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SYPHILIS IN PREGNANCY: PHARMACOLOGICAL AND THERAPEUTIC CHALLENGES

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ABSTRACT: *Syphilis is a chronic, multistage sexually transmitted disease caused by the spirochete Treponema pallidum. Infection during pregnancy can lead to transplacental spread (congenital syphilis) and may be associated with adverse foetal outcomes, such as early foetal loss (miscarriages), stillbirths, neonatal deaths, low-birth-weight infants, and other sequalae of infection if left untreated or incompletely treated. Rising rates of congenital syphilis emulate general increases in the rate of primary and secondary syphilis among females and remains a global health concern, particularly in lower middle-income countries (LMIC). Treatment with benzathine penicillin G remains the treatment of choice in the absence of alternative suitable antimicrobials. However, in the past few years, treatment with penicillin has been affected by poor availability due to manufacturing challenges, supply chain issues and stock-outs in some settings. In this article, we highlight the pharmacological and therapeutic challenges during pregnancy, and reflect on challenges associated with alternative antimicrobial therapy.*

KEYWORDS: Congenital syphilis, pregnancy, penicillin, antimicrobials.

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INTRODUCTION

Syphilis is a chronic, multistage sexually transmitted disease caused by the spirochete *Treponema pallidum*.[1] Mother-to-child transmission (MTCT) of syphilis poses an additional risk of transplacental spread to the foetus (congenital syphilis) and remains a global health concern, particularly in lower and middle-income countries (LMIC). Despite the availability of tests and effective treatment with penicillin since the early to mid-1900s, approximately 1.5 million women are infected with probable active syphilis during their pregnancies each year, and approximately half of this cohort will experience adverse fetal outcomes, such as early fetal loss (miscarriages), stillbirths, neonatal deaths, low-birth-weight infants, and other clinical sequalae of infection.[2]

Background

Extensive research on syphilis infection has been conducted over a long period; however, our understanding of the ultrastructure, physiology, and membrane biology of *T. pallidum* remains incomplete. Physiological changes associated with pregnancy, transplacental dynamics of therapeutic agents and the teratogenic potential of antimicrobial therapy pose unique challenges to suitable alternate antimicrobial therapy. The challenges facing the effective treatment of syphilis during pregnancy are therefore multifactorial and further include inter alia, the unique characteristics of the *Treponema pallidum* subspecies, poor access to penicillin in some settings, and the lack of robust data on the safety and efficacy of alternate antimicrobial agents.

Methodology

To obtain information on congenital syphilis, penicillin, and alternative antimicrobial agents, we conducted a narrative review by searching the literature from the following databases: PubMed, Google Scholar, and the Cochrane Library. These databases were searched for information on the biological characteristics of *Treponema pallidum*, physiological alterations during pregnancy, adverse pregnancy outcomes among untreated women with seroreactivity for *Treponema pallidum* infection, penicillin stock-outs and alternate antimicrobials for the treatment of syphilis during pregnancy. Keywords used in the search included syphilis, pregnancy, penicillin, and antimicrobials. Using a total of 39 author references, a narrative review is presented with reference to syphilis during pregnancy and the pharmacological challenges associated with alternate antimicrobial therapy for safe and effective treatment.

FINDINGS

Challenges to the treatment of syphilis, inter alia, relate to the characteristics of *Treponema pallidum* and the physiologic and pharmacokinetic changes in pregnancy.

Characteristics of *T. pallidum*

The propensity of the syphilis spirochete for early dissemination and immune evasion has earned it the designation, 'the stealth pathogen.'[3] *T. pallidum* has a thick phospholipid membrane which holds most of the antigens under its surface, thus impairing the recognition of antigens as foreign. The membrane also lacks lipopolysaccharide (LPS) glycolipids necessary for inflammatory reactions which alert the immune system to act or produce notable symptoms.[4] This binary allows *Treponema pallidum* to enter the body relatively

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asymptomatically, allowing time to disseminate with little resistance. During pregnancy, both local and systemic nonspecific suppressor mechanisms may down-regulate maternal immune responses without significantly impairing the ability to fight infections.[5] Although the mode of action and the lethal targets for β-lactams are incompletely understood, *T. pallidum* has remained sensitive to penicillin which continues to be the drug of choice for syphilotherapy.[6] Penicillin and other β-lactams are bactericidal via their ability to inhibit cytoplasmic membrane-bound enzymes (penicillin-binding proteins) involved in peptidoglycan biosynthesis.[7] Generally, bacteria contain several penicillin-binding proteins (PBP's) that are classified as high molecular weight or low molecular weight penicillin-binding proteins.[8] The lethal targets for β-lactams in *T. pallidum* infection, however, require further investigation, notwithstanding its established efficacy in clinical use.

Physiologic and Pharmacokinetic Changes in Pregnancy

Pregnancy is associated with physiological changes in many of the organ systems which influence the pharmacokinetic and pharmacodynamic properties of antimicrobials and other medications. Physiologic changes during pregnancy include: increased maternal fat and total body water, decreased plasma protein concentrations, increased maternal blood volume, cardiac output, and renal blood flow and decreased blood pressure.[9] Moreover, a physiologic anaemia and haemodilution occur due to the larger proportional increase in maternal blood volume compared with the corresponding increase in red blood cell mass.[10] Other physiologic changes include: increased tidal volume, partially compensated respiratory alkalosis, delayed gastric emptying and gastrointestinal motility, and altered activity of hepatic drug metabolizing enzymes.[9]

DISCUSSION

Some authors suggest that increased maternal dosing or shorter dosing intervals should be considered for penicillin G and other antibiotics.[11] Nevertheless, there is limited data on the optimal therapeutic regimen during pregnancy, and studies in this area remain challenging due to ethical considerations involving research in human subjects. Pharmacologic considerations indicate that an interval of 7–9 days between doses, if feasible, might be preferred. [12] Delayed doses are not optimal for pregnant women receiving therapy for latent syphilis, and pregnant women who experience delays of more than 9 days between doses should repeat the full course of therapy.[12] If a pregnant woman does not return for the subsequent dose on day 7, every effort should be made to contact her and commence immediate treatment within two days to avoid a retreatment schedule. Pregnant women who miss a dose of therapy should repeat the full course of therapy.[12] Some authors suggest that additional therapy is beneficial for pregnant women to prevent congenital syphilis in certain cases.[13] For women who have primary, secondary, or early latent syphilis, a second dose of benzathine penicillin G 2.4 million units IM can be administered 1 week after the initial dose.[13] Other authors suggest that a second dose is advisable if the diagnosis is made in the third trimester as the physiological changes in pregnancy results in a low level of penicillin concentrations.[14]

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Implications for Practice

Evidence to date suggests that a single dose of benzathine penicillin G (BPG) ends syphilis infectivity in adults with no documented risk of antibiotic resistance.[15] The recommended treatment for syphilis in pregnant women currently is BPG, and although it is available at low-cost, congenital syphilis remains a significant contributor to early infant mortality, particularly in low- and middle-income countries. The reasons for the treatment deficit are multifactorial; however, a global shortage of BPG is a known contributing factor in affected countries. Data from the World Health Organisation (WHO) and the Clinton Health Access Initiative (CHAI) suggest some of the reasons for penicillin unavailability.[15] A sole sourcing model poses challenges to alternative supply when there are production, quality, regulatory, or specification changes within a country's supply chain.[15] Moreover, access to technology, research and development, and intellectual property issues from a sole supplier may provide marketplace advantages or a competitive advantage. BPG also commands a market price of pennies per dose and is expensive to manufacture as a sterile injectable, leading manufacturers to either abandon BPG production or implement stringent ordering protocols that compromise supply to low- and middle-income countries.[15] Inaccurate country forecasts, weak procurement systems, and clinical knowledge gaps about syphilis treatment have also compromised demand and procurement of BPG.[15] Noting the challenges with penicillin, it is imperative that research and development should focus on alternate drugs, especially amoxicillin and third generation cephalosporins, which have been used safely in pregnancy.[16] Data from limited case studies of patients treated with β-lactam antibiotics show that both the mother and child can been treated successfully.[16]

FUTURE RESEARCH

Penicillins belong to the β-lactam class of antibiotics and act by specifically hindering bacterial cell wall synthesis.[17] Penicillins and β-lactam inhibitors can cross the placental barrier and reach the foetus in sufficient quantities to be detected in foetal blood and amniotic fluid.[17] Earlier evidence shows that a single dose of benzathine penicillin G or procaine penicillin G for 10 days for the treatment of asymptomatic congenital syphilis was not associated with treatment failure with either regimen and there was no significant difference in outcomes between the two groups.[18] Penicillin has been consistently effective for the treatment of syphilis in human since the 1940s;[19] however, challenges such as penicillin sensitivity and poor access have prompted the consideration of other antibiotics, although robust data on their effectiveness and safety in pregnancy are lacking. Drugs such as amoxicillin, cephalosporins, and macrolides have been described for the treatment of syphilis infection in case series and reports; however, their treatment efficacy and prevention of congenital syphilis require further evaluation in large scale studies. There appears to be some maternal response to therapy with macrolide use, but congenital syphilis may still be observed in cases treated with erythromycin or azithromycin, probably due to poor placental passage of the drug.[16] Furthermore, resistance has been detected with macrolide specific genomic strains of syphilis, although no penicillin-resistant lineages have been identified.[20] Katanami et al. describe encouraging data on the use of oral amoxicillin, although their series is limited to 2 patient reports only.[21] In their patients of 13 weeks and 6 weeks of gestation respectively, amoxicillin, probenecid and ceftriaxone were used according to a specific protocol. Both patients had appreciable decline in titres at 6 months after treatment and the newborns had no evidence of congenital syphilis.[21]

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Cephalosporins also have a β-lactam ring structure and exert bactericidal effects by inhibiting the biosynthesis of the bacterial cell wall. Cephalosporins are also capable of passing through the placenta and can be detected in bactericidal concentrations in the amniotic fluid.[17] In a slightly larger series of 11 pregnant women with primary or secondary syphilis, Zhou et al. administered treatment with intramuscular ceftriaxone, and reported successful treatment in case-patients, including new-borns who had no evidence of congenital syphilis.[22] Berkovitch et al. suggest that exposure to cefuroxime during the first trimester is probably not associated with an increased risk of malformations or spontaneous abortions; however, larger studies are needed to confirm these findings.[23] Treatment with cephalosporins (mainly oral cephalexin) during pregnancy does not seem to present a detectable teratogenic risk to the fetus. However, further studies are also needed to clarify the teratogenic and fetal toxic effects of different cephalosporins separately.[24] In an 18-month follow-up of pregnant women treated with cefuroxime axetil, Manka et al. did not demonstrate physical or mental developmental abnormalities of concern in any of the children, and no abnormality that was attributable to the treatment the mother had received.[25]

Macrolides are bacteriostatic antibiotics that inhibit protein biosynthesis through reversible binding to the bacterial 50S ribosomal subunit; however, lower levels of macrolides reach the foetus due to their size.[17] Erythromycin is a member of the macrolide group and is considered safe for use during pregnancy, and a suitable alternative for those who are allergic to penicillin.[26] However, there is less encouraging and limited data on macrolide and azalide antibiotics for the complete treatment of syphilis in pregnancy. Fenton et al. and Hashisaki et al. reported cases of women at 32- and 26-week gestation with syphilis and syphilis chancre respectively, who were treated with oral erythromycin stearate according to specific protocol.[27,28] Whilst the former patient had a 4-fold decline in RPR titer, the new-born had evidence of secondary syphilis at 11 weeks of life. In the latter patient, the chancre did not improve despite repeated treatment. Successful treatment was subsequently achieved with penicillin desensitization and benzathine penicillin G.[27,28] Other macrolides include roxithromycin, clarithromycin and azithromycin. These agents are characterised primarily by improved bioavailability and tolerance, fewer side effects (e.g., gastrointestinal side effects) and an extended antibacterial spectrum.[29] Earlier studies suggest that azithromycin has a long plasma half-life (68 h in adults), is active against T pallidum in vitro,[30] effective in treating experimental syphilis,[31] and aborts incubating syphilis.[32] The placental transfer of azithromycin also appears to be similar to erythromycin in placental perfusion models.[33] However, the limited data on the use of azithromycin for the treatment of syphilis in pregnancy does not appear promising. In a case series of 5 pregnant women treated with azithromycin, according to specific protocol, all 5 new-borns had evidence of congenital syphilis, despite successful maternal treatment.[34] Tetracyclines are a broad-spectrum class of bacteriostatic antibiotics that penetrate bacterial cells by passive diffusion and inhibit bacterial growth by interfering with protein synthesis or by destroying the membrane.[35] Mascola et al. describe a single case of tetracycline treatment for a urinary tract infection at 8 months of pregnancy in a patient with a negative initial syphilis prenatal test.[36] At delivery, the patient tested positive for syphilis; however, the neonate had nonreactive serologies. At 10 weeks of age, the infant was diagnosed with congenital syphilis through positive serologies.[36] Definitive conclusions cannot be drawn from the case and it must be noted that tetracyclines cross the placental barrier, can accumulate in bones and teeth and can lead to teratogenic defects.[17] Owing to the reported risks associated with tetracycline treatment during pregnancy, this class of antibiotics should not be administered to pregnant women.[37]

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CONCLUSION

Prenatal screening and treatment of seropositive mothers is important for the prevention of congenital syphilis. Despite the availability of other antibiotics, penicillin remains the most studied agent for the treatment of syphilis in pregnancy. It is effective in treating syphilis during pregnancy; however, more research is needed on the best dosage and duration of treatment. Shortages of penicillin compromise the treatment and prevention of congenital syphilis and countries should strengthen their procurement strategies to ensure an uninterrupted supply of treatment. Penicillin shortages are most likely to affect developing countries where efficacious and cost-effective alternatives are necessary. If research and development into alternatives is not feasible in both developed and developing countries, governments should amplify efforts to increase the availability of penicillin by attending to manufacturing and supply chain issues as well as preventing stock-outs of penicillin.

There appears to be space for the utilisation of cephalosporins during pregnancy; however, further investigation is required. Doxycycline and tetracycline have teratogenic effects on bone and tooth enamel formation and are contraindicated in pregnancy, whilst erythromycin is unable to adequately and predictably cross the placenta to maintain therapeutic levels in the fetus.[38] There is a paucity of data comparing the effectiveness of different doses of penicillin or comparing penicillin with other antibiotics.[39] To date, satisfactory treatment for penicillin-allergic pregnant patients with syphilis is desensitization followed by administration of penicillin, although this must be practised with caution.[38] Further research is needed to evaluate the causes of treatment failure, poor compliance and the influence of HIV and other co-infections. Further research should be conducted, particularly with the β-lactam group of antimicrobials and other oral formulations of treatment. This is motivated by the emergence of potential drug resistance, unavailability of penicillin or interruptions in the regular supply of needles and syringes, particularly in middle and low income countries.

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