The importance of preterm births for peri- and neonatal mortality in rural Malawi

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Summary

Peri- and neonatal mortality remain high in developing countries, especially in sub-Saharan Africa. In the present study, we quantified and identified the most important predictors of early mortality in rural Malawi. Data were obtained from a community-based cohort of 795 pregnant women and their 813 fetuses, followed prospectively from mid-pregnancy. In this group, peri- and neonatal mortality rates were 65.3 deaths per 1000 births and 37.0 deaths per 1000 live births respectively. When controlled for month of birth, maternal age and selected socio-economic variables, preterm birth was the strongest independent predictor of both peri- and neonatal mortality (adjusted odds ratios 9.6 for perinatal and 11.0 for neonatal mortality; 95% confidence intervals: [4.4, 21.0] and [3.7, 32.7] respectively). Weaker risk factors for mortality included a maternal history of stillbirth and abnormal delivery. Preterm delivery was associated with primiparity and peripheral malaria parasitaemia of the mother, and it accounted for 65% of the population-attributable risk for perinatal and 68% of the neonatal mortality. Successful intervention programmes to reduce peri- and neonatal mortality in Malawi have to include strategies to predict and prevent prematurity.

Introduction

Although childhood mortality has declined markedly in developing countries during the past 30–40 years, the positive development has not affected all age groups equally. Most improvements have been in the post-neonatal mortality rates, whereas deaths within the perinatal period (from the 22nd week of pregnancy up to the seventh day after birth) or neonatal period (first 28 days of life) have remained largely unaltered.[1] According to a World Health Organisation estimate, during the past 20 years, the average perinatal mortality rate in all developing countries has declined only from 64 to 57 deaths/1000 births and the neonatal mortality rate from 40 to 36 deaths per 1000 live births.[1] Currently, these rates in developing countries are approximately 10 times higher than those in industrialised countries.[1]

A number of factors, such as delivery complications, low birth weight or preterm delivery, have been associated with early mortality in developing countries.[2–17] However, the relative importance of these underlying factors remains largely unknown, because most studies are based on deliveries in hospitals or other modern health care facilities.[2–4,6,8–11] In areas with scarce resources and a large proportion of children being born at home, hospital-based results may not apply to the whole population. Therefore, to design successful intervention programmes, further community-based data on the magnitude and causes of peri- and neonatal mortality are urgently needed. To provide such information, we conducted a prospective, population-based cohort study in Malawi, a poor south-east African country with high childhood mortality.[18,19]

Subjects and methods

Study area

The study was carried out in Lungwena, a rural area of approximately 100 km^2 in the southern part of Malawi. The 17 000 inhabitants are mainly subsistence farmers.

A government health centre providing free primary care is located in the middle of the area. The curative and antenatal services are used frequently, but only about 30% of the deliveries take place in modern health care facilities. Most occur in the villages, usually assisted by traditional birth attendants who have received some complementary training in modern delivery care. Malaria is endemic throughout the year.

Participants

All pregnant women presenting for antenatal care at Lungwena health centre between June 1995 and August 1996 were eligible for the study. Before enrolment, informed consent was obtained verbally from each participant. The study plan was approved by the Malawi National Health Science Research Committee.

Collection of background information and antenatal follow-up

The organisation of the study and collection of data on maternal socio-economic and obstetric background or energy intake at the 32nd gestation week are described in detail elsewhere.[20,21] Enrolled pregnant women were seen at approximately monthly intervals at the health centre antenatal clinic. At each visit, a nurse-midwife enquired about any episodes of recent ill health, and measured women's weight and blood pressure with digital instruments accurate to the nearest 100 g and 1 mmHg respectively. Routine obstetric examination included external fundal palpation, auscultation of the fetal heart and measurement of the fundal height with a tape measure accurate to the nearest 0.5 cm. Two nurse-midwives and one investigator (T.K.) shared the duty of performing clinical examinations. The methods were standardised during a 3-month pilot study. All suspicious fundal height measurements were verified by the investigator.

At the first antenatal visit, a capillary blood sample was taken for laboratory analysis. Peripheral malaria parasitaemia was assessed from Giemsa-stained thick and thin blood smears by microscopy of 100 high-power fields/sample. Anaemia was assessed by determining packed cell volumes (haematocrits) using a microcapillary method after 5 min centrifugation with a hand-operated centrifuge (Jabric, Primary Diagnostics, Ash Barn, Devon, UK). HIV antibodies were screened from filter paper-impregnated blood samples using two standard enzyme-linked immunosorbent assays (Genetic Systems LAV EIA, Genetic Systems Corporation, USA, and Wellcozyme HIV 1 + 2 GACELISA VK61, Murex, UK). Women whose samples were reactive in both tests were considered to be HIV infected. HIV testing was done with pre- and post-test counselling, and the result was released in private to those few wishing to know it.

Syphilis reactivity was assessed from separated sera with rapid plasma reagin tests (Macro-Vue RPR Card Tests, Becton Dickinson Microbiology Systems, Maryland, USA). A subsample of sera was tested with Treponema Pallidum Haemagglutination assay (TPHA reagents, Fujirebio, Tokyo, Japan). Women with a positive screening test for syphilis and their sexual partners were treated with a 2.4-mU intramuscular injection of benzathine penicillin as soon as the results were available. Babies born to syphilis-reactive mothers received a similar injection (50 kU/kg) after birth.

In accordance with national policy, all women attending the antenatal clinic routinely received tetanus toxoid immunisation, iron supplements and sulphadoxine-pyrimethamine as malaria chemoprophylaxis.

Delivery events and newborn measurements

Within approximately 1 week of delivery, a research assistant visited the mothers to collect information on delivery events and the baby. Newborn weights, measured with spring scales accurate to the nearest 100 g, were considered as birthweights if taken within 1 week of the delivery. Otherwise, no birthweight was recorded. The surviving newborns were medically examined within 4 weeks from birth by a member of the research team. Peri- and neonatal outcomes were documented by research assistants during home visits made 1 month after delivery.

The length of gestation was estimated by the fundal height at each mother's first antenatal visit.[22,23] This method was chosen because ultrasound was not available, and most women did not remember the dates of their last menstrual period. Maturity scores were not feasible, because most babies were born at home, and cultural habits often prevented a home visit during the first week of life.

Statistical methods

Data entry and analyses were performed using EPI-INFO 6.04b, Microsoft Excel 7.0 and SPSS 7.5 computer programs.

Table 1 shows a summary of socio-economic, antenatal and obstetric variables tested for their association with peri- and neonatal mortality. This evaluation was limited to singleton newborns. In univariable analyses with dichotomous variables, we calculated relative risks and their 95% confidence intervals [CI] and assessed statistical significance with chi-square tests.

For multivariable modelling of peri-and neonatal mortality, logistic regression was used. The models included variables that were statistically significantly ($P < 0.05$) associated with mortality in univariable analyses as well as some potential confounding variables. Because farming, fishing and domestic animals contribute to food security in the study area,[20,21] variables describing the presence of a fisherman in the family, the size of cultivated land area and ownership of domestic animals were included in the models. Birthweight was excluded because it was unknown for a large number of infants and because there was an association between the known birthweights and gestational ages at birth (correlation coefficient 0.44, Pearson correlation). Maternal weight gain was excluded because several women (especially those with preterm delivery) had insufficient follow-up time to determine average weekly gain. Month of birth was modelled as a categorical variable (each month forming one category) and all others as dichotomous variables.

Population-attributable risks (PAR%) for predictors of mortality were calculated from adjusted odds ratio (AOR) and appropriate prevalences (p) using the standard mathematical formula: $PAR\% = (AOR-1)/[AOR + (100-p)/p] \times 100\%$.[24]

Results

Enrolment and success of follow-up

Of the 799 women attending for antenatal care at Lungwena Health Centre during the study period, 797 (99.7%) chose to participate. Two of the women were not pregnant, and 18 were carrying twins. Thus, the total number of enrolled women and fetuses was 795 and 813 respectively. Fifteen mothers and fetuses (1.9%) discontinued the follow-up during their pregnancies, two mothers aborted before the 22nd gestational week, and 36 babies were stillborn. Of the 760 liveborn infants, three (0.4%) were lost to follow-up during the neonatal period. Thus, 796 births and 757 live births could be evaluated for perinatal and neonatal outcome respectively (Fig. 1).

Active surveillance through local traditional birth attendants and study participants identified only 37 pregnant women who were not receiving antenatal services from Lungwena. Thus, 95.6% (795/832) of all pregnant women in the area were eligible for study. There were no socio-economic differences between

Table 1. Variables analysed as predictors of peri-and neonatal mortality among singleton infants

Socio-economic variables	Antenatal maternal variables	Obstetric/newborn variables
Age of parents	Number of antenatal clinic visits	Duration of pregnancy at delivery
Educational level of parents	Time of antenatal clinic enrolment	Month of birth
Literacy of parents	Parity	Place of delivery
Occupation of parents	Height	Attendant of delivery
Religion of parents	Weight and weight gain	Mode of delivery
Number of people in the household	Mid–upper arm circumference	Presentation of the fetus
Gender of the head of the family	Symphysis–fundal (S–F) height and S–F height gain	Delivery complications
Present marital status of the mother	Blood pressure and its changes	Gender of the child
Size and building material of the house	Haematocrit level at first antenatal visit	Weight of the newborn
Source of drinking water	Malaria status at first antenatal visit	
Presence of pit latrine at home	HIV status at first antenatal clinic visit	
Size of cultivated land area	Syphilis reactivity at first antenatal visit	
Ownership of domestic animals	Number of tetanus toxoid immunisations	
Distance between home and health centre	Number of malaria prophylaxis received	
Age of mother at first pregnancy	Energy intake at 32 gestation weeks	
Age of previous child at new delivery		
Number of previous infant deaths in family		
Number of under-5 deaths in family		

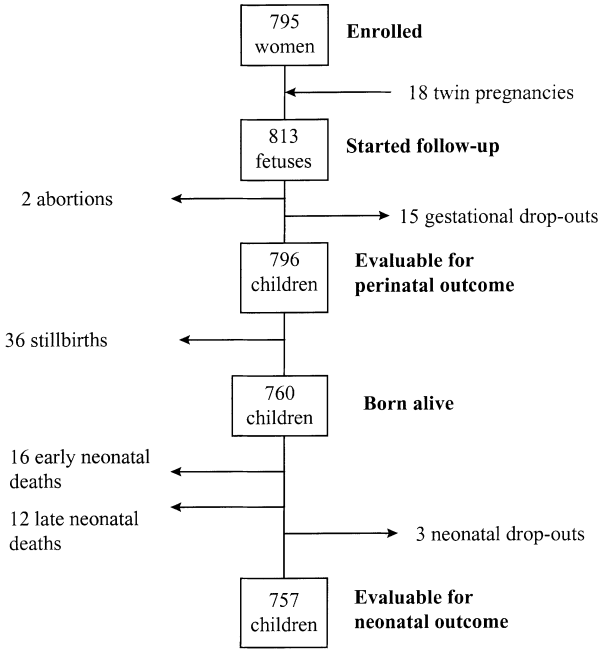

Figure 1. Outcomes of enrolled children.

those women who attended Lungwena Health Centre and those who did not, nor were there any significant differences in the peri- or neonatal mortality of their newborn children.

Table 2 summarises the relevant background information and the prevalence of potential predictor variables for peri- and neonatal mortality in the study cohort.

Mortality rates

Of the 796 births, 36 were stillborn, 16 died within 7 days of delivery and another 12 before the 28th day. Thus, the perinatal mortality rate was 65 deaths per 1000 births, and the neonatal mortality rate was 37 deaths per 1000 live births.

Sex-specific mortality rates are summarised in Table 3. Boys appeared to have an increased risk of dying during the peri- and neonatal period, but numbers were too small to draw definitive conclusions about the differences ($P = 0.29$ and 0.14 for peri- and neonatal mortality, respectively, Pearson chi-square test). Twins had a higher risk of death than singletons, but statistical significance was reached only for perinatal mortality ($P = 0.012$, Pearson chi-square test).

Determinants of mortality

Table 4 lists the environmental, socio-economic and ante- or perinatal variables associated with peri- and neonatal mortality among singleton newborns. Preterm birth (before the 38th gestation week) bore the strongest association with both peri- and neonatal death. Other risk factors for perinatal mortality included low birthweight of the child, obstetric problems and maternal anaemia at antenatal clinic enrolment. Neonatal mortality was also associated with low fetal birthweight and young maternal age, primiparity, anaemia, malaria parasitaemia and problems at delivery (Table 4).

Table 2. Background characteristics of the study cohort

Variable	Value	*n*
Mean (SD) maternal age (years)	25.7 (3.7)	794
Proportion of under-20-year-old mothers	21.8%	789
Proportion of primiparous mothers	23.6%	795
Mean (SD) timing of ANC enrolment (gest.weeks)	24.1 (4.5)	782
Mean (SD) duration of pregnancy (gest.weeks)	38.9 (3.8)	776
Proportion of preterm deliveries (before 38th gest.week)	21.8%	782
Proportion of abnormal deliveries	21.4%	777
Proportion of hospital deliveries due to delivery complications	5.0%	780
Proportion of mothers with peripheral malaria parasitaemia	30.0%	791
Proportion of mothers with HIV infection	18.0%	782
Proportion of mothers with positive syphilis test	27.0%	785
Proportion of anaemic mothers (PCV $<$ 34%)	48.6%	784
Mean (SD) gestational weight gain of mothers (g/week)	246.5 (203.5)	708
Mean (SD) birthweight of singleton newborns (g)	3099.5 (505.9)	476
Proportion of low birthweight ($\leqslant$ 2500g) singleton babies	15.1%	476

SD, standard deviation; ANC, antenatal clinic; HIV, human immunodeficiency virus; PCV, packed cell volume.

Table 3. Peri- and neonatal mortality rates in Lungwena

Group		Boys	Girls	All
PMR	Singletons	69.4 (27/389)	51.2 (19/371)	60.5 (46/760)
	Twins	158.9 (3/19)	66.7 (1/15)	166.7 (6/36)
	All	73.5 (30/408)	51.7 (20/387)	65.3 (52/796)
NMR	Singletons	45.9 (17/370)	25.3 (9/356)	35.8 (26/726)
	Twins	118.6 (2/17)	0.0 (0/14)	64.5 (2/31)
	All	49.1 (19/387)	24.3 (9/370)	37.0 (28/757)

PMR, perinatal mortality rate; NMR, neonatal mortality rate. Rates are given per 1000 births for perinatal mortality and per 1000 live births for neonatal mortality. The absolute numbers of observed deaths/number of evaluable children are shown in parentheses. No sex data were available for two children who died perinatally.

Table 4. Variables associated with peri-and neonatal mortality among singleton newborns in Lungwena

	Deaths/total number of children				
	Exposed	Unexposed	RR[a]	[95% CI]	*P*-value[b]
Predictors of perinatal mortality					
Birth before 38th gestation week	29/168	17/577	6.0	[3.4, 10.7]	< 0.001
Birthweight ⩽ 2500 g[c]	4/72	4/404	5.6	[1.4, 22.0]	0.005
Abnormal delivery[d]	24/166	22/593	3.9	[2.2, 6.8]	< 0.001
Maternal history of stillbirths or abortions	18/143	28/619	2.8	[1.6, 4.9]	< 0.001
Maternal anaemia (PCV < 0.34)[e]	34/393	17/394	2.0	[1.1, 3.5]	0.013
Predictors of neonatal mortality					
Birth before 38th gestation week	17/167	9/592	6.7	[3.0, 14.8]	< 0.001
Maternal malaria at ANC enrolment	16/224	9/531	4.2	[1.9, 9.4]	< 0.001
Birthweight < 2500 g[c]	4/70	7/404	3.3	[1.0, 11.0]	0.041
Maternal anaemia (PCV < 0.34)[e]	20/391	7/393	2.9	[1.2, 6.7]	0.010
Maternal primiparity	11/179	15/580	2.4	[1.1, 5.1]	0.022
Abnormal delivery[d]	10/165	16/591	2.2	[1.0, 4.8]	0.037
Maternal age < 20 years	10/166	16/589	2.2	[1.0, 4.8]	0.039

[a]RR, relative risk.
[b]*P*-value, Pearson chi-square test.
[c]Only children who were weighed within a week after delivery were analysed.
[d]Includes abnormal presentation of the child, abnormal mode of delivery or complications to the mother.
[e]PCV, packed cell volume.

In a multivariable analysis controlling for a number of socio-economic variables, such as month of delivery, maternal age, HIV infection and positive syphilis screening test, preterm birth was the strongest predictor of perinatal mortality (AOR 9.6). Other independent predictors included maternal history of earlier stillbirths or miscarriages, problems related to the current delivery and maternal anaemia. For neonatal mortality, preterm birth was the only statistically significant independent predictor (AOR 11.0). Maternal peripheral malaria parasitaemia at antenatal clinic enrolment also appeared to be associated with neonatal mortality, although this finding just failed to reach statistical significance (Table 5).

To estimate the community impact, we calculated the PAR% for mortality. Results from this analysis indicated that preterm birth contributed 65% to perinatal and 68% to neonatal mortality. Abnormal delivery accounted for 38% of perinatal deaths.

Predictors of preterm delivery

Univariable analyses indicated that primiparity, maternal age < 20 years and maternal peripheral malaria parasitaemia were all associated with preterm delivery (relative risks 2.3, 1.6 and 1.9, respectively; $P < 0.001$ for each variable, Pearson chi-square test). When controlled for each other as well as month of delivery

Table 5. Adjusted odds ratios (AOR) for predictors of peri-or neonatal mortality among singleton newborns in Lungwena

	Prevalence	AOR	[95% CI]	*P*-value
Perinatal mortality ($n = 731$)				
Birth before 38th gestation week	21.3%	9.6	[4.4, 21.0]	< 0.001
Abnormal delivery[a]	22.0%	4.0	[1.9, 8.4]	< 0.001
Maternal history of stillbirths or abortions	18.6%	3.7	[1.6, 8.6]	< 0.001
Maternal anaemia (PCV < 0.34)[b]	48.6%	2.4	[1.2, 5.4]	0.020
Neonatal mortality ($n = 726$)				
Birth before 38th gestation week	21.3%	11.0	[3.6, 32.4]	< 0.001
Maternal peripheral malaria parasitaemia	29.6%	2.9	[1.0, 8.6]	0.055
Abnormal delivery[a]	22.0%	2.6	[1.0, 7.0]	0.063
Maternal anaemia (PCV < 0.34)[b]	48.5%	2.2	[0.8, 6.2]	0.139
Maternal age < 20 years	21.8%	1.3	[0.3, 6.4]	0.682
Maternal primiparity	23.4%	0.7	[1.2, 3.3]	0.651

Results from logistic regression models include the dichotomous variables shown as well as maternal age (< 20 or ⩾ 20 years), HIV infection (yes/no) and syphilis screening (positive/negative), distance between mother's home and health centre (⩽ 5 or > 5 km), household cultivated land area, presence of a fisherman in the family (yes/no), ownership of domestic animals (yes/no) and latrine (yes/no), source of drinking water (safe/unsafe) and month of child's birth (categorised in 12 categories).

[a]Includes abnormal presentation of the child, abnormal mode of delivery and complications to the mother.

[b]PCV, packed cell volume.

and all potentially confounding variables listed in Table 5, primiparity was the only independent predictor of preterm delivery (AOR 2.7, $P = 0.002$). Maternal malaria infection appeared to have an independent effect as well, but the finding failed to reach statistical significance (AOR 1.5, 95% CI [0.9, 3.3], $P = 0.07$).

Discussion

Malawi has the eighth highest under-5-year mortality rate in the world.[18] Data from several, mainly hospital-based or surveillance studies suggested that a large share of early childhood mortality occurs during the peri-and neonatal periods.[4,15] We confirmed this observation with a community-based prospective cohort study with high coverage (99.7%) and a very low drop-out rate (1.9%). The number of unnoticed perinatal deaths was likely to be small, as most women enrolled relatively early for antenatal care. Thus, the observed peri- and neonatal mortality rates of 65 deaths per 1000 births and 37 deaths per 1000 liveborns were representative of the population in Lungwena. As average national figures for infant and under-5 mortality rates are 137 and 215, respectively, our data suggest that neonatal deaths account for approximately 25% of infant and 15% of all under-5-year mortality in the study area.[18]

Preterm birth was the strongest predictor of both peri- and neonatal mortality. At a population level, preterm births accounted for as much as two-thirds of peri- and neonatal mortality, much more than adverse delivery events or other harmful antenatal or delivery exposures. This is in marked contrast to many studies from developing and industrialised countries, which tend to emphasise the importance of delivery events on early mortality.[3,6,8,11,13] Theoretically, part of the difference might be explained by the methods used for gestational age assessment. In our study, the length of gestation was estimated from maternal fundal height at the first antenatal visit. While such an approach may give inaccurate results for some individuals with poorly growing babies, the method has been shown to be reliable at the population level in developing countries.[22,23] Thus, a more likely explanation for the apparent discrepancy in the importance of prematurity was our community-based enrolment at mid-pregnancy. This approach ensured inclusion in the analysis of preterm and other home deliveries that may easily have been missed in hospital-based studies in developing countries. Furthermore, complicated deliveries were not selectively concentrated in the cohort, as may occur in hospital samples from areas where only a minority of deliveries take place in health facilities.

As in many other studies, low birthweight was associated with increased peri- and neonatal mortality in the present cohort.[3,4,6,7,9–16] In fact, the correlation between gestational age and birthweight suggests that

part of the increased mortality risk for preterm infants was explained by their low birthweight. Unfortunately, an assessment of the individual impact of the variables was not possible because of the large number of unknown birthweights. Thus, we could not evaluate the importance of growth retardation among term babies. However, the main conclusion that preterm birth, usually associated with low birthweight, was a major risk factor for peri- or neonatal mortality remains valid.

In areas such as Malawi, endemic maternal malaria infection, especially if manifested as placental parasitaemia, is known to predispose towards preterm delivery and low birthweight.[25,26] Primigravid mothers are at greatest risk, apparently because they have not yet acquired selective immunity, which develops during subsequent pregnancies.[25,27] In our subjects, preterm deliveries and peripheral malaria parasitaemia at antenatal clinic enrolment were both markedly more common among primigravid women. Furthermore, even when adjusted for parity, maternal malaria parasitaemia appeared to predict preterm birth. We therefore suggest that malaria contributed significantly to prematurity in the cohort, despite the routine malaria prophylaxis given to all pregnant women. This hypothesis is consistent with a recent finding from rural Malawi that one or two antenatal doses of sulphadoxine-pyrimethamine have little influence on malaria parasitaemia at term,[28] although it has been shown to clear the infection for some weeks.[28,29] The potential role of malaria is further substantiated by the fact that most other studies in the developing world that emphasise the importance of prematurity in causing peri-or neonatal mortality have also been carried out in a malaria-endemic area.[5,9,10,14,15]

Taken together, we have documented high levels of peri- and neonatal mortality in a rural community in Malawi. Preterm birth was the most important determinant of this mortality. Children born to primigravid women were at greatest risk of preterm birth, possibly because of placental malaria parasitaemia. In view of these results, improved malaria control and other antenatal interventions for predicting and preventing preterm deliveries, especially among primigravidae, are likely to result in the largest reductions in peri- and neonatal mortality. Improved delivery care may also have a positive effect, but its relative impact on mortality would be smaller than that of improvements in antenatal follow-up.

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