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P. Gichangi, MD, Department of Human Anatomy, and Obstetrics and Gynecology, University of Nairobi, Nairobi, Kenya, L. V. Renterghem, PhD, Department of Microbiology and Immunology, Ghent University, Belgium, J. Karanja, MD, Department of Obstetrics and gynaecology, Nairobi, Kenya, J. Bwayo, MD, PhD, Department of Medical Microbiology, University of Nairobi, Nairobi, Kenya, D. Kiragu, MD, Pumwani Maternity Hospital, Nairobi City Council, Nairobi, Kenya and
M. Temmerman, MD, PhD, International Centre for Reproductive Health (ICRH), Department of Obstetrics and Gynaecology, Ghent University, Belgium

Request for reprints to: Dr. P. Gichangi, Department of Human Anatomy, Obstetrics and Gynaecology, University of Nairobi, P.O Box 2631, KNH 00202, Nairobi

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P. GICHANGI, L. V. RENTERGHEM, J. KARANJA, J. BWAYO, D. KIRAGU and M. TEMMERMAN

ABSTRACT

Objective: **To assess adverse pregnancy outcome associated with maternal syphilis and congenital syphilis rate based on FTA-ABS-19s-IgM.**
Design: **Descriptive cross-sectional study.**
Setting: **Pumwani Maternity Hospital (PMH), the largest maternity unit in Nairobi, Kenya.**
Subjects: **Rapid Plasma Reagin reactive women and their live born infants.**
Main outcome measures: **Syphilis serology in pregnant women, FTA-ABS-19s-IgM in cord blood and pregnancy outcome.**
Results: **Three hundred and seventy seven out of 12,414 women (3%) were RPR+. 4.0% of RPR+ and 1.4% of RPR- women delivered a stillbirth (OR 3.0, p<0.001). 19% of RPR+ and 10% of RPR- had low birth weight deliveries (OR 2.1, p<0.001). Mothers untreated for syphilis during pregnancy had significantly more preterm births (18.5% vs 9.2%, OR 2.3, p=0.026), and more stillbirths (5.4% vs 1.0%, OR 6.3, p=0.044). Of the 200 randomly selected cord bloods of RPR+ women, 142 (72%) were TPHA+. Nine (6.3%) of the 142 TPHA+ cords were FTA-ABS-19s-IgM+.**
Conclusions: **Stillbirth and low birth weight rates were high in RPR+ untreated pregnant women and treatment significantly improved pregnancy outcome. Based on very stringent laboratory criteria (FTA-ABS-19s-IgM), 6.3% of live born infants with TPHA+ cord blood were considered syphilis infected.**

INTRODUCTION

Syphilis screening and treatment is well-recognised intervention in routine antenatal care. Infection with *Treponema pallidum* during pregnancy is an important risk factor for poor pregnancy outcome including miscarriage, preterm birth, low birth weight, stillbirth, perinatal death and congenital syphilis. The rationale of a syphilis screening and treatment program in pregnant women is to prevent congenital syphilis and other adverse obstetrical outcome(1-4).

The risk of transmission of *T. pallidum* to the fetus varies considerably according to the stage of untreated syphilis in the mother. The obstetric history of a woman with untreated syphilis is that of first trimester abortion or stillbirth, while other trimester infections end in term infants with congenital syphilis(5,6). The diagnosis of congenital syphilis is problematic, especially in poor resource settings. Clinical diagnosis and criteria based upon maternal serological syphilis status are most often used. Clinical diagnosis in the newborn is difficult because of the rare event of classic signs and symptoms of congenital syphilis(7). Maternal serological criteria are of limited value because of transplacental transfer of maternal IgG to the infant and low sensitivity and specificity of IgM testing(7). Currently, there is no serological gold standard for the diagnosis of congenital syphilis at birth except identification of *T. pallidum.*

Seroepidemiological studies among pregnant women in Kenya since the early nineties show that the syphilis prevalence has gone down from 7.3% to 3.0%, suggesting a significant reduction in congenital syphilis(8). The risk of congenital syphilis in infants of syphilis seroreactive women in Kenya is unknown. As part of a larger study to assess the impact of maternal syphilis on obstetrical outcome(9), cord blood samples were analysed using fluorescent antibody (FTA-ABS-19s-IgM) to determine the rate of vertical transmission of *T. pallidum* among RPR reactive pregnant women in Nairobi.

MATERIALS AND METHODS

The study was conducted at Pumwani Maternity Hospital (PMH), Nairobi, Kenya. PMH serves as the major referral maternity hospital for the city and its environs, with referrals from 54 Nairobi City Council antenatal clinics, as well as self referred women of lower socio-economic strata. On average, 60 deliveries take place per day.

Women who gave birth at PMH between April 1997 and April 1998 were tested for syphilis after informed consent for the study was obtained. Data on prior syphilis testing and treatment during pregnancy was obtained from the antenatal records. A structured questionnaire was used to elect socio-demographic data, sexual history, past obstetrical performance and date of last normal menstrual period (LMP). LMP and clinical examination at delivery were combined to assess gestational age of the infants at delivery. These data has been published elswhere(2). At delivery, cord blood was obtained from all live born infants and stored. Upon delivery of the placenta, the umbilical cord was wiped with clean gauze wet with normal saline and blood was obtained from the umbilical vessels with a vacutainer. Two hundred randomly selected cord blood samples of infants whose mothers were RPR reactive were analysed for congenital syphilis using FTA-ABS-19s-IgM. Centre for Disease Control (CDC) 1997 revised criteria for presumptive congenital syphilis surveillance was also used to make diagnosis of presumptive congenital syphilis(10). All 200 infants from mothers RPR reactive at delivery were examined for stigmata of congenital syphilis using a check list of the known early clinical stigmata for congenital syphilis(11). Mothers RPR reactive at delivery rather than mothers with confirmed syphilis (RPR and TPHA positive) were included since TPHA testing is not widely available especially in rural health settings in Kenya. Syphilis (RPR and TPHA) tests were carried out at the Department of Medical Microbiology, University of Nairobi. Later, frozen samples of cord blood were transported to the Ghent University, Belgium, where fluorescent antibody (FTA-ABS-19s-IgM) testing was done. Infants whose cord blood had a positive serologic (TPHA) test for syphilis, and a reactive FTA-ABS-19s-IgM were classified as having congenital syphilis. For all mothers who were found to be RPR reactive irrespective of their previous treatment for syphilis during pregnancy and their infants, they were treated for syphilis with Benzathine penicillin and given follow up appointments. Ethical clearance for the study was obtained from the Kenyatta National Hospital ethics and review committee.

Laboratory procedures: Syphilis serology on maternal and cord blood samples was performed using the Rapid Plasma Reagin card test (RPR, Becton Dickson, Maryland, USA) and all positive samples were confirmed with *Treponema Pallidum* Haemaglutination assay (TPHA, Randox Laboratories, UK). Cord blood samples were tested by FTA-ABS-19s-IgM at Ghent University (Biomerieux).

Statistical analysis: Data were entered and analysed in SPSS version 10 for windows (SPSS, Chicago, IL, USA). For univariate analysis the Pearson Chi-square test was used to compare proportions. Odds ratios (OR) and their 95% confidence intervals (CI) were used to measure strength of associations. Yates corrected or Fischer's exact 2-tail test, were used where appropriate.

RESULTS

During the study period, a total of 22, 466 women gave birth at PMH of whom, 12,414 delivered during working hours and were invited to the study. Birth weight was not available for 6.5% of the deliveries (808/12,414). The RPR test was positive in 377/12,414 (3.0%). The rate of low birth weight (<2500g) was 10.1% (1140/11,242) in the RPR negative group and 19.0% (70/368) in RPR positive women (OR 2.1, 95% CI 1.6-2.8, p<0.001). The stillbirth rate was 1.4% (166/12,037) and 4.0% (15/377) respectively (OR 3.0, 95% CI 1.7-5.2, p<0.001).

Of the 377 RPR reactive women, 28% (105/377) had not been tested for syphilis during the index pregnancy, 41% (155/377) had been found RPR negative, whereas 31% (117/377) were RPR seroreactive during pregnancy. One hundred and twelve of the 117 (95.7%) of the women RPR reactive who had been identified during pregnancy had received treatment for syphilis during the index pregnancy. Two hundred and sixty five of the 377 (70.3%) women RPR positive at delivery were untreated for syphilis during the index pregnancy, thus infants born of these women were classified as having presumptive congenital syphilis according to CDC 1997 case definition of presumptive congenital syphilis.

Tablel 1

Cord blood RPR,TPHA and FTA-ABS-19s-IgM results

Test	Cord blood RPR positive		Cord blood RPR negative	
	No.	(%)	No.	(%)
TPHA test				
Positive	120	81.0	22	43.0
Negative	26	17.0	27	53.0
Indeterminate	3	2.0	2	4.0
FTA-ABS-19s-IgM test*				
Positive	9	7.5	0	
Negative	111	92.5	22	100.0

*FTA-ABS-19s-IgM=Fluorescent antibody IgM test, which was done for TPHA *(Treponema Pallidum* Haemaglutination assay) positive samples only, RPR = Rapid Plasma Reagin test

Table 2

Correlation of maternal RPR titre, and cord blood FTA-ABS-19s-IgM for the 142 infants with positive cord blood TPHA

Maternal RPR Titre (N=142)	Cord FTA-ABS-19s-IgM (N=142) (IgM+/n)	(%)
1:1	0/7	0
1:2	1/28	3.6
1:4	1/26	3.8
1:8	0/22	0
1:16	0/23	0
1:32	7/35	19.4

Chi-square of trend 14.6, p=0.012, LBW = Low birth weight, TPHA = Treponema Pallidum Haemaglutination assay, RPR = Rapid, Plasma Reagin

Data on fetal outcome were missing for 7(2.6%) of the 265 mothers untreated for syphilis during pregnancy and two (1.8%) of the 112 mothers treated for syphilis during pregnancy. Forty five of the 244 (18.4%) mothers untreated for syphilis during pregnancy had preterm delivery as compared to 9.2% (10/109) among mothers treated for syphilis during pregnancy (OR 2.2, 95%CI 1.1-4.6, p=0.027). Untreated mothers also had more stillbirth deliveries 5.5% (14/257) as compared to those treated for syphilis during pregnancy 1% (1/110) (OR 6.3, 95%CI 0.8-48.2, p=0.045).

From the three hundred and seventy seven infants born to RPR positive women, of the 200 cord bloods of live born neonates tested for RPR and TPHA; 142 (72%) were TPHA positive, 53 (26%) TPHA negative and five (2%) indeterminate. Of the 142 TPHA positive samples, 6.3% (9/142) were positive FTA-ABS-19s-IgM. Table I shows cord blood RPR, TPHA and FTA-ABS-19s-IgM test results. Among the nine infants FTA-ABS-19s-IgM cord bloods positive, five (56%) were from mothers who had tested RPR negative during pregnancy, hence possibly infected during pregnancy after testing. Two were from infants born to mothers found RPR positive during pregnancy, of whom one was treated at 30 weeks gestation and the other did not receive treatment. Two were from infants born to mothers not tested for syphilis during pregnancy. None of the nine babies had clinical stigmata of congenital syphilis. About 7.7% (7/91) of the babies born of mothers untreated for syphilis during pregnancy as compared to 3.9% (2/51) born to mothers treated during pregnancy were FTA-ABS-19s-IgM positive (OR 2.0, 95%CI 0.4-20.8, p=0.376).

Rapid Plasma Reagin titres of the nine infants were either equal or lower than maternal RPR titre. None of the cord bloods had a RPR titre 4-fold higher than the maternal RPR titre. Table 2 shows the correlation of maternal RPR titre and cord blood FTA-ABS-19s-IgM. Mothers with RPR titre >1:8 were nine times more likely to deliver infants with FTA-ABS-19s-IgM positive cord bloods (20.0% versus 2.7%, OR 9 .1, 95% CI 1.8-58.8, p =0.002). A maternal RPR titre of > 1:8 was significantly associated with the likelihood of the infants cord blood being RPR and TPHA positive (96.7% (29/30) versus 81.3% (91/112), OR 6.7, 95% CI 1.0-286.2, Fisher exact 2-tail p=0.045). Four (44.4%) of the nine babies were born preterm, as compared to 12.8% (17/133) babies whose cord blood was FTA-ABS-19s-IgM negative, (OR 5.5, 95% CI 1.3-22.4, p=0.010).

DISCUSSION

The syphilis seroprevalence was 3.0% in women delivering at Pumwani Maternity Hospital in Nairobi, Kenya. This prevalence is similar to the RPR rates reported earlier in Nairobi(8), and in Harare(12), but much higher than 0.2% reported by Sombie *et al*(13) in women attending urban antenatal clinics in Burkina Faso. RPR seroreactive women in our study were three times more likely to have a stillbirth or low birth weight outcome. These findings confirm the adverse effects of syphilis infection on pregnancy outcome and underline the public health importance of syphilis control in pregnancy(14,15).

Because of the difficulty of isolating *T. pallidum* from infected patients, serologic tests have played a major role in diagnosis of congenital syphilis. Measurement of infant serum IgM levels at or shortly after birth has been used. However, IgM levels are non-specific and may result from other intrauterine infections(16). The fluorescent treponema antibody absorption (FTA-ABS-IgM) test originally thought to be highly specific for IgM antibodies to *T. pallidum is* technically difficult, and has had problems with sensitivity and specificity(17). The presence of rheumatoid factor (fetal IgM against maternal IgG) in the baby has resulted in false-positive FTA-ABS-IgM test(18) and competitive inhibition of IgM by maternal IgG has resulted in false-negative FTA-ABS-IgM test(19). Refinement of FTA-ABS-IgM test by removing maternal blocking antibodies and rheumatoid factor has resulted in FTA-ABS-19S-IgM test, with better sensitivity and specificity. Stoll *et al*(20) evaluating three diagnostic tests for diagnosis of congenital syphilis (FTA-ABS-19S-IgM test, IgM capture ELISA for *T. pallidum* and reverse enzyme linked immunospot (RELISPOT), did not find any single diagnostic test sufficiently sensitive for treatment decisions. Although the assays were useful in confirming the clinical diagnosis of syphilis in symptomatic neonates, they do not solve the problem of the asymptomatic but possibly infected neonates(20). Rawston and Bromberg(21) comparing maternal and cord blood/infant RPR titres reported failure of the RPR test to identify babies at risk for congenital syphilis. A third of the new-borns of mothers with a reactive syphilis serology had indeed non-reactive tests(21).

Our finding of a vertical transmission rate of 6.4% among syphilis positive women is the first report on vertical transmission of syphilis in Kenya based on FTA-ABS-19s-IgM testing. Other reports on congenital syphilis in Kenya were based on clinical data(22), serology(23) or estimated from maternal syphilis prevalence(24). Wafula and Bwibo(23) reported a congenital syphilis prevalence of about 1% while Bwibo(22) acknowledged lack of clinical stigmata for congenital syphilis. None of the infants positive for FTA-ABS-19s-IgM had clinical stigmata of congenital syphilis. Based on this test, the rate of vertical transmission of *T. pallidum* in live born neonates is around 6.4%, which is an underestimate of the overall transmission rate because of the exclusion of abortions and stillbirths(25-28).

According to the CDC 1997 surveillance case definition, a presumptive case of congenital syphilis includes any infant whose mother had untreated or inadequately treated syphilis at delivery, regardless of signs and symptoms in the infant(10). This broad definition includes some asymptomatic infants who are not infected. Applying the CDC 1997 congenital syphilis case definition to our women, 70.3% of the infants born to RPR reactive women were classified as having presumptive congenital syphilis, which is close to an estimate of 69.0% reported from Baltimore, USA, 1998 using the CDC case definition(29). Using strict laboratory criteria (FTA-ABS-19s-IgM test), only 6.4% of the infants were classified as having presumptive congenital syphilis. The CDC 1997 cases definition (epidemiological diagnosis) grossly overestimates the true number of cases of congenital syphilis. Our data however based on very stringent laboratory criteria may underestimate the true prevalence of congenital syphilis as it has been shown that congenital syphilis can exist in the absence of fetal IgM(28). Despite this limitation, with declining syphilis prevalence, rarity of classical syphilis presentation, strict laboratory criterion is likely to have a role in identifying true cases of CS. FTA-ABS-19s-IgM is technically demanding, expensive and not readily available in poor resource settings. Use of FTA-ABS-19s-IgM at the moment is not feasible outside research settings in resource limited countries.

CONCLUSION

This study has confirmed the deleterious effect of maternal syphilis on pregnancy outcome. In addition, the vertical transmission rate of *T. pallidum* based on FTA-ABS-19s-IgM was found to be lower than the epidemiological definition. More research is needed to develop a simple test to select children at birth who need further treatment and follow-up because of prenatal exposure and inadequate treatment of *T. pallidum.*

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