Research

Adverse birth outcomes in United Republic of Tanzania — impact and prevention of maternal risk factors

Deborah Watson-Jones,[a] Helen A Weiss,[a] John M Changalucha,[c] James Todd,[a] Balthazar Gumodoka,[d] Judith Bulmer,[e] Rebecca Balira,[b] David Ross,[a] Kokungoza Mugeye,[f] Richard Hayes[a] & David Mabey[a]

Objective To determine risk factors for poor birth outcome and their population attributable fractions.
Methods 1688 women who attended for antenatal care were recruited into a prospective study of the effectiveness of syphilis screening and treatment. All women were screened and treated for syphilis and other reproductive tract infections (RTIs) during pregnancy and followed to delivery to measure the incidence of stillbirth, intrauterine growth retardation (IUGR), low birth weight (LBW) and preterm live birth.
Findings At delivery, 2.7% of 1536 women experienced a stillbirth, 12% of live births were preterm and 8% were LBW. Stillbirth was independently associated with a past history of stillbirth, short maternal stature and anaemia. LBW was associated with short maternal stature, ethnicity, occupation, gravidity and maternal malaria whereas preterm birth was associated with occupation, age of sexual debut, untreated bacterial vaginosis and maternal malaria. IUGR was associated with gravidity, maternal malaria, short stature, and delivering a female infant. In the women who had been screened and treated for syphilis, in between 20 and 34% of women with each outcome was estimated to be attributable to malaria, and 63% of stillbirths were estimated as being attributable to maternal anaemia. Screening and treatment of RTIs was effective and no association was seen between treated RTIs and adverse pregnancy outcomes.
Conclusion Maternal malaria and anaemia continue to be significant causes of adverse pregnancy outcome in sub-Saharan Africa. Providing reproductive health services that include treatment of RTIs and prevention of malaria and maternal anaemia to reduce adverse birth outcomes remains a priority.

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Introduction

Adverse birth outcomes such as low birth weight (LBW) and prematurity are associated with increased infant morbidity and mortality.[1] Maternal risk factors that are likely to be particularly important in sub-Saharan Africa include reproductive tract infections (RTIs), malaria and human immunodeficiency virus (HIV) infection.[2–5] The impact of these infections is likely to be high because they are so prevalent. Up to 50% of stillbirths, for example, have been attributed to untreated maternal syphilis.[6,7] Other RTIs associated with adverse birth outcomes include bacterial vaginosis (BV), gonorrhoea, and *Chlamydia trachomatis* and *Trichomonas vaginalis* infections.[8–12]

A few studies have documented other maternal factors associated with adverse pregnancy outcomes in sub-Saharan Africa.[13–20] However, there are few data on the examination of multiple determinants of birth outcome and the proportion of adverse birth events attributable to these factors from the study region, partly because of a lack of simple, inexpensive diagnostic methods.

We conducted a study to determine the effectiveness of syphilis screening and treatment in preventing adverse pregnancy outcomes in women in Mwanza city, north-west United Republic of Tanzania.[21] This study allowed the concomitant measurement of the importance and impact of other maternal factors in this population.

Methods

Study design and participants

The study methods have been described in detail elsewhere.[21] In summary, a prospective cohort of 1688 women attending an antenatal clinic (ANC) was recruited from the main ANC in Mwanza city from 1997 to 2000 to examine the effectiveness of antenatal screening and treatment of syphilis. Women were

[a] Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, England. Correspondence to Dr Mabey (email: David.Mabey@lshtm.ac.uk).
[b] National Institute for Medical Research, Mwanza, Tanzania.
[c] African Medical & Research Foundation, Mwanza, Tanzania.
[d] Bugando Medical Centre, Mwanza, Tanzania.
[e] School of Clinical and Laboratory Sciences (Pathology), University of Newcastle upon Tyne, England.
[f] Municipal Office of Health, Mwanza, Tanzania.

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screened at the ANC for syphilis by the rapid plasma reagin assay (RPR). RPR-positive women were treated with a stat dose of benzathine penicillin G, 2.4 MU, by intramuscular injection. Inclusion criteria for enrolment included informed consent, residence in Mwanza city for at least 1 month and a viable pregnancy confirmed by ultrasound. Exclusion criteria included more than one fetus or congenital fetal abnormality seen on ultrasound, maternal diabetes, hypertension or a history of vaginal bleeding in the current pregnancy. For each RPR-positive woman consecutively enrolled, the next two RPR-negative eligible women were recruited. Women were interviewed about their sociodemographic characteristics, obstetric history, RTI symptoms and recent antibiotic treatment. On examination, vaginal and cervical specimens were collected. Women diagnosed with *T. vaginalis* and/or *Candida albicans* on vaginal wet preparations were offered immediate treatment. ANC attendees were provided with iron and folate supplements and chloroquine 300-mg base following the Tanzanian national guidelines at that time. At a follow-up visit 2 weeks later, participants were treated for any RTIs identified in reference laboratory tests done following national guidelines. Syphilis testing was repeated at the STD reference laboratory in Mwanza. Women who were RPR-negative following the initial ANC screening, but who were found to be RPR-reactive at the reference laboratory were treated with benzathine penicillin G, 2.4 MU, by intramuscular injection.

A second RTI screen and treatment and an ultrasound examination were offered to women recruited before 32 weeks gestation. Free treatment was offered to the sexual partners of women with RTIs. Participants were followed to delivery. As soon as possible after admission, a 10-ml venous blood sample and a finger-prick sample for a malaria thick film and haematocrit were collected. A placental blood smear and a 10 mm^3 placental biopsy from the maternal placental surface were taken after delivery. Data were collected on birth outcomes and signs of congenital syphilis. Stillbirth was defined as a fetal death after 22 weeks gestation, intrauterine fetal death (IUFD) as fetal death at or before 22 weeks gestation, LBW as birth weight less than 2500 g, prematurity as delivery before 37 weeks gestation and intrauterine growth retardation (IUGR) as an LBW infant born at or after 37 weeks gestation.[14,22,23] Gestational age was estimated by ultrasound and date of the last menstrual period. To treat potential congenital infections, infants of RPR-positive mothers were given benzathine penicillin G (0.5 mg/kg, intramuscular) as soon as possible after birth.

Laboratory analysis

Serum samples taken at the ANC were tested on-site using a qualitative RPR test. Serum samples from all the women recruited were tested at the reference laboratory by the same RPR test and by the *Treponema Palliidum* haemagglutination assay (TPHA) and a fluorescent treponemal antibody assay if the results of the RPR test and TPHA were positive and negative, respectively.

Gram-stained vaginal smears were examined for candidiasis and also for BV using the Nugent method.[24] As previously described, trichomoniasis was diagnosed using wet preparations and culture, *Neisseria gonorrhoeae* by culture and *C. trachomatis* by an enzyme immunoassay antigen detection test to allow early treatment of infected women.[21] First-void urine samples (the first few mls of urine passed when voiding the bladder) were tested by the polymerase chain reaction (PCR) for *C. trachomatis* and *N. gonorrhoeae*. Anonymous testing for human immunodeficiency virus (HIV) using screening (Vironostika HIV Uni-Form II, Organon Teknika, Boxtel, the Netherlands) and confirmatory ELISA (Enzygnost® Anti-HIV 1/2 Plus, Behring, Marburg, Germany) was performed on stored maternal serum collected at delivery.

Anaemia at delivery was diagnosed by measuring the percentage packed cell volume (PCV). A PCV of 37% or more was considered normal, 33–36% was defined as mild anaemia, 24–32% as moderate anaemia and below 24% as severe anaemia.

Peripheral and placental blood smears were examined for asexual malaria parasites. Placental malaria, diagnosed by examining placental biopsies, was classified as: uninfected (no parasites or pigment); active (parasites in intervillous spaces); active-chronic (parasites in maternal erythrocytes and pigment in fibrin or cells within fibrin and/or chorionic villous syncytiotrophoblast or stroma); past-chronic (no parasites and pigment confined to fibrin or cells within fibrin).[25]

Statistical analysis

Data were entered in dBase IV (Ashton-Tate, USA) and analysed in STATA8 (STATA Corporation, Texas, USA). Univariate analysis was performed to compare sociodemographic and maternal factors in women who were followed to delivery with those lost to follow-up, and between treated RPR-positive and RPR-negative women. Comparison of proportions was done by the χ^2 test and Fisher's exact test. Means of normally distributed continuous variables were compared using the *t*-test.

Potential risk factors for stillbirth, LBW, IUGR and preterm birth were examined separately for women followed to delivery. These were not stratified by syphilis serostatus because it had previously been demonstrated that there was no difference in birth outcome between women treated for serological syphilis and seronegative women.[21] To examine potential risk factors for adverse pregnancy outcomes, crude and adjusted odds ratios (OR) were obtained using multiple logistic regression. Statistical significance was assessed using the likelihood ratio test. Factors significant at $P < 0.1$ on univariate analyses were entered in a multivariate model. Factors which remained significant ($P < 0.10$) were included in the final model for each outcome, together with variables of a priori interest (i.e. age, gravidity and HIV status).

The proportion of outcomes in the population attributable to the exposure (population attributable fraction (PAF)) was estimated for malaria, anaemia and HIV at delivery using a modification of the methods outlined by Benichou and Gail.[26] The adjusted PAF = p (R'–1)/R' where p is the prevalence of exposure among cases in the total population and R' is the adjusted relative risk (RR). Bootstrapping techniques were used to calculate the 95% confidence interval for the adjusted PAF. Sampling weights equal to the inverse of the sampling fraction were applied to both the RPR-positive and RPR-negative women to allow for the sampling strategy.

Results

Cohort recruitment and follow-up

Recruitment and follow-up have been described elsewhere.[21] In total, 1688 women were recruited into the cohort: 559 were diagnosed as RPR-positive

and 1127 RPR-negative by reference laboratory testing. Two women had incomplete serology and were excluded from further analysis.

A third trimester screen for RTIs was performed on 1283 (76.1%) women. One hundred and fifty women (8.9%) were lost to follow-up before delivery. Women lost pre-delivery were younger than those followed up (mean age 22.8 versus 23.8 years, $P = 0.01$), more likely to be primigravidae (41.3% versus 28.3%, $P = 0.001$) and not currently married (24.7% versus 14.3%, $P = 0.001$). Of the 1536 women followed to delivery, 1205 (78.5%) delivered in hospital and 331 delivered at home or elsewhere. Two women died after giving birth (0.1%), both as a result of postpartum haemorrhage. Birth weight was recorded for 1260 (84.3%) of the 1494 infants born alive.

Baseline sociodemographic characteristics

Further analysis was restricted to the 1536 women who were followed to delivery. Sociodemographic and maternal factors according to ANC RPR status are shown in Table 1. The mean age of the women was 23.8 years and most (86%) were currently married. Only 17.5% attended for antenatal care before 20 weeks gestation. The mean gestational age at recruitment was 25.4 weeks (standard deviation (SD) 6.1; range 7.1–42.0 weeks).

There was a high prevalence of RTIs at enrolment, especially BV (29.9%), *T. vaginalis* (20.5%) and *C. albicans* (29.6%). PCR testing showed that only 2.2% of the women had gonorrhoea and 7.4% had *C. trachomatis*.

Prevalence of HIV, malaria and anaemia at delivery

Of 1518 women who had an HIV result at delivery, 177 (11.7%) were HIV positive. Of the 1152 women for whom the results of placental biopsy were available, 451 (39.2%) had evidence of placental malaria (Table 1). Overall 113/1138 (9.9%) women had maternal malaria (peripheral blood parasitaemia) at the time of delivery. Anaemia was observed in 772/1189 (64.9%) women for whom haematocrit results were available, and 402 (33.8%) had moderate or severe anaemia.

There was a borderline association between HIV and maternal malaria at delivery (14.3% of HIV-positive women had malaria whereas 9.3% were HIV-negative; $P = 0.075$). An association was noted between parasite density and HIV status: of 126 HIV-positive women for whom a white blood cell count (WBC) had been recorded, 6.4% had a parasite count of $\geq 50/200$ WBC at delivery compared to 1.9% of 1002 HIV-negative women ($P = 0.002$). The geometric mean parasite density in women with malaria was 12.1/200 WBC in HIV-negative women and 36.8/200 WBC in HIV-positive women ($P = 0.04$).

There was no association between placental malaria and HIV status (41.4% of HIV-positive versus 38.8% HIV-negative women; $P = 0.56$). However, 5.6% of the 126 HIV-positive women had a parasite count in active placental malaria infection of $> 50/200$ WBC at delivery compared to 1.2% of 1009 HIV-negative women ($P = 0.04$) whereas the geometric mean parasite densities were 36.7/200 WBC and 11.4/200 WBC, respectively ($P = 0.01$).

Risk factors for adverse pregnancy outcomes

In total 230 (18%) of women had an adverse birth outcome. Univariate and multivariate analyses of the association of sociodemographic and biological variables with adverse birth outcomes are shown in Table 2.

Stillbirth and intrauterine fetal death

Overall, 42/1536 (2.7%) women experienced a stillbirth or IUFD. Two cases of IUFD diagnosed at 19 weeks gestation were combined with stillbirth for this analysis. On univariate analysis, stillbirth was strongly associated with a past history of stillbirth, occupation, being a smoker at recruitment, short stature, and maternal HIV infection and maternal anaemia at delivery.

On multivariate analysis, stillbirth was independently associated with short stature (odds ratio (OR): 2.64), a past history of stillbirth (OR: 7.50) and maternal anaemia (OR: 3.74). Although few women smoked, there was some evidence that those who did were at increased risk of stillbirth (OR: 8.51; 95% confidence interval, 0.9–78.4). There was also a borderline association with being a primigravida and with placental malaria; the highest risk was seen in women with active placental malaria (OR = 7.74) compared with no placental malaria.

Premature birth

Twelve per cent of mothers who had live births gave birth preterm. On univariate analysis, prematurity was associated with younger age (test for trend $P = 0.01$), occupation, marital status, snuff use, gravidity, untreated BV during pregnancy, peripheral maternal malaria, active chronic placental malaria and maternal anaemia at delivery.

Independent risk factors for preterm birth were occupation, sexual debut after age 15 years, untreated BV during pregnancy (OR: 2.95) and maternal malaria (OR: 3.19). Women with HIV infection were not at a significantly increased risk of preterm birth (OR: 1.06).

Low birth weight

Overall, 8.2% of live births for whom birth weight was recorded were LBW. On univariate analysis, giving birth to an infant with LBW was associated with younger age, non-Sukuma ethnicity, occupation, never having been married, short stature, low gravidity, taking metronidazole during pregnancy, untreated BV during pregnancy, not having chlamydia during pregnancy, maternal malaria, active chronic placental malaria and maternal anaemia. Receiving penicillin at enrolment and testing RPR-positive at enrolment were associated with a lower risk of LBW in the univariate analysis. These two variables were strongly associated since RPR-positive women were treated with penicillin.

Independent risk factors for LBW were non-Sukuma ethnicity, occupation (staying at home compared to having employment), short stature (OR: 1.80), being a primigravida (OR: 1.76), not having *C. trachomatis* infection and maternal malaria (OR: 5.44).

Intrauterine growth retardation

Analyses of IUGR were based on the 1117 women who had full-term live births. Of these, 4% were defined as having IUGR which was associated with younger age, non-Sukuma ethnicity, occupation, short stature, low gravidity, female sex of baby, maternal malaria and placental malaria.

Independent risk factors were occupation, short stature (OR: 1.94), being a primigravida (OR: 2.14), a female baby (OR: 2.11) and maternal malaria (OR: 2.83).

Table 1. **Characteristics of 1536 women recruited during pregnancy and seen at delivery by rapid plasma reagin assay (RPR) status at recruitment**

	Total	%	RPR+	%	RPR−	%	*P*
Age group							
13–19 years	303	19.7	97	19.3	206	19.9	0.57
20–24 years	634	41.3	204	40.6	430	41.6	
25–29 years	378	24.6	134	26.7	244	23.6	
⩾ 30 years	221	14.4	67	13.4	154	14.9	
Marital status[a]							0.88
Married	1 316	85.7	430	85.7	886	85.8	
Not married	129	8.4	41	8.2	88	8.5	
Widowed/divorced/separated	90	5.9	31	6.2	59	5.7	
Education							
None	205	13.4	103	20.5	102	9.9	< 0.001
Primary	1 154	75.1	369	73.5	785	75.9	
Secondary	175	11.4	29	5.8	146	14.1	
Tribe							
Sukuma	540	35.2	229	45.6	311	30.1	< 0.001
Other	996	64.8	273	54.4	723	69.9	
Residence in Mwanza							
⩽ 1 year	280	18.2	105	20.9	175	16.9	0.06
> 1 year	1 256	81.8	397	79.1	859	83.1	
Gravidity							
1–2	828	53.9	251	50.0	577	55.8	0.05
3–5	566	36.9	207	41.2	359	34.7	
⩾ 6	142	9.2	44	8.8	98	9.5	
Housing (building material)							
Concrete	872	56.8	237	48.1	635	62.4	< 0.001
Mud/wood	639	41.6	256	51.9	383	37.6	
Literate							
Yes	1 229	80.0	358	71.3	871	84.2	< 0.001
No	307	20.0	144	28.7	163	15.8	
No. of sexual partners in last year							
1	1 375	89.5	431	85.9	944	91.3	0.001
⩾ 2	161	10.5	71	14.1	90	8.7	
Prevalence of RTI at recruitment							
Candida albicans[b]	454	29.6	138	27.5	316	30.6	0.21
Trichomonas vaginalis	315	20.5	143	28.5	172	16.6	< 0.001
Bacterial vaginosis	459	29.9	158	31.5	301	29.1	0.34
Neisseria gonorrhoeae[c]	33	2.2	14	2.8	19	1.8	0.23
Chlamydia trachomatis[c]	114	7.4	43	8.6	71	6.9	0.24
Prevalence of maternal factors at delivery							
HIV[d]	177	11.7	73	14.7	104	10.2	0.01
Placental malaria[e]	451	39.2	174	48.3	277	35.0	< 0.001
Peripheral malaria[f]	113	9.9	32	9.1	81	10.3	0.51
Anaemia[g]	772	64.9	270	73.0	502	61.3	< 0.001

[a] 1 woman missing marital status.
[b] 2 missing results.
[c] 1 missing result.
[d] 18 missing results.
[e] 384 missing results.
[f] 369 missing, 29 indeterminate results.
[g] 357 missing results; sample taken before actual delivery.

Table 2. **Multivariate analyses of factors associated with adverse birth outcomes**

	Stillbirth[a]	Prematurity[b]	Low birth weight[c]	Intrauterine growth retardation[d]
Age (years)	*P* = 0.71	*P* = 1.00	*P* = 0.74	*P* = 0.57
< 20	1	1	1	1
20–24	1.56 (0.5–5.0)	0.98 (0.6–1.7)	0.72 (0.4–1.3)	0.62 (0.3–1.5)
25–29	1.56 (0.3–7.1)	0.99 (0.5–1.9)	0.80 (0.4–1.8)	0.92 (0.3–3.0)
⩾ 30	0.79 (0.1–5.4)	1.06 (0.5–2.3)	0.76 (0.3–2.1)	1.19 (0.3–4.8)
Ethnicity	*P* = 0.28	*P* = 0.91	*P* = 0.03	*P* = 0.10
Non-Sukuma	1	1	**1**	1
Sukuma	0.58 (0.2–1.6)	0.98 (0.7–1.5)	**0.56 (0.3–1.0)**	0.53 (0.2–1.1)
Occupation	*P* = 0.71	*P* = 0.08	*P* = 0.007	*P* = 0.07
At home	1	1	**1**	1
Skilled	0	0.43 (0.2–1.0)	**0.28 (0.1–0.9)**	0.19 (0.1–1.5)
Manual/farmer	1.22 (0.4–3.3)	0.84 (0.5–1.4)	**0.45 (0.2–0.9)**	0.50 (0.2–1.4)
Age at sexual debut (years)	*P* = 0.13	*P* = 0.01	*P* = 0.50	*P* = 0.79
⩽ 15	1	**1**	1	1
16–17	1.81 (0.6–5.4)	**2.17 (1.2–3.8)**	1.33 (0.7–2.3)	0.80 (0.3–1.9)
18–30	0.64 (0.2–2.4)	**1.99 (1.1–3.6)**	1.00 (0.5–1.9)	1.06 (0.4–2.5)
Smoker	*P* = 0.13	*P* = 0.90	*P* = 0.36	
No	1	1	1	–
Yes	8.51 (0.9–78.4)	1.16 (0.1–9.5)	3.17 (0.4–28)	–
Height	*P* = 0.03	*P* = 0.31	***P* = 0.01**	***P* = 0.05**
⩾ 156 cm	**1**	1	**1**	**1**
< 156 cm	**2.64 (1.1–6.3)**	1.22 (0.8–1.8)	**1.80 (1.1–2.9)**	**1.94 (1.1–3.8)**
Gravidity	*P* = 0.09	*P* = 0.76	*P* = 0.06	*P* = 0.08
Multigravida	1	1	1	1
Primigravida	2.62 (0.9–8.0)	0.92 (0.6–1.5)	1.76 (1.0–3.2)	2.14 (0.9–5.1)
Past stillbirth	*P* = 0.003	*P* = 0.21	*P* = 0.66	*P* = 0.74
No	**1**	1	1	1
Yes	**7.50 (2.3–24.3)**	1.64 (0.8–3.4)	1.29 (0.4–3.9)	0.71 (0.1–5.6)
Sex of baby	*P* = 0.56	*P* = 0.60	*P* = 0.39	*P* = 0.03
Male	1	1	1	**1**
Female	0.78 (0.3–1.8)	0.90 (0.6–1.3)	1.22 (0.8–1.9)	**2.11 (1.1–4.2)**
Chlamydia trachomatis[e]	*P* = 0.27	*P* = 0.43	*P* = 0.03	
No	1	1	**1**	–
Yes – untreated	0.97 (0.1–7.9)	0.59 (0.2–2.0)	**0.19 (0.1–1.5)**	–
Yes – treated	3.65 (1.1–12.0)	1.15 (0.5–2.6)	**0.33 (0.1–1.2)**	–
Trichomonas vaginalis[e]	*P* = 0.12	*P* = 0.39	*P* = 0.66	*P* = 0.28
No	1	1	1	1
Yes – treated	2.32 (1.0–5.7)	1.27 (0.8–2.0)	1.11 (0.6–1.9)	0.61 (0.2–1.5)
Yes – untreated	5.57 (0.5–66.1)	2.38 (0.5–12.1)	–	–
Bacterial vaginosis[e]	*P* = 0.18	*P* = 0.04	*P* = 0.44	*P* = 0.79
No	1	**1**	1	1
Yes – treated	1.79 (0.8–4.2)	**0.91 (0.6–1.4)**	1.08 (0.7–1.8)	1.09 (0.6–2.2)
Yes – untreated	–	**2.95 (1.3–6.6)**	2.02 (0.7–5.7)	
HIV[f]	*P* = 0.74	*P* = 0.84	*P* = 0.31	*P* = 0.49
No	1	1	1	1
Yes	1.24 (0.4–4.4)	1.06 (0.6–1.9)	1.47 (0.7–3.0)	1.45 (0.5–4.0)
Maternal malaria[f]	*P* = 0.15	***P* < 0.001**	***P* < 0.001**	*P* = 0.03
No	1	**1**	**1**	**1**
Yes	2.30 (0.8–6.7)	**3.19 (1.9–5.2)**	**5.44 (3.1–9.5)**	**2.83 (1.2–6.7)**
Placental malaria[f]	*P* = 0.09	*P* = 0.35	*P* = 0.16	*P* = 0.49
No	1	1	1	1
Past chronic	1.84 (0.6–5.2)	1.11 (0.7–1.8)	1.17 (0.6–2.1)	1.33 (0.6–3.0)
Active chronic	1.92 (0.5–6.9)	1.53 (0.7–3.2)	1.65 (0.7–3.8)	2.24 (0.7–7.3)
Active	7.74 (1.8–32.7)	0.61 (0.2–2.1)	0.38 (0.1–1.9)	0.76 (0.1–7.1)

(Table 2, cont.)

	Stillbirth[a]	Prematurity[b]	Low birth weight[c]	Intrauterine growth retardation[d]
Maternal anaemia[f]	*P*=0.02	*P*=0.11	*P*=0.18	*P*=0.93
No	**1**	1	1	1
Yes	**3.74 (1.1–12.8)**	1.40 (0.9–2.1)	1.42 (0.8–2.4)	1.03 (0.5–2.1)

Note: bold type indicates a statistically significant result.

[a] Adjusted for age, height, gravidity, history of stillbirth, HIV at delivery and maternal anaemia. Based on 1166 women with complete data for these variables.

[b] Adjusted for age, occupation, gravidity, bacterial vaginosis during pregnancy, HIV at delivery and maternal malaria. Based on 1102 women with complete data for these variables.

[c] Adjusted for age, tribe, occupation, height, gravidity, *Chlamydia trachomatis* at recruitment, HIV at delivery and maternal malaria. Based on 1090 women with complete data for these variables.

[d] Adjusted for age, tribe, occupation, height, gravidity, baby's sex, maternal malaria and HIV at delivery. Based on 964 women with complete data for these variables.

[e] At recruitment or follow-up during pregnancy.

[f] On admission for delivery.

Population attributable fractions

The proportions of adverse outcomes attributable to malaria, anaemia and HIV are shown in Table 3. The presence of malaria in pregnancy, either maternal or placental, was associated with statistically significant PAFs of 34% for stillbirth, 20% for prematurity, 28% for LBW and 22% for IUGR. For prematurity, LBW and IUGR, the main associations were with peripheral maternal malaria and active chronic placental malaria. In contrast, stillbirth appeared to be attributable to both peripheral and active or chronic placental malaria. A substantial proportion of stillbirths were attributable to maternal anaemia (PAF 63%). The proportion of adverse outcomes attributable to HIV was 5% or less for each outcome.

Discussion

There is a high incidence of adverse birth outcomes in northern United Republic of Tanzania, even in women who receive a package of reproductive health care as part of the antenatal services. Risk factors for adverse birth outcomes are multifactorial and only some of them are preventable or treatable.

Documented risk factors for stillbirth in sub-Saharan Africa include low socioeconomic status, nulliparity, maternal syphilis, LBW, mode of delivery, a previous late fetal or early neonatal death and malaria, as well as anaemia and short stature as observed in this study.[7,13,27] However, in many African populations without access to screening, maternal syphilis will remain the most important preventable cause of stillbirth.[7] Efforts to screen and treat for this infection must be a priority.[28,29] Where syphilis screening and treatment is being implemented effectively, as in this study where adverse birth outcomes attributable to syphilis were effectively prevented, anaemia and placental malaria infection remain as other potentially preventable causes of stillbirth.

The risk factors for LBW and IUGR in this study were similar to those described in a previous review which showed that ethnic group, nutrition, low weight pre-pregnancy, parity, young maternal age, short stature and malaria were important determinants of growth in utero in developing countries.[14] In contrast to research findings in Uganda,[30] our study did not find any significant association on multivariate analysis between metronidazole treatment and LBW or preterm birth.

Our study showed a strong association between preterm birth and the potentially preventable factors of BV and maternal malaria. Other determinants for prematurity in developing countries are unclear except for pre-pregnancy weight, maternal age and socioeconomic status. Vitamin A deficiency, which was not measured in our study, may also influence premature births in sub-Saharan Africa.[17]

The results of this study highlight several key points. First, as in other studies in sub-Saharan Africa, there was a high prevalence of RTIs in pregnancy.[31,32] However, apart from untreated BV, these had no significant association with adverse pregnancy outcome. Untreated RTIs have been associated with all the adverse pregnancy outcomes documented in this study. Treating RTIs in pregnancy with a single dose of ceftriaxone in Nairobi has been shown to increase birth weight and reduce the incidence of postpartum endometritis.[33] A study of mass treatment of RTIs in pregnant women in Uganda reported an increase in birth weight, and a reduction in rates of preterm birth and neonatal death in the intervention arm.[32] In our study, in which treatment of RTIs was provided at several points in pregnancy, RTIs were not independent risk factors for adverse birth outcomes. This emphasizes the importance of intervening against RTIs as a routine part of antenatal services because their impact on adverse outcomes can be prevented so effectively. This can be done through simple syndromic management at several points during antenatal care, but the use of rapid screening tests for RTIs, once available, may be more effective because they will identify asymptomatic infections. Re-screening women later in pregnancy and efforts to treat contacts should also be intensified.

Second, in a population in which the impact of maternal syphilis in pregnancy has been prevented, and in which most pregnant women have been treated for RTIs at the ANC, malaria and anaemia become the most significant preventable causes of adverse birth outcome. In this study, maternal malaria at delivery was a stronger independent risk factor for prematurity, LBW and IUGR than placental malaria, although active placental malaria infection was associated with stillbirth. In cases of maternal malaria, LBW can result from either IUGR or premature delivery.[34,35] Infection acquired close to the time of delivery results in preterm birth, whereas antenatal infection acquired earlier increases the risk of IUGR.[24]

Table 3. **Population attributable fractions[a] for the association of maternal and placental malaria, anaemia and HIV infection with adverse pregnancy outcomes**

	Adjusted prevalence[b]	Stillbirth	Prematurity	Low birth weight (LBW)	Intrauterine growth retardation (IUGR)	Any adverse outcome[c]
Peripheral malaria	10.2%	13% (0–37%)	**14% (6–22%)**	**25% (14–36%)**	**17% (5–28%)**	**15% (9–22%)**
Placental malaria						
Past chronic	20.8%	10% (0–31%)	1% (0–11%)	2% (0–13%)	3% (0–10%)	3% (0–11%)
Active chronic	11.4%	9% (0–30%)	10% (0–25%)	14% (0–38%)	13% (0–28%)	**11% (2–23%)**
Active	3.8%	7% (0–18%)	0% (0–4%)	0% (0–2%)	0% (0–9%)	0% (0–5%)
Any malaria[d]	37.9%	**34% (1–68%)**	**20% (5–35%)**	**28% (10–46%)**	**22% (7–36%)**	**22% (8–35%)**
Maternal anaemia	62.2%	**63% (26–100%)**	19% (0–45%)	22% (0–52%)	13% (0–34%)	**23% (3–43%)**
Maternal HIV infection	10.5%	4% (0–21%)	0% (0–9%)	5% (0–13%)	4% (0–12%)	3% (0–9%)

Note: bold type indicates a statistically significant result.

[a] Calculated by bootstrapping the formula p(OR–1)/OR where p is the proportion of cases exposed in the target population, and the odds ratio (OR) is the adjusted OR in Table 3. Estimates are based on 1000 bootstrap samples.

[b] Prevalence of exposure in the target population, adjusted for the weighted sample of rapid plasma reagin assay (RPR)-positive and negative women selected into the study.

[c] Any pregnancy ending in a stillbirth or delivery of a preterm or a low-birth-weight infant or an infant with intrauterine growth retardation.

[d] Evidence of placental and/or peripheral maternal malaria infection.

In contrast to other studies in sub-Saharan Africa, this study did not show any independent risk of adverse pregnancy outcome associated with maternal HIV infection.[36] However, an association between HIV status and both peripheral and placental malaria and higher parasite densities in HIV-infected individuals was seen in this study as well as in several previous studies.[37–39] Parity-specific immunity appears to be reduced in HIV-positive women; women of all parities have a higher relative risk for malaria if they are HIV-positive.[27,37,39,40] This in turn may lead to an even higher rate of adverse pregnancy outcomes, although we did not observe this, with the exception of a univariate effect of HIV on stillbirth. Any effect on pregnancy outcome may be partially mediated through the effect of HIV infection on malaria and/or anaemia. Malaria prophylaxis may not be effective in this situation because placental parasitaemia was more common in HIV-positive than in HIV-negative pregnant women treated with sulfadoxine–pyrimethamine in Kenya.[38] Similar findings have been reported from Malawi.[40]

In developing countries, maternal anaemia is usually the result of iron deficiency and/or malaria. Hookworm infection and poor diet are believed to be important causes of iron deficiency.[41,42] Iron supplementation during pregnancy is therefore generally recommended and has been shown to increase the haemoglobin level and PCV in the mother's blood post-delivery and to increase the mean birth weight of infants.[43] Maternal anaemia was not prevented in our study and this may relate to poor adherence to treatment with iron supplements or failure to control malaria adequately because of chloroquine resistance.

Both malaria and HIV can affect pregnancy outcomes indirectly because they are risk factors for maternal anaemia.[2,42,44,45] Malaria prophylaxis in pregnancy can reduce the incidence of third-trimester anaemia[38] and is generally recommended as a part of prenatal care in malaria-endemic areas.[46] This has been effective in reducing the incidence of LBW infants, especially those born to primigravidae, and in reducing maternal anaemia.[47–49] Trials of sulphadoxine–pyrimethamine have reduced placental malaria and may explain how chemoprophylaxis increases birth weight[38,50] Malaria prophylaxis has had little effect on the rate of other birth outcomes such as stillbirths or neonatal deaths.[48] In our study, chloroquine was the recommended chemoprophylactic but had limited effectiveness in preventing infection because chloroquine resistance is common.[34] Efforts are now being made in many parts of sub-Saharan Africa to change to more effective regimens.[49] The potential impact of an effective intervention will be significant at the population level because more than one third of LBW and stillbirth cases and nearly a quarter of IUGR cases were attributable to malaria. Given the relationship between malaria and HIV in pregnant women infected with both, it will be important to document the effectiveness of antiretroviral therapy for HIV on pregnancy outcomes and on the prevalence and severity of malaria in pregnancy in sub-Saharan Africa as programmes of antiretroviral therapy are implemented. ■

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Résumé

Issues défavorables de l'accouchement en Tanzanie - Influence et prévention des facteurs de risque maternels

Objectif Déterminer les facteurs de risque pour diverses issues défavorables de l'accouchement et les fractions attribuables en population de ces issues.

Méthodes 1688 femmes bénéficiant de soins anténataux ont été incluses dans une étude prospective visant à évaluer l'efficacité du dépistage de la syphilis et de son traitement. Pendant leur grossesse, ces femmes ont toutes été soumises à un dépistage de la syphilis et ont éventuellement été traitées contre cette maladie ou d'autres infections de l'appareil reproducteur. Elles ont également fait l'objet d'un suivi jusqu'à l'accouchement, en vue de mesurer l'incidence des mortinaissances, des retards de développement intra-utérins, des faibles poids à la naissance et des naissances avant terme.

Résultats Parmi les 1536 accouchements, 2,7 % ont donné un enfant mort-né, 12 % un enfant prématuré vivant et 8 % un enfant de faible poids à la naissance. La mortinaissance était associée de manière indépendante aux facteurs suivants : antécédents d'accouchement d'un enfant mort-né, et faible stature ou anémie maternelles. Le faible poids à la naissance pouvait être associé à une petite stature de la mère, à son origine ethnique, à sa profession, au nombre de grossesses et à la présence du paludisme chez la mère, tandis que la naissance avant terme pouvait être mise en relation avec la profession, l'âge au début de l'activité sexuelle et la présence d'une vaginite bactérienne non traitée ou d'un paludisme chez la mère. Le retard de croissance intra-utérin pouvait être corrélé avec le nombre de grossesses, la présence d'un paludisme chez la mère, une faible stature maternelle et la mise au monde d'une fille. Parmi les femmes chez lesquelles on avait détecté et traité une syphilis, 20 à 24 % des issues défavorables de l'accouchement ont été considérées comme imputables au paludisme et 63 % des mortinaissances à une anémie maternelle. Le dépistage et le traitement des infections de l'appareil reproducteur se sont révélés efficaces et aucune association n'a été relevée entre ces infections et des issues défavorables de la grossesse.

Conclusion Le paludisme et l'anémie maternels restent des causes importantes d'issues défavorables de la grossesse en Afrique subsaharienne. L'apport de services de santé génésique comprenant le traitement des infections de l'appareil reproducteur et la prévention du paludisme et de l'anémie chez la mère demeure une priorité pour réduire les issues défavorables de l'accouchement.

Resumen

Desenlaces adversos del parto en la República Unida de Tanzanía: impacto y prevención de los factores de riesgo maternos

Objetivo Identificar los factores de riesgo de desenlace adverso del parto y sus fracciones poblacionales atribuibles.

Métodos En un estudio prospectivo sobre la eficacia de la detección y tratamiento de la sífilis se incluyeron 1688 mujeres que esperaban recibir atención prenatal. Todas ellas fueron sometidas a pruebas de detección y tratamiento de la sífilis y de otras infecciones del aparato reproductor durante el embarazo, y fueron observadas hasta el parto para determinar la incidencia de muerte fetal, retraso del crecimiento intrauterino, bajo peso al nacer y parto antes del término.

Resultados Entre las 1536 mujeres observadas hasta el parto hubo un 2,7% de muertes fetales, un 12% de nacidos vivos antes del término y un 8% de recién nacidos con bajo peso al nacer. La muerte fetal se asoció de forma independiente a los antecedentes de muerte fetal y a la anemia y la baja estatura de la madre. El bajo peso al nacer se asoció a la baja estatura de la madre, su etnia y ocupación, el número de embarazos anteriores y los antecedentes de paludismo, mientras que el parto antes del término se asoció con la ocupación, la edad de inicio de las relaciones sexuales, la vaginosis bacteriana no tratada y los antecedentes de paludismo. El retraso del crecimiento intrauterino se asoció con el número de embarazos anteriores, el paludismo, la baja estatura de la madre y el sexo femenino del recién nacido. En estas mujeres sometidas a pruebas de detección y tratamiento de la sífilis, entre un 20 y un 34% de cada uno de los desenlaces adversos fueron atribuibles al paludismo, mientras que el 63% de las muertes fetales fueron atribuibles a la anemia materna. La detección y tratamiento de las infecciones del aparato reproductor fue eficaz y no se observó ninguna asociación entre las infecciones tratadas y los desenlaces adversos del embarazo.

Conclusión El paludismo y la anemia materna siguen siendo causas importantes de desenlace adverso del embarazo en el África subsahariana. La prestación de servicios de salud reproductiva que incluyan el tratamiento de las infecciones del aparato reproductor y la prevención de la malaria y la anemia materna siguen siendo prioritarias para reducir los desenlaces adversos del embarazo.

ملخص

الحصائل الضائرة للولادات في جمهورية تنزانيا المتحدة: أثر عوامل الاختطار الأمومية والوقاية منها

الهدف: التعرف على عوامل الاختطار للحصائل السيئة للولادات وأجزائها المعزوة للسكان.

الطريقة: شملت دراسة استباقية لفعالية تحري الزهري ومعالجته 1688 مريضة زارت مرافق الرعاية السابقة للولادة، وقد تم تحرّي جميع النساء ومعالجتهن للإصابة بالزهري وبغيره من العداوى للقناة الإنجابية خلال الحمل وتلو الولادة لقياس معدل حدوث الإملاص (موت الجنين داخل الرحم)، وتأخر النمو داخل الرحم، ونقص وزن الوليد عند الولادة، وولادة الأحياء الخدّج (قبل تمام الحمل).

الموجودات: عانى 2.7% من بين 1538 حاملاً من الإملاص، فيما عانى 12% منهن من الخداج و8% من نقص وزن الوليد عند الولادة. وقد ترافق الإملاص مع سوابق للإملاص وقصر قامة الأمهات وفقر الدم، فيما ترافق نقص وزن الوليد عند الولادة بقصر قامة الأمهات وبالإثنية (الانتماء لعرق ما) والمهنة وتعدد الحمول والملاريا لدى الأمهات، وترافق الخِداج مع المهنة والعمر عند أول ممارسة للعلاقة الجنسية، وأمراض المهبل غير المعالَجَة والملاريا لدى الأمهات. وترافق تأخر النمو داخل الرحم بتعدد الحمول والملاريا لدى الأمهات وقصر القامة لديهن وولادتهن للأنثى. ومن بين النساء اللواتي تم مسحهن ومعالجتهن لإصابتهن بالزهري قدر أن من 20% إلى 34% من النساء اللاتي لديهن واحدة من جميع الحصائل يقدَّر أنهن قد يُعزَيْن إلى الملاريا، وأن 63% من الإملاص يعزى إلى فقر الدم الناجم عن الملاريا. وقد كان تحري العداوى للقناة الإنجابية فعالاً، ولم يلاحظ ترافق بين العداوى الالتهابية في القناة الإنجابية وبين الحصائل الضائرة للحمل.

الاستنتاج: لاتزال الملاريا وفقر الدم بين الأمهات من المسببات الهامة للحصائل الضائرة للحمل في البلدان الواقعة في جنوب الصحراء الأفريقية. ويستدعي الأمر تقديم خدمات الصحة الإنجابية، والتي تشمل معالجة عدوى السبيل الإنجابي والوقاية من الملاريا وفقر الدم لدى الأمهات، بهدف الحد من الحصائل الولادية الضائرة، واعتبار كل ذلك من الأولويات.

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