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Predictors of stillbirth among HIV-infected Tanzanian women

Roland Kupka[1,2], **Tarik Kassaye**[3], **Elmar Saathoff**[4], **Ellen Hertzmark**[5], **Gernard I. Msamanga**[6], and **Wafaie W. Fawzi**[1,5]

[1]Department of Nutrition, Harvard School of Public Health, Boston, MA, USA

[2]United Nations Children's Fund, Regional Office for West and Central Africa, Dakar, Senegal

[3]Unaffiliated

[4]Department of Infectious Diseases and Tropical Medicine, University of Munich, Munich, Germany

[5]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

[6]Department of Community Health, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania

Abstract

Objective—To determine maternal risk factors for stillbirth among pregnant HIV-infected women in sub-Saharan Africa.

Design—Prospective cohort study nested within a micronutrient trial. At enrollment, maternal sociodemographic, obstetric, immunologic, clinical, and nutritional variables were measured. Women were followed through monthly clinic visits until delivery. Multivariate predictors of stillbirth were identified in Poisson regression models.

Setting—Antenatal clinic in a tertiary care hospital in urban Dar es Salaam, Tanzania.

Population—*N* = 1,078 women enrolled between 12 and 27 weeks of gestation.

Main outcome measures—Stillbirth (delivery of dead baby ≥ 28 weeks' gestation), fresh stillbirth, and macerated stillbirth.

Results—Among 1,017 singleton pregnancies, there were 49 stillbirths, yielding a stillbirth risk of 50.0 per 1,000 deliveries (95% Confidence Interval(CI) = 37.2, 65.6). Of stillbirths with known type, 53.7% were fresh and 46.3% macerated. In multivariate analyses, baseline measures of late (≥ 21 weeks' gestation) study entry (Relative Risk (RR) = 2.13, 95% CI = 1.17, 3.87), CD3 count ≥ 1,179 cells/ml (RR = 2.15, 95% CI = 1.16, 4.01), stillbirth history (RR = 3.53, 95% CI = 1.30, 9.59), primiparity (RR = 3.65, 95% CI = 1.83, 7.29), and syphilis infection (RR = 2.06, 95% CI = 1.09,

Correspondence: Roland Kupka, UNICEF Regional Office for West and Central Africa, P.O. Box 29720, Dakar-Yoff, Senegal. rkupka@post.harvard.edu.

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3.88) predicted increased stillbirth risk. Late study entry, illiteracy, stillbirth history, primiparity, CD3 count ≥ 1,179 cells/ml, gonorrhea infection, and previous hospitalization predicted increased risk of fresh stillbirth, while living alone and syphilis infection predicted increased risk of macerated stillbirth.

Conclusions—Applying antenatal screening and preventive tools for the socioeconomic, obstetric, immunologic, and clinical risk factors identified may assist in reducing the high incidence of stillbirth among HIV-infected women in urban sub-Saharan Africa.

Keywords

Predictors; pregnancy; HIV; stillbirth; Tanzania

Introduction

Worldwide, more than 3.3 million stillbirths occur each year. Developing countries account for over 97% of these deaths, while sub-Saharan Africa, the geographic region with the highest incidence of stillbirth in the world, contributes more than one-fourth to the worldwide total (1).

Maternal HIV infection may increase the risk of stillbirth (2). Given that 13 million women of reproductive age currently live with HIV in sub-Saharan Africa (3), HIV infection and its ramifications may account for a high toll of stillbirths. Nevertheless, little is known on predictors of stillbirth among HIV-infected women (4).

Moreover, no studies among HIV-infected women have comprehensively assessed etiologic factors separately for macerated stillbirths, which occur antepartum, and fresh stillbirths, which generally occur intrapartum. This separation is important, as the causes of endpoints may vary over the course of pregnancy (5). Inadequate access to vital obstetric care is an important risk factor for intrapartum stillbirth in sub-Saharan Africa (6), whereas chromosomal abnormalities, infection, and maternal demographic and behavioral factors may underlie antepartum stillbirths (7).

Identifying risk factors for stillbirth among HIV-infected women could inform specific preventive and curative actions during antenatal care (8). Therefore, we examined a wide range of maternal predictors of overall stillbirth risk, as well as of risks of macerated and fresh stillbirth, in a cohort of 1,017 HIV-infected Tanzanian women.

Material and methods

The study design has been described in detail (9). Study participants were HIV-infected pregnant women, presenting for the first prenatal visit between 12 and 27 weeks' gestation, were residents of Dar es Salaam, and intended to stay in the city until delivery and for a year thereafter. Those who gave informed consent to participate in the trial were randomized to a daily dose of one of the following regimens: (1) vitamin A + β-carotene (30 mg of beta carotene + 5,000 IU of preformed vitamin A); (2) vitamins B, C, and E (20 mg of vitamin B_1, 20 mg of vitamin B_2, 25 mg of vitamin B_6, 100 mg of niacin, 50 μg of vitamin B_{12}, 500 mg of vitamin C, 30 mg of vitamin E, and 0.8 mg of folic acid); (3) vitamins B, C, and E + vitamin A + β-carotene; or (4) placebo. Participants were enrolled from April 1995 to July 1997.

In accordance with national guidelines for antenatal care at the time, during pregnancy all women received 400 mg of ferrous sulfate (equivalent to 120 mg of ferrous iron) and folate (5 mg) daily for anemia prophylaxis, and weekly doses of 500 mg of chloroquine phosphate (equivalent to 300 mg of chloroquine base) for malaria prophylaxis. Syphilis infection was

treated with benzathine penicillin among women and their partners, while hypertension during pregnancy was treated with methyldopa. Antiretroviral therapy to reduce the risk of mother-to-child transmission of HIV or to slow HIV disease progression was not available at the time of the study.

During the baseline visit, trained research nurses conducted structured interviews to collect information on obstetric history and sociodemographic factors such as age, literacy, education, marital status, living arrangements, and expenditure on food. They also collected information on history of morbidities, symptoms, and hospitalizations during the current pregnancy. The research staff aided women in the recollection of their date of last menstrual period. This date was used to calculate gestational age and season at conception. Study physicians carried out a complete medical examination and collected blood, urine, stool, and vaginal swab specimens. The stage of HIV disease was assigned in accordance to the World Health Organization (WHO) staging system (10). Trained nurses measured the women's blood pressure (to the nearest 1 mmHg) and anthropometry. They measured height and mid-upper arm circumference to the nearest 0.1 cm and weight to the nearest 100 g. Body mass index was calculated as weight (kg)/height $(m)^2$.

Study participants were followed during monthly visits to the clinic and were asked to deliver at Muhimbili National Hospital, where they received care in accordance with the national standard of care at the time.

Laboratory methods

Baseline specimens were used to determine the presence of HIV infection and levels of hemoglobin, T-lymphocytes (total lymphocytes; CD3, CD4, and CD8 subsets), serum retinol, serum vitamin E, and erythrocyte sedimentation rate. At baseline, the presence of malaria, intestinal parasites, and sexually transmitted diseases was also determined.

HIV-1 serostatus was determined by ELISA (Well-cozyme, Murex Biotech. Ltd., Dartford, UK) and positive results were confirmed by the Western blot test (Bio-Rad Laboratories Ltd., Herfordshire, UK). Hemoglobin concentrations were measured by the CBC5 Coulter Counter (Coulter Corp., Miami, FL) or the cyanmethaemoglobin colorimetric method (Corning Inc., Corning, NY). Absolute counts of T-lymphocytes were quantified with the FACS count system (Becton-Dickinson, San Jose, CA). Serum retinol and vitamin E concentrations were determined with high performance liquid chromatography (HPLC), and erythrocyte sedimentation rate with the Westergren method.

Active syphilis was defined as positive results for sera antibodies in the Venereal Diseases Research Laboratory (VDRL) slide test (Murex Diagnostic, Dartford, UK) or the *Treponema palladium* hemag-glutination (TPHA, Fujirebio, Tokyo, Japan) test. Vaginal and cervical swabs were examined for infection by *Neisseria gonorrhea*, *Candida albicans*, and *Trichomonas vaginalis*. The presence of malaria parasites was ascertained from Giemsa-stained thick and thin smear blood films. The level of parasite density per cubic millimeter was estimated from the number of malarial parasites identified per 300 leukocytes and assuming a leukocyte count of 8,000/mm^3 of blood. Stool specimens were examined for the presence of pathogenic protozoans and helminths. Macroscopic examinations were conducted for worms, whereas eggs, trophozites, and cysts were detected microscopically using saline and iodine wet mount, and the formalin-ether concentration technique.

Outcome definitions

Stillbirth was defined as the delivery of a dead baby ≥ 28 weeks' gestation, in accordance with previous work in this setting (9,[11]). Fresh stillbirths were characterized as death at birth without

signs of skin disintegration or maceration; deaths with such signs were characterized as macerated stillbirths (12). Miscarriages (delivery <28 weeks' gestation) and live births born at <28 weeks' gestation were not in the risk set for stillbirths.

Data analyses

A total of 1,078 women participated in the parent multivitamin supplementation trial. Of the 1,041 (97%) women with a known pregnancy outcome, the 1,017 (94.3%) with singleton pregnancies constituted the study cohort.

Maternal predictors were evaluated at the baseline visit, which occurred between 12 and 27 weeks' gestation. Conventional cutoffs were used to categorize predictors; when these were not available, the median was used to classify variables, in line with previous publications by our group. Poisson regression models with robust variance were used to estimate relative risks and 95% Confidence Intervals (CIs). Variables with univariate $p < 0.2$ were included in multivariate regression models and retained if $p < 0.05$. We used time-varying Cox proportional hazards models to determine whether predictors varied significantly between final models for fresh and macerated stillbirth.

Observations with missing data were kept in analyses using the missing indicator method (13). Given that the multivitamin regimen tested in the original trial significantly reduced the risk of stillbirth (9), we included an indicator variable for receipt of multivitamin trial regimen in all regression models. For stillbirth incidence, 95% CIs were calculated using exact methods for binomial proportions. Statistical significance was defined as $p < 0.05$. Statistical analyses were performed using SAS software version 9.1 (SAS Institute Inc., Cary, NC).

The study was approved by the College Research and Publications Committee of Muhimbili University College of Health Sciences (now the Institutional Review Board at Muhimbili University of Health Sciences and Allied Sciences), the ethics committee of the National AIDS Control Program of the Tanzanian Ministry of Health, and the Institutional Review Board of the Harvard School of Public Health.

Results

On average, women were 24.7 (SD = 4.8) years old and entered the study at 20.4 (SD = 3.3) weeks' gestation (Table I). Primiparas comprised 36.5% of the cohort; among multiparas, 10.8% had a history of stillbirth. The mean CD4 cell count was 420 (SD = 203) cells/mm^3 and most women (80.6%) were at HIV Stage I. The prevalence of sexually transmitted diseases at baseline was 38.1%.

Of the 1,017 singleton pregnancies, 49 resulted in stillbirths, yielding a stillbirth risk of 50.0 (95% CI: 37.2, 65.6) per 1,000 deliveries (Figure 1). There were 22 (44.9%) fresh stillbirths and 19 (38.8%) macerated stillbirths; the timing was unknown for 8 (16.3%). Among all stillbirths, 35 (71.4%) were preterm and 14 (28.6%) were term. The mean gestational age at birth was lower for stillbirths (34.4 weeks, SD = 4.4) compared to livebirths (38.7 weeks, SD = 3.1) ($p < 0.0001$).

In multivariate analyses examining risk factors for stillbirth, an approximately two-fold increased risk of stillbirth was noted among women with entry into the study ≥ 21 weeks gestation, CD3 cell count ≥ 1,179 cells/mm^3, and syphilis infection (Table II). Previous stillbirth and primiparity were related to approximately 3.5-fold increased risks in comparison to multiparas without previous stillbirth. When macerated stillbirths were examined separately, not living with a partner and syphilis infection were identified as significant multivariate risk factors (Table III). In multivariate analyses for fresh stillbirth, significant risk factors were

entry into the study ≥ 21 weeks gestation, illiteracy, previous stillbirth, primiparity, CD3 cell count ≥ 1,179 cells/mm^3, gonorrhea infection, and previous hospitalization during the same pregnancy (Table IV).

Time-varying analyses comparing predictors of macerated and fresh stillbirths also demonstrated that syphilis infection was a significant risk factor for macerated, but not fresh stillbirth ($p = 0.05$). There were no other significant interactions when comparing predictors for macerated stillbirth with those for fresh stillbirth.

Discussion

We assessed the incidence of stillbirth and its sociodemographic, obstetric, immunologic, clinical, and nutritional determinants among HIV-infected Tanzanian women. The risk of stillbirth among these women was 50 per 1,000 deliveries. This risk is higher than the aggregate risk for sub-Saharan Africa, estimated at 32 per 1,000 births, which is the highest of all regions in the world (14). HIV infection may account for this higher risk (2); however, risk of fetal loss (including both miscarriages and stillbirths) in the present study cohort did not differ from the risk in a contemporaneous cohort of HIV-uninfected women (15). The higher risk in our cohort may be due to better documentation than in population-based estimates, which are likely to underestimate the true risk of stillbirth (1).

In this cohort, 71.4% of stillbirths occurred before 37 weeks' gestation. Other studies support that the majority of stillbirths occur preterm (16). For instance, Chi et al. described that 66% of stillbirths occurred preterm in a multicenter study from sub-Saharan Africa among predominantly HIV-infected women (4). The proportion of fresh stillbirths in our study was four to five times higher than in developed countries, but was similar to that described by Chi et al. (4). The higher proportion of fresh stillbirths in sub-Saharan Africa is likely caused by deficiencies in care during delivery (7).

Late entry into the trial(≥ 21 weeks' gestation) was related to an increased risk of stillbirth overall and of fresh stillbirth. Women entered the trial after their first antenatal visit, so that entry into the trial is related to the duration of antenatal care. Thus, it appears that the duration of antenatal care was of benefit. Similarly, in a study from Brazil, fewer antenatal visits were related to an increased risk of stillbirth (17). Nevertheless, it is unclear whether the content of antenatal care was the causal factor for improved reproductive outcomes, or whether women who reported early represented a lower-risk group.

Illiteracy was related to increased risks of fresh stillbirth. Poor socioeconomic and educational status is associated with increased risk of stillbirth (18,[19]), partly because women with low socioeconomic status are less likely to make use of antenatal care, even if it is officially free as in Tanzania (20).

Living without a partner was related to an increased risk of macerated stillbirth. In North America, pregnancy outcomes are poorer among single women compared to those who are married or unmarried but cohabiting (21). The underlying factors are unknown, but may relate to increased stress level during pregnancy, harmful behaviors during pregnancy, or poorer socioeconomic status among single women (21). These factors may also be at work in our setting.

Maternal syphilis infection at baseline was strongly related to stillbirths overall and to macerated but not fresh stillbirths. The causative agent, *T. pallidum*, may be transmitted to the fetus transplacentally and may decrease blood flow to the fetus (22). However, we were unable to perform placental assessments and, therefore, unable to confirm these mechanisms. Up to half of all stillbirths may be due to syphilis among unscreened women in Tanzania, and

treatment for serological syphilis during pregnancy can reduce the risk of adverse pregnancy outcomes to that of seronegative women (23). It is unclear why syphilis infection remained predictive of macerated stillbirth in our study despite the availability of treatment. One possible explanation is that fetal infection had already occurred by the time women were recruited into the study; alternatively, some women may have reacquired the infection after the initial treatment.

Gonorrhea infection was related to fresh stillbirth in this study. This infection is generally not considered to be a risk factor for abortion and stillbirth; however, gonorrhea has been associated with prematurity and low birth weight (24). Our findings indicate that gonorrhea infection may also be a risk factor for fresh stillbirth among HIV-infected women, but the number of endpoints to examine this association was small.

A history of stillbirth was a strong risk factor for stillbirth. This is in line with evidence from different settings that describe a strong disposition to repeat adverse reproductive outcomes (16). Primiparity was a risk factor of similar magnitude. Possibly, primiparous women are less aware to detect warning signs during pregnancy. In North America, improved access to and quality of antenatal as well as obstetric care has reduced the risk of reproductive failure among primiparous women to that of multiparous women (25). In our setting, primiparity and a history of reproductive failure should trigger special attention during antenatal care while care overall improves.

Elevated CD3 cell count was related to increased risks of stillbirth overall and of fresh stillbirth. The CD3 complex is expressed on CD4 and CD8 cells as well as their immature precursor cells (26). Higher CD3 cell counts may suggest prior exposure to infectious agents or advanced stage of HIV disease, which may result in a higher risk of stillbirth. The lack of association between stillbirth and other markers of advanced HIV disease stage, such as elevated CD8 cell count or reduced CD4 count, does not support an association between advanced disease stage and stillbirth, though. Chance may therefore serve as an alternative explanation of the observed association.

Malarial infection at baseline was not related to risk of stillbirth. Malaria infection during pregnancy increases the risk of preterm delivery and low birth weight (27,[28]), but only active placental malaria appears to increase the risk of stillbirth (29). Even though HIV infection increases the risk of malaria during pregnancy (30), our findings are in line with other evidence that maternal malaria does not independently predict reproductive failure.

Maternal anemia early in pregnancy is related to increased risks of low birth weight and prematurity among HIV-uninfected women (31) and may also increase stillbirth risk (32). There is little evidence from HIV-infected populations, and our current analyses indicate that maternal anemia in the first two trimesters is not predictive of fetal loss.

We described high risks of reproductive failure in this cohort of HIV-infected pregnant and we were able to identify maternal risk factors not only for macerated stillbirth, which have traditionally been related to pregnancy complications or maternal disease, but also for fresh stillbirth. In particular, our results indicate that among HIV-infected women from sub-Saharan Africa, improving intrapartum care needs renewed attention and that initiation of antepartum care in the first half of pregnancy may be beneficial. Our findings support the benefit of improving maternal immunologic status and the prevention and treatment of syphilis and gonorrhea for pregnancy outcomes. Implementing these interventions into antenatal care may reduce the unacceptably high incidence of stillbirths among HIV-infected women in sub-Saharan Africa.

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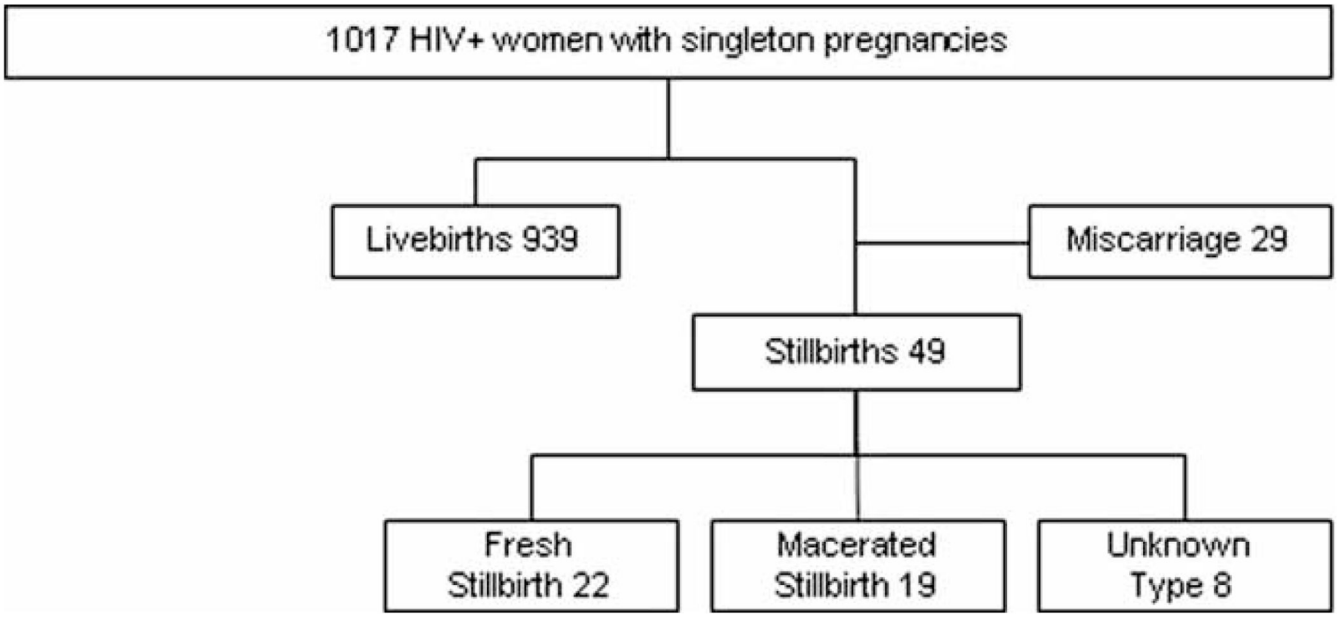

Figure 1.
Study profile.

Table I

Background characteristics at baseline.

Characteristic	Women with baseline data (*n*)	Mean (SD) or%
Age (years)	1,017	24.7 (4.8)
Gestational age at study entry (weeks)	1,017	20.4 (3.3)
Literacy (%)	1,012	91.6
Primiparity (%)	948	36.5
History of stillbirth (%)[a]	631	10.8
CD4 cell count	956	420 (203)
HIV stage ≥ 2 (%)	1,015	80.6
Presence of sexually transmitted disease (%)[b]	985	38.1
Height (cm)	1,001	156.6 (5.9)
Mid-upper arm circumference (cm)	914	25.6 (2.9)
Hemoglobin (g/dl)	999	9.4 (1.7)

[a] Among multiparous women.

[b] Defined as infection with Treponema palladium, Neisseria gonorrhea, or Trichomonas vaginalis.

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Table II

Univariate and multivariate maternal baseline predictors of stillbirth[a].

Risk factor	Pregnancies, *n*	Stillbirths, *n* (%)	Univariate model, Relative risk (95% CI)	*p*	Multivariate model, Relative risk (95% CI)	*P*
Age (years)						
<20	128	12 (9.4)	2.77 (1.23, 6.22)	0.01		
20–24	395	19 (4.8)	1.40 (0.66, 2.97)	0.38		
25–29	296	10 (3.4)	1			
≥30	161	8 (5.0)	1.48 (0.60, 3.66)	0.40		
Literacy						
No	81	7 (8.6)	1.90 (0.88, 4.12)	0.10		
Yes	894	41 (4.6)	1			
Lives with partner						
No	114	10 (8.8)	1.92 (0.99, 3.75)	0.05		
Yes	866	39 (4.5)	1			
Gestational age at study entry						
<21	479	15 (3.1)	1		1	
≥21	501	34 (6.8)	2.17 (1.20, 3.92)	0.01	2.13 (1.17, 3.87)	0.013
Season at conception						
Rainy (Mar–May, Nov–Dec)	381	24 (6.3)	1.49 (0.86, 2.58)	0.15		
Dry (Jan–Feb, Jun–Oct)	599	25 (4.2)	1			
CD3 count (per mm^3)						
<1,179	470	14 (3.0)	1		1	
≥1,179	452	32 (7.1)	2.40 (1.30, 4.43)	0.005	2.15 (1.16, 4.01)	0.02
Obstetric history						
Multiparous without previous stillbirth	553	12 (2.2)	1		1	
Multiparous with previous stillbirth	59	5 (12.5)	3.77 (1.41, 10.13)	0.008	3.53 (1.30, 9.59)	0.01
Primiparous	319	23 (7.2)	3.31 (1.67, 6.55)	0.001	3.65 (1.83, 7.29)	<0.001
Syphilis infection						
No	792	35 (4.4)	1		1	
Yes	155	13 (8.4)	1.87 (1.01, 3.47)	0.05	2.06 (1.09, 3.88)	0.03
Previous hospitalization						

Risk factor	Pregnancies, *n*	Stillbirths, *n* (%)	Univariate model, Relative risk (95% CI)	*p*	Multivariate model, Relative risk (95% CI)	*P*
No	968	46 (4.8)	1			
Yes	11	3 (27.3)	5.59 (1.94, 16.10)	0.001		
Abnormal vaginal discharge						
No	793	30 (3.8)	1			
Yes	124	8 (6.5)	1.67 (0.79, 3.55)	0.18		
Diastolic blood pressure (mmHg)						
<90	951	46 (4.8)	1			
≥90	26	3 (11.5)	2.16 (0.68, 6.83)	0.19		

[a]From Poisson regression models with robust variance. Variables with univariate $p < 0.2$ were included in multivariate regression models and retained if $p < 0.05$. Univariate and multivariate models were adjusted for multivitamin trial regimen.

Table III

Univariate and multivariate maternal baseline predictors of macerated stillbirth[a].

Risk factor	Pregnancies, *n*	Macerated stillbirths, *n* (%)	Univariate model, Relative risk (95% CI)	*p*	Multivariate model, Relative risk (95% CI)	*p*
Lives with partner						
No	112	5 (4.5)	2.72 (0.99, 7.46)	0.05	3.24 (1.16, 9.04)	0.03
Yes	860	14 (1.6)	1		1	
CD3 count (per mm^3)						
<1,179	467	6 (1.3)	1			
≥1,179	449	13 (2.9)	2.27 (0.87, 5.91)	0.09		
Syphilis infection						
No	786	11 (1.4)	1		1	
Yes	154	8 (5.2)	3.66 (1.49, 9.01)	0.005	3.65 (1.43, 9.34)	0.007

[a]From Poisson regression models with robust variance. Variables with univariate $p < 0.2$ were included in multivariate regression models and retained if $p < 0.05$. Univariate and multivariate models were adjusted for multivitamin trial regimen. The variable 'obstetric history' could not be examined as there were no cases among multiparous women with a previous stillbirth.

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Table IV

Univariate and multivariate maternal baseline predictors of fresh stillbirth[a].

Risk factor	Pregnancies, *n*	Fresh stillbirths, *n* (%)	Univariate model, Relative risk (95% CI)	*P*	Multivariate model, Relative risk (95% CI)	*p*
Age (years)						
<20	121	5 (4.1)	2.39 (0.71, 8.10)	0.16		
20–24	384	8 (2.1)	1.19 (0.39, 3.60)	0.76		
25–29	291	5 (1.7)	1			
≥30	157	4 (2.6)	1.48 (0.40, 5.42)	0.56		
Gestational age (weeks)						
<21	468	4 (0.9)	1		1	
≥21	485	18 (3.7)	4.34 (1.48, 12.71)	0.008	4.26 (1.64, 11.08)	0.003
Literacy						
No	78	4 (5.1)	2.49 (0.86, 7.20)	0.09	2.82 (1.02, 7.79)	0.05
Yes	871	18 (2.1)	1		1	
Season at conception						
Rainy (Mar–May, Nov–Dec)	370	13 (3.5)	2.24 (0.96, 5.21)	0.06		
Dry (Jan–Feb, Jun–Oct)	583	9 (1.5)	1			
Obstetric history						
Multiparous without previous stillbirth	545	4 (0.7)	1		1	
Multiparous with previous stillbirth	58	4 (6.9)	8.94 (2.36, 33.79)	0.001	8.02 (2.01, 32.06)	0.003
Primiparous	305	9 (3.0)	4.00 (1.24, 12.86)	0.02	4.13 (1.24, 13.78)	0.02
CD3 count (per mm^3)						
<1,179	461	5 (1.1)	1		1	
≥1,179	436	16 (3.7)	3.43 (1.27, 9.28)	0.02	3.71 (1.25, 11.06)	0.02
CD8 count (per mm^3)						
<565	296	4 (1.4)	1			
≥565	602	17 (2.8)	2.07 (0.70, 6.09)	0.19		
Gonorrhea infection						
No	938	20 (2.1)	1		1	
Yes	8	1 (12.5)	7.58 (1.33, 43.28)	0.02	9.74 (2.52, 37.59)	0.001
Previous hospitalization						

Risk factor	Pregnancies, *n*	Fresh stillbirths, *n* (%)	Univariate model, Relative risk (95% CI)	*P*	Multivariate model, Relative risk (95% CI)	*p*
No	941	19 (2.0)	1		1	
Yes	11	3 (27.3)	13.0 (4.17, 40.68)	B0.0001	11.76 (5.97, 23.17)	<0.0001

[a]From Poisson regression models with robust variance. Variables with univariate $p = < 0.2$ were included in multivariate regression models and retained if $p < 0.05$. Univariate and multivariate models were adjusted for multivitamin trial regimen.