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Association of previous severe low birth weight with adverse perinatal outcomes in a subsequent pregnancy among HIV-prevalent urban African women*

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Abstract

Objective—To evaluate the association between severity of prior low birth weight (LBW) delivery and adverse perinatal outcomes in the subsequent delivery among an HIV-prevalent urban African population.

Methods—A retrospective cohort study was conducted among 41 109 women who had undergone two deliveries in Lusaka, Zambia, between February 1, 2006, and May 31, 2013. The relationship between prior LBW delivery (<2500 g) and a composite measure of adverse perinatal outcome in the second pregnancy was assessed using multivariate logistic regression.

Results—Women with prior LBW delivery (n=4259) had an increased risk of LBW in the second delivery versus those without prior LBW delivery (n=37 642). Such risk correlated with the severity of first delivery LBW. The adjusted odds ratio (AOR) was 2.89 (95% confidence interval [CI] 2.05–4.09) for a birth weight of 1000–1499 g, 3.05 (95% CI 2.42–3.86) for a birth weight of 1500–1999 g, and 2.02 (95% CI 1.81–2.27) for a birth weight of 2000–2499 g. Previous LBW delivery also increased the risk of adverse perinatal outcome, with an AOR of 1.4 (95% CI 1.2–1.7).

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AUTHOR CONTRIBUTIONS

MCS, MCDS, EMS, and JSAS were involved in design, planning, data analysis, and manuscript writing. YA and BV were involved in the conduct of the present study and manuscript writing.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

Conclusion—Severe prior LBW delivery conferred substantial risk for adverse perinatal outcomes in a subsequent pregnancy.

Keywords

HIV; Low birth weight; Perinatal morbidity; Perinatal mortality; Recurrence risk; Stillbirth

1. INTRODUCTION

Low birth weight (LBW) is defined by WHO as delivery at a weight of less than 2500 g.¹ On a global scale, LBW affects 20 million pregnancies each year, making it a major contributor to perinatal mortality.^{2,3} Preterm delivery (at <37 weeks) and intrauterine growth restriction (IUGR) have both been implicated as causes of LBW, either alone or in combination.⁴ Estimates suggest that 96% of all LBW deliveries occur in low-resource countries.⁴ Because gestational dating is rarely confirmed with early pregnancy ultrasonography in low-resource areas, it is often difficult to distinguish between preterm delivery and IUGR. For example, a neonate weighing 2200 g could be preterm and appropriate for gestational age, a term neonate who is growth restricted, or a preterm neonate who is growth restricted. Without confirmation of gestational dating with ultrasonography, it is very difficult to distinguish these clinical scenarios.

An infant with LBW is 20 times more likely to die than its peers of normal birth weight, a disparity that is amplified in low-resource countries, which frequently lack the facilities required to care for affected individuals.⁴ For those who do survive, LBW can have lifelong implications, including increased risk of neonatal morbidity from feeding problems, increased risk of infection and respiratory problems,^{5,6} impaired childhood growth and cognitive development,⁷ and increased risk of chronic conditions such as cardiovascular disease, hypertension, and diabetes mellitus.^{8,9} Indeed, the risk associated with LBW might even span generations because some data suggest that girls born LBW are more likely to deliver LBW newborns than are girls born at normal weight.^{10,11}

The presence of LBW in a prior pregnancy is one of the strongest known risk factors for LBW in the subsequent pregnancy.^{12,13} Other maternal risk factors for recurrence of LBW or small for gestational age include low prepregnancy weight, short stature, smoking, and black ethnic origin.^{14–16} However, the data supporting these associations were derived from high-resource counties in Europe or North America where gestational age is routinely confirmed and pregnancy care, nutrition and exposure to infectious disease are in marked contrast with the situation experienced by pregnant women in Sub-Saharan Africa. Whether severity of LBW in the first delivery confers an increased risk of LBW or adverse perinatal outcomes (e.g. stillbirth and neonatal morbidity) in the second delivery remains unclear for such low-resource settings. This disparity is particularly true for the 2 million pregnant women affected by HIV in Sub-Saharan Africa.¹⁷ Both untreated HIV and the use of antiretroviral therapy have been linked to LBW in this population;^{18–20} nevertheless, little is known about the impact of first delivery LBW severity or mother-to-child transmission of HIV on LBW recurrence risk. The ability to potentially stratify risk by severity of prior

LBW might aid identification of women with a high likelihood of recurrent LBW or adverse perinatal outcomes and so enable targeted interventions.

Approximately 12% of all newborns in Zambia weigh less than 2500 g⁴ and 15% of all reproductive-aged women test positive for HIV.²¹ The aim of the present study was, therefore, to investigate the predictors of LBW recurrence (e.g. severity of the first LBW delivery) and adverse perinatal outcomes (e.g. mother-to-child transmission of HIV) in this low-resource HIV-prevalent setting.

2. MATERIALS AND METHODS

A retrospective study was conducted among a cohort of women who had undergone singleton deliveries in their first and second pregnancies. These deliveries were recorded at 26 facilities in Lusaka, Zambia, between February 1, 2006, and May 31, 2013. The present study was approved by the Institutional Review Boards of the University of Zambia School of Medicine (Lusaka, Zambia) and the University of North Carolina at Chapel Hill (Chapel Hill, NC, USA). Consent was not required for the present study owing to the retrospective design.

The Zambia Electronic Perinatal Record System (ZEPRS) was used to create the retrospective cohort.²² This networked, patient-level electronic medical record system is used for monitoring, reporting, quality improvement, and research. Information captured by ZEPRS includes patient demographics, medical and obstetric history, results of laboratory tests, delivery data, and some postnatal data. The database covers mothers and infants receiving prenatal care and delivery services at 25 public-sector facilities and at the University Teaching Hospital (a tertiary referral center) in Lusaka, the capital city of Zambia.²³ As in most low-resource settings, obstetric ultrasonography is not routinely available in Lusaka; therefore, estimates of gestational age were predominantly based on last menstrual period and symphysis–fundal height.

The present analysis defined first-delivery LBW as a weight of less than 2500 g.¹ Birth weight, rather than gestational age, was chosen as the primary outcome because this variable was reliably measured and recorded for most women included in the ZEPRS database. First-delivery LBW was stratified as 1000–1499 g, 1500–1999 g, and 2000–2499 g on the basis of previously reported outcomes in low-resource settings.^{24–26} Women who underwent only two singleton deliveries during the present study period were selected from ZEPRS to precisely characterize the association of first-delivery birth weight with the subsequent delivery birth weight. Women with a first-delivery birth weight of less than 1000 g were excluded from the present analysis because such deliveries might be categorized as spontaneous abortions and the fetuses were not reliably weighed at delivery (n=101).

The data were analyzed using SAS version 9.3 (SAS Institute, Cary, NC, USA). Maternal characteristics and perinatal outcomes were compared using the Pearson χ^2 , Fisher exact, or Wilcoxon rank-sum tests, as appropriate. A non-parametric additive model was created to examine the predicted probability of LBW in the second pregnancy according to the continuous variables of birth weight at first delivery and HIV infection status. Maternal age,

maternal body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), and estimated gestational age at the first prenatal visit were categorized rather than used as continuous variables on the basis of an exploratory analysis of the data and previously reported non-linear relationship.²⁷ Stepwise logistic regression with backwards deletion was performed to create an adjusted model to estimate the odds of LBW recurrence by birth weight at first delivery. Independent variables found to be statistically significant in bivariate analyses were included in the model, as were clinically important variables. The multivariate logistic regression models were used to estimate the association between prior LBW and other adverse perinatal outcomes. These outcomes included stillbirth, neonatal death at less than 24 hours, a 5-minute Apgar score of less than 7, and admission to the neonatal intensive care unit. The outcomes were assessed both as a composite measure and individually. All models were adjusted for maternal age, HIV infection status, maternal BMI, syphilis serology, baseline hemoglobin level, hypertension during the prenatal period or delivery, and interpregnancy interval. $P < 0.05$ was considered statistically significant.

3. RESULTS

The retrospective cohort comprised 41 901 women (Fig. 1). Prior LBW delivery was recorded for 4259 (10.2%) women, with birth weights of 2000–2499 g ($n=3452$ [8.2%]), 1500–1999 g ($n=559$ [1.3%]), and 1000–1499 g ($n=248$ [0.6%]). The remaining 37 642 (89.8%) women did not experience prior LBW delivery. The birth weights in this group were 2500–3999 g ($n=35 596$ [85.0%]) and 4000 g or higher ($n=2046$ [4.9%]). Of the women with prior LBW delivery, 672 (16.0%) experienced a recurrence of LBW in their second delivery. Of the women without prior LBW, 2877 (7.6%) experienced LBW in their second delivery.

The characteristics of the retrospective cohort are presented in Table 1. In all, 9856 (23.5%) of the women tested positive for HIV. When compared with the women without prior LBW delivery, those with LBW in the first delivery tended to be older (8.2% vs 1.6% for age ≥ 35 years; $P < 0.001$) and underweight (2.6% vs 1.9% for BMI < 18.5 ; $P < 0.001$).

Table 2 shows the risk of LBW in the second delivery. Women with prior LBW delivery had a twofold to threefold increased risk of subsequent LBW delivery compared with those without prior LBW delivery. Women with previous macrosomic delivery (> 4000 g) and those who were overweight or obese had a decreased risk of LBW in the second pregnancy. Additional independent risk factors for LBW in the second delivery were advanced maternal age (≥ 35 years), underweight (BMI < 18.5), HIV-positive status, chronic hypertension, and profound anemia (hemoglobin < 50 g/L). Both syphilis diagnosis with treatment and no syphilis testing were associated with LBW recurrence; however, syphilis diagnosis without treatment was not associated with an increased risk. Although short and prolonged interpregnancy intervals were associated with increased LBW recurrence in the unadjusted models, only prolonged interpregnancy interval (> 60 months) was associated with increased risk in the adjusted model.

The predicted probability of LBW recurrence was increased among women who tested positive for HIV (Fig. 2). For example, an HIV-positive woman whose first neonate weighed 1500 g had a 24.4% predicted probability of delivering a second LBW neonate. The probability dropped to 16.6% when the first neonate weighed 2500 g. An HIV-negative woman with the same birth history had a 19.5% and 10.5% predicted probability, respectively, of an LBW neonate in the second pregnancy.

The risk of adverse perinatal outcomes in the second delivery is outlined in Table 3. Women with prior LBW delivery were more likely to have an adverse perinatal outcome than were the women without prior LBW delivery (4.0% vs 2.9%). The adjusted odds ratio was 1.4 (95% confidence interval 1.2–1.7). Among HIV-positive women with information available on perinatal HIV transmission at 6 weeks after delivery (n=2409), there was no difference in HIV transmission rates among women with or without prior LBW.

4. DISCUSSION

The present study found that prior LBW delivery conferred substantially increased risk of recurrent LBW delivery and that this risk increased with the severity of the first LBW child. Prior LBW delivery was also associated with adverse perinatal outcomes in the subsequent delivery. Limited data are available on the impact of first LBW severity on the risk of LBW recurrence and adverse perinatal outcomes in low-resource settings. Consequently, the present study provided novel insight into this issue in the context of an HIV-prevalent urban African population.

The present findings corroborated those of Bratton et al.,¹² who found a markedly increased risk of second LBW delivery among women whose first child had a very LBW (<1500 g). Another study found that, in combination, prior preterm delivery and prior LBW increased the risk of subsequent preterm delivery by approximately threefold; however, the role of HIV was not considered.²⁸ The findings of the present study contradicted those of a Danish study in which survival of the second child of women with prior LBW improved compared to those of women without a history of LBW.¹³

As a composite measure of both preterm delivery and IUGR, LBW is a key contributor to perinatal morbidity and mortality in low-resource settings.^{2,28} Reducing LBW and adverse perinatal outcomes, including stillbirth, is vital to reducing perinatal mortality. In Sub-Saharan African countries, understanding the role of HIV and increased risk of LBW recurrence and adverse perinatal outcome is critical. Although both the United Nations Millennium Development Goal 4 and the United Nations General Assembly Special Session on Children identified reduction of LBW as critical for improving maternal and child health, trends in the worldwide incidence of LBW have remained unchanged over the past two decades.⁴

The main strength of the present study was the large number of women included from a single public health system who delivered at various sites, including clinics and hospitals, in which almost all newborns had their birth weight recorded. In low-resource countries, most neonates are not routinely weighed.⁴ Although the present study captured deliveries in the

public health sector, the cohort did not include home deliveries, women who delivered in the public health sector but did not attend prenatal care, and those who delivered in the private sector. A limitation of the present study was that ZEPRS does not reliably capture all of the maternal comorbidities that are known risk factors for LBW. Although hypertensive disorders were included in the present analysis, the contribution of this known risk factor for LBW was probably underestimated.

As with most population-based studies conducted in low-resource countries, the majority of women in the present cohort had no confirmation of gestational dating by ultrasonography and those that did primarily underwent ultrasonographic examination late in the second trimester or during the third trimester. Given the unreliability of estimated gestational age, the present study used birth weight to develop the models, because this variable was both routinely measured and reproducible. Although LBW is generally not used in high-resource settings in favor of small for gestational age, the present study had only limited access to early ultrasonography to confirm gestational age. The ZEPRS perinatal database probably underestimated the number of extremely LBW (<1000 g) and very LBW (<1500 g) neonates because they might have been categorized as spontaneous abortions.¹ Although some neonates delivered at the tertiary care center in Lusaka might be admitted to the neonatal intensive care unit, the majority born at a weight of less than 1000 g are not recorded in ZEPRS. Underestimates of very LBW neonates in ZEPRS could also explain the decreased risk of recurrence among women with prior LBW of 1000–1499 g versus those with prior LBW of 1500–1999 g.

The present finding that women with a reactive syphilis serology who received antibiotic treatment had an increased risk of LBW delivery contradicts another Zambian study, which found that syphilis treatment reduces adverse perinatal outcomes, including LBW.²⁹ This discrepancy might be explained by the fact that most women in the public-health sector with reactive syphilis serology are treated empirically and no confirmatory testing is performed owing to prohibitive laboratory costs. However, it is possible that some of the women in the present study might have undergone confirmatory testing, with negative results not included in ZEPRS.

In conclusion, LBW is a critical public-health indicator that reflects overall maternal health and nutritional status and access to quality prenatal care. In resource-limited settings, particularly those with a high prevalence of HIV, using the weight of the first child might aid identification of women at high risk of recurrent LBW and adverse perinatal outcomes, including stillbirth. Women with prior LBW delivery (particularly those with newborns weighing <2000 g) might need to be seen more frequently than the four prenatal visits currently recommended by WHO³⁰ and/or be stratified into a high-risk category and followed at a tertiary care center. Furthermore, nutritional supplementation could be beneficial as, in the present study, both underweight and profound anemia were risk factors for LBW recurrence and adverse perinatal outcomes. Further research is required to assess whether such approaches might prevent subsequent adverse perinatal outcomes. Finally, both the present findings and those of other studies suggest the need for a large cohort study of pregnant women in a low-resource setting with early ultrasonographic gestational dating

confirmation to establish the true incidence of LBW and its associated risk factors and likelihood of recurrence.

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FIGURE 1.

Flow of a Zambian cohort of pregnant women and their delivery outcomes from 25 public sector sites between February 1, 2006, and May 31, 2013. Abbreviations: ZEPRS, Zambia Electronic Perinatal Record System; LBW, low birth weight.

FIGURE 2.

Predicted probability and 95% confidence intervals for birth weight in second pregnancy in relation to birth weight in first pregnancy by HIV status (n=41 901).

TABLE 1

Characteristics of the retrospective cohort of Zambian women (n=41 901)^{a,b}

Characteristic	Prior LBW (n=4259) ^c	No prior LBW (n=37 642) ^c	P value ^d
Maternal age, y			<0.001
<20	616 (14.5)	4203 (11.2)	
20–34	3582 (84.1)	32 837 (87.2)	
35	61 (1.4)	602 (1.6)	
Prior	77 (1.8)	202 (0.5)	<0.001
Birth weight in second pregnancy, g			<0.001
1000–1499	68 (1.6)	280 (0.7)	
1500–2499	604 (14.2)	2597 (6.9)	
2500–3999	3554 (83.4)	33 884 (90.1)	
4000	33 (0.8)	881 (2.3)	
Interpregnancy interval, mo			<0.001
0–6	145 (3.4)	665 (1.8)	
7–59	2885 (67.7)	26 021 (69.1)	
60	802 (18.8)	7198 (19.1)	
Missing	427 (10.1)	3758 (10.0)	
Maternal body mass index at first prenatal visit ^e			<0.001
Underweight (<18.5)	110 (2.6)	724 (1.9)	
Normal weight (18.5–25.0)	2070 (48.6)	16 968 (45.1)	
Overweight (26.0–30.0)	566 (13.3)	6317 (16.8)	
Obese (>30.0)	141 (3.3)	1708 (4.5)	
Missing	1372 (32.2)	11 925 (31.7)	
Syphilis serology			0.107
Non-reactive	2953 (69.3)	26 417 (70.2)	
Reactive with treatment	74 (1.7)	579 (1.5)	
Reactive with no treatment	46 (1.1)	290 (0.8)	
Test not done or no test result available	1186 (27.9)	10 356 (27.5)	
HIV infection status			0.002
Negative	3121 (73.3)	27 594 (73.3)	
Positive	1031 (24.2)	8825 (23.5)	
Unknown	107 (2.5)	1223 (3.2)	
Hypertension during the prenatal period or delivery	85 (2.0)	462 (1.2)	<0.001
Missing	737 (17.3)	5883 (15.6)	
Baseline hemoglobin level, g/L			<0.001
100	1924 (45.2)	17 565 (46.7)	
80–90	194 (4.6)	1691 (4.5)	
<80	32 (0.8)	234 (0.6)	

Characteristic	Prior LBW (n=4259) ^c	No prior LBW (n=37 642) ^c	P value ^d
Missing	2109 (49.5)	18 152 (48.2)	

Abbreviation: LBW, low birth weight.

^aValues are given as number (percentage) unless indicated otherwise.

^bSecond pregnancies with or without prior LBW recorded at 26 facilities in Lusaka, Zambia, between February 1, 2006, and May 31, 2013.

^cLBW defined as a birth weight of <2500 g.

^dKruskal–Wallis or χ^2 tests, as appropriate; $P < 0.05$ denotes an association between prior LBW and the listed variable.

^eCalculated as weight in kilograms divided by the square of height in meters.

TABLE 2

Risk of low birth weight (<2500 g) in the second pregnancy among the retrospective cohort of Zambian women (n=41 901).^a

Characteristic	Crude OR (95% CI) ^b	Stepwise adjusted OR (95% CI) ^c
Birth weight in first pregnancy, g		
1000–1499	3.15 (2.32–4.29) ^d	2.89 (2.05–4.09) ^d
1500–1999	3.28 (2.67–4.03) ^d	3.05 (2.42–3.86) ^d
2000–2499	2.01 (1.81–2.22) ^d	2.02 (1.81–2.27) ^d
2500–3999	1.00	1.00
4000	0.70 (0.58–0.85) ^d	0.64 (0.52–0.80) ^d
Maternal age, y		
<20	0.99 (0.89–1.11)	1.05 (0.93–1.19)
20–34	1.00	1.00
35	1.69 (1.35–2.12) ^d	1.34 (1.01–1.78) ^d
Maternal BMI at first prenatal visit ^e		
Underweight (<18.5)	1.53 (1.25–1.88) ^d	1.48 (1.18–1.85) ^d
Normal weight (18.5–25.0)	1.00	1.00
Overweight (26.0–30.0)	0.67 (0.60–0.75) ^d	0.68 (0.61–0.76) ^d
Obese (>30.0)	0.69 (0.57–0.84) ^d	0.69 (0.56–0.85) ^d
Syphilis serology		
Non-reactive	1.00	1.00
Reactive with treatment	1.79 (1.42–2.24) ^d	1.85 (1.45–2.36) ^d
Reactive with no treatment	1.40 (0.99–1.98)	1.13 (0.77–1.65)
Test not done or no test result available	1.12 (1.04–1.21) ^d	1.12 (1.03–1.22) ^d
HIV infection status		
Negative	1.00	1.00
Positive	1.85 (1.71–1.99) ^d	1.65 (1.52–1.80) ^d
Unknown	1.18 (0.96–1.44)	1.15 (0.92–1.44)
Hypertension during the prenatal period or delivery	1.43 (1.25–1.63) ^d	1.52 (1.32–1.75) ^d
Interpregnancy interval, mo		
0–6	1.34 (1.06–1.69)	1.24 (0.97–1.58)
7–59	1.00	1.00
60	1.33 (1.22–1.45) ^d	1.21 (1.10–1.32) ^d
Baseline hemoglobin level, g/L		
100	1.00	1.00
80–90	1.73 (1.51–1.98)	1.29 (0.85–1.95)

Characteristic	Crude OR (95% CI) ^b	Stepwise adjusted OR (95% CI) ^c
<80	1.92 (1.37–2.71) ^d	1.37 (1.18–1.61) ^d

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index.

^a Second pregnancies with or without prior low birth weight recorded at 26 facilities in Lusaka, Zambia, between February 1, 2006, and May 31, 2013.

^b Logistic regression.

^c Logistic regression; adjusted for birth weight of the first delivery, maternal age, maternal BMI, syphilis serology, HIV infection status, hypertension during the prenatal period or delivery, interpregnancy interval, and baseline hemoglobin level.

^d $P < 0.05$.

^e Calculated as weight in kilograms divided by the square of height in meters.

TABLE 3

Risk of adverse perinatal outcomes in the second pregnancy among the retrospective cohort of Zambian women (n=41 901).^{a,b}

Characteristic	No prior LBW (n=37 642) ^c	Prior LBW (n=4259) ^c	Adjusted OR (95% CI) ^d
Composite measure of adverse perinatal outcomes	1090 (2.9)	173 (4.1)	1.4 (1.2–1.7) ^e
Individual measures of adverse perinatal outcomes			
Stillbirth	626 (1.7)	97 (2.3)	1.3 (1.1–1.7) ^e
5-min Apgar score <7	239 (0.6)	31 (0.7)	1.1 (0.7–1.7)
Missing	666 (15.6)	5201 (13.8)	
NICU admission	301 (0.8)	56 (1.3)	1.7 (1.2–2.3) ^e
Neonatal death <24 h after delivery	89 (0.2)	19 (0.4)	1.8 (1.1–3.1) ^e
Maternal transmission of HIV by 6 wk after delivery ^f	126/2153 (5.9)	16/256 (6.2)	1.09 (0.6–2.0)

Abbreviations: LBW, low birth weight; OR, odds ratio; CI, confidence interval; NICU, neonatal intensive care unit.

^aValues are given as number (percentage) or number/total number (percentage), unless indicated otherwise.

^bSecond pregnancies with or without prior LBW recorded at 26 facilities in Lusaka, Zambia, between February 1, 2006, and May 31, 2013.

^cLBW defined as a birth weight of <2500 g.

^dLogistic regression; adjusted for maternal age, HIV infection status, maternal body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), syphilis serology, baseline hemoglobin level, hypertension during the prenatal period or delivery, and interpregnancy interval.

^e $P < 0.05$.

^fAdjusted odds ratios for outcome in second pregnancy among HIV-positive women with complete data for mother-to-child transmission and all covariates (n=2409).