who was treated with oral erythromycin ethylsuccinate 800 mg four times daily for 15 days. The chancre did not improve with the treatment course; therefore, investigators prescribed an additional course of oral erythromycin stearate 500 mg, 4 times daily for 15 days.¹⁵ Despite that repeated treatment, she developed a macular rash and ultimately was successfully treated with penicillin desensitization and benzathine penicillin G.¹⁵ In a series of 5 pregnant case patients, researchers reported on 3 case patients treated with oral azithromycin 1 g daily for 1, 5, and 10 days each and 2 case patients treated with intravenous azithromycin 1 g for 3 and 7 days; 3 of the 5 case patients received a second course of azithromycin between 28 and 32 weeks of gestation.¹⁶ All 5 newborns were born with evidence of congenital syphilis, despite successful maternal treatment.¹⁶

Tetracycline

Mascola et al¹⁷ described one case of tetracycline treatment. The case patient had initial prenatal labs that were negative for syphilis.¹⁷ During her eighth month of pregnancy, she was treated for a urinary tract infection with oral tetracycline 500 mg four times daily for a 2-week course.¹⁷ At the time of delivery, 3 weeks later, the patient tested positive for syphilis with a venereal disease research laboratory test titer of 1:4 and a reactive microhemagglutination assay-*Treponema pallidum*; however, the neonate had nonreactive serologies.¹⁷ Investigators treated the mother with 2.4 million units of benzathine penicillin G. At 10 weeks of age, the infant was diagnosed with congenital syphilis through positive serologies, including a venereal disease research laboratory test titer of 1:128.

THE WAY FORWARD

Overall, we found very limited published evidence for alternative treatments of maternal syphilis. We found 21 cases of patients treated with penicillin alternatives (13 with beta-lactam antibiotics, 7 with macrolide antibiotics, 1 with tetracycline). The 13 treated with beta-lactam antibiotics had successful treatment. We found no randomized controlled trials comparing the established and accepted standard of care, benzathine penicillin G, against any other antibiotic, despite the development of hundreds of new antibiotics since the 1950s.

Based on our findings, certain classes of antibiotics should be prioritized for further clinical research for syphilis in pregnant patients. Amoxicillin is structurally very similar to penicillin and has demonstrated promising results.¹² Amoxicillin would likely be preferred due to its high oral bioavailability, although it should be noted that pregnant patients may require higher doses of amoxicillin and the optimal dose is unknown.¹⁸ Amoxicillin does pass through the placenta and achieve high levels in amniotic fluid.¹⁹ However, in the reported cases oral probenecid was used with amoxicillin. Probenecid is not readily available in most parts of the world. Additionally, amoxicillin will not address the concern of treatment in the case of penicillin allergy; however, it could increase access to treatment, particularly in regions without reliable access to benzathine penicillin G.^{10,11}

Third-generation cephalosporins should also be considered as potential alternative treatments with the limited evidence that ceftriaxone can adequately treat syphilis during pregnancy.¹³ Ceftriaxone has been accepted as an alternative in nonpregnant patients.⁸ The CDC states that the alternative treatment course in nonpregnant patients is 10–14 days of intramuscular or intravenous ceftriaxone, which poses a significant burden on health systems

and the patient.⁵ An oral third-generation cephalosporin, like cefixime, which has demonstrated high transplacental transfer, may be more practical and advantageous.²⁰ Due to the absence of clinical studies, cefixime is not currently recommended as an alternative treatment in nonpregnant patients. We are conducting a phase 2 trial of cefixime 400 mg by mouth twice daily for 10 days in patients with early syphilis. Early results are promising.²¹ A phase 1/2 trial by the World Health Organization will begin recruiting in later 2019 to test cefixime at the same dose, frequency and duration in nonpregnant women with early syphilis.²² If cefixime is efficacious in those trials in nonpregnant populations, we expect that cefixime will move into clinical trials in pregnant patients. Planning for those trials should start now.

Macrolide and azalide (azithromycin) antibiotics have been explored as treatment for syphilis in pregnancy, but we found 9 cases of treatment failure in the prevention of congenital syphilis.^{14–16} Furthermore, a pharmacokinetic study showed that macrolide and azalide antibiotics (erythromycin, roxithromycin, and azithromycin) had limited transplacental transfer (<5%); therefore, the authors of that study did not recommend those antibiotics for the treatment of maternal infections due to their unlikely fetal benefit.²³ Further making the use of macrolide or azalide antibiotics challenging has been the development of azithromycin-resistant strains of *Treponema pallidum* documented worldwide.^{24,25}

One case report of tetracycline failure was described; however, the interpretation of that case report may be limited because tetracycline was incidentally prescribed for a urinary tract infection, and it is unknown when the patient contracted syphilis.¹⁷ If she was infected during the course of antibiotic treatment or shortly after, she would have received inadequate treatment. In the treatment of nonpregnant populations, doxycycline is an accepted alternative for the treatment of syphilis.⁵ Historically, tetracyclines, including doxycycline, have been labeled as US Food and Drug Administration Category D in pregnancy due to the side effects of maternal hepatotoxicity and teratogenicity, including stunted bone growth and permanent teeth discoloration in the developing fetus.²⁶ However, in a systematic review conducted by Cross and colleagues regarding the safety of doxycycline in pregnancy and young children, there was no documented evidence of those dangerous side effects.²⁶ Doxycycline was developed after the tetracycline class was associated with those adverse effects and was never separately studied.²⁶ Regardless, it is uncertain the medical community would be willing to study doxycycline given the risk of teratogenicity with tetracycline when other potential treatment alternatives do not pose significant fetal risk.

Although there is very little published research on alternatives to benzathine penicillin G syphilis treatment in pregnancy, there are several studies exploring alternative syphilis treatments in nonpregnant patients.^{7,8,27,28} Pregnant patients are viewed as a vulnerable population, and systematically omitted from studies to avoid undue maternal and fetal harm; however, it can be argued that this approach has resulted in potentially worse outcomes for pregnant patients and their unborn children due to fewer established treatment options. In fact, this knowledge and research gap has been acknowledged by the National Institutes of Health (NIH), which has established the Task Force on Research Specific to Pregnant Women and Lactating Women.²⁹ We advocate that pregnant patients and newborns would greatly benefit from additional research into alternative treatments of syphilis in pregnant patients. Pregnant women need to be a priority population for syphilis treatment research.

In order to adequately address the growing epidemic of maternal and congenital syphilis in the global setting of a benzathine penicillin G shortages, we will need to identify alternative treatments of syphilis in pregnant patients. We propose that research should be

focused on amoxicillin and third-generation cephalosporins, which are already considered safe in pregnancy. Although our conclusion is based on limited case studies of patients treated with beta lactam antibiotics, in all the cases found, both the mother and child were treated successfully. To achieve to identify new evidence-based treatments, the medical community will need to support research in pregnant patients, which will hopefully be championed by advocates, community leaders and NIH's new task force.

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