

Syphilis in Pregnancy in Tanzania. I. Impact of Maternal Syphilis on Outcome of Pregnancy

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To measure the impact of maternal syphilis on pregnancy outcome in the Mwanza Region of Tanzania, 380 previously unscreened pregnant women were recruited into a retrospective cohort at delivery and tested for syphilis. Stillbirth was observed in 18 (25%) of 73 women with high-titer active syphilis (i.e., women with a rapid plasma reagin titer $\geq 1:8$ and a positive *Treponema pallidum* hemagglutination assay or indirect fluorescent treponemal antibody test result), compared with 3 (1%) of 233 uninfected women (risk ratio [RR], 18.1; $P < .001$). Women with high-titer active syphilis were also at the greatest risk of having low-birth-weight or preterm live births (RR, 3.0 and 6.1, respectively), compared with women with other serological stages of syphilis. Among unscreened women, 51% of stillbirths, 24% of preterm live births, and 17% of all adverse pregnancy outcomes were attributable to maternal syphilis. Syphilis continues to be a major cause of pregnancy loss and adverse pregnancy outcome among women who do not receive antenatal syphilis screening and treatment.

Screening and treatment for syphilis in pregnant women have been recommended as a potentially feasible and cost-effective intervention to reduce fetal and perinatal mortality and other adverse outcomes [1–3]. Information on the current impact of untreated syphilis in sub-Saharan Africa is needed before examining the effectiveness of syphilis screening programs that have been introduced to many countries in the region. The fraction of adverse outcomes that can be potentially averted if syphilis is adequately treated is expected to be particularly high in sub-Saharan Africa, because syphilis seropositivity among pregnant women from this region is common, with 2.5%–17.0% of antenatal clinic (ANC) attenders testing positive for syphilis [4–12].

Maternal syphilis has been associated with perinatal morbidity and mortality in many parts of sub-Saharan Africa [4, 5, 13–15]. Forty-two percent of stillbirths and 19% of spontaneous abortions after 20 weeks of gestation in Zambia and 21% of perinatal deaths in Malawi have been attributed to maternal syphilis [6, 13]. However, not all studies have demonstrated that women who are seropositive for syphilis have an increased risk of adverse pregnancy outcome. In The Gambia, no association was found between maternal syphilis seropositivity and stillbirth or neonatal death [16], suggesting that these women may have had partially treated syphilis or a non-venereal treponemal infection. There are further difficulties in comparing results from different countries, because studies have used different definitions of serological syphilis, and a range of rapid plasma reagin (RPR) titer cutoffs have been taken to define active syphilis. Because the RPR test is not specific for *Treponema pallidum*, studies that rely on the RPR test alone to define syphilis may include women with biological false-positive (BFP) RPR results. Furthermore, many studies have not examined the potential confounding effects on pregnancy outcome of factors such as other reproductive tract infections (RTIs), human immunodeficiency virus (HIV) infection, and maternal malaria or anemia.

The aims of this study were to determine the proportion of adverse pregnancy outcomes (i.e., stillbirth, low birth weight [LBW], preterm delivery, and intrauterine growth retardation [IUGR]) attributable to syphilis in pregnant women in Tanzania and to determine which serological criteria were the most important in determining the risk of adverse pregnancy outcomes.

Received 7 January 2002; revised 18 April 2002; electronically published 3 September 2002.

Presented in part: 14th meeting of the International Society for Sexually Transmitted Diseases Research, Berlin, Germany, 24–27 June 2001 (abstract T042).

Ethical clearance was obtained from the Tanzanian National Medical Research Coordinating Committee and the London School of Hygiene and Tropical Medicine. Informed consent was obtained from all participants who signed or fingerprinted the consent form after the aims of the study had been explained to them.

Financial support: D.W.-J. was supported by a Wellcome Trust Research Training Fellowship in Clinical Tropical Medicine.

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An accompanying study [17] reports on the effectiveness of antenatal syphilis screening and treatment with single-dose benzathine penicillin to prevent adverse pregnancy outcomes attributable to maternal syphilis in the same region of Tanzania.

Subjects and Methods

Recruitment of study subjects. This retrospective cohort study was conducted in the Mwanza Region of northwestern Tanzania. Study participants were recruited in the delivery suites of the 2 main government hospitals in Mwanza City and of a district hospital serving a rural population in Sengerema, 30 km west of Mwanza. Antenatal health information cards were examined for every woman admitted for delivery, to check whether she had been screened for syphilis during antenatal care. Eligible women who were admitted during week days and who had not been tested during their pregnancy were offered an RPR test after the purposes and benefits of syphilis screening were explained to them. Women were considered to be eligible if they were Tanzanian, resided in the Mwanza Region, were ≥ 13 years old, did not have any indications of multiple gestation or preeclampsia, and were not known to be diabetic. Every RPR-positive woman and the next 2 RPR-negative women who were admitted for delivery at the same site were invited to participate in the study after giving their informed consent. Consenting participants underwent a confidential interview in Swahili, using a pretested, structured questionnaire. Information was collected on sociodemographic and biological factors, including age, obstetric history, literacy, sexual behavior, history of genital ulceration, and drugs taken during the current pregnancy.

Clinical procedures and specimen collection. Maternal blood pressure was measured at admission, and a 10-mL venous blood sample was collected from eligible women for a screening RPR test. A fingerprick blood sample was taken for a thick malaria smear and a hematocrit, and women were asked to provide a first-void urine sample into a sterile urine container. At delivery, the duration of labor, type of delivery, sex of the infant, birth weight in grams, and gestational age were recorded. After delivery, a thick placental blood smear and a 1-cm² placental biopsy specimen were taken from the maternal placental surface.

To determine preterm birth and because many women could not accurately recall the date of their last menstrual period (LMP), all live-born infants had a gestational age assessment, the Dubovitz examination [18], performed by 2 independent examiners within 5 days of birth. In the case of discrepant results, the score given by 1 of the 6 more-experienced examiners was taken as the definitive result; otherwise, the average score was used if both assessments were done by less-experienced examiners. If the Dubovitz examination could not be performed (for example, in the case of a stillbirth), the gestational age was estimated by measuring the difference between the date of delivery and the reported LMP date of the woman.

Stillbirth was defined as the delivery of a dead fetus of >22 weeks gestation, intrauterine fetal death (IUFD) was defined as a fetal death at ≤ 22 weeks gestation, and LBW was defined as <2500 g. Preterm birth was defined as a delivery at <37 weeks gestation, and IUGR was defined as a birth weight <2500 g with a gestational age of ≥ 37 weeks [19–21].

Each infant was examined for signs of congenital syphilis, including pseudoparalysis, nasal discharge, hepatosplenomegaly, and a rash. RPR-positive mothers and their infants were treated with an intramuscular injection of 2.4 million units and 50,000 U/kg benzathine penicillin G, respectively, as soon as possible after birth. Women with positive RPR test results were given contact slips for their partners to receive free syphilis treatment.

Syphilis serologic testing. At the delivery suites, maternal serum samples were screened qualitatively by RPR test (Syfacard-R; Murex Diagnostics). Serum samples from recruited women were also tested at the reference laboratory of the National Institute for Medical Research, Mwanza, with a second quantitative RPR test, using the same commercial kit and following the manufacturer's instructions. The reported titer was the highest dilution that gave a positive result.

In addition, serum samples from enrolled women were tested with a specific treponemal test (MicrosyphTM-TP 1000; Porton Cambridge), using an indirect hemagglutination method, according to the manufacturer's instructions. Samples that were RPR positive and *T. pallidum* hemagglutination assay (TPHA) negative were tested by the indirect fluorescent antibody technique (FTA-ABS) with another specific treponemal assay (Trepo-Spot IF; bioMérieux). Women who were positive by both the RPR test and a specific treponemal test were defined as having active syphilis. This was classified as high-titer active infection if the RPR titer was $\geq 1:8$ and as low-titer active syphilis if the RPR titer was $<1:8$. Women who were positive by a specific treponemal assay but negative by RPR testing were interpreted as having previously treated or resolved infection. Women whose RPR test result was positive but who had negative TPHA and FTA-ABS test results were classed as having BFP reactions. Those who were seronegative by both RPR and TPHA tests were considered to be uninfected.

Anemia and malaria diagnosis. Finger-prick blood samples were collected into a heparinized capillary tube and centrifuged at 11,800 rpm for 5 min. The percentage of packed cell volume (PCV) was recorded using a microhematocrit reader. A PCV of $\geq 37\%$ was considered to be normal. Peripheral blood films and placental smears were stained with Giemsa stain and examined by light microscopy. The presence of asexual malaria parasites was recorded. Smears were considered to be negative for malaria if no asexual parasites were seen after 200 white blood cells had been counted.

Placental biopsy specimens taken from the maternal placental surface were stored immediately in 20 mL of a 10% solution of neutral buffered formalin. Sections were processed and examined histologically for malaria pigment and parasites, according to the method described by Bulmer et al. [22]. Placental malaria was defined as the presence of parasites and/or malaria pigment on the biopsy specimen or parasites on the placental smears.

Other RTIs. Maternal serum samples were labeled with a unique study number and the date. An aliquot of maternal serum was stored and later anonymously tested for HIV-1 by an EIA (Vironostika HIV Uni-Form II; Organon Teknika) at the reference laboratory. Positive samples were confirmed by a second EIA (Enzygnost Anti-HIV 1/2 Plus; Behring). Results were linked on the unique study number to the data set at final analysis.

First-void urine samples were immediately stored at 2°C–4°C before being transported to the Mwanza reference laboratory and frozen at -20°C until they were tested for *Chlamydia trachomatis*

Table 1. Maternal age, delivery site, and birth outcome, by syphilis status.

Variable	Total (n = 380)	Seronegative (n = 233)	High-titer ^a active syphilis (n = 73)	Low-titer ^b active syphilis (n = 27)	Past/treated syphilis (n = 9)	BFP (n = 38)
Age, mean years ^c	24.5	23.9	24.0	28.3	25.6	24.6
Age groups						
<20 years	105 (28)	67 (29)	24 (33)	2 (7)	2 (22)	10 (26)
20–24 years	120 (31)	79 (34)	20 (27)	5 (19)	2 (22)	12 (31)
25–29 years	72 (19)	41 (18)	12 (16)	7 (26)	4 (45)	8 (22)
30–34 years	50 (13)	24 (10)	13 (18)	9 (33)	0	4 (10.5)
≥35 years	34 (9)	24 (9)	4 (6)	4 (15)	1 (11)	4 (10.5)
Delivery site						
Sengerema	279 (73)	164 (70)	61 (84)	20 (74)	6 (67)	28 (74)
Mwanza	101 (27)	69 (30)	12 (16)	7 (26)	3 (33)	10 (26)
Birth outcomes						
All infants						
Any adverse outcome ^d	71 (19)	26 (11)	36 (49)	1 (4)	1 (11)	7 (18)
Stillbirth	22 (6)	3 (1)	18 (25)	0	0	1 (3)
Live-born infants only						
LBW	49 (14)	23 (10)	18 (33)	1 (4)	1 (11)	6 (16)
Premature	20 (6)	7 (3)	11 (20)	0	0	2 (5)
IUGR	29 (8)	16 (7)	7 (13)	1 (4)	1 (11)	4 (11)
Total live births	358	230	55	27	9	37

NOTE. Data are no. (%) of women, except where noted. "Active syphilis" is defined as positive test results for both rapid plasma reagin (RPR) and *Treponema pallidum* hemagglutination assay (TPHA)/fluorescent antibody technique (FTA). "Past/treated" syphilis is defined as a negative RPR test result and a positive TPHA/FTA result. "BFP" (biological false-positive) is defined as a positive RPR test result and a negative TPHA/FTA result. IUGR, intrauterine growth retardation; LBW, low birth weight.

^a RPR titer ≥1:8.

^b RPR titer <1:8.

^c One seronegative woman who did not know her age was omitted from analysis.

^d Includes live births and stillbirths.

and *Neisseria gonorrhoeae* by the AMPLICOR CT/NG polymerase chain reaction (PCR) assay (Roche Diagnostics Systems). Urine samples were thawed and processed according to the manufacturer's instructions. Samples that tested positive for *N. gonorrhoeae* were confirmed using a second primer (16S rRNA).

Statistical analysis. Data were double-entered using Dbase 4 (Ashton-Tate) and were cleaned and analyzed using STATA software (version 6.0; StataCorp). Syphilis-positive and -negative mothers were compared for sociodemographic factors and biological characteristics, including history of pregnancies, current RTIs, and birth outcomes. Proportions and means were compared using χ^2 , Fisher's exact, and Student's *t* tests, as appropriate. To examine the association between syphilis and specific adverse pregnancy outcomes, binomial regression with a log-link was used to estimate crude and adjusted risk ratios (RRs). The attributable fraction for cohort women with high-titer active syphilis and for the population were calculated for different adverse pregnancy outcomes, using a modification of the methods outlined by Bruzzi et al. [23].

Results

Cohort recruitment and syphilis serostatus. From 1 June 1998 through 31 April 2000, 22,180 women were admitted for delivery at the 3 hospitals, of whom 18,456 (83.2%) had been screened for syphilis prenatally. RPR screening at the delivery suites was performed for 1809 previously unscreened women, of whom 144 (8.0%) tested RPR positive. Testing was not done for 1915 previously unscreened women for the following rea-

sons: admission when there was no team member on duty (*n* = 1169), cesarean section (*n* = 450), being non-Tanzanian or a nonresident (*n* = 118), having a false labor, declining screening or being discharged before screening (*n* = 80), or having twins or complications of pregnancy (*n* = 98). In total, at delivery, 126 RPR-positive and 254 RPR-negative women underwent complete syphilis serologic testing and were recruited into the cohort. The remaining RPR-positive women were not recruited because they had false labor at admission or a twin birth, were discharged from hospital prior to full data collection, refused to participate, or were not enrolled by hospital staff. After reference laboratory testing, 28 of 254 women who were found to be RPR negative by the delivery screening test were reclassified as RPR positive, and 16 women who were found to be RPR positive by the delivery screening test were reclassified as RPR negative. In total, by the reference laboratory tests, there were 138 RPR-positive and 242 RPR-negative women. Seventy-three (52.9%) of the 138 RPR-positive women were defined as having high-titer active syphilis, 27 (19.6%) were defined as having low-titer active syphilis, and 38 (27.5%) had a BFP RPR test result. Of the 242 RPR-negative women, 9 were TPHA positive, and 233 were TPHA negative and were classed as seronegative. Reference laboratory results were used for all further analyses.

Overall, 73.4% of mothers in the cohort were recruited in Sengerema, and the remaining 26.6% mothers were recruited in Mwanza. Nearly 60% of the women were <25 years old, and

9% of them were >34 years old. Women with low-titer active syphilis had a higher mean age, compared with women in the other serological groups (table 1). Most women (79%) were married, 35% were primigravidae, 14% were secundigravidae, and 52% were multigravidae (i.e., ≥ 3 pregnancies). Two hundred ninety-nine (79%) study participants had sought antenatal care during the pregnancy. Among these mothers, the mean gestational age for the first ANC visit was 5.8 months (range, 2–9 months). Only 8% of women were admitted for a reason other than labor pains, such as an elective admission for a cesarean section ($n = 2$), premature rupture of membranes ($n = 5$), or other reasons ($n = 24$). Drug consumption during pregnancy was common. Three hundred and nineteen women (84%) reported that they had taken some form of medicine orally during their pregnancy; of these, 40 (13%) believed that they had taken a capsule or tablet fitting the description of tetracycline, and 69 (22%) believed that they had taken another type of antibiotic.

Only 6% and 2% of women had positive urine PCR tests for *C. trachomatis* and *N. gonorrhoeae*, respectively, and 4% were HIV positive. However, at delivery, 81 (22%) of 369 women had peripheral malaria parasitemia, and 250 (68%) of 369 had evidence of placental malaria infection. Both maternal and placental malaria were negatively associated with age ($P < .001$, trend test) and gravidity ($P < .001$, trend test).

Birth outcomes and syphilis status. Twenty-two (5.8%) women had a stillbirth. There were no cases of IUFD. The highest proportion of stillbirths was seen in the women with high-titer active syphilis (18/73 [24.7%]), compared with seronegative women (3/233 [1.3%]; $P < .001$; table 1). Seventeen women whose RPR titer was $\geq 1:32$ had stillbirths. Stillbirths were uncommon in the mothers from other serological groups. Only 1 (2.6%) woman with a BFP RPR result had a stillbirth, and there were no stillbirths among women with low-titer active syphilis or past/treated syphilis.

Excluding the 22 women who had a stillbirth, 23 (10.0%) of 230 seronegative women had a live LBW infant, compared with 18 (32.7%) of 55 women with high-titer active syphilis and 1 (3.7%) of 27 women with low-titer active syphilis. Although a greater proportion of live LBW infants whose condition was attributed to IUGR were observed in women with high-titer active syphilis, compared with seronegative women, this difference was not statistically significant (12.7% vs. 7.0%; RR, 1.8; $P = .16$). All live-born LBW infants of mothers with low-titer active syphilis and past/treated syphilis were attributed to IUGR. Four women (10.8%) with BFP RPR results had infants with IUGR.

There were 20 preterm infants in the cohort, all of whom were LBW. There was a significant difference in the proportion of premature births between women who had high-titer active syphilis and those who were seronegative (20.0% vs. 3.0%, respectively; $P < .001$). Eight (72.7%) of 11 women with high-titer syphilis who had a premature birth had an RPR titer $\geq 1:32$.

There were no cases of premature birth in mothers with low-titer or past/treated syphilis. Two women (5.4%) with BFP RPR results had an infant born prematurely.

Overall, 36 (49.3%) of 73 women with high-titer active syphilis had an adverse pregnancy outcome (stillbirth, IUGR, or premature delivery), compared with 11.2% of seronegative women, 11.1% of women with past/treated syphilis, and 3.7% of women with low-titer active syphilis. There was no significant association between low-titer active syphilis and the risk of any adverse pregnancy outcome ($P = .33$). Women with BFP RPR results had a higher proportion of adverse outcomes, compared with seronegative women, but this difference was not significant (18.4% vs. 11.2%; $P = .2$). Experiencing an adverse pregnancy outcome in women with active syphilis was positively associated with higher RPR titers ($P < .001$, trend test).

Live-born infants were examined at delivery. One child of a mother with high-titer active syphilis had hepatosplenomegaly, and 2 infants whose mothers had BFP RPR test results had jaundice. The remaining live-born infants of mothers with positive syphilis serologic test results had no clinical signs of congenital syphilis.

Comparability of other factors affecting birth outcomes. Most adverse pregnancy outcomes occurred in women who had high-titer active syphilis. Because there was no evidence of excess birth outcome risk in the other serological groups, women with high-titer active syphilis were compared with seronegative women for other factors potentially influencing pregnancy outcome (table 2). Women with high-titer active syphilis were more likely to be from the Sukuma ethnic group, and active infection was associated with variables suggesting that they had a lower socioeconomic and educational level, such as poorer housing and illiteracy. A self-reported history of a previous stillbirth among multigravidae was strongly associated with high-titer active syphilis, as was a history of having an abortion or having any genital ulceration. *C. trachomatis* infection was significantly more common among women with high-titer active syphilis. However, no significant association was observed between syphilis and maternal gonorrhoea, HIV infection, malaria, or anemia. Comparing women with high-titer active syphilis and uninfected women, there was no significant difference in the proportion of women taking any form of medication during the pregnancy (82.2% vs. 81.6%; $P = .9$) or taking antibiotics in the previous 2 years (24.7% vs. 18.5%; $P = .25$). Other maternal factors known to be associated with poor birth outcomes—such as smoking, alcohol consumption, and maternal height and blood pressure—were not significantly associated with syphilis serostatus.

High-titer active syphilis and adverse birth outcomes. By univariate analysis (table 3), there was an extremely strong association between stillbirth and high-titer active syphilis (RR, 19.1; 95% confidence interval [CI], 5.8–63.2). There was also a strong association between high-titer active syphilis and LBW live births (RR, 3.2; 95% CI, 1.9–5.5). The association of syphilis with LBW

Table 2. Selected sociodemographic and maternal characteristics, stratified by syphilis serostatus.

Characteristic	Seronegative (n = 233)	High-titer ^a active syphilis (n = 73)	P
Gravidity			.45
1	92 (40)	22 (30)	
2	29 (12)	12 (16)	
3–5	72 (31)	23 (32)	
≥6	40 (17)	15 (22)	
Sukuma ethnic group ^b	141 (61)	61 (84)	<.001
Concrete/brick house ^c	55 (24)	6 (8)	.004
Illiterate	73 (31)	36 (49)	.005
Previous abortion ^d	32 (23)	18 (35)	.08
Previous stillbirth ^d	7 (5)	13 (25)	<.001
History of genital ulcer	15 (6)	21 (29)	<.001
Maternal height <156 cm	103 (44)	30 (41)	.62
Drank alcohol during pregnancy	48 (21)	10 (14)	.19
<i>Chlamydia trachomatis</i> positive ^e	10 (4)	8 (11)	.03
<i>Neisseria gonorrhoeae</i> positive ^e	4 (2)	1 (1)	1.00
HIV positive ^e	7 (3)	4 (6)	.30
Maternal malaria ^e	50 (22)	17 (25)	.60
Placental malaria ^e			.09
None	71 (31)	24 (34)	
Past chronic	71 (31)	13 (18)	
Active chronic/active ^f	85 (37)	24 (48)	
Maternal anemia ^e	153 (66)	48 (68)	.83

NOTE. Data are no. (%) of women. HIV, human immunodeficiency virus.

^a Rapid plasma reagin titer ≥1:8.

^b Non-Sukuma ethnic groups include Jita (n = 11), Zinza (n = 27), Kara (n = 12), Haya (n = 13), Jaluo (n = 8), Kuria (n = 5), and others (n = 28).

^c Concrete or brick houses vs. mud or wood houses; excludes 3 women for whom data on house type are missing.

^d Includes 51 multigravidae women with high-titer active syphilis and 141 seronegative multigravidae women.

^e Data are missing for test results for HIV (n = 2), polymerase chain reaction (n = 2), maternal malaria (n = 11), placental malaria (n = 11), and hematocrit (n = 3).

^f There was histological evidence of current placental malaria and chronic changes indicative of malaria infection earlier in the pregnancy.

was predominantly due to a strong association with preterm birth among women with syphilis, compared with women without syphilis (RR, 6.6; 95% CI, 2.7–16.2). There was also an excess number of live-born infants with IUGR among women with high-titer active syphilis, compared with seronegative women (13% vs. 7%), but this difference was not significant (RR, 1.8; 95% CI, 0.8–4.2). Overall, women with high-titer active syphilis were at a 4-fold increased risk of any adverse pregnancy outcome, compared with seronegative women (49.3% vs. 11.2%; RR, 4.4; 95% CI, 2.9–6.8).

There was little confounding of the relationship between high-titer active syphilis and stillbirth, LBW, and premature delivery by other variables that are known to be associated with pregnancy outcome, and no factors changed the crude RR by >10%. By multivariate analysis, adjusting for minimal confounding effects of gravidity, delivery site, and several other factors, high-titer active syphilis was associated with an 18-fold increased risk of stillbirth (RR, 18.1; 95% CI, 5.5–59.6), a 3-fold increased risk of LBW in live-born infants (RR, 3.3; 95% CI, 2.0–5.4), a 6-fold increased risk of premature live births (RR, 6.1; 95% CI, 2.5–15.3), and a 2-fold increased risk of

IUGR (RR, 2.1; 95% CI, 1.0–4.2). Women with high-titer active syphilis were 4 times more likely to have an adverse pregnancy outcome (RR, 4.4; 95% CI, 2.8–6.9), compared with seronegative women (table 3). Other potential confounders for adverse birth outcome did not have any appreciable effect on the multivariate model.

Impact of untreated maternal syphilis. Adjusted RRs of the association between high-titer active syphilis and adverse pregnancy outcomes were used to calculate the following attributable fractions. Overall, 94% of stillbirths and 77% of any adverse pregnancy outcome in women with untreated high-titer active syphilis were attributable to the infection. Among live births to women with high-titer active infection, maternal syphilis accounted for 70% of LBW infants, 84% of premature births, and 52% of infants with IUGR.

Population attributable fractions (PAFs), the proportions of outcomes in the study population (i.e., women who had not attended for ANC syphilis screening) attributable to the exposure, were calculated for each outcome associated with maternal syphilis, using the adjusted RR presented in table 3. The prevalence of high-titer active syphilis in women who had not been screened for syphilis during pregnancy was calculated by estimating the proportion of RPR-positive and -negative mothers tested at delivery who had high-titer active syphilis. Of 126 women who were RPR positive at the initial RPR screening test at delivery, 69 (55%) were classified as having high-titer active syphilis. Four (1.6%) of 254 women who were RPR negative at delivery were also classified as having high-titer active syphilis by reference laboratory testing. Assuming that 79 (55%) of 144 RPR-positive women and 27 (1.6%) of 1665 RPR-negative women identified by delivery screening had high-titer active syphilis, then the prevalence of high-titer active syphilis in women who had not been screened during pregnancy would be (79 + 27)/1809 (i.e., 5.9%). With this prevalence, the PAF for stillbirth was 51% (table 3). Among live-born infants, 24% of premature infants, 5% of infants with IUGR, and 12% of LBW infants were attributable to high-titer active syphilis. Overall, 17% of all adverse pregnancy outcomes in women who had not been screened for syphilis in their pregnancy were attributable to high-titer active maternal syphilis.

Discussion

The results of this study confirm that maternal syphilis is associated with an extremely high risk of adverse pregnancy outcomes, especially stillbirth and premature birth, in this study population. Despite widespread use of antibiotics in this population, which might have been expected to at least partially treat and ameliorate the sequelae of syphilis, maternal infection still had a devastating impact on the developing fetus. A quarter of women with high-titer active syphilis infection had stillbirths, and another quarter had LBW live infants. Only half the women with high-titer active syphilis had a normal pregnancy

Table 3. Association of adverse pregnancy outcomes and high-titer active syphilis.

Pregnancy outcomes	Women with high-titer ^a syphilis, %	Seronegative women, %	RR (95% CI)	Adjusted RR (95% CI)	PAF ^b (95% CI)
All deliveries ^c					
All adverse outcomes ^d	49.3	11.2	4.4 (2.9–6.8)	4.4 (2.8–6.9)	16.7 (8.3–25.1)
Stillbirth only ^e	24.7	1.3	19.2 (5.8–63.2)	18.1 (5.5–59.6)	51.4 (19.4–83.1)
Live births only ^f					
LBW ^g	32.7	10.0	3.2 (1.9–5.5)	3.3 (2.0–5.4)	11.6 (3.3–19.9)
Prematurity ^c	20.0	3.0	6.6 (2.7–16.2)	6.1 (2.5–15.3)	24.1 (5.5–43.2)
IUGR ^h	12.7	7.0	1.8 (0.8–4.2)	2.1 (1.0–4.2)	5.2 (–3.3 to 13.7)

NOTE. CI, confidence interval; IUGR, intrauterine growth retardation; LBW, low birth weight; RR, risk ratio.

^a Rapid plasma reagin titer $\geq 1:8$.

^b PAF (population attributable fraction) was calculated for adverse pregnancy outcomes attributable to maternal syphilis, with a prevalence of active syphilis of 5.9%. $PAF = Rp/[p(R-1)+1] \times (R'-1)/R'$, where p is the prevalence of high-titer active syphilis in population, R is the crude RR, and R' is the adjusted RR. The 95% CI for the adjusted PAF was estimated using a Taylor series approximation to the variance.

^c There were 73 women with high-titer syphilis and 233 seronegative women.

^d Includes all stillbirths, premature deliveries, and infants with IUGR; RR adjusted for gravidity, delivery site, and placental malaria.

^e RR adjusted for gravidity and delivery site.

^f There were 55 women with high-titer syphilis and 230 seronegative women.

^g RR adjusted for gravidity, delivery site, antibiotics during pregnancy, and housing type.

^h RR adjusted for gravidity, delivery site, antibiotic during pregnancy, and maternal stature.

outcome. Women with this stage of syphilis had 18 times the risk of stillbirth, 3 times the risk of having LBW infants, 6 times the risk of preterm delivery, and 2 times the risk of IUGR.

Historical data suggest that the risks and sequelae of congenital transmission are highest in primary and secondary syphilis and decrease with the duration of untreated maternal infection [24, 25]. Evidence that the duration of infection is important is supported by the observation that mothers with high nontreponemal test titers, as seen in earlier stages of infection, are most at risk of passing on infection to their infants [26–28]. Support for these findings comes from the present study, in which the most important stage of syphilis, in terms of pregnancy outcome, was active infection with an RPR titer of $\geq 1:8$ and a positive specific treponemal test result. Indeed, within this group, most adverse outcomes occurred in women with RPR titers $\geq 1:32$. High-titer active infection in this study is presumed to indicate early latent infection, since these women did not have signs or symptoms of primary or secondary syphilis. Historically, untreated, early latent maternal syphilis infection has been estimated to result in stillbirths (10% of cases), preterm births (20% of cases), congenital infection (40% of cases), neonatal deaths (4% of cases), and healthy uninfected infants (20% of cases) [25]. Tanzanian women with high-titer active syphilis experienced a higher proportion of stillbirths, but there was a similar proportion of preterm births. Syphilis has been associated with prematurity in some other studies [14, 29] and was the strongest predictor of premature delivery in Malawi [29].

It is believed that even late latent syphilis, up to 4 years after the secondary stage, can result in fetal infection [27, 28, 30]. At this stage of infection, the proportion of adverse pregnancy outcomes has been estimated as 10% stillbirths, 9% premature births, 10% congenital infection, and 1% neonatal deaths [25].

In contrast, Tanzanian women who were RPR negative and TPHA positive or who had low RPR titers and a positive specific treponemal test result, interpreted as late latent infection, had no increased risk of adverse birth outcomes, compared with seronegative women. The proportion with a history of stillbirth was similar among women with high- and low-titer active syphilis, suggesting that the low-titer group had progressed from a previously infectious stage, when they experienced stillbirths, to a late, less-infectious stage.

The present study included women from both urban and rural populations and can be considered to be reasonably representative of women from this region of Tanzania who give birth in hospitals. Many of the observed cohort characteristics, including socioeconomic status, educational level, and prevalence of other infections in the study population, are also found in pregnant women from other parts of sub-Saharan Africa [31]. Our findings are likely to be generalizable to many other regions in the continent that share similar population characteristics. The risks for adverse outcomes in women with high-titer active syphilis in this study are similar to those seen in Zambia and South Africa [4, 11]. They are higher than those reported recently in Nairobi, where 23% of women with untreated syphilis (RPR- and TPHA-positive) and 7% of seronegative women had one adverse outcome (either a stillbirth or a LBW infant) [32], compared with 49% and 11%, respectively, in the Mwanza Region. The Kenyan study used a broader definition of syphilis, irrespective of RPR titer, and therefore included women with less-infectious syphilis who would be at lower risk of adverse outcomes. The results in Mwanza Region also contrast with those observed in The Gambia, where there was a lack of association between positive serologic test results and poor pregnancy outcome [16]. The strong association seen in the Tanzanian study provide reas-

urance that the serological tests used are detecting sexually transmitted infection with *T. pallidum* and not a nonvenereal treponemal infection, which may have explained the Gambian findings.

The impact of syphilis on pregnancy outcome in women who have not been screened for syphilis in pregnancy is extremely high in this population but is likely to be underestimated in this study for several reasons. Women were only recruited at delivery in a hospital, and, therefore, data would have been missed on earlier pregnancy losses due to second trimester miscarriage. Difficulties in determining whether an infant has asymptomatic infection may also have underestimated the impact of untreated syphilis. Women giving birth at home may have a higher or a lower prevalence of high-titer active syphilis than women giving birth in a hospital, potentially underestimating or overestimating the proportion of adverse outcomes attributable to maternal infection.

Measures of impact, such as PAF analyses, assume that the relationship between syphilis and an outcome is causal and that there is complete control of confounding. Most of the factors examined as potential confounders in the current study failed to alter the relationship between high-titer active syphilis and stillbirth, LBW, IUGR, or prematurity. This provides evidence for a significant direct relationship between the serological results and poor pregnancy outcome.

The validity of these results depends on the correct classification of outcomes. This should have been accurate for stillbirth and the measurement of LBW. The Dubovitz gestational age scoring system is a proxy marker for defining preterm birth and may have misclassified some cases of preterm birth as full-term and vice versa. Distinguishing the 2 types of LBW into preterm and IUGR has been used in other studies [31] and was considered to be the most practical method for defining these subgroups in this study, although it is possible that some preterm infants also had IUGR in utero and were therefore considered to be "small-for-dates."

Maternal syphilis is a significant cause of adverse pregnancy outcomes in Tanzanian women who fail to receive antenatal syphilis screening. An effective syphilis screening program would reduce stillbirths by 51% and preterm births by 24% in an unscreened population that satisfies the study's inclusion criteria and with a similar syphilis prevalence to that of Mwanza Region. Antenatal syphilis screening is a highly cost-effective intervention [33, 34] and should be prioritized as an essential part of antenatal care throughout sub-Saharan Africa. Health education messages for pregnant women should continue to reinforce the message that untreated maternal syphilis is a danger to the unborn infant, that it can be diagnosed and treated, and that women should attend an ANC that can perform syphilis screening as soon as they suspect that they are pregnant.

Acknowledgments

We thank the principal secretary of the Ministry of Health, the manager of the National AIDS Control Programme, and the director gen-

eral of the National Institute for Medical Research, Tanzania, for permission to conduct and publish the results of this study. We gratefully acknowledge the assistance of the labor ward teams at Bugando Medical Centre (Sekou Toure Regional Hospital, Sengerema Designated District Hospital) and the statistical and laboratory staff of the National Institute for Medical Research, Mwanza. We would also like to thank Tamara Hurst, William Rudibuka, Judith Bulmer, Rosanna Peeling, France Bernier, Michel Alary, Danielle Fortin, Eddy Van Dyck, Angela Hunt-Cooke, Julie Tucker, and the women who participated in the study. We thank the referees for their useful comments.

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