

# Treatment of Syphilis in Pregnancy and Prevention of Congenital Syphilis

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**Studies about the management of syphilis during pregnancy were reviewed. They lacked uniformity in diagnostic criteria and study design. Currently recommended doses of benzathine penicillin G are effective in preventing congenital syphilis in most settings, although studies are needed regarding increased dosing regimens. Azithromycin and ceftriaxone offer potential alternatives for penicillin-allergic women, but insufficient data on efficacy limit their use in pregnancy. Ultrasonography provides a noninvasive means to examine pregnant women for signs of fetal syphilis, and abnormal findings indicate a risk for obstetric complications and fetal treatment failure. Ultrasonography should precede antepartum treatment during the latter half of pregnancy to gauge severity of fetal infection. However, optimal management of the affected fetus has not been established; collaborative management with a specialist is recommended. Antepartum screening remains a critical component of congenital syphilis prevention, even in the era of syphilis elimination.**

Syphilis in pregnancy is an infection with widespread complications for both the infected woman and her fetus. Maternal syphilis has been associated with obstetric complications such as hydramnios, abortion, and preterm delivery; fetal complications such as fetal syphilis, hydrops, prematurity, fetal distress, and stillbirth; and neonatal complications such as congenital syphilis, neonatal death, and late sequelae. Although congenital syphilis has been studied and described for many years, our understanding of the pathophysiology of maternal transmission of *Treponema pallidum* is still incomplete. Furthermore, the natural history of in utero treponemal infection of the fetus, amniotic fluid, and placenta is poorly described compared with our knowledge of neonatal and congenital syphilis. These gaps in fundamental

concepts of fetal infection and its response to treatment underscore difficulties in our understanding of the optimal therapeutic approach to syphilis in pregnancy.

Antepartum syphilis is a chronic maternal bacterial infection that is associated with a completely curable fetal infection. Our lack of knowledge of fetal syphilis has been due in part to an inability to accurately examine the fetus in utero. Targeted fetal ultrasonography, amniocentesis, and fetal blood testing by percutaneous umbilical blood sampling have provided means to improve our understanding of fetal syphilis. In utero infection accompanies maternal early syphilis approximately half the time, but it is difficult to assess the severity of fetal infection [1–3].

Thus, antepartum syphilis management must consider that both maternal and fetal infection is present. We usually use 2 simple end points, resolution of maternal infection and prevention of congenital syphilis, to examine the efficacy of syphilis treatment in pregnancy. The maternal stage of syphilis and quantitative syphilis serology titers are crude surrogates of the risk of fetal infection. Until we have more accurate estimates

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of the actual rates of fetal infection, we will probably overestimate the true efficacy of maternal treatment for fetal syphilis.

During the past 20 years, the Centers for Disease Control and Prevention (CDC) has convened expert panels to examine the clinical evidence on which to base treatment guidelines for the management of syphilis in pregnancy. Those guidelines were last updated in 1993 [4] and 1998 [5], and the last published comprehensive review of antepartum treatment was in 1995 for the 1993 guidelines [6]. The present article summarizes the available data since the 1998 treatment guidelines regarding the management of syphilis in pregnancy. It does not address issues regarding the management of congenital syphilis.

## MATERIALS AND METHODS

A computerized search on MEDLINE was conducted for articles published from 1998 through September 2000 that related to antepartum syphilis, congenital syphilis, and treatment of syphilis. In addition, abstracts relevant to antepartum syphilis treatment that were presented at an Interscience Conference on Antimicrobial Agents and Chemotherapy, International Society of Sexually Transmitted Disease Research, Society of Maternal-Fetal Medicine, Infectious Diseases Society for Obstetrics and Gynecology, or International AIDS meeting during the period of 1998–2000 were examined.

Using these references and a comprehensive review prepared from the 1993 guidelines revision, we formulated a series of questions to address the key issues regarding the optimal treatment and management of maternal syphilis in pregnancy. In the creation of the key questions and efforts to answer them, the opinions of investigators with recognized expertise and interest in syphilis in pregnancy were solicited. Where necessary, reference was made to older, published studies. Tables of evidence were created from available studies.

## KEY QUESTIONS AND REVIEW OF EVIDENCE

***Is 2.4 million units of benzathine penicillin G (BPG) effective therapy for antepartum, primary, secondary, and early latent syphilis?*** There is no prospective evidence to change the current recommendations for the use of 2.4 million units of BPG for most cases of antepartum syphilis. There have been no prospective randomized clinical trials published to compare alternate regimens in pregnancy.

There are 3 prospective cohort studies that have described the efficacy of treatment of antepartum infection at various stages with BPG to prevent congenital syphilis (table 1) [1, 7, 8]. The largest cohort involved 340 women and observed an overall efficacy of 98% [7]. The effectiveness of 2.4 million units of BPG was lower (95%) for maternal secondary syphilis.

Another cohort of gravidas with syphilis at  $\leq 20$  weeks' gestation described uniformly successful treatment with 4.8 million units of BPG over 2 weeks in all 8 cases [1]. The third prospective cohort described the efficacy of a planned regimen of 7.2 million units of BPG over 3 weeks in 180 gravidas with antepartum syphilis [8]. No maternal staging of infection was performed, but all women had quantitative rapid plasma regain (RPR) titers of at least 1:8. Women who remained pregnant long enough to receive 2 or 3 of the planned weekly BPG injections had lower rates of prematurity and neonatal mortality but not fewer cases of congenital syphilis compared with gravidas who received only 1 BPG injection. The rates of prematurity and neonatal mortality after a single BPG injection were comparable to those observed when no maternal treatment was given. Most of the incompletely treated women delivered  $< 4$  weeks after their injection, and they also had the worst neonatal outcome. Adverse outcomes associated with shorter treatment clustered in early attendees of prenatal care (before the 28th week of gestation) and gravidas with initial RPR titers  $> 1:16$ .

There are 6 retrospective series (table 1) [8–12] and 1 case report [13] that provide some useful information regarding antepartum treatment. Several studies concentrated on reductions in neonatal complications such as preterm birth, stillbirth, and neonatal mortality, in addition to prevention of congenital infection. One study found that treatment failures tended to occur in women with early latent infection, Venereal Disease Research Laboratory titers  $\geq 1:32$ , and treatment after 30 weeks' gestation [14].

There are no new data to indicate an increased risk of maternal infection after antepartum treatment. However, most cohorts do not describe long-term clinical or serological maternal follow-up during or after the pregnancy. There are insufficient reports of antepartum syphilis treatment with concomitant HIV infection to draw conclusions about therapy to prevent congenital syphilis or cure maternal infection in the coinfecting grvida.

***Is 4.8 million units of BPG over 2 weeks effective therapy for antepartum early syphilis?***

One US study described 100% efficacy in 8 women treated with 4.8 million units of BPG over 2 weeks in early pregnancy [1]. Another US retrospective matched-control study found no improvement in prevention of congenital syphilis with additional treatment in the high-risk setting of secondary syphilis [15]. There was no difference in the percentage of women with a 4-fold drop in titer, in delivery titer, or in the percentage seronegative by delivery in 20 women given 4.8 million units of BPG over 2 weeks compared with 40 matched controls given 2.4 million units of BPG. Donders et al. [8] found little benefit after a single treatment with 2.4 million units of BPG in preventing preterm birth, stillbirth, and congenital syphilis in women with an RPR of at

**Table 1. Data from reports on the efficacy of antepartum treatment of syphilis.**

Reference, study design	Population and setting	Intervention and treatment	Outcome measure	Results (%)	Comments
[7], Pro. cohort	340 Gravidas with syphilis	1°, 2°, and EL: 2.4 mU BPG; LL: 7.2 mU BPG over 3 weeks	Efficacy in prevention of CS by stage of infection	1°, 27/27 (100); 2°, 71/75 (95); EL, 100/102 (98); LL, 136/136 (100); total, 334/340 (98)	Large cohort
[10], Retro. cohort	685 Female inmates, 190 treated, 17 gravidas	2.4 mU BPG	NYC CS Surveillance System record review	8 Live births, 7/8 (87) successful treatments; 1 failure due to reinfection	Low follow-up rate
[11], Pro. cohort	11 Gravidas at <20 weeks' gestation	Amniocentesis for AF RIT and PCR to detect <i>T. pallidum</i> ; 4.8 mU BPG; newborn exam and treponemal WB IgM	Rate of in utero infection; prevention of CS	4/11 (36) AF infection; 8/8 (100) successful treatments	Small sample size, early pregnancy bias
[8], Pro. cohort	180 pregnant South Africans, HIV-negative	Diagnosis by RPR ≥1:8; BPG over 3 weeks indicated in all cases	Pregnancy outcome, PTB and CS rate	1 BPG vs. ≥2 BPG; PTB RR, 8.5; 95% CI, 2.5–28; mortality RR, 20.5; 95% CI, 2.3–184; CS RR, 2.0; 95% CI, 0.6–6.8	Recommend 2 BPG over 2 weeks; confusing management scheme; analysis by theoretic PG durations of 1 BPG injection, 3 weeks; no maternal clinical staging
[9], Retro. survey	British GU physicians and pediatricians	Pregnant women treated for transmissible syphilis and CS cases	Number of transmissible cases treated and CS cases	139 Maternal cases (22% transmissible) and 17 CS; 9 presumptive and 8 possible CS	
[11], Retro. cohort	Serological results in Edinburgh	Chart review	Stage of maternal syphilis and prevention of CS in newborns	15 Cases; 8 LL and 7 serofast serologies; 8/8 (100) successful treatments	Review of serological data bank; small sample
[13], Case report	Single patient with EL syphilis (RPR 1:128)	7.2 mU BPG from 14 to 16 weeks' gestation	Delivery at 41 weeks; maternal RPR 1:32; normal newborn exam and WR RPR	Apparent success of treatment but infant developed florid CS diagnosed at age 10 weeks (RPR >1:256)	Well-described early treatment failure
[12], Retro. cohort	Pumwani Maternity Hospital, Kenya	Antenatal and delivery record review; treatment, 2.4 mU BPG	Adverse outcomes (AO); <2500 g or SB) by delivery RPR	275 Cases and 275 controls; RPR neg, 6% AO; Treat RPR neg, 8% AO; Treat RPR pos, 15% AO; RPR pos, 26% AO	No staging of infection; no CS rates; unclear definitions and outcomes; ? false positives
[15], Retro. case-control (1:2 match)	20 Women with 2° syphilis	4.8 mU BPG (n = 20) vs. 2.4 mU BPG (n = 40)	Treatment efficacy; serological response	4.8 mU BPG, 95%; 2.4 mU BPG, 90%; no difference in rate of 4-fold drop, delivery titer, or seronegative titer	Matched controls with high rate of treatment failure; small study
[14], Retro. cohort	43 Syphilis treatment failures	Record review	Maternal and fetal characteristics	Maternal 42% EL and 28% 2° stage; pretreatment VDRL, 1:32; EGA, 30 weeks; bimodal treatment to delivery interval, 14 and 60 days	

**NOTE.** 1°, primary syphilis; 2°, secondary syphilis; AF, amniotic fluid; AO, adverse outcome; BPG, benzathine penicillin G; CS, congenital syphilis; EGA, estimated gestational age; EL, early latent syphilis; GU, genitourinary; LL, late latent syphilis; NYC, New York City; PG, penicillin G; PTB, preterm birth; Pro., prospective; Retro., retrospective; RIT, rabbit infectivity test; RPR, rapid plasma reagen test; RR, relative risk; SB, stillbirth; VDRL, Venereal Disease Research Laboratory; WB, Western blot; WR, weakly reactive.

**Table 2. References on alternate treatment in pregnancy: azithromycin and penicillin desensitization.**

Reference, study design	Population and setting	Intervention and treatment	Outcome measure	Results	Comments
[24], Pro. cohort; cross-sectional PK	20 Gravidas, elective cesarean delivery	1-g azithromycin at intervals pre-op to 168 h; spinal anesthesia	Maternal serum, urine, tissue, and CSF and fetal serum azithromycin (ng/mL) levels by HPLC	6 h: maternal, 311 ± 170; cord, 19 ± 6; 12 h: maternal, 144 ± 79; cord, 26 ± 16; 24 h: maternal, 63 ± 37; cord, 27 ± 13; 72 h: maternal, 60 ± 31; cord, 19 ± 7; 168 h: maternal, <10; cord, <10; no levels in maternal CSF	Well-designed protocol; no AF placenta, or fetal tissue levels
[25], Pro. cohort; cross-sectional PK	21 Gravidas, elective cesarean delivery	1-g azithromycin at intervals pre-op to 168 h; spinal anesthesia	Maternal serum, urine, tissue, and CSF and fetal serum, placenta, and AF azithromycin levels by HPLC	6 h: 311 ng/mL; 24 h: 63 ng/mL; maternal tissue, >500 ng/mL at 72 h; fetal serum levels, 19–38 ng/mL in first 72 h	Pro., cross-sectional analysis; limited fetal tissue level testing
[23], Placental perfusion model	21 Term placentas	2-h nonrecirculating perfusion of a single cotyledon; maternal azithromycin, 0.3 µg/mL	Mean TPT for 120 min by HPLC	TPT (steady state), 2.6%; TPT (absolute), 32%; no difference from erythromycin rates	Nonrecirculating system design, no tissue levels
[32], Retro. cohort	16 Penicillin desensitizations in pregnancy	Record review of 11 oral and 6 IV procedures; 2.4-mU BPG treatment	Complications, cost, treatment efficacy	1/11 anaphylaxis with oral route; oral, \$144; IV, \$319; oral is easier and less costly	No mention of neonatal outcome

**NOTE.** AF, amniotic fluid; BPG, benzathine penicillin G; EL, early latent; HPLC, high-pressure liquid chromatography; IV, intravenous; PK, pharmacokinetics; pre-op, preoperative; Pro., prospective; Retro., retrospective; TPT, transplacental transfer.

**Table 3. Jarisch-Herxheimer reaction after antepartum treatment of syphilis.**

Reference, study design	Population and setting	Intervention and treatment	Outcome measure	Results	Comments
[42], Retro. cohort	Prenatal patients hospitalized for treatment	2.4 mU BPG, 24 h FHR monitoring	Frequency of J-H reaction and FHR abnormalities	50 Women and 31 FHR tracings; 40% J-H reaction; 42% contractions; 39% variable FHR decelerations	Only 1 fetal infection

**NOTE.** NOTE. BPG, benzathine penicillin G; FHR, fetal heart rate; J-H, Jarisch-Herxheimer; mU, million units, Retro., retrospective.

least 1:8. Two benzathine penicillin injections 1 week apart were comparable with 3 injections at preventing prematurity and mortality but not significantly preventing congenital syphilis. The authors concluded that an injection of 2.4 million units of BPG (treponemicidal penicillin concentrations lasting  $\leq 3$  weeks) is not sufficient therapy for pregnant women with syphilis. To obtain treponemicidal activity  $>3$  weeks, the authors recommend administration of 2 injections of 2.4 million units of BPG at least 1 week apart, if possible  $\geq 4$  weeks before delivery. This therapy was stressed for women commencing prenatal care before 28 weeks' gestation or when RPR titers are  $>1:16$ . Methodological issues, the use of hypothetical penicillin levels, and imprecise case definitions make the Donders report difficult to interpret.

Available clinical data do not support replacing 2.4 million units of BPG with 4.8 million units of BPG over 2 weeks. Further research is needed in this area, because there are theoretic pharmacokinetic advantages to an increased penicillin dose. Maternal penicillin levels are variable after 2.4 million units of BPG at term [16]. Nathan et al. [16] found no significant difference in mean penicillin levels at day 1, days 2–3, or day 7 for maternal serum, maternal CSF, cord serum, or amniotic fluid. The mean penicillin concentration in maternal serum declined from  $0.14 \pm 0.04 \mu\text{g/mL}$  1 day after injection to  $0.08 \pm 0.06 \mu\text{g/mL}$  7 days after injection. The proportion of patients with a penicillin concentration  $\geq 0.018 \mu\text{g/mL}$  (the desired treponemicidal concentration) in the maternal serum declined significantly from day 1 to day 7, and 36% of the 25 women had serum penicillin levels that declined to  $<0.018 \mu\text{g/mL}$  by day 7. Weeks et al. [17] have reported on penicillin levels after 4.8 million units of BPG in one setting for group B streptococcal chemoprophylaxis near term. None of the patients had serum penicillin levels  $<0.20 \mu\text{g/mL}$  30 days after treatment, and cord blood levels were  $\sim 50\%$  lower than maternal levels. In all but 3 subjects, who delivered  $>100$  days after treatment, cord-blood levels were  $>0.06 \mu\text{g/mL}$ .

There are no data on the maternal or fetal pharmacokinetics after 4.8 million units of BPG given over 2 weeks. Mainly on the basis of opinion and clinical experience, the current guidelines already mention that some experts recommend an additional dose of BPG for treatment of primary, secondary, and early latent syphilis [5].

**Are there alternatives to BPG antepartum therapy?** There

have been no clinical trials or reports of azithromycin or ceftriaxone treatment in pregnancy, but studies are ongoing regarding maternal and fetal azithromycin pharmacokinetics (table 2). Azithromycin has a long plasma half-life (68 h in adults), is active against *T. pallidum* in vitro [18], is effective in treating experimental syphilis [19], aborts incubating syphilis [20], and may be effective in treating early syphilis in adults [21, 22]. The azithromycin daily dose and duration of therapy in adults has not been established. In a placental perfusion model, the placental transfer of azithromycin appears to be similar to erythromycin [23].

Ramsey [24, 25] reported on 21 gravidas who received 1 g azithromycin orally at term up to 168 h before a scheduled cesarean delivery. Maternal serum levels of azithromycin peaked ( $311 \text{ ng/mL}$ ) at 6 h after administration of 1 g orally, and they declined rapidly by 24 h ( $63 \text{ ng/mL}$ ). In contrast, maternal myometrial, adipose, and placental levels had longer half-lives, with higher, sustained drug levels ( $>500 \text{ ng/mL}$ ) at 72 h. Fetal azithromycin serum levels were low ( $19\text{--}38 \text{ ng/mL}$ ) during the first 72 h, and amniotic fluid levels peaked at 6 h ( $151 \text{ ng/mL}$ ) and declined rapidly. Further studies on fetal tissue levels of drug are in progress. Any recommendation change should await fetal tissue pharmacokinetic studies and clinical trials in pregnancy.

If azithromycin is recommended for the treatment of adults with primary or secondary syphilis, it is likely to be used inadvertently in pregnant women. Penicillin G remains the treatment of choice in pregnancy, and any nonpenicillin antepartum treatment should be followed by neonatal evaluation and treatment for possible congenital syphilis, according to current recommendations [5].

Ceftriaxone is an alternate for syphilis treatment in adults, and its serum concentration leading to 50% immobilization of *T. pallidum* is low ( $0.01 \mu\text{g/mL}$ ) [26]. Pharmacokinetic studies in gravidas have indicated that the half-life ( $\sim 6$  h) and maternal serum levels achieved (peak  $138 \mu\text{g/mL}$ ) after 1 g parenterally are treponemicidal [27–31]. Fetal serum and amniotic fluid ceftriaxone levels are  $\sim 10\%$ – $20\%$  of maternal serum levels and also are probably treponemicidal.

There was a single report on penicillin desensitization in pregnancy that described the outcome of 16 nonrandomized gravidas who had 11 oral and 6 intravenous desensitizations (table 2) [32]. There were no significant differences between the groups with respect to duration of time in a monitored

bed or length of hospital stay. There was only 1 complication—anaphylaxis early during an oral desensitization that was followed by ceftriaxone for 14 days. The oral desensitization regimen was less expensive than the intravenous regimen (\$144 vs. \$319). Although both methods were effective for penicillin-allergic gravidas, the investigators preferred the oral route because of its ease of administration and substantial cost savings.

**Should an ultrasound examination for signs of fetal syphilis precede treatment after 20 weeks' gestation?** Most cases of maternal syphilis probably are associated with an uninfected fetus, incubating fetal infection, asymptomatic fetal syphilis, or mild fetal disease that is cured by maternal treatment. The current recommendations state that the risk of treatment failure is increased with sonographic signs of fetal syphilis. Prospective studies of fetal syphilis have shown an association with hepatomegaly, ascites, hydrops, and in utero infection with *T. pallidum* [1–3]. These fetuses are at increased risk of having congenital syphilis at delivery, and the anatomic abnormalities from fetal infection are detectable by ultrasonography. Pregnancies of <20 weeks' gestation may be associated with fetal syphilis, but the ultrasonographic abnormalities are rare and treatment is nearly uniformly successful [1, 6, 33].

There have been numerous small cohorts and case reports of fetal syphilis or hydrops that have been unsuccessfully treated antepartum [2, 3, 33–39]. Some of these affected fetuses also had abnormal antepartum fetal heart rate testing that indicated fetal distress or an impending demise that precluded maternal therapy prior to delivery (see next section). No “symptomatic” fetus was successfully treated, and all survivors had neonatal treatment for probable or possible congenital syphilis. Current experience is too limited to estimate the magnitude of risk, but the relative risk of treatment failure probably increases with severity of fetal disease.

The current evaluation for other maternal infections that cause congenital infection, such as toxoplasmosis, cytomegalovirus, human parvovirus B19, and varicella zoster virus includes sonographic fetal examinations [40, 41]. In managing antepartum syphilis, the ultrasound should be used as a tool to “stage” the extent of fetal disease during the second half of pregnancy. Assessment of the severity of fetal involvement will aid in maternal counseling about efficacy and complications of treatment. Management may be facilitated by consultation with an obstetrician or maternal-fetal medicine subspecialist to perform the targeted ultrasound examination. Scheduling the fetal sonographic examination should not delay the maternal treatment unduly.

**How should the fetus with signs of syphilis be treated?** The reports and studies mentioned above have shown that fetal abnormalities detected by ultrasound are predictive of fetal syphilis and treatment failure. Penicillin G is clearly the choice for significant fetal disease; however, evidence is insufficient to

determine whether a specific regimen is optimal. No studies have been done to determine whether more-intensive therapy is beneficial in this circumstance, and further clinical research is needed.

Several of the reports of syphilitic fetal hydrops described intravenous penicillin G treatment [35, 36, 38, 39] and weekly injections of 2.4 million units of BPG until fetal sonographic abnormalities resolved [3, 37]. Consultation with an obstetrician or maternal-fetal medicine subspecialist may be reasonable, because some of the complications, such as preterm labor, preterm premature ruptured membranes, fetal distress, and stillbirth, may be precipitated by treatment. Furthermore, intravenous penicillin G or ceftriaxone treatment may be associated with the rapid appearance of a Jarisch-Herxheimer reaction. In general, maternal treatment should follow the standard guidelines for syphilis in pregnancy. The risks of fetal treatment failure are higher in the fetus with hydrops, so a thorough evaluation of the newborn for congenital infection is indicated.

If the fetal ultrasound is abnormal, antepartum fetal heart-rate testing is indicated before treatment. In some cases of hydrops, fetuses had spontaneous late decelerations or non-reactive nonstress testing that invariably led to fetal distress soon after maternal treatment. Sonographic signs of fetal syphilis with abnormal antepartum testing probably identify a severely affected fetus with an impending fetal demise. In this setting, consultation with a neonatologist should occur with consideration given to an untreated preterm delivery and treatment in the nursery.

**What is the normal serological response to treatment in pregnancy?** There is no evidence of a different serological response in pregnant women compared with nonpregnant women, despite a common perception that this is the case. In the past, it was recommended that quantitative titers be followed monthly to assure adequacy of treatment [4]. However, there is no evidence that any maternal serological response predicts fetal treatment failure. After treatment, measurement of quantitative titers during the third trimester (28–32 weeks) and at delivery should be adequate. Monthly titers in pregnancy should be reserved for surveillance for reinfection that may be clinically atypical or asymptomatic. In patients at risk for reinfection or in communities where the prevalence of syphilis is high, monthly quantitative titers may be beneficial.

In general, serological follow-up testing and response to treatment should be appropriate for the stage of disease. A <4-fold titer drop over a 6-month period after primary, secondary, or early syphilis therapy should alert the clinician of a possible risk of maternal treatment failure. Further clinical and serological evaluation should be performed according to current recommendations. Most women will deliver before there has been sufficient time for serological assessment of maternal treat-

ment adequacy. This may confound decisions for the evaluation of possibly infected asymptomatic newborns.

***Should specific recommendations be made about prevention of the Jarisch-Herxheimer reaction to prevent preterm labor, fetal distress, or stillbirth during pregnancy?*** There has been one retrospective, observational report of a cohort of women observed for 24 h after antepartum syphilis treatment (table 3) [42]. Forty percent of the 50 women had Jarisch-Herxheimer reactions during their hospitalization. Forty-two percent developed uterine contractions at a median of 10 h posttherapy, and 39% had recurrent variable fetal heart-rate decelerations. Contractions were associated with higher maternal temperatures. Decelerations were associated with earlier gestational ages (29.6 vs. 32.3 weeks). There were no cases of fetal distress, and most fetal heart-rate abnormalities spontaneously resolved within 24 h of treatment. One woman ultimately delivered a fetus with congenital syphilis, and the fetal heart-rate tracing did not return to a reassuring pattern until after an additional 48 h of observation. No interventions were described for management of the Jarisch-Herxheimer reactions.

No new recommendations regarding the prevention or management of the Jarisch-Herxheimer reaction can be made. Routine hospitalization is not recommended for fetal monitoring after treatment, unless the fetus has sonographic signs of fetal syphilis as above. In general, women in early pregnancy should be advised to stay well hydrated, rest, and take acetaminophen for uterine cramping, pelvic pain, or fever. Gravidas at >20 weeks' gestation with normal sonographic evaluations can be counseled to seek obstetric evaluation if they experience fever, decreased fetal movement, or regular contractions within 24 h of treatment. Maternal management during a Jarisch-Herxheimer reaction may include hydration, supplemental oxygen, antipyretics, and continuous heart-rate surveillance of the fetal status [43]. Evidence is insufficient to recommend prophylactic measures to prevent these reactions.

***Are women coinfecting with HIV and syphilis more likely to transmit either infection? Do they need additional syphilis treatment?*** There is insufficient evidence to estimate an altered risk of transmission of HIV in the setting of coinfection with syphilis and HIV infections (table 4). The maternal/fetal syphilitic immune response is characterized by placental inflammation and vasculitis [44, 45], so syphilis has the potential to increase the risk of perinatal HIV transmission. One HIV-infected maternal cohort of 40 women experienced a seeming continuum of risk of perinatal HIV transmission for women with current syphilis (100%), a history of syphilis (21%), and no syphilis (14%) [46]. Several of the studies reviewed included some women coinfecting with syphilis and HIV infection, but none reported HIV transmission clearly. There was no association between genital ulcer disease (including syphilis) and perinatal HIV transmission in an analysis of maternal risks from

the AIDS Clinical Trial Group 185 study cohort [47]. Another analysis observed increased rates of perinatal HIV transmission with maternal genital ulcer disease (odds ratio [OR], 3.57; 95% confidence interval [CI], 1.28–9.66) and placental membrane inflammation (adjusted OR, 2.87; 95% CI, 1.04–7.90) [48]. The investigators estimated that 34% of HIV transmission could be prevented by treatment of placental membrane inflammation in nonimmunocompromised women. The magnitude of the effect of syphilis on HIV perinatal transmission, if any, is not quantified currently. Furthermore, the effect of treatment on modifying any risk is unknown, but the gravida coinfecting with HIV and syphilis should be treated promptly and aggressively for both infections.

There are no reports of congenital syphilis rates in women with HIV infection. No recommendations can be made about additional evaluation or maternal treatment in this setting to prevent congenital syphilis. There are no reports of inadequate maternal therapy, so the risks of maternal treatment failure should be similar to the risks of nonpregnant adults. In general, syphilis treatment should be similar to that in pregnancy and follow-up similar to that for adults with HIV infection.

***When should syphilis serological testing be performed?***

Prenatal syphilis screening is recommended by the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics at the first prenatal visit and again at 32–36 weeks, if the woman is at risk for syphilis [49]. Current CDC guidelines recommend syphilis testing at the first prenatal visit and, for patients at high risk, again during the third trimester and at delivery [5].

There has been a recent reexamination of the costs and benefits of routine antenatal syphilis testing in the setting of declining rates of syphilis in women and congenital syphilis in the United Kingdom. Several groups have concluded that the alternative of targeted testing is impractical to implement and would save little money, while missing stillbirths and congenitally infected infants [9, 11, 50, 51]. Furthermore, in developing countries, the treatment of prenatal syphilis also may be associated with reductions in other adverse outcomes [8, 12, 52], in addition to prevention of congenital syphilis.

Control of infectious syphilis in women is crucial to reduce rates of congenital syphilis, and the National Plan to Eliminate Syphilis is ambitiously marching toward both goals in the United States [53]. Prenatal syphilis testing early during pregnancy has been shown to be cost-effective at maternal rates of infection as low as 5/100,000 in Norway [54]. In 1999 the rate of primary and secondary syphilis in women in the United States declined to 2.0/100,000, and the rate of congenital syphilis was 13.4/100,000 live births [55].

There is no current evidence to support changing recommendations for prenatal syphilis screening. However, if current

**Table 4. HIV infection and antepartum syphilis.**

Reference, study design	Population and setting	Intervention and treatment	Outcome measure	Results	Comments
[46]. Retro. cohort	44 HIV-infected gravidas; 4 HIV-coinfected	Record review, all syphilis treated	Pediatric HIV and CS rates in those with syphilis, history of syphilis, or no syphilis	2.2° and 2 EL; 0/4 CS; with syphilis 4/4 (100%), history of syphilis, 3/14 (21%), and no syphilis 5/35 (14%) perinatal HIV transmission; all maternal VDRL $\geq$ 1:128; only 1/4 received zidovudine	Small cohort; HIV monotherapy prophylaxis
[47]. Pro. cohort secondary analysis of ACTG 185	480 Women and infants who received zidovudine	Univariate and multivariate analysis	Perinatal HIV transmission	134 (33%) had STD; no association with antepartum STDs (4.5% vs. 5.2%); HIV-1 RNA is best predictor	Composite STD risk factor; unable to ascertain treatment status; no mention of CS rates
[48]. Pro. cohort analysis	172 HIV-infected women and their infants	No intervention; placental membrane and villous histology from all deliveries	Rates of membrane and villous inflammation, immunosuppression, and GUD	Overall: 23% transmission; no effect of villous inflammation; immunosuppression OR, 3.07; 95% CI, 1.42–6.67; amnionitis OR, 1.87; 95% CI, 0.88–3.99; amnionitis, not immune suppressed, OR, 2.87; 95% CI, 1.04–7.90; amnionitis, immunosuppressed, OR, 3.87; 95% CI, 2.16–4.96; GUD OR, 3.76; 95% CI, 1.35–10.66	Limited obstetric information about duration of membrane rupture, EGA; breast-feeding not included; no breakdown of GUD etiology

**NOTE.** 2°, secondary syphilis; CI, confidence interval; CS, congenital syphilis; EGA, estimated gestational age; EL, early latent syphilis; GUD, genital ulcer disease; OR, odds ratio; Pro., prospective; Retro., retrospective; STD, sexually transmitted disease; VDRL, Venereal Disease Research Laboratory test.



declines continue, examination of the cost effectiveness of antenatal syphilis testing in the United States will be necessary.

## DISCUSSION

There are no data from prospective, comparative studies about management of syphilis in pregnancy to make major changes to the current treatment recommendations necessary. Penicillin G remains the treatment of choice for treating maternal syphilis and preventing congenital syphilis. There are data that support the need for pharmacokinetic studies of larger BPG doses than are currently recommended, but it is unclear whether these studies would translate into improved clinical outcomes. Penicillin desensitization followed by penicillin G is the preferred method for penicillin allergic gravidas, but ceftriaxone and azithromycin may offer theoretically effective potential alternatives. There are insufficient data concerning increased rates of congenital syphilis or perinatal transmission of HIV to make any changes in therapy in the setting of coinfection with HIV and syphilis in pregnancy.

The major changes in the new recommendations involve increased obstetric involvement in evaluation for signs of fetal syphilis before treatment. Ultrasonographic fetal examination for signs of syphilis is recommended prior to therapy after 20 weeks' gestation. Fetal hepatomegaly, ascites, hydrops, hydramnios, and placental thickening are all sonographic findings that indicate a high risk of fetal syphilis. Fetal treatment failure is higher in this setting, and counseling and management will be improved by fetal ultrasonographic evaluation before treatment. Coordination of care is critical to assure that ultrasonographic examination does not delay needed treatment.

Overall, the decreases in infectious syphilis in the United States have heralded a welcome decrease in congenital syphilis. As the Syphilis Elimination Program continues, rates of syphilis in women and newborns are likely to decline further. Clearly, the most effective method to reduce congenital syphilis is to reduce the rates of primary, secondary, and latent syphilis in women of reproductive age. However, we must not lose sight of the fact that prenatal syphilis serological testing is an essential component of identifying infected gravidas who need antepartum treatment. Prenatal testing to prevent congenital syphilis must not fall in our priorities as the rates of infectious syphilis in women approach elimination.

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