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GUIDELINES FOR PREVENTION OF ADVERSE OUTCOMES OF  
PREGNANCY DUE TO SYPHILIS



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## INTRODUCTION

Syphilis is a systemic, chronic infectious disease with a spectrum ranging between florid manifestations on one hand and years of latent asymptomatic infection on the other. It is transmitted through sexual intercourse, from mother to unborn child during pregnancy and through transfusion of infected blood. It is one of the two most damaging STD during pregnancy; other being human immunodeficiency virus (HIV) infection. Since the advent of penicillin in the 1940s, syphilis is a fully curable infection (1).

## 1. EPIDEMIOLOGY OF MATERNAL SYPHILIS

Despite easy availability of penicillin and other treponemicidal antibiotics, venereal syphilis continues to be a serious public health problem in many countries (2).

In several African nations high rates of infectious maternal syphilis ranging between 5 and 15 percent have been reported (table 1). Corresponding high rates of congenital syphilis, the offshoot of maternal syphilis, have also been reported. For example, congenital syphilis was diagnosed among 5.5% of hospitalised children between 0 and 2 years in Cameroon, 2.2% of live births and 11.0% of sick children between 0 and 4 years of age in Ethiopia, and 1.0% of all live births and 8.6% of hospitalised children under 6 months of age in Zambia (7,18-20). In some countries in Africa, syphilis is the foremost risk factor associated with 20-30% of perinatal mortality (20). By comparison, one of every 10,000 live-born infants in the United States in 1986 had congenital syphilis and while 40.0% of these infants died the proportion of stillbirths attributed to syphilis was unknown (21).

Table 1: Syphilis seroprevalence among prenatal women

Country: city (year) (reference)	No. Tested	% Reactive RPR/VDRL
Brazil: Niteroi (1974) (3)	200	16.0
Gabon: Libreville (1985) (4)	623	14.0
Swaziland: Mbabane (1986) (5)	283	13.1
Zambia: urban and rural (1983) (6)	1437	12.8
Ethiopia: Addis Ababa (1976) (7)	337	12.7
Fiji: Suva (1985-86) (8)	440	8.9
South Africa: Johannesburg (1985) (9)	7912	8.1
Thailand: Chantaburi (1984) (10)	3910	4.9
India: Bombay (1988-89)*	10181	4.6
Cape Verde: Santa Cruz (1983) (11)	316	3.8
Chile: Santiago (1974) (12)	21052	3.4
Malaysia: Kuala Lumpur (1973-75) (13)	10096	3.3
Rwanda: Butare (1972) (14)	862	3.2
Nigeria: Ilorin (1984) (15)	566	0.9
Saudi Arabia: Riyadh (1984) (16)	4361	0.9
Poland: Bialystock (2)	140000	0.27
Australia: Melbourne (1980-81) (17)	4600	0.04
United Kingdom: Scotland (1985) (2)	64404	0.03

\* J Maniar personal communication

As seen with other STD, the highest age-specific attack rate of infectious syphilis is in adolescence and early adulthood; the reproductive period. A Zambian report showed that one-sixth of women acquired syphilitic infection the in latter half of pregnancy, and the source of infection usually was their husbands. The men acknowledged having intercourse both with their wives and extramarital sexual partners during pregnancy (22).

## 2. ADVERSE OUTCOMES OF MATERNAL SYPHILIS

Syphilis does not appear to produce unusual manifestations among women during pregnancy (23). The maternal spirochaetaemia peaks in the first two years of infection and decreases slowly thereafter as a result of acquired immunity. Although infectiousness to sexual partners ceases after about 2 years of infection, the risk to the fetus lasts longer. The duration of untreated maternal syphilis is inversely correlated with the risk of congenital infection (24). Thus, a fetus is almost always infected in utero in early maternal syphilis (25).

The effects of untreated maternal syphilis on the fetus depend on the stage of maternal disease and the stage of pregnancy when the infection was acquired. The adverse outcomes of untreated maternal syphilis may be one of the following:

- (a) Abortion in the second trimester, commonly around 20 weeks of gestation, sometime after the fetus becomes immunocompetent. Ratnam et al attributed 18.0% of spontaneous abortions to syphilis (26).
- (b) Intrauterine death at later gestational age results in a stillbirth. A study conducted in the United States showed that stillbirths were four times more common among syphilitic women as compared to the general population (27).
- (c) Risk of prematurity in syphilitic pregnancies is reported to be 12 times higher in two African studies (20,28).
- (d) Infant may be born with clinical features of congenital syphilis. Based on the criteria for diagnosis of early congenital syphilis (29), Zambia reported that one out of every 100 liveborn infants had clinical features of congenital syphilis in 1981 (20).
- (e) Delivery of an apparently healthy infant who may manifest signs of infection within 6 months or much later in childhood (tardive form). Presumably, in such cases infection occurs very late in pregnancy and development of spirochaetaemia occurs slowly.
- (f) In long-standing maternal infection, the fetus may escape infection.

The best estimates of adverse pregnancy outcomes of syphilis come from two studies summarised in table 2. One study was published in pre-penicillin era in 1917 from Western-world data and the other was the study conducted in Zambia, Africa in 1987(30,31). Both studies showed that about 40 percent of syphilitic pregnancies had no adverse outcomes. The agreement between the two studies is remarkable given the wide disparity of 70 years. The newer study resulted in lower percentage of syphilitic infants presumably due to two reasons: firstly, an appreciable number of women may have received penicillin or other antibiotics since these are widely available. Secondly, distribution of women in early and late syphilis does produce wide disparity in pregnancy outcomes (32).

In Zambia, 20 to 30 percent of the total perinatal mortality of 50/1000 total births is attributable to syphilis (20). In other words, 1 to 1.5 percent of all pregnancies which extend beyond 20 to 27 weeks end in syphilis attributable death. In absolute numbers, 4000 to 6000 fetal and neonatal deaths are directly caused each year by syphilis in Zambia. In Ethiopia, it is reported that 15,000 fetal and infant deaths are caused each year by syphilis (33).

Table 2: Percentage Distribution of the Outcomes of Untreated Maternal Syphilis

Outcome	Study 1 (1917)	Study 2 (1987)
Stillbirth or late miscarriage	17%	22%
Infant death	23%	No data
Prematurity or Low birth weight	No data	33%
Syphilitic infant	21%	2% (at birth)
Non-syphilitic infant	39%	43%

### 3. DETERMINANTS OF ADVERSE PREGNANCY OUTCOMES

The determinants of adverse pregnancy outcomes are the prevalence of syphilis among pregnant women, the vertical transmissibility of infection and the barriers to prevention programme.

#### 3.1. Prevalence of syphilis among pregnant women

The prevalence of syphilis among pregnant women varies between countries depending upon the prevalence of infectious syphilis in each country. The latter depends upon the level of STD control efforts and the emphasis placed on syphilis control activities. Universally, low prevalences are reported from the developed countries and while high rates are reported from developing countries, the situation is insufficiently documented (table 1).

#### 3.2. Materno-fetal transmissibility of syphilis

It was long believed that the fetus was protected until the 16th week of gestation (34). However, this theory is widely discounted since Silverstein demonstrated in 1962 that infection of the fetus may occur at any gestational age but the pathologic effects of congenital syphilitic infection manifest only after the immune system of the fetus becomes operative at about 16 weeks of gestation (35). Transmissibility of infection from an early maternal syphilis is between 80 and 100 percent (25,32)). Subsequently, in untreated late latent stage of maternal syphilis, transmission may occur in a quarter of cases (32).

#### 3.3. Barriers to prevention programme

Adverse pregnancy outcomes due to syphilis are preventable through routine serologic screening and early treatment. However, in Zambia (1981), it was shown from two urban and two rural hospitals that despite 90-92% of pregnant women attended prenatal services, less than 30% had a syphilis screening test performed and of those found seropositive, less than one-third were treated (6). Thus, in developing countries, there are several barriers to prevention programme:

- \* Late attendance of women at prenatal clinics is a major limiting factor. In developing countries in Africa, less than 10% of women seek prenatal care before 16 weeks of pregnancy. A majority of late attenders believe it to be unnecessary to seek prenatal care early in pregnancy.
- \* Syphilis screening test is not performed on some prenatal attenders due to a variety of reasons ranging from sporadic or frequent nonavailability of needles, syringes, containers, test kits to lack of appreciation among health workers (possibly due to lack of training) to sheer apathy to perform the testing.
- \* Failure to provide treatment to seropositive women and their sexual partner(s). Again, not much data is available from developing countries as to what percent of seropositive women eventually receive adequate treatment.
- \* Failure to recognise infections acquired late in pregnancy i.e. after initial screening. A Zambian study showed that almost one-sixth of infections were acquired during pregnancy (6) and a study from the United States reported that 37% of maternal syphilis was acquired after serologic screening test performed at first visit (27).

#### 4. PREVENTION OF ADVERSE PREGNANCY OUTCOMES

The adverse pregnancy outcomes can be averted by primary prevention and early detection of infection. The strategy includes health education/ information, prenatal screening and case finding, adequate treatment, counselling seropositive women and cost-benefit of intervention.

##### 4.1. Primary prevention

The goal of primary prevention is through education to prevent women of child-bearing age from acquiring syphilis. Health education programmes aimed at modifying sexual behaviour or those aimed at promoting condom use have not been very successful. However, the growing importance of incurable, viral STD, particularly HIV, has renewed interest in behaviour modification and condom promotion and efforts should be made to implement these methods of control.

##### 4.2. Detection of syphilis in pregnancy

Two general approaches should be used for control of syphilis during pregnancy: reducing the prevalence of syphilis in the general community, thereby reducing its prevalence in pregnant women, and detecting and treating infected pregnant women.

##### 4.2.1. Health promotion

While health promotion is an essential component of strong STD control programmes which are aimed at reducing the prevalence of syphilis in the general community, there is need for new and focussed health education aimed at motivating early and frequent attendances to prenatal clinics. The latter should also improve the health care seeking behaviours of pregnant women. Again, in addition to

community-based health education programmes which should include topics on importance of optimum prenatal care and sexually transmitted diseases, there is need to continue with health education at the institutional level that is targeted at three specific groups: sexually active women attending prenatal, family planning and under-five clinics; sexually active men and women attending general outpatients; and elderly men and women attending outpatients/ various departments. The latter group is specifically important in developing countries where elderly men and women are considered to be influential in motivating behavioural change among younger people.

The health promotion messages are best developed with the assistance of local leaders. Messages should be kept simple, accurate, clear and repetitive. Use of local words, pictures and stories are encouraged. All communication material should be pre-tested to find out if the target groups understand the idea, believe the message, and think it relates to them. Several educational methods such as lectures (with or without flip charts), pictorial tales, question and answer sessions, brain storming, handouts, audio/video messages, group discussions or one-to-one preventive counselling can be used.

#### 4.2.2. Prenatal screening and case finding

Every pregnant women attending prenatal care should a the syphilis screening test performed using the appropriate test chosen for the country (See section 5). The syphilis test should be performed twice during pregnancy; initial at first visit and repeated in early third trimester. In developing countries which generally have a high seroprevalence of maternal syphilis, Rapid Plasma Reagin (RPR) card test is best suited since midwives or other health workers can be trained to perform the test while pregnant women wait for the results. This system not only eliminates the delays in obtaining reports from central laboratories which as such are overburdened but also increases the efficiency of the prenatal programme because those women who tested seropositive can be immediately treated. In these setups, high default rates at followup visits is the main obstacle in treating the seropositive women. In developed countries where seroprevalence is generally low, confirmatory treponemal tests are be performed in central laboratories. At these laboratories, arrangements should be made for prenatal specimens to be tested on a priority basis. In these setups, few women default at followup visits and these can be reached through social workers. Moreover, in countries like Norway with extremely low seroprevalence of 0.02%, the second screening test in third trimester is not necessary (36).

It is important to consider that a certain percent of pregnant women, generally higher in developing countries, may miss the syphilis screening during prenatal care or may not seek prenatal care at all. For countries or populations with high seroprevalence rates, intervention among these women should be: for babies born of women who did not have prenatal care, cord blood should be screened; for women who did not seek healthcare either for prenatal care or for delivery, their infants should be screened for syphilis at the first contact with health services.

#### 4.2.3. Adequate treatment of prenatal syphilis

The duration of treatment of a seropositive pregnant woman and her sexual partner(s) will depend on accurate history of STD and accompanying presence or absence of clinical lesions. Since a majority of women are in latent stage, there is difficulty in distinguishing early from late latent stage. Hence, when in doubt, it is generally agreed to overtreat than undertreat. The schedule for treatment is:

		<u>Early syphilis</u>	<u>Late syphilis</u>
Not allergic to: penicillin	Benzathine penicillin inj 2.4 million units	single im	3 doses at weekly intervals
Allergic to: penicillin	Erythromycin 2g daily oral	3 weeks	4 weeks

#### 4.2.4. Counselling seropositive women

Counselling seropositive women is an integral part of management. The midwives or full-time counsellors at specialised STD centres should be responsible for this activity. The contents of counselling are: factual information about syphilis and other sexually transmitted infections, status of her syphilitic infection, implications of infection emphasising the possible adverse effects on the fetus, availability of drugs for complete cure, importance of her husband or sexual partner(s) being treated simultaneously, practical approach which she may consider when discussing her syphilis test result with her sexual partner(s), reasons for eliminating or reducing the high risk behaviour.

A Zambian study showed that subsequent to one-to-one counselling of seropositive women, almost two-third of women brought their husbands or sexual partners for treatment, generally within a week. In most cases men came with their wives, knew about the syphilis test results of their wives, and confirmed that they had come for treatment (31).

#### 4.2.5. Cost-benefit of intervention

The Zambian demonstration project showed that under field conditions in a developing country, the prevention programme outlined above helped to reduce the adverse pregnancy outcomes by two-thirds (31). The programme was relatively inexpensive considering that the cost of the intervention was US\$ 0.60 for every pregnant woman (table 3). If this intervention was perfectly effective in a country or population with a seroprevalence of 10%, it would prevent 17 spontaneous abortions, 19 perinatal deaths, and 14 syphilitic infants for every 1000 pregnant women (table 4). Thus cost of averting an adverse outcome was US\$ 12 (US\$ 600 for 50 adverse outcomes averted).

Table 3: Cost of maternal syphilis intervention in a developing country with a seroprevalence of 10%

The estimated costs per 1000 pregnant women are:

* Two tests per attendee at \$0.1 per test	200
* Treatment of all seropositive at first visit at \$1/per treatment	100
* Treatment of subsequent visit at \$1/per treatment assuming 20% will be retreated	20
* Treatment of spouses at \$1/per treatment assuming 67% of spouses of seropositive women at first and second trimester will be treated	80
* Amortized cost for development and printing of behavioural and educational material	100
* Amortized cost for microcentrifuges and lamps	100
	-----
	Total US\$ 600

Table 4: Reproductive outcome model assuming a 10% seropositivity in 1000 pregnant women

	Seropositive pregnant women -----	Seronegative pregnant women -----
Pregnancies	100	900
Spontaneous abortions in 2nd or early 3rd trimester	20 (20%)	27 (3%)
*Excess spontaneous abortions due to syphilis	17	--
Pregnancies extending beyond 27 weeks	80	873
Perinatal deaths	24 (30%)	52 (6%)
*Excess perinatal deaths due to syphilis	19	--
*Syphilitic infants	14 (24%)	--

In Norway, the cost of screening is estimated at US\$ 4.60 per participating woman. With prenatal seroprevalence at 0.02% among 50,000 pregnancies, approximately 10 new cases of early infection are identified each year. The cost of every adverse outcome averted is US\$ 28,700 (US\$ 230,000 for 8 adverse outcomes averted). Yet, considering the direct and some of the indirect costs of 8 adverse outcomes, the economic benefits are nearly four times the cost of the programme. Thus, if the prevalence of maternal syphilis is 0.005%, the benefits will equal the costs of the intervention programme (36).

#### 5. CHOICE OF TESTS FOR PRENATAL SCREENING

Countries with high rates of syphilis should choose nontreponemal tests (eg VDRL or RPR) as screening tests because these are simpler, quicker, and cheaper to perform. The rapid plasma reagin (RPR) card test or its variations are technically less demanding and can be effectively performed by trained health workers. The rates of biologic false positive results (BFP) with the nontreponemal tests are within acceptable limits. The reported BFP results in high prevalence countries vary between 5 and 10 percent (5,31). Quantitative titres on positive specimens should always be done.

In countries with rates of syphilis lower than 1%, a positive nontreponemal test (VDRL or RPR) should always be confirmed with a treponemal test. The Treponema pallidum haemagglutination assay (TPHA) is a preferred treponemal antibody test because it is easy to perform, its low cost compared with Fluorescent Treponemal Antibody - Absorption (FTA-Abs) test, and is highly sensitive and specific.

#### 6. PROGRAMME COMPONENTS

The components of the programme are management, training and evaluation of the programme.

### 6.1. Management of the programme

Control of maternal syphilis can be achieved objectively by close collaboration between STD control and MCH programmes. The activities for prevention of adverse pregnancy outcomes should be integrated within the broad framework of primary health care. Either of the two programmes can take the leadership. The implementation of an intervention strategy in developing countries is hindered by scarcity of resources. It is the responsibility of programme managers to develop good plans of action and obtain resources from international agencies.

### 6.2. Training

Formal training in problem-oriented approach and STD control should be introduced in the curricula of all cadres of the medical profession. For example, medical students, physician assistants/clinical officers, nurses, and laboratory technicians' curricula should have adequate training built in their curricula.

Specially designed seminars and workshops are required to train primary health care workers (including STD and MCH staff) to problem-oriented approach for effective management of STD, to be able to perform RPR card tests, and to undertake preventive activities.

The managers of STD control and MCH programmes should identify the personnel for short- or long-term retraining. This should include topics like methods of health promotion, epidemiology, reporting, prenatal syphilis screening, performing nontreponemal tests in prenatal clinics, problem-oriented approach to management of STD, evaluation, etc.

### 6.3. Evaluation

Evaluation of the programme for the prevention of adverse pregnancy outcomes due to maternal syphilis includes programme performance and quality control of syphilis tests.

#### 6.3.1. Programme performance

The main issue to be addressed is to define the parameters for programme performance. Changes in some of the following parameters help in process and outcome evaluation: number of prenatal attenders, their pattern of seeking prenatal care, coverage of syphilis testing (district-wise), number of seropositive women treated, availability of drugs for treatment, impact of the programme in terms of maternal syphilis rates, perinatal mortality rate, and incidence of congenital syphilis.

As part of the primary health care system, the district hospital is essential. For the purpose of evaluation of programme performance, there is need to build-in a monthly or quarterly report on some or all the parameters outlined above from the district hospital to the national coordinating centre. At the national coordinating centre, the reports should be compiled quarterly or annually to look at trends of parameters. Additionally, sentinel serosurveillance for maternal syphilis should be conducted at selected sites.

### 6.3.2. Quality control for syphilis tests

The national STD reference laboratory established under the STD control programme should maintain quality control for syphilis tests being performed for prenatal attenders. This should help to correct over- or under-reading of nontreponemal tests and identify the needs for retraining of staff at various levels of primary health care. Additionally, vigilance must be kept to avoid outdated tests being used at PHC level.

## 7. COORDINATION BETWEEN MATERNAL SYPHILIS CONTROL PROGRAMME AND THE HIV PREVENTION PROGRAMME

The structure/system for maternal syphilis prevention programme should be linked with HIV prevention programme. The areas of possible linkage should be: (a) health promotion for syphilis prevention including prevention for HIV; (b) selected prenatal clinics utilised for HIV sentinel surveillance; and (c) depending on the cultural and political acceptability of the concept, prenatal attenders to be screened for HIV infection. However, the latter concept will require counselling services and pregnancy termination services to be in place for HIV infected pregnant women.

## 8. GUIDELINES FOR EFFECTIVE PROGRAMME MANAGEMENT

- \* Prenatal screening and treatment of pregnant women with syphilis is cost-effective, not only in high prevalence areas in Africa, the Caribbean and parts of Asia, but also in low prevalence areas. It is recommended to be applied globally.
- \* In areas, where syphilis is common, screening is recommended at the first prenatal visit and repeated in the third trimester. However, where syphilis is uncommon retesting in third trimester is not necessary.
- \* Intensive health education is effective in motivating women to attend prenatal care early in pregnancy.
- \* The syphilis screening test should be performed on-site by any trained health worker and seropositive women should be treated at the same visit.
- \* Seropositive women should be counselled to bring in their sexual partner(s) for treatment.
- \* Unless both parents have been treated, a baby born to a seropositive mother should be treated.
- \* There is need to integrate STD control and MCH activities under primary health care.
- \* The programme manager has the responsibility to seek adequate resources.
- \* There is urgent need to strengthen STD control programmes in developing countries where such programmes exist and to launch such programmes in countries where these are non-existent.

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