Antibiotics for syphilis diagnosed during pregnancy (Review)

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ABSTRACT

Background
Congenital syphilis is an increasing problem in many developing countries and in the transitional economies of Eastern Europe and the former Soviet Union. In several countries this increase has been aggravated by HIV/AIDS. While the effectiveness of penicillin in the treatment of syphilis in pregnant women and the prevention of congenital syphilis was established shortly after the introduction of penicillin in the 1940s, there is uncertainty about the optimal treatment regimens.

Objectives
To identify the most effective antibiotic treatment regimen (in terms of dose, length of course and mode of administration) of syphilis with and without concomitant infection with HIV for pregnant women infected with syphilis.

Search strategy
The Cochrane Pregnancy and Childbirth Group Trials Register (March 2006), the Cochrane Infectious Diseases Group Trials Register (March 2006), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2006, Issue 1), MEDLINE (1966 to March 2006), EMBASE (1974 to March 2006) and the references of traditional reviews. Experts in specialist units were also contacted.

Selection criteria
It was planned that any trial in which an attempt is made to allocate treatment for syphilis during pregnancy by a random or quasi-random method would be included in this review.

Data collection and analysis
Information was extracted using a data extraction sheet and this included entry criteria, the source of controls, and whether the authors stratified by the stage of pregnancy when the diagnosis of syphilis was made.

Main results
Twenty-nine studies met the criteria for detailed scrutiny. However, none of these met the pre-determined criteria for comparative groups and none included comparisons between randomly allocated groups of pregnant women.

Authors' conclusions
While there is no doubt that penicillin is effective in the treatment of syphilis in pregnancy and the prevention of congenital syphilis, uncertainty remains about what are the optimal treatment regimens.

Further studies are needed to evaluate treatment failure cases with currently recommended regimens and this should include an assessment of the role of HIV infection in cases of prenatal syphilis treatment failure. The effectiveness of various antibiotic regimens for the treatment of primary and secondary syphilis in pregnant women need to be assessed using randomised controlled trials which compare them with existing recommendations. This should include treatment with oral antibiotics which could be particularly relevant in resource-poor countries where the availability of safe needles and syringes cannot be guaranteed.

PLAIN LANGUAGE SUMMARY

Penicillin is effective in curing syphilis during pregnancy but more research is needed on the best dosage and duration of treatment

Syphilis is a potentially fatal, sexually transmitted disease that passes from a pregnant woman to her unborn baby. If the woman is untreated, her baby may be born with the disease, suffer permanent disability and be disfigured. The effectiveness of penicillin in curing infection with syphilis in pregnant women and preventing the baby being born with congenital syphilis was established soon after its introduction in the 1940s and before the widespread use of randomised controlled trials. Although rare in developed countries, the incidence of syphilis is high and increasing in many developing countries, particularly where HIV/AIDS is common. The review of trials found no trials comparing the effectiveness of different doses of penicillin or comparing penicillin with other antibiotics. More research is needed to find the best dosage and duration of treatment.

BACKGROUND

Characteristics of syphilis infection

Syphilis is a complex systemic disease with protean manifestations and virtually any organ in the body can be involved. It has been described in medicine as the great imitator or the great imposter in view of the multiple possible clinical manifestations, many of which are severe. It is caused by the spirochete, Treponema pallidum (T. pallidum), and is usually transmitted by sexual contact. Unlike most infectious diseases, it is rarely diagnosed by isolation and characterisation of the causative organism (Tramont 1990). Humans are the natural hosts of T. pallidum and also act as the vector.

Treponema pallidum penetrates usually abraded or damaged skin or mucous membrane although less often it can penetrate intact mucous membrane and the organisms rapidly become disseminated. The extremes of the incubation period are usually given as 10 to 90 days, although in practice it is generally around 28 days (Csonka 1990).

Infection with syphilis is characterised by several stages (Garnett 1997). The development of clinical syphilis is usually denoted by the appearance of a chancre, which is the classical lesion of primary syphilis at the site of inoculation. Most, but not all, patients with primary syphilis develop secondary syphilis. This is a systemic illness characterised by an array of signs and symptoms including fever, malaise, generalised lymphadenopathy and a rash and mucosal lesions. Even without treatment the manifestations of both primary and secondary syphilis resolve spontaneously over a few weeks, but recur in about a quarter of patients usually during the second year of infection. This is then followed by a latent period when the patient has few or no signs or symptoms. This is frequently divided into an early period (usually one year following the resolution of the secondary stage) and a late latent period. About a third of untreated patients with latent syphilis, subsequently develop tertiary manifestations of the disease, which can include neurosyphilis (tabes dorsalis and general paresis), cardiovascular involvement, or gummatous disease at many possible sites.

Unlike most other common bacterial infections, T. pallidum cannot be cultured sufficiently quickly or cheaply to assist diagnosis. T. pallidum is very difficult to visualise using light microscopy and instead requires visualisation by darkfield microscopy, but even this depends crucially on the type of specimen and how it has been obtained. Partly as a consequence of the limited availability of microscopic methods for diagnosis, as well as some patients with secondary syphilis and all patients with more advanced stages of the disease not having lesions which can be microscopically examined, serologic testing is the mainstay of syphilis screening and diagnosis (Sparling 1971; Hutchinson 1990; Hook 1992; Peeling 2004). There are two main types of serologic tests for syphilis; the non-treponemal and the treponemal tests. Non-treponemal tests detect antibodies to reagin, a cholesterol-lecithin-cardiolipin antigen that cross-reacts with antibodies present in the sera of patients with syphilis. The first syphilis serologic test was developed by Wasserman in 1906, but it was later realised that the antibodies detected by this test were not specific for syphilis. This led to the development of more specific and sensitive non-treponemal tests, of which the two commonly used today are the VDRL (Venereal Disease Research Laboratory) and the RPR (Rapid Plasma Reagin) tests. In most people with syphilis, non-treponemal serologic tests become reactive in early syphilis, at about four to seven days following the appearance of lesions. However, these tests are non-reactive in 13 to 41 per cent of individuals presenting with primary disease (Hutchinson 1990). These tests are almost always reactive in people with secondary syphilis. Antibody titers usually peak during the secondary or latent phases of the disease, after which even when not treated they decline and with long follow up and even without treatment around 25 per cent eventually become non-reactive in the late stages. In people who are treated for syphilis the RPR declines to become non-reactive more rapidly, usually between three and 12 months after treatment.

The main advantages of non-treponemal tests are that they are relatively inexpensive, easy to perform, and sensitive, making them useful as screening tests and, in addition, they are quantitative and can be followed over time to monitor response to treatment (Fiumara 1978). A disadvantage of non-treponemal tests is that false positives, often of a transitory nature, can be caused by acute viral

infections such as hepatitis and measles, and sustained false positive tests can be caused, particularly by auto-immune conditions. The diagnosis of syphilis should be confirmed in people with a positive non-treponemal test result by testing with a treponemal serologic test such as the FTA-ABS (fluorescent-treponemal antibody-absorbed test). Treponemal tests usually become reactive before reaginic tests. In most people, the treponemal tests remain positive indefinitely, whether the person has been treated or not. The treponemal tests are more expensive than the reaginic tests and can be technically more difficult to carry out. Antibody titers measured by reaginic tests vary during the natural history of untreated syphilis, becoming detectable shortly after the primary stage and climbing to their highest levels during the secondary or early latent stages (Hook 1992). Recent technological advances have resulted in improved serodiagnostic tools for syphilis (Peeling 2004).

Studies of the sexual partners of people with syphilis document infection risks of 10 to 60 per cent; a useful estimate is that syphilis develops in about a third of those exposed to early syphilis. Sexual contact with patients who have early syphilis is associated with the highest risk of developing the disease, whereas sexual contact with those who have latent disease is associated with lower risk (Hook 1992).

Syphilis is common among people infected with the human immunodeficiency virus (HIV), and the converse is also true. The relationships between syphilis and HIV are complex, with several areas of potential interaction. For instance, syphilis may predispose individuals to HIV acquisition, or transmission of either disease could be potentiated by the presence of the other (Fenton 2002; Goh 2005; Karumudi 2005). In addition, in HIV infected people with clinical features of syphilis, laboratory manifestations or the response to currently recommended syphilotherapy may be modified.

Infection with HIV, as with syphilis, produces a protean disease and the two interact on a number of levels. Syphilitic genital ulcers may enhance the acquisition and transmission of HIV; the natural history of syphilis may be modified in people co-infected with HIV; the results of laboratory tests for syphilis may be different in HIV-infected persons; and currently recommended therapy for syphilis may be less reliable for persons who are co-infected with HIV. Given the progressive decline of host defence that characterises the natural history of HIV infection, interactions between the two diseases may also depend on the degree of HIV-related immunosuppression present at the time of contact with syphilis (Hook 1992; Karumudi 2005).

Magnitude of the problem of syphilis infection

The reported rates of syphilis vary greatly from country to country. The rates for industrialised countries are better documented, whereas there are fewer data for developing countries, where the disease is more widespread. For example, in 1990, the incidence of primary and secondary syphilis in the United States was 20 per 100,000 population, far less than the 360 per 100,000 estimated for parts of Africa (Hook 1992).

Syphilis was a major public health problem in Europe and North America until the 1950s and its late complications were major causes of neurologic and cardiovascular disease. During the early part of the 20th century more than 20 per cent of patients in mental institutions in the United States had tertiary syphilis (Hutchinson 1990; Hook 1992). Annual incidence reached a peak during the second world war with 575,000 cases being reported in 1943, a rate of 4/1,000 population (Zenker 1990). With the introduction of penicillin after the second World War in the United States, the incidence of syphilis decreased.

In the United States, in the late 1950s and early 1960s, the number of cases increased again, fluctuating between 19,000 and 26,000 cases per year until 1978. The rates increased slightly in the late 1970s and early 1980s, and a disproportionate number of cases occurred in homosexual men. In the mid-1980s, primarily because of behavioural changes adopted in response to the acquired immunodeficiency syndrome (AIDS) epidemic, it is presumed syphilis declined among homosexual men, as did the male to female ratio of cases (Hook 1989). However, from the late 1980s the disease became more common and has been linked epidemiologically with HIV infection (Hook 1992; St Louis 1996). Around 1985 the incidence of syphilis among heterosexual men and women began to increase rapidly. From a peak in 1990 rates of primary and secondary syphilis fell after control measures were strengthened and in 1999 the rate was the lowest ever recorded with 6,657 cases of primary and secondary cases of syphilis being reported to the Centers for Disease Control and Prevention - CDC - (CDC 1999b). This led to the question being raised of whether possible "elimination of endemic syphilis transmission (is) a realistic goal for the USA" (Hook 1998) and more recently a 'National Plan to Eliminate Syphilis from the United States' has been developed by the Surgeon General (CDC 1999c).

In England and Wales a similar pattern has been seen with a peak number of annual cases being reported shortly after the second World War, at 27,761 in 1946 (Macfarlane 1984). During the 1950s incidence was low but, after this, numbers gradually increased and peaked in the late 1970s at just under 4,000 (Adler 1995). Since then numbers have fallen to very low levels and, in 1997, 150 new diagnoses of primary and secondary syphilis (100 males and 50 females) were reported by genitourinary medicine clinics (CDSC 1999). During the 1980s, syphilis became a subject of renewed concern due to rapidly increasing syphilis rates in North America and Europe. This was partly because the disease has been epidemiologically linked with HIV infections, and as a result of indications that currently recommended treatment regimens may not be sufficient to reliably eradicate syphilis, particularly in patients with concomitant HIV infection (Hutchinson 1990). The increase in syphilis infections in Europe from very low

levels has continued during the first decade of the 21st century (Eurosurveillance2004).

Syphilis infection rates in Eastern Europe have increased dramatically in recent years (Linglof 1995; Deayton 1997).

The World Health Organisation estimates that at least 12 million people are infected with syphilis globally each year (WHO 2001). The majority of these are in South and Southeast Asia (5.8 million) and Sub Saharan Africa (3.5 million). It is possible that the availability of penicillin in developing countries and its use in mass campaigns such as that directed against yaws in the 1950s and 1960s had some temporary effect on the prevalence and incidence of syphilis, but this had no long term impact. Syphilis remains at levels that were seen in developed countries a century ago.

Syphilis in pregnancy and congenital syphilis

The infection can be transmitted vertically from an infected pregnant woman to her fetus and at least two-thirds of all babies born to untreated women with syphilis are infected (Zenker 1990). However, the risk to the fetus or baby varies considerably according to the stage of untreated syphilis of the mother (Ingall 1990). The general obstetric history of a woman with untreated syphilis (known as Kassowitz's law) is that early pregnancies end in abortion or a stillborn child, later pregnancies in full-term infants with congenital syphilis and even higher parities in unaffected infants. In other words the natural history, in terms of perinatal outcome, of untreated syphilis in women is that the infectivity and severity become less with each successive pregnancy (Ingall 1990; Schulz 1992).

Congenital syphilis is a systemic infection in which a baby might have been delivered prematurely and the classic description of the congenital syphilitic baby is a severely infected premature infant with marasmus, a pot belly, 'old man facies' and withered skin. Congenital syphilis is a serious condition which if not fatal at a young age, can cause permanent impairment, debilitation and disfigurement from the stigmata associated with this condition. The clinical state of failure to thrive may be correlated with the frequently encountered pathologic finding of intense pancreatitis and inflammation of the gastrointestinal tract (Ingall 1990).

Syphilis can be transmitted transplacentally at all stages during the course of untreated maternal disease, from incubation, through primary, secondary, latent and to tertiary syphilis (Tsui 1997). The precise pathogenesis of congenital syphilis is unclear. It is usually thought that infection of the fetus by a syphilitic mother does not occur before the fourth month of pregnancy because treponemes from the maternal circulation are unable to pass through the Langhans' cell layer of the early placenta. When the Langhans' cell layer begins to atrophy during the fourth month of pregnancy, the fetus is exposed to the first risk of infection, but infection is most likely after the sixth month, when complete atrophy has occurred (Woltz 1946; Ingall 1990).

In the United States from the mid-1980s there were dramatic increases in congenital syphilis with the reported incidence increasing from 4.3 cases per 100,000 live births (158 cases) in 1983 to 107.0 cases per 100,000 live births (4,398 cases) in 1991 (Dunn 1993). Since 1991 the congenital syphilis rate has steadily declined (a decline of about 78 per cent between 1992 and 1998) and, in 1998, 801 cases were reported giving a rate of 20.6 per 100,000 live births (CDC 1999a). However, in Baltimore there was an epidemic of congenital syphilis in 1996-1997 with the rate rising to 282 per 100,000 live births (CDC 1998b). Since the implementation of 'National Plan to Eliminate Syphilis from the United States' there have been substantial declines in syphilis including congenital syphilis. In the United Kingdom, the incidence of congenital syphilis has remained low (five cases in 1992 and for 1994 to 1997 seventeen children meeting case definitions for congenital syphilis, but none had definitive syphilis, nine were presumptive and eight were possible cases; Hurtig 1998) and with only two cases reported in 1996 (CDSC 1998). This low incidence is ascribed largely to control of early acquired infectious syphilis in women through the screening of all pregnant women for syphilis (Adler 1995). In the period 1994 to 1997 it is estimated that more than two million women were screened as part of antenatal care in the UK and of the 139 women who were reported to have been treated for syphilis during or within three months of pregnancy 121 were identified by antenatal screening alone (results from the British Co-operative Clinical Group Survey of Syphilis among Pregnant Women quoted in CDSC 1998).

Recent epidemics of syphilis in Eastern Europe have affected pregnant women and for instance in Moscow the prevalence of syphilis among pregnant women increased from 0.02% in 1990 to 0.33% in 1995 (quoted in CDSC 1998). There have been equally dramatic increases in reported congenital syphilis in the Russian Federation from 29 in 1991 to 743 in 1999 (Tikonova 2003).

In developing countries congenital syphilis has continued to be a serious health hazard (Mascola 1985). For instance, reports indicate that a substantial proportion of perinatal mortality is caused by syphilis and in Zambia almost 9 per cent of infants seen at the University Teaching Hospital had congenital syphilis (Chattopadhyay 1988) and in the Central Hospital of Maputo, Mozambique about one per cent of neonates had congenital syphilis (Bastos dos Santos 92). Reported prevalences among women attending antenatal clinics in African, Asian and Latin American countries with positive sero-reactivity for syphilis range up to 19 per cent (Islam 1995; Luthra 1992; Maggwa 1992; Schulz 1992; Desperthes 2004, Gichangi 2004). While there are very few time series, it appears that, the incidence of congenital syphilis is increasing in many developing countries; for instance Faundes (Faundes 1992) reports a 10-fold increase in congenital syphilis in the Brasilian Federal District from 0.17 per 100,000 inhabitants in 1980 to 1.7 in 1984. It is probable that these rates are underestimates of the actual situation and are unlikely to be due to cross reactivity with nonvenereal treponemal infections (Schulz 1992). Lack and poor

quality of antenatal care appear to be an important risk factor for increasing numbers of mothers giving birth to babies with congenital syphilis (Wilkinson 1998; Walker 2002).

The costs of treating and not treating syphilis in pregnancy

The hospital costs of caring for newborn infants with congenital syphilis are considerable (Bateman 1997) and cost benefit studies in developed countries indicate the substantial advantages of screening pregnant women for syphilis (Stray-Pedersen 1983; Williams 1985). This has led several people to emphasise the importance of continued routine screening programmes in, for instance, North America (Ray 1995; Schmid 1996; Sanchez 1997; Sheffield 1999; Genc 2000) and the United Kingdom (Nicoll 1994; Sweeney 1994; Hurtig 1998; Welch 1998). Although, in view of the low incidence in the UK, it has been suggested that targetted screening might be more cost-effective. The United Kingdom National Screening Committee has considered a 'systematic review and national options appraisal' dealing with antenatal syphilis screening in the UK carried out by the PHLS Communicable Disease Surveillance Centre and decided that "screening should continue" and that "antenatal screening was effective and that only a small amount (of resources) would be saved by withdrawing the service" (NSC 2000).

In the early 1990s, it was estimated that in many developing countries an adverse outcome associated with syphilis during pregnancy could be averted at a cost of US$12, which includes the cost of the diagnostic test (rapid plasma reagin) and penicillin. This compares favourably with cost estimates per-childhood-death-prevented for measles of US$41, pertussis US$100 and neonatal tetanus US$153 for immunisation (Schulz 1992).

Treatment of early infection with syphilis

Treatment of syphilis with penicillin was a notable early success and has remained the preferred treatment of all types of syphilis since its first use for this indication by Mahoney in 1943 (Thomas 1949; Willcox 1981; Hutchinson 1990; Adler 1995; Rolfs 1995). Prior to this, the standard treatment for syphilis during pregnancy was arsenic therapy involving a series of injections usually of neoarsphenamine plus bismuth often, with side effects (Paley 1937). The success of penicillin for the treatment of syphilis in pregnant women was established soon after it became available (see summaries of early experience with penicillin in pregnancy: Beerman 1945; Ingraham 1948a; Ingraham 1948b; Goodwin 1950; Stokes 1950; Kampmeier 1981b; Jefferiss 1963). However, in strict terms of evidence from randomised controlled trials, neither the optimal dose nor the optimal duration of administration is known (Zenker 1990).

Studies carried out in the 1940s indicated that the doubling time for T. pallidum was 30-33 hours in early disease (Magusen quoted in Zenker 1990). Idsoe (Idsoe 1972) after extensive review of treatment studies suggested that effective treatment of early syphilis required the maintenance of a minimal serum concentration of 0.03 I.U. of penicillin/ml (0.018 mug/ml) for 7-10 days without interruption for more than 24 hours, however it was admitted that the choice of this minimal treponemicidal level was rather arbitrary. There have been concerns raised that the "resurgence in the incidence of congenital syphilis in the United States" was because of inadequate levels of penicillin following recommended guidelines. A small study showed "a wide range of penicillin levels ...in gravidas at term in the maternal serum, cerebro-spinal fluid, umbilical cord serum, and amniotic fluid within one week after 2.4 million units of benzathine penicillin G intra-muscularly (i.m.)" (Nathan 1993). The precise penicillin regimens for the treatment of early syphilis and syphilis during pregnancy and congenital syphilis remain controversial issues (CDC 1993; Rolfs 1995; Crowe 1997). For instance in the United States, depot preparations of penicillin, usually benzathine penicillin G (BPG), are preferred for the treatment of early syphilis (one dose of 2.4 million units i.m.), because they are easier to administer, are inexpensive, and do not require frequent readministration (Hook 1992; CDC 1993). While in the United Kingdom treatment with daily injections of procaine penicillin (0.6 to 0.9 million units daily for 10 to 14 days intramuscularly) is preferred (Adler 1995; Crowe 1997; CDSC 1998; CDC 2002). The regimen of benzathine penicillin G recommended by the CDC for treatment of early syphilis, one dose of 2.4 million units intramuscularly (CDC 1993; CDC 1998a), has been criticised on the grounds that it does not achieve treponemicidal levels in CSF (Smith 1956; Polinikorn 1980; Hook 1992; Rolfs 1995). This debate about appropriate penicillin preparations and adequate dosage regimens to treat syphilis has been reopened in the light of reports of inadequately treated cases of syphilis in patients who are seropositive to HIV, despite following agreed treatment schedules (Hook 1992; Crowe 1997). Although a randomised trial of two treatments (2.4 million units of penicillin G and that therapy enhanced with a 10-day course of amoxicillin and probenecid) for early syphilis in non-pregnant people with and without HIV infection found that the enhanced treatment "...did not improve outcomes" (Rolfs 1997). The high seroconversion rates for both syphilis and HIV during pregnancy found in certain populations has led to the suggestion that screening of women twice during a pregnancy for these diseases might be justified (Qolahle 1995).

The 2002 CDC 'Guidelines for Treatment of Sexually Transmitted Diseases' (CDC 2002) are similar to earlier CDC guidelines (see CDC 1998a. CDC is due to publish updated Guidelines for Treatment of Sexually Transmitted Diseases in Spring 2006) recommend that "treatment during pregnancy should consist of the penicillin regimen appropriate for the stage of syphilis". These are: for primary and secondary syphilis, benzathine penicillin G 2.4 million units i.m. in a single dose; early latent syphilis, benzathine penicillin G 2.4 million units i.m. in a single dose, late latent syphilis or latent syphilis of unknown duration, benzathine penicillin G 7.2 million units total, administered as three doses of benzathine penicillin G 2.4 million units i.m. each at one week intervals. It is recommended that treatment of primary and secondary syphilis in HIV-infected persons should be "... with ben-

zathine penicillin G , 2.4 million units i.m., as for HIV-negative patients". The CDC Guidelines note that "parenteral penicillin G is the only therapy with documented efficacy for neurosyphilis or for syphilis during pregnancy.... Penicillin is effective for preventing maternal transmission to the fetus.... Evidence is insufficient to determine whether specific, recommended penicillin regimens are optimal.... Some experts recommend additional therapy in some settings. A second dose of penicillin 2.4 million units i.m. may be administered one week after the initial dose for women who have primary, secondary, or early latent syphilis".

The CDC guidlines (CDC 2002) note that "the efficacy of penicillin for the treatment of syphilis was well established through clinical experience before the value of randomized controlled clinical trials was recognized. Therefore, almost all the recommendations for the treatment of syphilis are based on the opinions of persons knowledgeable about STDs and are reinforced by case series, clinical trials, and 50 years of clinical experience. Parenteral penicillin G has been used effectively for more than 50 years to achieve clinical resolution (i.e., healing of lesions and prevention of sexual transmission) and to prevent late sequelae. However, no comparative trials have been adequately conducted to guide the selection of an optimal penicillin regimen (i.e., the dose, duration, and preparation). Substantially fewer data are available for nonpenicillin regimens. Parenteral penicillin G is the only therapy with documented efficacy for syphilis during pregnancy. Pregnant women with syphilis in any stage who report penicillin allergy should be desensitized and treated with penicillin. Penicillin is effective for preventing maternal transmission to the fetus and for treating fetal infection. Evidence is insufficient to determine whether the specific, recommended penicillin regimens are optimal."

In the United Kingdom (UK) treatment guidelines for pregnant women with syphilis recommend a different penicillin regimen to the American CDC i.e. i.m. procaine penicillin G 750mg (Jenacillin A 3 ml or Jenacillin O 2.5 ml) daily x 10 days (AGUM, MSSVD 2002).

In 2003 the European Office of WHO published a review of different antibiotic regimens (principally using penicillin) for treating syphilis followed in different countries (WHO Euro 2003).

WHO Geneva in 2003 as part of "Guidelines for the Management of Sexually Transmitted Infections" recommended that for syphilis "pregnant patients at all stages of pregnancy, who are not allergic to penicillin, should be treated with penicillin according to the dosage schedules recommended for the treatment of nonpregnant patients at a similar stage of the disease" which give those recommended by CDC and as alternatives those proposed in the UK (WHO 2003).

Reservations have been raised particularly over the past 10 or so years regarding whether recommended schedules for the treatment of syphilis during pregnancy are adequate (Hardy 1970; Rawstron 1991; Monif 1994; Galan 1997; Conover 1998; Hollier 1998; Tourneux 2001; Richardson 2002; Sheffield 2002).

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Treatment of syphilis in pregnancy can lead to development of the Jarisch-Herxheimer reaction (Myles 1998; Brocklehurst 1999). "The Jarisch-Herxheimer reaction is similar in frequency, character, and intensity to that in non-pregnant adults, but gravidas may have increased uterine activity and transient alterations in fetal well-being. The pregnant patient with a severely affected fetus with congenital syphilis may experience preterm labor, preterm delivery, or fetal death in association with the Jarisch-Herxheimer reaction" (Klein 1990).

A separate issue is allergy to penicillin which in the United States is estimated to be between five and 10 per cent (Wendel 1985). However, desensitisation, under close supervision, with increasing oral doses of pencillin over four to six hours (Wendel 1985) or a slowly increasing infusion of penicillin G (Ziaya 1986), and then treatment with penicillin appear safe and effective.

There is limited experience with antibiotics other than penicillin for the treatment of syphilis during pregnancy (Montgomery 1959; Willcox 1962; Holder 1972; Thompson 1976b). Other antibiotics which have been used for the treatment of syphilis in pregnancy include: spectinomycin (Lucas 1967); amoxycillin (Hay 1990); erythromycin (Montgomery 1961); azithromycin (Hook 1999); and cephalosporins (Gonzalez-Ochoa 1967; Oller 1967; Katsambas 1987; Hook 1988; Schofer 1989). Erythromycin has been associated with a high failure rate when used to treat pregnant women (South 1964; Fenton 1976; Hashisaki 1983; Hartmann 1984; Mascola 1984; Chattopadhyay 1988; Hook 1992; Sanchez 1997).

Problems with studying syphilis treatment

Syphilis is a difficult disease to study as the natural history in an individual can often cover several decades and both the diagnosis and the outcome are usually made on the results of serology and not clinically or bacteriologically. Because the development of neurosyphilis (or other late sequelae) cannot be predicted, long-term follow up is needed to measure treatment efficacy (Garnett 1997). Instead of performing long-term follow up and observation, investigators usually monitor titers of non-treponemal antibody to assess the response to treatment.

Because of penicillin's immediate clinical success very few further clinical trials after an initial period of intensive investigation were carried out and over time the recommended penicillin regimens have changed only slightly (Thompson 1976a; CDC 1993; CDC 1998a). Furthermore, because the early studies occurred before modern clinical-trial methodology was fully developed, interpretation of the results is problematical (Zenker 1990). As a result, while current regimens for syphilis therapy appear to be largely effective, they may or may not be optimal. With the accumulation of reports of treatment failures and the appearance of HIV, current regimens for the treatment of syphilis are being questioned.

Zenker (Zenker 1990) has noted the evaluation of syphilis treatment trials is complicated by three factors: first, many studies lack the essentials of good study design: randomisation, blinding, an adequate number of patients (i.e. statistical power), and inclusion of a control group; second, because Treponema pallidum cannot be routinely cultured, diagnosis of active disease often relies on serology tests; third, the natural history of syphilis necessitates long-term follow up to assess treatment efficacy. Because of the last two factors, studies should have clearly defined entry and outcome criteria, but rarely do. As a result, treatment trials are difficult to evaluate, and optimal treatment regimens are difficult to determine (Zenker 1990).

In 2005 the results of a randomised controlled trial of a single 2 g oral dose of azithromycin compared to 2.4 million units of penicillin G given intramuscularly for the treatment of early syphilis among high-rsk populations (72 percent of the 328 included in the trial were women) in Mbeya, Tanzania were published (Riedner 2005). This concluded that the RCT "...provided clear evidence that a single 2 g dose of azithromycin is as effective as a 2.4 MU dose of penicillin G benzathine for the treatment of early syphilis....given logistical advantages conferred by this oral treatment, particularly in resource-poor settings in developing countries,...our findings support the wider use of this alternative regimen in syphilis-control programs." However the authors and others have raised concerns about the recent emergence of azithromycin-resistant Treponema pallidum (Ballard 2006; Holmes 2005; Riedner 2006).

In view of increasing incidence of syphilis and reports of apparent non-response to current antibiotic regimens, questions have been more frequently raised about whether the established regimens to treat pregnant women with syphilis and babies born with congenital syphilis are optimal and effective (McCraken 1974; Giles 1979; Mascola 1984; Van Eijk 1987; Musher 1988; Hook 1989; Zenker 1990; Rawstron 1991; Hook 1992; Rolfs 1995; CDC 2002).

OBJECTIVES

The objective of this review is to identify the most effective antibiotic treatment regimen (in terms of dose, length of course and mode of administration) of syphilis with and without concomitant infection with HIV for pregnant women infected with syphilis.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

It was planned that any trial in which an attempt is made to allocate treatment for syphilis during pregnancy by a random or quasi-random method would be included in this review.

Types of participants

Pregnant women with a clinical diagnosis of primary, secondary or late stage syphilis confirmed by nontreponemal and treponemal tests and with and without concomitant infection with HIV.

Types of intervention

Any antibiotic treatment versus no treatment; comparison of two different antibiotic drug treatments; systemic versus oral antibiotic treatment; comparison of different doses and lengths of course of treatment.

Types of outcome measures

Maternal: resolution of clinical symptoms; changes in titers for quantitative reaginic serologic tests i.e. VDRL or RPR and follow up at three months, six months, one year and two years and above.

Fetal and infant: miscarriage with and without evidence of an infected fetus, stillbirth with and without evidence of an infected fetus, neonatal death with and without evidence of congenital syphilis, and baby born with congenital syphilis or suspicion of congenital syphilis. The initial case definition of congenial syphilis includes all infants (aged < 12 months of age) with one of the following: (1) a reactive nontreponemal serologic test for syphilis confirmed by a reactive treponemal test, (2) a positive darkfield microscopic examination on a non-oral mucous membrane or (3) a positive fluorescent antibody examination for Treponema pallidum on any lesion.

Side-effects: development of Jarisch-Herxheimer reaction in the mother with possible preterm labour, delivery and fetal or neonatal death.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

The Cochrane Pregnancy and Childbirth Group Trials Register was searched by contacting the Trials Search Co-ordinator (March 2006).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:
(1) quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
(2) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness search of a further 37 journals.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Search strategies for identification of studies'

section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

In addition, the Cochrane Infectious Diseases Group Trials Register (March 2006), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2006, Issue 1), MEDLINE (1966 to March 2006) and EMBASE (1974 to March 2006) were searched, using the highly sensitive search strategy detailed in the Cochrane Handbook (Higgins 2005) combined with the terms syphilis and pregnancy.

The reference lists of traditional reviews (Idsoe 1972; Zenker 1990; Rolfs 1995; Hollier 1998; Wendel 2002) were searched and specialist centres and groups including the 'sexually transmitted infections' (STIs) group in the Reproductive Health and Research Department, Family and Community Health cluster at the World Health Organization, Geneva, the Cochrane Sexually Transmitted Diseases Group, the Division of STD Prevention, the National Center for HIV, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, USA and the Centre for Infections of the British Health Protection Agency were contacted to identify additional published and unpublished trials.

Language restrictions were not applied.

These searches provided a list of potential studies. Hard copies were retained and reviewed to see if they met the inclusion criteria.

METHODS OF THE REVIEW

Papers that potentially met the inclusion criteria were scrutinised for a second time. Information was extracted using a data extraction sheet and this included entry criteria, the source of controls, and whether the authors stratified by the stage of pregnancy when the diagnosis of syphilis was made.

DESCRIPTION OF STUDIES

Twenty-nine studies met the criteria for hard copy scrutiny. However, none of these met the pre-determined criteria for comparative groups and none included comparisons between randomly allocated groups of pregnant women. The details of the 29 studies are given under the excluded studies section.

METHODOLOGICAL QUALITY

No randomised controlled trials were identified.

RESULTS

No randomised controlled trials were identified.

DISCUSSION

Syphilis in pregnancy with the consequent likelihood of severe long-term morbidity in the mother and fatal or severely debilitating sequelae in her fetus has been largely controlled in recent years in affluent countries through effective screening and treatment programmes (CDC 1999c; NSC 2000). In countries of Eastern Europe and the former Soviet Union and to an even greater extent in many developing countries the morbidity caused by syphilis and particularly congenital syphilis is increasing and significant. This has become even more of a burden in populations where the HIV/AIDS epidemic is severe. This is tragic because since the introduction of penicillin in the 1940s a very effective means of treatment of syphilis and of the prevention of congenital syphilis has been available.

In an ideal situation, treatment policies for pregnant women who are infected with syphilis should be based on research which compares an intervention group and a control group of pregnant women with syphilis who are randomly allocated to treatment by different schedules or doses, or both, of antibiotics. However, the efficacy of penicillin in the treatment of particularly early syphilis in pregnant women in terms of curing the infection in the woman and also preventing a baby being born with congenital syphilis was established shortly after the introduction of penicillin. The effective treatment of syphilis including pregnant women with the infection was a notable early success of the use of penicillin during the 1940s. The recommended penicillin regimen for the treatment of syphilis in pregnant women developed at this time (Cole 1946; Cole 1949; Cross 1949; Ingraham 1946) has changed very little over the past 60 or so years and certainly since the development of long-acting preparations of penicillin G in the early 1950s (Jackson 1962). A recent case series has generally confirmed the effectiveness of benzathine penicillin G for the treatment of maternal infection with syphilis and the prevention of congenital syphilis (Alexander 1999). Although this study found the ".. highest risk of fetal treatment failure exists with maternal secondary syphilis".

However, as noted by Rolfs "though the efficacy of penicillin is firmly established, the scientific evidence for specific recommendations is weak by current standards for clinical investigation" (Rolfs 1995). Rolfs (Rolfs 1995) also notes that "although these early studies did not utilize methods considered standard practice for acceptable clinical trials today - particularly randomized, concurrent

comparisons between different therapy regimens - many were carefully conducted and involved large numbers of patients. Several conclusions can be drawn from these early studies: (1) both duration and dosage of therapy were important, (2) re-treatment rates were lowest for primary infections and highest for patients with second-stage infection, (3) long acting preparations were probably as effective as regimens using multiple injections of aqueous crystalline or procaine penicillin G."

The latest CDC 'Guidelines for Treatment of Sexually Transmitted Diseases' (CDC 2002) recommend that "treatment during pregnancy should be the penicillin regimen appropriate for the stage of syphilis". These are: for primary and secondary syphilis, benzathine penicillin G 2.4 million units i.m. in a single dose; early latent syphilis, benzathine penicillin G 2.4 million units i.m. in a single dose, late latent syphilis or latent syphilis of unknown duration, benzathine penicillin G 7.2 million units total, administered as three doses of benzathine penicillin G 2.4 million units i.m. each at one-week intervals. It is recommended that treatment of primary and secondary syphilis in HIV-infected persons should be "... with benzathine penicillin G , 2.4 million units i.m., as for HIV-negative patients". The CDC Guidelines note that "penicillin is effective for preventing maternal transmission to the fetus.... Evidence is insufficient to determine whether specific, recommended penicillin regimens are optimal.... Some experts recommend additional therapy in some settings. A second dose of penicillin 2.4 million units i.m. may be administered one week after the initial dose for women who have primary, secondary, or early latent syphilis". The high seroconversion rates for both syphilis and HIV during pregnancy found in South Africa led to the suggestion that screening of women twice during a pregnancy for these diseases is justified (Qolahle 1995). It has also been suggested that a second dose of penicillin 2.4 million units should be given as standard practice (Mascola 1985; Markovitz 1986; Genc 2000). In the United Kingdom treatment of primary, secondary and early latent syphilis is usually with daily injections of procaine penicillin (0.6 to 0.9 million units daily for 10 to 14 days i.m.) and for late latent and tertiary syphilis (excluding neurosyphilis) the daily injections are continued for 17 to 21 days (Adler 1995; Crowe 1997; CDSC 1998, AGUM, MSSVD 2002). The incidence of congenital syphilis in the United States in 1999 was 14.3 cases per 100,000 live births (CDC 2000) compared to 6.2 in the United Kingdom for the three years 1994 to 1996 (results from the British Co-operative Clinical Group Survey of Syphilis among Pregnant Women quoted in CDSC 1998). Clearly many factors other than the antibiotic regimen used to treat syphilis during pregnancy such as the coverage of antenatal care could explain these differences. However, concerns have been raised on several occasions that the standard dose of benzathine penicillin G (2.4 million units) recommended by CDC does not achieve adequate concentrations in the cerebrospinal fluid and may not be the most effective therapy regimen. These concerns have been heightened as treatment failures appear to be more common in women with HIV and those who deliver soon after treatment has begun (Rawstron 1991; Hook 1992; McFarlin 1994; Rolfs 1995; Crowe 1997).

An underlying issue is that uncertainty continues about what are the appropriate treatment regimens for syphilis during pregnancy as, in strict terms of evidence from randomised controlled trials, neither the optimal dose nor the optimal duration of administration is known (Zenker 1990).

AUTHORS' CONCLUSIONS

Implications for practice

No randomised trials were identified to guide a decision on whether recommended antibiotic (penicillin) treatment schedules for women who have syphilis and are pregnant should be changed.

Implications for research

Further studies are needed to evaluate treatment failure cases with currently recommended regimens and this should include an assessment of the role of HIV infection in cases of prenatal syphilis treatment failure.

The effectiveness of various antibiotic regimens for the treatment of primary and secondary syphilis in pregnant women needs to be assessed using randomised controlled trials which compare them with existing recommendations. These studies should also document possible side-effects of the various treatments. The comparisons could include one and two injections of 2.4 million units of benzathine penicillin G, daily injections of procaine penicillin 0.6 to 0.9 million units for 10 to 14 days, one injection of 2.4 million units of benzathine penicillin G followed by a course of amoxicillin/ampicillin and probenecid or high-dose amoxicillin/ampicillin and probenecid for syphilis.

These comparisons could be carried out for the treatment of primary and secondary syphilis detected before the last trimester and probably more importantly for those detected in the last trimester.

Consideration could also be given to trials which assess the effectiveness of treatment with oral antibiotics such as 2 g single-dose azithromycin compared to benzathine penicillin G or procaine penicillin, or both. Treatment with oral antibiotics could be particularly relevant in resource-poor countries where the availability of safe needles and syringes cannot be guaranteed.

FEEDBACK

Sankar, October 2002

Summary

In the background, you discuss development of the Jarisch-Herxheimer reaction as a complication of treatment of syphilis and

imply desensitisation with penicillin may protect against this reaction. The Jarisch-Herxheimer reaction is not due to penicillin allergy. The references quoted (Wendel 1985, Ziaya 1986) relate to desenitisation for penicillin allergy. There are no data to suggest that desensitisation has any ameliorating effect on the Jarisch-Herxheimer reaction.

[Summary of comment received from Nathan Sankar, October 2002]

Author's reply

The relevant section has been corrected.

[Reply from Godfrey Walker, November 2002]

Contributors

Nathan Sankar

POTENTIAL CONFLICT OF INTEREST

None known.

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TABLES

Characteristics of excluded studies

Study	Reason for exclusion
Akorbian 1969	A non randomised trial carried out in the 1960s in Tashkent, USSR and including 272 patients (168 men and 104 women with no mention whether pregnant or not) with primary, secondary or tertiary syphils and comparing three types of penicillin (bicillin 3, 4 and 6).
Alexander 1999	A non randomised trial to evaluate prospectively the 1988 Centers for Disease Control and Prevention (CDC) recommended regimens for the treatment of antepartum syphilis and prevention of congenital syphilis. This was a prospective evaluation of recommended syphilis treatment regimens carried out from September 1, 1987, to August 31, 1989, at Parkland Memorial Hospital, Dallas, Texas, U.S.A. Women with syphilis were staged and treated according to CDC recommendations. Treatment included 2.4 million units of intramuscular (i.m.) benzathine penicillin G for primary, secondary, or early latent (less than 1 year) syphilis. Women with late latent (uncertain or longer than 1 year) syphilis were treated with 7.2 million units of benzathine penicillin G i.m. over 3 weeks. During the study period, 448 of 28,552 women (1.6%) who delivered were diagnosed with syphilis. One hundred and eight were diagnosed at delivery and treated postpartum. The remaining 340 (75.9%) gravidas with untreated syphilis attending the prenatal clinic comprised the study group. The success of therapy in preventing congenital syphilis was as follows: primary syphilis, 27 of 27; secondary syphilis, 71 of 75; early latent syphilis, 100 of 102; and late latent syphilis, 136 of 136. The success rate for all stages of syphilis was 334

	of 340 (98.2%). The success rate of therapy in secondary syphilis was significantly different from that of the other groups (P = .03). Two of the six fetal treatment failures produced preterm stillborns. Only one maternal treatment failure occurred, in a human immunodeficiency virus-infected woman. The authors conclude that the CDC-recommended regimens for the prevention of congenital syphilis and treatment of maternal infection are effective, but the highest risk of fetal treatment failure exists with maternal secondary syphilis.
Aron 1947	A case series of 36 pregnant women all of whom presented with lesions of early syphilis infection to the Chicago Intensive Treatment Center, U.S.A. during 1945 and early 1946. Syphilis was confirmed by dark field examination in 35 of the cases. The remaining patient had "...lesions indubitably characteristic of secondary syphilis but unsuitable for dark field examination". All women received 2,400,000 units of penicillin over a period of 15 days. The results of the treatment of these 36 women are presented. "In a group of 35 infants that were delivered of women who were treated with penicillin for early infectious syphilis during pregnancy, congenital syphilis did not develop in any infant. One infant was stillborn, possibly because of syphilitic infection (2.8 per cent failures)."
Bundesen 1950	Comparison of two penicillin treatment regimens for pregnant women with "dark field-positive primary, secondary or relapsing syphilis". From February 1945 to August 1946 women attending the Chicago Intensive Treatment Center of the Venereal Disease Control Program, U.S.A. were treated with schedule A (2,400,000 units of aqueous penicillin over a period of 15 days with a total of 160,000 units in 24 hours) and from July 1946 to November 1947 schedule B was used (4,800,000 units of aqueous penicillin over a period of seven and a half days with a total of 640,000 units during 24 hours). 130 women were treated while they were pregnant, 75 with schedule A and 55 with schedule B. Information was available on all but one of the pregnancy outcomes i.e. 129, 74/75 for schedule A and 55/55 for schedule B. For those receiving schedule A, the outcomes were slightly worse i.e. 1 case of congenital syphilis and three stillbirths probably or possibly related to syphilis than for those treated with schedule B, no cases of congenital syphilis and one stillborn with "a possibility that syphilis played some role in the unfavourable outcome of this pregnancy".
Cole 1946	A case series of 730 patients attending the University and City Hospitals in Cleveland, U.S.A. from October 1943 until late 1945 with early syphilis and treated with penicillin is presented. Of these patients 47 were pregnant women. Various dosages of penicillin were given ranging from 60,000 units to 2,000,000 units. Full figures are not given for outcomes in relation to dose of penicillin, however, the following statements are made: "the general experience with 60,000 units in acute syphilis is that sooner or later there will be a relapse"; "even with 300,000 units (used in three cases) there was a relapse in the form of early congenital syphilis"; "nine patients were treated with 1,200,000 units, and there are no relapses so far"; "eight patients were treated with 1,600,000 units, and 1 relapse"; "seventeen patients have been treated with a dosage of 2,400,000 units and 2 cases of stillbirth but unfortunately no examination of the fetuses were made"; "certainly the patient should receive at least 2,400,000 units and perhaps even more".
Cole 1949	Pooled results of three large studies carried out before 1947 in Cleveland, Chicago and New York City in the USA in which pregnant women with serologically confirmed syphilis and not previously treated were treated with penicillin. A case series with no controls. The paper is based on 414 'outcomes' of pregnancies in terms of live births, abortions, miscarriages and stillbirths, but the number of pregnant women is not stated. The summary states that "... previously untreated patients (were) given amounts of penicillin varying from 200,000 to 10,000,000 units". "A status based on clinical and serologic evidence was established at 90 days or later in 311 of the outcomes. It was found that 11 of those 3.5 percent were diagnosed as syphilitic." "Of the 216 known outcomes of patients treated for primary and secondary infection, 4.2 percent were found to be syphilitic, while congenital syphilis was diagnosed in 2.1 percent of the outcomes of patients treated for early latent syphilis." "Best results were obtained from treatment schedules employing at least 2,400,000 units of penicillin." Statistical tests are not presented in support of this.
Cole 1950	Pooled results of three large studies carried out before 1947 in Cleveland, Chicago and New York City in the USA in which women with serologically confirmed syphilis had been treated with penicillin before they became pregnant and the subsequent outcome of their pregnancies are given. A case series with no controls. The paper is based on 311 'outcomes' of pregnancies in terms of live births, abortions, miscarriages and stillbirths, but the number of pregnant women is not stated. Treatments varying from 600,000 to 9,600,000 units of penicillin were given and 58 patients also received 320 to 360 mg of arsenoxide. However, the outcome status could

	only be definitely established for 229 'outcomes', and among this group the authors state that "one congenital syphilis, representing a treatment-failure incidence of 0.4 percent of the 229 'outcomes' in which the status was established, indicates that no great likelihood of danger exists for a child born of a mother who has had satisfactory treatment for syphilis before she became pregnant, provided the woman has not relapsed during pregnancy."
Cross 1949	A case series of 39 pregnant women treated from July 1946 until probably the end of 1947 in Georgia, U.S.A. and followed for at least four months after delivery. Each woman had early syphilis and was treated with a total dose of 4.8 million units of crystalline penicillin G in doses of 80,000 units every three hours i.e. 60 injections in seven and a half days. In more than a third of the patients treatment was started after the 32nd week of pregnancy. "Six patients went into premature labour during penicillin therapy and two of their children were born with congenital syphilis. One patient developed a serologic relapse prior to parturition and delivered a syphilitic child. Five (12.8 per cent) of the 39 mothers have shown evidence of a relapse of their syphilitic infection. The results obtained in this series of patients with early infectious syphilis treated in the late stage of pregnancy indicate that crystalline penicillin G is an effective therapeutic agent in prenatal syphilis."
Donders 1997	The outcome of pregnancy was assessed in a case series of 212 HIV seronegative women diagnosed with active syphilis attending for antenatal care at Kalafong Hospital, Pretoria, South Africa between January 1988 and December 1990 and who received either no treatment with penicillin or one to three weekly injections of 2.4 million units of benzathine penicillin G (BPG). Outcome information from 180 women was included in the study. Twenty two women did not deliver at Kalafong Hospital and could not be traced. Two women with twin pregnancies, one with a premature neonatal death due to a placental abruption and seven with severe preeclampsia were excluded from the study. Fifty five women received no prenatal treatment with penicillin; 19 received one injection of 2.4 million units of BPG; 24 received two injections of BPG; and 82 received three such injections. The authors conclude that the "... women receiving two or three weekly intra-gluteal injections of benzathine penicillin G had a favourable pregnancy outcome. However, after only one injection, lower birth weight, increased immaturity, prematurity, and total preterm birth rate resulted. Total pregnancy loss and perinatal mortality were also increased.
Goodwin 1946	A case series of 31 pregnant women from Baltimore, U.S.A. recruited prior to September 1945, all of whom had early infectious (primary or secondary) syphilis at the time of treatment. These women from Baltimore are compared with the Philadelphia series (26 mothers) of Ingraham (1946). Both series were similar with regard to: type of infection, primary 7/57, secondary 50/57; single course of penicillin 52/57 and multiple courses 5/57; duration of treatment 4 to 15 days; duration of pregnancy 14/57 < 16 weeks, 31/57 16-32 weeks, 12/57 > 32 weeks. Most (48/57) received 1.2 to 2.4 million units of penicillin. Of the 57 women three had two pregnancies during the period covered by the article and thus there were 60 infants born and only in one was a diagnosis of congenital syphilis made. A comparison is also made with an historical case series carried out in the 1930s of pregnant women with syphilis treated with metal chemotherapy ('standard' arsenic-bismuth-mercury) in terms of arsphenamine. Depending on the stage of pregnancy this was administered by weekly, or three times weekly or by intravenous drip or multiple syringe injection over five to 10 days. The cure figures are given for different doses of arsphenamine. These range for early syphilis (71 cases) from: no treatment 5% normal infant and 95% almost certainly syphilitic, to for 3+ gm arsphenamine 95% almost certainly normal and 5% almost certainly syphilitic; and for late (usually latent) syphilis (579) cases from: no treatment 35% almost certainly normal and 65% almost certainly syphilitic, to 3+ gm arsphenamine 98% almost certainly normal and 2% almost certainly syphilitic. The article recommends that "... in syphilitic pregnant women penicillin be used routinely for the prevention of prenatal syphilis, other methods of treatment being abandoned." "The total dose of penicillin should not be less than 2.4 million units administered intramuscularly and over not less than seven and a half days."
Haagsma 1956	A case series of 928 syphilitic women with 978 pregnancies of whom information was obtained on 746 from 734 pregnancies in 696 women from 1947 until about 1955 in Amsterdam. Women were treated with penicillin or neo-arsphenamine with bismuth. The authors conclude that "treatment during pregnancy only with at least 4,800,000 U of penicillin, if not started too late, may in all probability prevent syphilis of the child or cure it before birth".
Ingraham 1946	Sequential case series of pregnant women receiving aqueous sodium penicillin (92) from the fall of 1943 and amorphous calcium penicillin in peanut oil-beeswax (46) from early 1946 up to mid 1947 in Pennsylvania, U.S.A. Those receiving aqueous penicillin had either 1.2 or 2.4 million units split over 3- to 4-hour intervals

	for 8 to 10 days. The women receiving amorphous calcium penicillin in peanut oil-beeswax had a total dosage of 4.8 million units over a period of nine days. The authors note that the "over-all results are approximately equivalent (for both treatments) .... with a failure rate of 4.9 percent (in terms of living syphilitic infants being born)". Although numbers are presented by stage of disease, gestational age when treatment begun, serologic response and perinatal outcome, it is not possible to derive comparable outcomes for the two series. The authors suggest that a minimum total dose of 2.4 million units of aqueous sodium penicillin is recommended to achieve cure of both mother and baby.
Ingraham 1947	A case series of the treatment of 49 pregnant women with syphilis in Pennsylvania, U.S.A. from 1943 up to 1946. Women ranged in age from 15 to 36 years; two had primary syphilis, 24 secondary, 19 early latent syphilis and three late latent syphilis; 46 had received no previous treatment for syphilis; 10 patients received 1.2 million Oxford units of sodium penicillin, 30 received 2.4 units and for 9 the dosages were individualised. The authors note that "at the time of compilation of these data" 39 of the 49 women in the study had reached "termination of their pregnancy" and "one woman has completed two pregnancies during the course of this study". "Only one living syphilitic child was born" and "this success which approaches 97 per cent ... indicates a result at least equal to that obtained by the arsenical-bismuth regimen now generally employed in the prevention of congenital syphilis."
Ingraham 1951	An article which summarises a case series concerned with the outcome of pregnancy of 1959 women with syphilis from the University of Pennsylvania, (484 women) and Philadelphia General Hospital (1475 women) U.S.A. and of which 1063 received penicillin. "All cases are included ... in which the surviving infant was followed for at least sixty days and in whom at the time of the last medical observation there seemed no reasonable doubt as to the presence or absence of syphilis." In addition "for adequate clinical statistical analysis of the value of penicillin in the prevention of congenital syphilis, it was felt that three types of control groups were necessary. In the first place, since normal, or non-syphilitic, pregnancy does not invariably result in the birth of a full term living infant it was felt that data on the results from a comparable group of pregnancies from which syphilis had been excluded, in so far as possible, were a requisite. This information was obtained through inclusion in the study of such a control group giving outcome of pregnancy in 10,323 mothers at the Philadelphia General Hospital for the years 1945 to 1949 inclusive, in whom syphilis was ruled out .... Secondly, it seemed necessary to obtain information concerning the effect of untreated syphilis on the outcome of pregnancy in comparable material over a period concurrent with the study ... In the ten years 1940 to 1949 inclusive it was possible to derive information at the Philadelphia General Hospital on the outcome of 302 untreated syphilitic pregnancies, 220 with early syphilis and 82 cases with late syphilis at the time of delivery ... In controlling the results of penicillin therapy in this field it also seemed highly desirable to have information in a comparable series of cases concerning the outcome of pregnancy when arsenic and bismuth, which it is proposed be replaced by penicillin, is employed. Such a group ... with early syphilis was found at Philadelphia General Hospital for the interval January 1940 to August 1946 inclusive ... This group of cases numbers 594." The authors conclude that: "the probability of pregnancy, uncomplicated by syphilis, resulting in a normal full term living infant is about 86 percent .... Untreated early syphilis ... resulted in a dead or diseased infant in about 82 percent of cases .... (and in) untreated women with late syphilis the likelihood of a normal full term infant was three in four (75 percent) and of a living full term syphilitic infant only 2.4 percent, though the stillbirth rate at 12.2 percent continued to remain higher than that of the normal control group ... Effective dosage of penicillin given to 663 women with early syphilis during pregnancy resulted in 92.5 percent normal full term living infants and only 1.5 percent living syphilitic infants. The most practical tested course for average use would consist in 600,000 Oxford units procaine penicillin G in oil with 2% aluminium monostearate once daily for 10 days ... An analysis of 267 pregnant women treated for early syphilis with more than 10 weeks arsenicals, with or without bismuth, in the period immediately preceding the introduction of penicillin yielded results not statistically different from the penicillin treated group. Nonetheless, ease of administration and short duration of therapy, lack of toxicity and the ability to cure in utero the already infected fetus, makes penicillin alone the preferred treatment in the prevention of congenital syphilis".
Jackson 1962	A case series of pregnant women with a positive serologic test for syphilis and who had early or latent infection and were treated with benzathine penicillin G (BPG) at the Jefferson Davis Hospital and the Social Hygiene Clinic, Houston, Texas, U.S.A. from December 1957 to August 1960. One hundred and thirty women were studied; 90 had received 2.4 million units BPG (group 1) and 40 either 4.8 or 7.2 million units BPG (group

	2). In addition "...20 pregnant women with evidence of syphilis who came to delivery without having had any antisyphilitic therapy" were included in the study (group 3). The outcome of these groups was: group 1: 77 infants with nonreactive serology at 3 to 8 months age, 1 with congenital syphilis (mother treated 6 days prior to delivery for secondary syphilis), 11 lost to follow-up, 1 complete abortion of nonsyphilitic fetus; group 2: 29 infants with nonreactive serology at 3 to 8 months age, 0 with congenital syphilis, 9 lost to follow-up, 2 infant deaths neither showed evidence of syphilis; group 3: 11 infants with nonreactive serology at 3 to 8 months age, 8 with congenital syphilis, 1 lost to follow-up, 0 deaths. The authors conclude that "a dosage of 2.4 mU of aqueous BPG given at the time of diagnosis can be recommended as an adequate form of treatment for early and latent syphilis in pregnancy. Following any therapeutic regimen, serologic and clinical evaluation of the baby should be carried out at the age of 3 to 6 months."
Kampmeier 1981 a	This paper is a long term follow-up (carried out between October 1977 and June 1980 i.e. at least 27 years since initial treatment) of 251 patients with acute syphilis who were treated in the U.S. Collaborative Penicillin Study of 1943 to 1950. Seventeen women were pregnant when admitted to the penicillin study and of these contact was made with 16 women. It is not explicitly stated but it appears that all were 'healthy' and there were no cases of late syphilis found.
Lentz 1944	A case series of fourteen pregnant women with early syphilis and treated with penicillin (six with 1,200,000 million units and one with 2,400,000) recruited from 19 November 1943 and followed until 29 June 1944 by which time seven had delivered. None of the infants born to these women had congenital syphilis although three had positive cord and neonatal blood positive serology. All became negative within a month of birth.
Mashkilleison 1994	A non randomised comparison carried out in Russia in the early 1990s of the treatment of 100 patients (men 65 and women 35 with no mention of whether pregnant or not) with 'early manifestations of syphilis' with either azithromycin, erythromycin or benzyl penicillin.
Moore 1944	A case series of 1,418 patients with early syphilis (of whom 58 were pregnant at the time of treatment) from September 1943 up to May 1944 as part of the U.S. multicentre study under the auspices of the Committee on Medical Research of the Office of Scientific Research and Development and directed by the Subcommittee on Venereal Diseases of the National Research Council and treated with penicillin. The authors note that due to the limited time period covered by the study "it is too early to speak of any results as to the outcome in the child".
Nelson 1956	A case series of children born late in 1950 or in 1951 living in Baltimore, U.S.A. and whose mothers were known to have had syphilis. The authors divide the children into three groups: group 1 - children of untreated mothers and of these they were able to establish the status of 199 out of 247 children and report that 13.4% had congenital syphilis; group 2 - children of inadequately treated mothers and of these they were able establish the status of 142 out of 174 children and report that 5.8% had congenital syphilis; group 3: children of adequately treated mothers and of these they were able establish the status of 654 out of 799 children and report that "no congenital infections were discovered among these 654 children". Of the 973 children whose mothers were treated for syphilis 489 received only penicillin (either 1,200,000 or 2,400,000 units of soluble penicillin or 4,800,000 units of procaine penicillin specific numbers are not given) and a further 171 also received "... a few doses of an arsenical and bismuth"; 313 received only a heavy metal and an arsenical and of these 174 received less than a complete course. A complete course is taken as varying between an intensive course of 30 injections of an arsenical (usually oxophenarsine [Marphasen] hydrochloride) and 10 injections of bismuth subsalicylate in 10 weeks to alternating courses of 8 weekly injections of an arsenical (usually neoarsphenamine) and 8 weekly injections of bismuth subsalicylate, to a total of 64 injections.
Olansky 1947	A case series of different antisyphilitic therapy schedules covering a total of 147 pregnant syphilitic women seen before 1946 at the Rapid Treatment Center, Washington D.C., U.S.A. Schedule 1a: arsenotherapy and bismuth, "five-day intravenous arsenotherapy plus bismuth subsalicylate in oil" given over eight weeks; schedule 1b: intravenous arsenotherapy plus bismuth subsalicylate in oil given over an eight day period; schedule 2: penicillin sodium, 40,000 units every three hours intramuscularly for 60 injections; schedule 3: combinations of penicillin, arsenic and bismuth. Results: schedule 1 a and b; the outcome was known in 65 of the 74 patients and of these there were 59 live births (6 premature), 4 stillbirths and 3 abortions, with no congenital syphilitics; schedule 2; the outcome was known in 21 of the 24 patients and of these there were 19 live births, 1 stillbirth and 1 abortion, with no congenital syphilitics; schedule 3: the outcome was known in 46 of the 49 patients and of these there were 44 live births, 1 stillbirth and 1 abortion, with 1 case of congenital syphilitis.

Phaosavasdi 1989	A case series of pregnant women seen at Chulalongkorn Hospital, Bangkok, Thailand from August 1984 to May 1985 and diagnosed to have syphilis and who were treated to assess the appropriateness of the U.S. Centers for Disease Control "1985" STD treatment guidelines. One hundred and ninety seven were identified who had "... a positive serological test for syphilis (and were) given benzathine penicillin G 2.4 million units intramuscularly, once weekly for 3 successive weeks". 184 women were treated with the above regimen of penicillin and 6 with erythromycin stearate orally 500 mgs four times a day for 30 days as they were allergic to penicillin. Of the 176 women who delivered at the study hospital,157 delivered a normal infant at term, 11 delivered premature infants, there were 2 stillbirths and 6 abortions. "Five neonates had a positive FTA-ABS IgM and might have had congenital syphilis. The authors conclude that "the intramuscular injection of benzathine penicillin G 2.4 million units weekly for 3 consecutive weeks to syphilitic pregnant women was again confirmed to be clinically effective for prevention of their neonates from congenital syphilis and well accepted as treatment for syphilis in pregnancy."
Robinson 1951	A non randomised comparison involving 71 primiparous pregnant women with syphilis (seven secondary, 56 early latent and eight late latent syphilis) of different treatment regimens at the University of Maryland, U.S.A. in the late 1940s. The treatment schedules were: (1) 300,000 units procaine penicillin in oil daily for 15 days (all treatments on an outpatient basis); (2) 300,000 units penicillin in oil and wax daily for 15 days (all patients hospitalised for duration of treatment); (3) 300,000 units penicillin in oil and wax with 0.6 gm of carinamide with each dose daily for 15 days (all patients hospitalised for duration of treatment); (4) 100,000 units of penicillin in buffered tablets three times daily for 15 days (all patients hospitalised); (5) 100,000 units of penicillin in buffered tablets three times daily with 2.0 gm carinamide with each dose for 15 days (all patients hospitalised). In group 1 there were 42 patients all except one completed the course (the one who did not was at term and only received one injection and delivered a stillborn infant), of the others, one who completed the treatment at the seventh month and delivered a baby with congenital syphilis all the other 40 delivered healthy babies. Twenty pregnant women were treated with penicillin in oil and wax (groups 2 and 3) and of these it was considered in terms of the titers in their serologic tests 10 benefited and 10 did not (of these one miscarried, one had a stillbirth and one had congenital syphilis). Nine women were treated with oral penicillin (groups 4 and 5) and of these three babies had congenital syphilis. Separate numbers are not given for these treated with the addition of carinamide.
Shafer 1954	A case series of 196 patients with early infectious syphilis which included 10 pregnant women from clinics in Chicago, Illinois, New Orleans, Louisiana and Durham, North Carolina, U.S.A. in 1951/52 treated with a single injection of 2,500,000 units of benzathine penicillin G. The authors comment that "although the number of cases is small, results indicate that N,N'-dibenzylethylenediamine dipenicillin G is effective in the treatment of syphilis in pregnancy. Ten women treated before or during pregnancy have now delivered. One pregnancy resulted in a non-syphilitic stillbirth at 71/2 months. The other nine pregnancies resulted in normal deliveries and the babies were serologically negative for syphilis from six weeks to seven months after birth. One woman was re-treated for sero-relapse four months after delivery, but the baby remained negative through six months of observation".
Speiser 1947	A case series of 259 patients attending the Rapid Treatment Center and other departments at Bellevue Hospital and the New York College of Medicine, U.S.A. around 1945 with early infectious syphilis (233) or latent syphilis (26) and treated with penicillin and followed up for two years. The patients were divided into three groups: group 1, 149 patients treated during pregnancy (123 early infectious syphilis and 26 latent syphilis); group 2, 84 patients treated prior to pregnancy (all early infectious syphilis); and group 3, 26 patients who were re-treated for relapse or reinfection following their initial treatment (23 relapsed or were reinfected during pregnancy and three relapsed prior to pregnancy). Various treatment schedules were used ranging from 600,000 units of penicillin to 4,000,000 units and in some cases arsenoxide was added. The results reported were: group 1: 114 non-syphilitic babies, 16 probably non-syphilitic babies but follow-up less than 16 weeks, 10 abortions or premature deliveries but syphilis was excluded as a cause in all of them; group 2: from 86 pregnancies in 84 women, 73 non-syphilitic babies, "4 mishaps that were not attributable to syphilis" and one congenital syphilis; group 3: three relapses after arsenoxide and fever therapy, at least six were re-infections and the re-treatment schedules were varied, the outcomes, 20 non-syphilitic babies, three probably non-syphilitic babies and two late abortions and one stillbirth, possibly due to syphilis. Among the conclusions of the authors were that "non-syphilitic babies may be obtained regardless of the period of gestation in which penicillin therapy is started".

Tucker 1949a	A case series from Baltimore, U.S.A. of 111 pregnancies among 88 women who had been treated between 1944 and March 1948 with penicillin for syphilis (72 primary and/or secondary syphilis and 16 either early latent or early asymptomatic neurosyphilis) before becoming pregnant. The 111 pregnancies resulted in 101 live births (of which three were premature infants and three neonatal deaths), three stillbirths and seven abortions. It was considered that these 10 "disasters (were) probably not due to syphilis". One baby with congenital syphilis was born. " With one exception, all received aqueous penicillin intramuscularly for 7.5 to 15 days and the majority received 3.0 million units or more".
Tucker 1949b	A case series of 149 pregnant women with early syphilis in Baltimore, U.S.A. between October 1943 and March 1948 were treated with either amorphous or crystalline penicillin in doses varying from 0.6 to 1.0 million units (1 patient) to more than 5 million units (5 patients) with most receiving 4.0 to 5.0 million units (91 patients). "Six women (4%) required retreatment with penicillin for relapse or reinfection, seroresistance, or serorelapse. Nearly three quarters were treated after the 4th month of gestation." Two abortions occurred but were not considered to be related to syphilis. No cases of congenital syphilis were identified up to four months after birth.
Wammock 1950	Two case series are presented, A of 281 pregnant women "in all stages of syphilis" treated in Philadelphia, U.S.A. from September 1946 until April 1948 with 2.4 million Oxford units of aqueous penicillin (crystalline G) given intramuscularly in 60 individual doses of 40,000 units each every three hours (71/2 days) and B "... 73 pregnancies in women who were treated for syphilis with penicillin prior to conception." The authors state "to evaluate even more thoroughly the results of penicillin therapy we have exercised three types of clinical control not generally employed in previous studies." These were group 1: the outcome of all non-syphilitic pregnancies occurring in the obstetrical service; group 2: outcome of pregnancy among syphilitic women who delivered during the period of the study without receiving any anti-syphilitic therapy; group 3: "... outcome of 390 pregnancies (401 infants) in which the syphilitic mother had been treated with varying amounts of arsenical and bismuth in the years just prior to the advent of penicillin treatment." The results were as follows: for group 1 (5,596 nonsyphilitic deliveries) 87.6% normal living infants, 170 neonatal deaths, 160 premature infants and 320 miscarriages; group 2, (75 untreated syphilitics, 90.4% with either latent or late syphilis), 29 normal live births, 21 congenital syphilitics, four neonatal deaths, 12 stillbirths, four premature infants and five miscarriages; group 3: 22 mothers with congenital syphilis were excluded from further analyses, 194 pregnant women with early syphilis who gave birth to 198 infants of whom 171 were normal, 13 had congenital syphilis, 3 neonatal deaths, 7 stillbirths and 4 premature infants; 174 pregnant women with latent syphilis who gave birth to 180 infants, 160 normal, none with congenital syphilis, 4 neonatal deaths, 10 stillbirths. Of the group of 281 syphilitic women treated with penicillin during pregnancy, 18 had early syphilis, 161 early latent syphilis and 88 late syphilis and 14 had congenital syphilis and were excluded from further analysis. Of the 179 with early or early latent syphilis: 171 delivered normal infants, 3 syphilitic living infants, 2 neonatal deaths, 2 stillbirths 2 premature infants and 1 miscarriage. The 88 pregnant mothers with late syphilis delivered 90 infants, 88 normal, none with congenital syphilis and 2 neonatal deaths. 71 women (with 73 infants) were treated with penicillin prior to being pregnant for syphilis and gave birth to 68 normal infants, one with congenital syphilis, 2 neonatal deaths, 1 stillbirth and 1 miscarriage. The authors conclude their article by stating that "in this study aqueous penicillin (crystalline G) was employed in total dosage of 2.4 million oxford units over a period of 71/2 days in 60 injections of 40,000 units each. Because of its ease of administration and effectiveness it should replace completely arsenical and bismuth treatment."
Zhou 2005	A case series of 11 HIV negative pregnant women with early syphilis and allergic to penicillin who attended the STD Institute, Shanghai, China between May 1997 and May 2001 were treated successfully with ceftriaxone.

GRAPHS AND OTHER TABLES

This review has no analyses.

INDEX TERMS

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