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## **Risks for preterm delivery and low birth weight are independently increased by severity of maternal anaemia**

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## Risks for preterm delivery and low birth weight are independently increased by severity of maternal anaemia

Hussein L Kidanto, Ingrid Mogren, Gunilla Lindmark, Siriel Massawe, Lennarth Nystrom

**Objective.** To estimate the effect of the severity of maternal anaemia on various perinatal outcomes.

**Design.** A cross-sectional study.

**Setting.** Labour Ward, Muhimbili National Hospital, Dar es Salaam, Tanzania.

**Methods.** The haemoglobin of eligible pregnant women admitted for delivery between 15 November 2002 and 15 February 2003 was measured. Data on socio-demographic characteristics, iron supplementation, malaria prophylaxis, blood transfusion during current pregnancy, and current and previous pregnancy outcomes were collected and analysed. Anaemia was classified according to the World Health Organization (WHO) standards: normal – Hb  $\geq 11.0$  g/dl; mild – Hb 9.0 - 10.9 g/dl; moderate – Hb 7.0 - 8.9 g/dl; and severe – Hb  $< 7.0$  g/dl. Logistic regression analysis was performed to estimate the severity of anaemia. The following outcome

measures were used: preterm delivery ( $< 37$  weeks), Apgar score, stillbirth, early neonatal death, low birth weight (LBW) ( $< 2500$  g) and very low birth weight (VLBW) ( $< 1500$  g).

**Results.** A total of 1 174 anaemic and 547 non-anaemic women were enrolled. Their median age was 24 years (range 14 - 46 years) and median parity was 2 (range 0 - 17). The prevalence of anaemia and severe anaemia was 68% and 5.8%, respectively. The risk of preterm delivery increased significantly with the severity of anaemia, with odds ratios of 1.4, 1.4 and 4.1 respectively for mild, moderate and severe anaemia. The corresponding risks for LBW and VLBW were 1.2 and 1.7, 3.8 and 1.5, and 1.9 and 4.2 respectively.

**Conclusion.** The risks of preterm delivery and LBW increased in proportion to the severity of maternal anaemia.

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Anaemia is the most widespread nutritional disorder in the world, affecting 30% of the global population, and is even more prevalent among pregnant women. Massawe *et al.* showed that 65% of pregnant women attending antenatal clinics in Dar es Salaam were anaemic;<sup>1</sup> this constitutes a public health problem that requires attention.

Anaemia has a significant impact on the health of mother and fetus especially if the condition is severe; however, the literature is conflicting about the association between anaemia and perinatal outcomes. Some studies<sup>2-4</sup> have demonstrated a strong association between low haemoglobin before delivery and adverse outcomes such as preterm delivery, low birth

weight (LBW), intra-uterine growth retardation, small-for-gestational-age and anaemia, while other studies found no association.<sup>5,6</sup> A meta-analysis showed that anaemia during early pregnancy, but not late pregnancy, is associated with slightly increased risk of preterm delivery and LBW.<sup>7</sup> Many studies have used different definitions and were performed in areas with a low prevalence of anaemia.<sup>7</sup> There is therefore insufficient information to conclusively assess the effect of maternal anaemia on perinatal outcomes.

Our study set out to investigate the effect of the severity of maternal anaemia on various perinatal outcomes in an area with a high prevalence of anaemia.

### Subjects and methods

Our study was conducted on pregnant women in the labour ward of Muhimbili National Hospital (MNH), Dar es Salaam, between 15 November 2002 and 15 February 2003. The hospital is a referral centre for Dar es Salaam and the coastal region but occasionally receives patients from elsewhere in the country. The MNH is a teaching hospital for the Muhimbili University of Health and Allied Sciences. The average number of deliveries per year ranges from 13 000 to 17 000.

Our initial sample totalled 3 275 women, from whom we selected all who met the inclusion criteria, i.e. attended outpatient care before 16 weeks' gestation, were aged  $\geq 16$  years, and had a singleton pregnancy with a complete medical record. Women with multiple gestations, antepartum haemorrhage, a previous history of preterm delivery, or chronic diseases such as tuberculosis, sickle cell anaemia

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and malignancy, and who were admitted in the second stage of labour or had eclampsia, were excluded to control for confounding factors. Accordingly, 1 721 women remained for analysis. All eligible women were informed of the aims of the study and were asked to participate.

Women were interviewed in Swahili using a pretested questionnaire. Information was collected on socio-economic characteristics, previous pregnancy outcome, iron supplementation, malaria prophylaxis and blood transfusion because of anaemia or treatment for malaria during the current pregnancy. The questionnaire was pretested on 33 women and was assessed as appropriate for the purposes of the study.

### Laboratory analysis

Although haemoglobin measurement was standard for pregnant women during antenatal care (ANC), this study required an additional collection of blood samples from all eligible women admitted to the labour ward to estimate the haemoglobin level for the purpose of standardisation. Venous blood samples were collected on admission to MNH, and the haemoglobin level was estimated using a Coulter machine. A thick blood film was also taken, fixed and Giemsa-stained, and malaria parasites were counted under the microscope as a ratio of number of parasites to 200 leucocytes. Measurement of haemoglobin was done by a senior laboratory technician; the Coulter machine was calibrated daily to ensure validity of the results.

### Statistical analysis

Epi Info and SPSS were used for data entry and statistical analysis, respectively. Pearson's chi-squared test was used to test the difference between two categorical variables. A logistic regression analysis was performed *separately* for each perinatal outcome to estimate the effect of mild, moderate and severe maternal anaemia. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated, using non-anaemic women as the reference category.

### Ethical clearance

Ethical clearance was obtained from the Ethical and Publication Committee of the Muhimbili University College of Health Sciences, Dar es Salaam.

### Definitions

**Anaemia in pregnancy** was defined according to the World Health Organization (WHO) standards as: normal – Hb  $\geq$ 11.0 g/dl; mild – Hb 9.0 - 10.9 g/dl; moderate – Hb 7.0 - 8.9 g/dl; and severe – Hb  $<$ 7.0 g/dl.

**Gestational age** was defined according to Naegle's formula as the duration of the pregnancy in weeks, i.e. from the first day of the last normal menstrual period (LNMP) to the date of delivery, and compared with first-trimester ultrasound as recorded in the patient's antenatal record.

**Preterm delivery** was defined using the international definition endorsed by the World Health Organization (WHO) in 1977 and the International Federation of Gynaecology and Obstetrics in 1986, where term pregnancy includes gestational age of 37 - 41 completed weeks (259 - 293 days), preterm pregnancy gestational age is  $<$ 37 weeks ( $<$ 259 days) and post-term pregnancy gestational age is  $\geq$ 42 weeks ( $\geq$ 294 days).

**Low birth weight (LBW) and very low birth weight (VLBW)** were defined as birth weight  $<$ 2 500 g and  $<$ 1 500 g respectively.

**Apgar score** was assessed at 1 and 5 minutes after birth.

**Early neonatal death** was defined as death during the first 7 days of life.

**Stillbirth** was defined as intra-uterine fetal death.

**Positive malaria test** was defined as the presence of malaria parasites in a thick blood film examined under microscope.

## Results

A total of 1 721 pregnant women participated; the median age 24 years (range 14 - 46 years), and median parity was 2 (range 0 - 17). The prevalence of anaemia and severe anaemia was 68% and 5.8%, respectively (Table I). There was no difference in the prevalence of anaemia and severe anaemia according to socio-demographic characteristics, with the exception of anaemia and occupation ( $p=0.003$ ).

The overall prevalence of positive blood slides for malaria was 6.4%; this increased from 5.5% in the non-anaemic group to 6.7%, 5.8% and 11% in the mild, moderate and severe anaemic groups, respectively; 23% had a history of at least one malaria episode during the index pregnancy. The prevalence of malaria decreased according to increasing age for women  $\leq$ 19, 20 - 29, 30 - 39 and  $\geq$ 40 years, to 8.3%, 6.5%, 4.6% and 4.3% respectively.

The prevalence of preterm delivery and LBW was 17% and 14%, respectively. The risk of preterm delivery increased significantly with severity of anaemia with ORs of 1.4, 1.4 and 4.1 for women with mild, moderate and severe anaemia, compared with women with normal haemoglobin levels (Table II). The corresponding risks for LBW and VLBW were 1.2, 1.7 and 3.8, and 1.5, 1.9 and 4.2 respectively. There was no association between severity of anaemia and Apgar score, stillbirths and early neonatal deaths.

## Discussion

Anaemia is a common problem during pregnancy in most developing countries. Pregnancy outcomes vary depending on its type and severity. Although the association between anaemia during pregnancy and adverse perinatal outcomes has been studied extensively, the literature is still conflicting. It has been reported that maternal anaemia diagnosed before mid-pregnancy is associated with an increased risk of preterm



**Table I. Prevalence of anaemia (Hb <11 g/dl) and severe anaemia (Hb <7.0 g/dl) by specified socio-demographic characteristics**

Socio-demographic characteristics	No. of women (%)	Anaemia		Severe anaemia	
		N	%	N	%
<b>Age (years)</b>					
≤19	329 (19.1)	237	72.0	12	3.6
20 - 29	986 (57.3)	677	68.7	67	6.8
30 - 39	348 (20.2)	216	62.1	18	5.2
≥40	23 (1.3)	16	69.6	2	8.7
<b>Marital status</b>					
Single	82 (4.8)	56	67.7	6	7.3
Married	1 008 (58.6)	682	67.7	54	5.4
Cohabiting	619 (36.0)	427	69.0	38	6.1
<b>Parity</b>					
0	747 (43.4)	492	65.9	35	4.7
1	469 (27.3)	332	70.8	28	6.0
2	248 (14.4)	176	67.3	19	7.7
≥3	246 (14.3)	177	72.0	18	7.3
<b>Education level</b>					
Illiterate	102 (5.9)	69	67.6	1	1.0
Schooling <7 years	99 (5.8)	75	75.8	9	9.1
Primary level (7 years)	1 159 (67.3)	800	69.0	68	5.9
Secondary level	305 (17.7)	197	64.6	18	5.9
Post secondary level	44 (2.6)	24	54.5	2	4.5
<b>Occupation</b>					
Housewife	1 321 (76.8)	927	70.2	77	5.8
Peasant	40 (2.3)	30	75.0	3	7.5
Casual worker	265 (15.4)	164	61.9	15	5.7
Professional job	87 (5.1)	49	56.3	4	4.6
<b>Total</b>	<b>1 721</b>	<b>1 174</b>	<b>68.2</b>	<b>100</b>	<b>5.8</b>

**Table II. Bivariate logistic regression analysis of the impact of severity of anaemia on the perinatal outcomes. Odds ratio (OR) and 95% confidence intervals (CI) using the non-anaemic group as reference group**

Perinatal outcome	Non-anaemic		Level of anaemia								
	(Hb ≥11.0 g/dl)		Mild (Hb 9.0 - 10.9 g/dl)			Moderate (Hb 7.0 - 8.9 g/dl)			Severe (Hb <7.0 g/l)		
	N=547	OR	N=671	OR	95% CI	N=403	OR	95% CI	N=100	OR	95% CI
Apgar at 1 min. <7	113	1	162	1.1	0.85 - 1.5	88	1.1	0.78 - 1.5	21	1.1	0.62 - 1.8
Apgar at 5 min. <7	78	1	108	1.2	0.84 - 1.6	54	0.93	0.64 - 1.4	15	1.1	0.61 - 2.0
Preterm delivery	68	1	112	1.4	1.01 - 1.9	67	1.4	0.96 - 2.0	37	4.1	2.5 - 6.6
Stillbirth	38	1	44	0.96	0.61 - 1.5	29	1.1	0.63 - 1.7	11	1.7	0.84 - 3.5
Early neonatal death	5	1	18	3.0	1.1 - 8.1	9	2.5	0.82 - 7.5	3	3.6	0.84 - 15
LBW	59	1	86	1.2	0.85 - 1.7	72	1.7	1.2 - 2.6	30	3.8	2.3 - 6.3
LBW; GA <37 weeks	33	1	54	1.02	0.68 - 1.5	35	0.75	0.37 - 1.5	22	2.2	0.8 - 5.7
LBW; malaria neg.	57	1	80	3.6	0.44 - 31	68	3.4	0.36 - 31	28	4.1	0.35 - 46
VLBW	7	1	13	1.5	0.60 - 3.9	10	1.9	0.73 - 5.1	5	4.2	1.3 - 14

Preterm delivery = gestational age <37 weeks of gestation; Early neonatal death = death during the first 7 days of life (cases of stillbirth excluded from analysis); Stillbirth = intra-uterine fetal death (early neonatal deaths excluded from the reference group); LBW = low birth weight, i.e. birth weight <2 500 g; VLBW = very low birth weight, i.e. birth weight <1 500 g.

delivery,<sup>8,10</sup> but other researchers found no association between anaemia during the last trimester and adverse pregnancy

outcomes;<sup>7</sup> however, most of these studies were not able to study anaemia according to severity of the disease.



In our study, the prevalence of anaemia and severe anaemia was high (68% and 5.8% respectively). A previous study in the same area indicated that a major proportion of women at reproductive age were anaemic before entering pregnancy.<sup>11,17</sup> It is therefore probable that many women were anaemic before their index pregnancy.

Preterm birth and LBW have been demonstrated to contribute significantly to early neonatal deaths.<sup>12,13</sup> At MNH, prematurity and birth asphyxia were the main causes of perinatal death. Some studies have demonstrated that severe anaemia (<7.0 g/dl) is associated with birth weight figures which are 200 - 400 g lower than in women with higher (>10 g/dl) haemoglobin values, but these studies generally have not excluded other factors that might also have contributed to LBW and severity of anaemia.<sup>4</sup>

The correlation between prematurity and birth weight points to a probable association with small-for-gestational-age (SGA). However, the SGA classification is meaningful only when gestational duration has been established by an appropriate method, e.g. gestational age assessed by ultrasound in the second trimester. The other requisite for an adequate SGA assessment is reference curves of fetal growth in the population under investigation. There were no such references available for the population in our study. To create them in this tertiary centre is possible but they will have low validity because of the selected population. The validity of birth charts is based on reliable estimation of gestational age expressed as completed weeks, in accordance with international recommendations.<sup>14</sup> This is not the case at MNH since not all women undergo confirmation of gestational age by ultrasound.

Our study was conducted in an area with a known high prevalence of anaemia during pregnancy,<sup>11</sup> which was an advantage concerning the research objective. Maternal anaemia detected during the later stages of pregnancy, especially the second trimester, often reflects the physiological expansion of maternal plasma. In this study, maternal haemoglobin was measured at delivery, at the end of the third trimester in most cases. Women included in the study had attended various ANC clinics using different methods of haemoglobin measurement. Furthermore, some women had had no antenatal haemoglobin measurements done during pregnancy. To ensure quality of data, we decided to measure haemoglobin on admission to standardise the measurement.

Although the study area was endemic for malaria, only 6.4% of the pregnant women had peripheral malaria; and the fact that 1 in 4 women had a positive history of treatment for malaria during their current pregnancy confirms that a thick blood film is not always a reliable test for malaria in pregnancy. The low laboratory figure may be attributed either to intermittent presumptive prophylaxis or placental localisation of the parasites, which we did not investigate. The mechanisms of malaria's serious effects in pregnancy have not yet been

fully established.<sup>15</sup> However, it appears probable that a major factor is the severe anaemia caused by malarial parasitaemia. Previous studies have indicated that malaria increases the risk of preterm birth, and 25% of the babies born are also anaemic.<sup>16</sup> Placental malarial infestation may lead to severe intra-uterine growth restriction of the fetus, which in turn predisposes to preterm birth.

Severe anaemia is an indicator of nutritional deficiency, and it contributes to several maternal diseases, all of which may affect pregnancy outcomes and fetal development. In particular, all maternal infections and parasitic diseases may directly cause preterm labour and retardation of fetal growth. The complications of preterm labour and pregnancy-related infections have a mutual causal effect. Maternal infections during pregnancy are well-known risk factors for preterm labour; examination of amniotic fluid or placental membranes shows the presence of bacteria or inflammatory cytokines, and appropriate treatment can reduce the adverse effects.<sup>16</sup> The scope of our study did not include investigating the impact of infections on premature labour and anaemia, which we consider to be a disadvantage. However, a previous study<sup>17</sup> conducted within the same catchment area revealed that, in addition to a range of micronutrient deficiencies, chronic infections such as HIV also contributed to the occurrence of anaemia, and C-reactive protein increased in most of the anaemic patients. Studies elsewhere<sup>18</sup> indicate that women with HIV have a small increased risk of miscarriage, stillbirth, perinatal and neonatal mortality, intra-uterine growth restriction and LBW babies. In our study area, where anaemia is caused by a combination of factors, HIV is only one of the infections that would impinge on maternal anaemia; consequently, information on HIV serostatus alone is probably of limited value since anaemia can only be expected in a later phase.

Our hospital-based study in the referral centre may not be representative of the Dar es Salaam population in general; however, our findings are consistent with previous community-based studies in the same area.<sup>17</sup>

The strong association shown in this study between anaemia, LBW and preterm delivery demonstrates that maternal anaemia should be seen as an important predictor for increased perinatal risk, although it is not possible to evaluate to what extent this relates to the maternal anaemic condition *per se*.

## Conclusions

The prevalence of anaemia and severe anaemia was high. The risks of preterm delivery and LBW were significantly and independently increased relative to the severity of maternal anaemia found on admission for delivery.

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