Syphilis In Pregnancy:

A Health Systems Intervention Trial

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Executive Summary

Sexually transmitted disease (STD) in pregnancy is a reproductive health issue of major importance in South Africa and the rest of the developing world. STDs pose a significant risk to both the pregnant woman and her fetus. Antenatal clinics, where women of reproductive age frequently seek care, may have a critical role to play in the prevention and treatment of these illnesses.

Screening for syphilis, a major cause of preventable pregnancy loss, is an important but frequently neglected component of antenatal care. About 40% of pregnant women with syphilis experience miscarriage, stillbirth or perinatal death if untreated. Appropriate care for syphilis consists of diagnosis, treatment, partner notification and related health education. Due to poor functioning of the health infrastructure in some places this does not always occur. We have shown that in Hlabisa more than 90% of pregnant women book for antenatal care. Although all women are screened for syphilis (prevalence 7-10%), in a recent study in a mobile antenatal clinic in Hlabisa only 49% were fully treated, largely because many women did not return to the clinic for their results. Unnecessary mortality attributable to syphilis (estimated at 27% of the district-wide perinatal mortality) is the result, despite high antenatal coverage and screening of all women.

This failure of service delivery is potentially remediable through on-site screening for syphilis with immediate treatment. Combined with improved health promotion and partner notification strategies, this approach would also offer a more comprehensive reproductive health approach to syphilis control, and it also could strengthen the capacity of the health system to begin to address other STDs in pregnancy. A pilot study of on-site testing in the mobile clinic referred to above

showed that the proportion of women adequately treated increased from 49% to 75% (p=0.004), and the perinatal mortality among women with syphilis was lower following on-site testing (6.8% vs 12%); due to the small sample size in this pilot study this reduction was not statistically significant (p=0.7).

This project will determine the feasibility, accuracy, and cost-effectiveness of on-site testing for syphilis in the community clinics of a rural South African health district. Impact will be measured through the key outcome measure, perinatal mortality, as well as process measures that include the proportion of women screened and treated, and the proportion of partners treated. The study design will be a clinic randomised trial. The study has the power to show a 50% reduction in mortality attributable to syphilis and a minimum reduction in total district perinatal mortality of 13.5%.

Literature Review

Syphilis is an important cause of morbidity and mortality in pregnancy. It may be responsible for up to 30% of perinatal mortality (1,2). Syphilis is common: the seroprevalence is often around 10% in African women who book for antenatal care (3). Without appropriate treatment, 5-8% of all pregnancies may have an adverse outcome due to syphilis (3).

Treponema pallidum, the cause of syphilis, usually crosses the placenta after the first trimester. If a woman books for antenatal care early, is diagnosed with syphilis and is appropriately treated with penicillin, the prognosis for the fetus is very good. Unfortunately, this sequence of events does not always occur.

In resource-poor settings, some women do not book for antenatal care at all, and the prevalence of syphilis is usually much higher in this group than in women who do book (4). Importantly, even women who do seek antenatal care often delay until the second or third trimester (5), leaving little time to adequately treat infection. Peripheral clinics often rely on central screening of blood samples (at district hospitals for example), with results reaching the clinic and the patient 1-4 weeks later (6). Even if the results do return to the clinic, the patient may not return for them, may delay in doing so, or the results may be misplaced. At times screening is omitted altogether. Such delays and basic errors may be common. For example, a recent study has shown that only 22% of pregnant women with syphilis at a South African teaching hospital were completely treated (7).

On-site testing for syphilis in women booking for antenatal care is possible (8). This intervention provides the advantage that treatment can be started immediately, and women can be counselled about the potential effects on the fetus, and about the need to bring partners for treatment. Partner notification strategies are notoriously difficult to implement successfully, and the opportunity to pursue these strategies in the context of antenatal care is important (9). At the same time, little is known about women's health care seeking behaviours during pregnancy and the factors that promote and inhibit these patterns. This is an area that requires further study in order to successfully implement new reproductive health strategies such as on-site testing for syphilis.

Proposals for prevention of congenital syphilis (especially on-site testing) in South Africa have been put forward (10). It is not only individual treatment that is important, however, but the opportunity to address this issue in a broader public health context. Prevention of congenital syphilis needs to be addressed within a district health system, where successful prevention and treatment efforts can be linked to broader reproductive health services.

Motivation For This Proposal

A study of the epidemiology of syphilis in pregnant women booking for antenatal care in one of the mobile clinic teams serving women who attend public sector antenatal clinics of Hlabisa Health district was recently conducted (11). This study provides the motivation for this study and a follow up pilot study also provides information critical to the design of appropriate intervention strategies.

The main finding of the study was that despite identifying all pregnant women with syphilis who attended this clinic, mortality attributable to syphilis still occurred. The reason was that 49% of women identified were not fully treated. The risk of an adverse pregnancy outcome was related to the number of doses of penicillin received. Treatment for maternal syphilis requires that women receive an initial penicillin injection and then return weekly for two more doses. In this study, most women who were not fully treated did not return for their 2nd and 3rd injections.

The fact that women do not return to complete treatment for syphilis has been well-documented. What we do not know is why this is so. While we can hypothesise that cost, lack of transport, and general inconvenience play a role in this, these factors have not been documented. Furthermore, the fact that awareness of syphilis specifically and STDs in general is low may also contribute to low return rates and poor compliance. The current proposal seeks to demonstrate that health promotion efforts, combined with improved service in the form of on-site testing, can improve awareness and health seeking behaviours of pregnant women, and hence improve pregnancy outcome.

In response to the findings of the Hlabisa study, we started a pilot project to examine the accuracy and feasibility of on-site testing in a mobile clinic setting.

528 consecutive women were screened for syphilis by rapid plasma reagin (RPR) test on plasma derived from whole blood by gravity. A battery-powered, solar-charging rotator mixed antigen with plasma. RPR test was repeated on serum in a reference laboratory for comparison. The on-site test was highly sensitive (86.7%; 95% confidence interval [CI] 72.5-94.5%) and highly specific (88.2%; 95%CI 84.9-90.9). Positive predictive value (40.6%; 95%CI 30.9-51.1) was low due to a large number of samples reported as "slightly positive" on-site being reported as "negative" in the laboratory. There were very few false negative results on-site (negative predictive value 98.6%; 95%CI 96.8-99.4). We conclude that on-site RPR screening for syphilis is highly accurate and easy to do. As the ost of the rotator is R3521 and reagent costs are 81 cents per woman, it is also cheap.

The study was then extended to determine the impact of on-site testing on treatment for syphilis. All 398 women attending the mobile clinic for their first antenatal clinic visit during 1996 were tested on-site as above. Pregnancy outcome data, collected by clinic staff and supplemented by home visits when necessary, was available for 378 (95%) women. Following introduction of on-site testing 51 of 68 (75%) on-site RPR positive women received all three penicillin doses, compared with 22 of 45 (49%) when testing was done in the laboratory in 1994 (p=0.004). The mean number of penicillin doses received by RPR positive women increased from 1.9 to 2.6 (p=0.0003). Far fewer women received zero or one penicillin dose (8/68, 11.7%) when testing was on-site than when it was laboratory based (13/45, 28.9%; p = 0.02). Indeed, with on-site testing all women received at least one penicillin dose, whereas with laboratory testing 10 (22.2%) did not receive any treatment (p=0.0001; Table). In 1994, when laboratory testing was

done, the perinatal mortality rate (PNMR) was 12.0% among RPR positive women and 1.3% among RPR negative women (p=0.003). In 1996, PNMR remained higher among RPR positive women (6.8%) than RPR negative women (2.5%), but not statistically significantly so (p=0.12). In 1996 the association between a positive RPR test and perinatal death (OR 2.8, p=0.07) was substantially weaker than the association in 1994 (OR11.8, p=0.006). We conclude that on-site testing substantially improves treatment for syphilis, and that there is some evidence that this may lead to reduced perinatal mortality - but that a larger study is required to confirm this.

Encouraged by the results we believe it is time to expand the intervention across the district. However it will be important to do this through a rigorous study design in order to carefully document the feasibility, accuracy and the cost-effectiveness of the intervention when brought up to scale. The proposed design is the only way to determine conclusively if on-site testing reduces syphilis-attributable mortality. This will be important as a way of providing strong data to inform health policy and good clinical practice in the area of reproductive health.

These findings indicate a need for intervention in two specific areas. First, strategies to ensure that all pregnant women with syphilis are treated must be put in place. These strategies will include on-site testing for syphilis and health promotion efforts designed to raise awareness among women of the dangers of syphilis to themselves, their pregnancies, their infants and their partners. Second, intensive health promotion efforts must be pursued to encourage women to book early for antenatal care.

Overall Goal

To determine the feasibility, accuracy cost-effectiveness and impact on pregnancy outcome of on-site syphilis testing and related health promotion strategies in the community antenatal clinics of a rural South African health district.

Specific Objectives

1. Through a pre-intervention phase, to document the current strategies for screening and treating maternal syphilis and other STDs in the antenatal clinics, and to determine their effectiveness.

2. To gain an understanding of women's health seeking behaviours during pregnancy through an assessment of 1) awareness and understanding of syphilis and other STDs and their impact on pregnancy, and 2) reasons why women often book late for antenatal care, or do not book at all.

3. To implement in six intervention clinics, on-site syphilis testing and health promotion strategies aimed at 1) increasing awareness of the impact of STDs, particularly syphilis, on pregnancy, 2) reducing the gestational age that women book for antenatal care, 3) increasing the number of women that book for antenatal care, 4) increasing the proportion of infected women who complete a course of treatment for syphilis.

4. To develop effective partner notification strategies within the context of antenatal care.

5. To evaluate the feasibility, accuracy, and cost-effectiveness of this strategy.

6. To implement the strategy in control clinics if the findings are positive.

7. To disseminate this data and thereby inform reproductive health policy and practice, and hence improve reproductive health status.

Methods

Setting

Hlabisa Health District is situated in northern KwaZulu/Natal, South Africa. The obstetric service includes a 450 bed district hospital, 12 community clinics, and 2 mobile clinic teams serving 20 clinic points throughout the district. Approximately 8000 women book for antenatal care each year. A recent community survey estimated that 95% of women in the district book for antenatal care, and that 83% deliver in either a clinic or the hospital (12). As part of routine antenatal care all women have blood taken to test for syphilis infection (rapid plasma reagin, [RPR]). Blood is sent to the hospital where the test is done, and results are returned to the clinic 1-4 weeks later. Women who test positive for syphilis in the antenatal clinics are counselled, treated, and asked to bring their partners for treatment. The treatment consists of 3 weekly doses of injectable penicillin. Awareness of syphilis and its impact on the fetus is low, and many women do not return for the second and third injections. Also, partner notification strategies are weak and few partners currently attend clinic for treatment.

Study Design

As part of the Hlabisa STD Intervention Studies 12 community clinics have been randomly assigned to receive (or not) an intervention designed to improve treatment of patients presenting with an STD. Clinics have been formed into matched pairs according to workload, syphilis prevalence and other socio-economic factors. This study design will be used for our study of on-site syphilis testing. This is the most rigorous study design possible to determine the effectiveness of health care interventions and its use will minimise selection bias and confounding.

A **six month pre-intervention phase** will define in detail the current approach and obstacles to effective syphilis screening and treatment. Current health promotion strategies in the clinics and the community will also be examined. The following will be measured:

- Number of women booking for antenatal care, and their gestation at booking;

- Proportion of these women screened for syphilis;

- The interval from screening to treatment;

- Proportion of screened women treated for syphilis, and number of doses of penicillin received;

- Number of partners treated per woman screened;

- Proportion of women in antenatal clinics with awareness of syphilis and other STDs, assessed through semi-structured questionnaire in antenatal clinics;

- Review of current clinic-based health education strategies (interviews and focus group discussions at clinics);

- Number of community health workers who currently provide education about STDs, including syphilis;

To estimate the impact that syphilis infection has on pregnancy outcome across the district we will measure rates of miscarriage and perinatal death in all women booking for antenatal care during this period.

During this time 2 other activities will go on. An in-depth investigation of the reasons for "late-booking" will be done through in-depth interviews and group discussions with different key

informants including women booking for antenatal care (early vs late bookers), and older women in the community who may help set the community norms. Younger, non-pregnant women will also be questioned, so that we understand how they would act, if and when they become pregnant.

Data on number of attendees at each clinic for 1) under-6 clinic, 2) minor ailments and 3) all clinic services will also be measured to examine trends in general consultation patterns. This is an important aspect of the control arm of the study.

This 6 month period will be critical. Not only as a period of formative research and baseline information gathering, but also because it will put in place the procedures for monitoring the impact of the intervention and it will act as a period of intense consultation, training and preparation for the clinic staff.

After six months the intervention will be implemented in the six randomly assigned clinics. The six control clinics will continue to measure the above variables without intervention.

The intervention

1. Health promotion strategies in the clinic and community, through community health workers and local health committees to encourage earlier booking for antenatal care.

2. On-site syphilis testing. Results of syphilis screening will be provided at the initial antenatal visit. Women who test RPR positive will receive an initial dose of penicillin immediately, will be intensively counselled regarding the positive RPR result, and will be informed that they need to return twice more for treatment at weekly intervals.

3. Partner notification by patient referral with the help of a card. The card will state that the woman has an infection that can put her baby at risk, that her partner may also have this infection and that a simple treatment is advised. Patients and partners will receive focused health education about STD and HIV.

4. Health promotion strategies directed at raising awareness of syphilis and other STDs in women attending antenatal clinics.

Outcome measures

The impact of the intervention will be determined in the following ways:

Primary outcome

Changes in pregnancy outcome among women with syphilis (mid-trimester abortion rates, perinatal mortality [still births plus deaths in the first week of life]).

Secondary outcomes

1. Changes in the proportion of women both screened and adequately treated (and the average number of doses of penicillin received).

2. Changes in the time interval from testing to treatment (with each dose received).

3. Changes in the number of partners treated.

4. Changes in the average gestation at booking.

6. Changes in community and clinic-based health promotion activities (average gestational age at booking).

These changes will be compared in intervention and control clinics, as well as before and after the intervention in the intervention clinics.

Trends in rates and patterns of other reasons for attending the clinics (under 6 clinic, minor ailments, total attendance) will also be monitored in order to be able to judge how much of any observed changes are due to the intervention. Using this study design any changes in the outcome measures will be attributable to the intervention alone.

Statistical justification

The perinatal mortality rate (PNMR) in Hlabisa district is 30-40 / 1000 total births. The PNMR recorded in the study that motivated this proposal recorded a PNMR of 12% (6/50) in the syphilis group and 2% (2/150) in the non-syphilis group: combined PNMR 30/1000. The attributable risk percent is calculated at 89.2% (the proportion of perinatal mortality that is due to syphilis). The population attributable risk percent is calculated at 27% (the proportion of perinatal mortality in the district that is due to syphilis, and hence the proportion of perinatal mortality that can be eliminated by effectively treating syphilis).

We have insight into the possible impact of onsite testing from the study done in the mobile clinic: the mortality among women who received 0 or 1 dose of penicillin was 38% (5/13) compared with 3% (1/32) among those who received 2 or 3 doses - a more than 10-fold reduction in mortality.

Furthermore, in the second pilot study, reported above, perinatal mortality in women with syphilis fell from 12% to 6.8% when on-site testing was started.

Sample size required to show a 50% reduction in mortality:

Assume ratio of exposed (on-site testing) to unexposed is 1:1

Incidence of perinatal death in unexposed is 12%

Incidence of perinatal death in exposed is 6%

= Sample size is 389 women (RPR positive) in intervention and control arms.

NB. If the impact of on-site testing is greater than a 50% reduction in mortality, and as reflected above there is evidence that this may be so, the sample size required to show the greater difference will be smaller.

Assuming a 50% reduction in mortality, we can use a 1-sided hypothesis test, and sample size is reduced to approximately 300 per arm.

It is however necessary to calculate an inflation factor to account for the cluster design (appendix), and this brings the sample size up to 380 per arm.

This number of women can be recruited within 18 months.

In the mobile clinic study described above, pregnancy outcome data was available (through clinic records and field work) for 94% of the 200 women studied. We estimate that follow up of around 85% will be achieved, so a corresponding number of women will need to be recruited.

We therefore conclude that this study design has the statistical power to detect a reduction in perinatal of at least 50%, and at least a 13.5% in the district -wide perinatal mortality rate.

Laboratory Methods

The on-site testing process will be as follows: blood will stand to allow plasma to separate from cells. Plasma will be mixed with RPR antigen on a battery-powered rotator and a qualitative (positive or negative) RPR result obtained. Serum will be sent to Durban (Department of Medical Microbiology) for definitive syphilis testing (RPR, TPHA and FTA, as appropriate). These results will be acted upon as they become available; thus if a woman test negative on-site, but positive in the laboratory, she will be treated.

As part of the intervention, clinic nurses will be trained by both laboratory technicians and nurses in the mobile clinic who already do on-site testing, to perform the RPR tests. Feedback of the results of the quality control done in Durban will be used as a way of maintaining standards and motivation.

Women who test RPR positive on-site will be treated with Penicillin 2.4 Mu im x 3 doses at weekly intervals. Those who do not attend expected visits will be traced and treated.

An analysis will be provided of outcome by on-site testing result and also of outcome by true syphilis status (gold standard defined in Durban). Accuracy of on-site testing will be determined by comparing results of the 2 testing strategies.

Economic evaluation

The cost and cost effectiveness of the intervention will be compared with the cost and cost-effectiveness of the current approach. Costs will be assessed from the perspective of the health service and the mother and her partner. Costs for the health service will include: value of time spent by community health workers and local health committees in promoting earlier booking for antenatal care; promotional materials such as booklets/leaflets/posters used to encourage earlier booking for care or to raise awareness of syphilis and other STDs; transportation costs associated with health promotion activities and delivery of samples; supplies and equipment used for testing; staff time involved in on-site testing and provision of counselling and education to the mother and her partner; laboratory staff time involved in analysis of samples; and cards for partner notification, and training of staff in on-site RPR testing. Costs to the mother and her partner include travel costs incurred in visiting clinics and any income lost through time spent away from informal or formal employment.

Cost-effectiveness will be assessed in five ways:

- cost/woman who completes a full course of penicillin treatment
- cost/partner who completes a full course of treatment
- cost/person who completes a full course of treatment (mothers and partners)
- cost/miscarriage, still birth or perinatal death prevented
- cost/year of life gained.

Ethics

The protocol will be submitted to the University of Natal Ethics Committee.

Dissemination And Impact

Results will be disseminated as follows:

1. As a peer-reviewed paper(s) in a scientific journal.

2. Through a workshop, involving national and provincial policy makers and senior practitioners.

3. Through a comprehensive technical report.

As part of the development of this project several key role players will be informed. They include national and provincial MCH and HIV/AIDS/STD managers and nurse/midwife trainers. The same people will be involved in the dissemination of project results.

We expect that this project will be of direct and immediate relevance to health system policy and practice. As a key reproductive health intervention, this project will improve the reproductive health of rural South African families.

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