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Risk factors and placental histopathological findings of term born low birth weight neonates

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ABSTRACT

Introduction: Low birth weight (LBW) is associated with increased neonatal morbidity and mortality. Hence, this condition should be well studied. The aims of this study were to identify the risk factors for term born LBW, as well as the placental histopathological lesions observed.
Methods: This case control study was carried out in the University Teaching Hospital and the Central Maternity, both of Yaoundé, Cameroon, from November 1st, 2013 to April 30th, 2014. Maternal medical records and placentas of term born (≥37 completed weeks) LBW (<2500 g at birth) or normal weight (3000–3500 g) were compared. The main variables recorded included maternal age and parity, maternal height, complications that occurred during pregnancy, maternal pre-gestational body mass index, the number of antenatal visits, the sex and birth weight of the newborn, the umbilical cord length, the placental weight and placental histology. Data were analyzed using Epi info 3.5.4. Fisher exact test, t-test and logistic regression were used for comparison. $P < 0.05$ was considered statistically significant.
Results: and Discussion: A total of 30 cases of LBW and the same number of controls were examined. Significant risk factors for LBW were primiparity (aOR 14.0, 95%CI 2.1–92.7), hypertensive diseases of pregnancy (aOR 18.1, 95%CI 1.02–322.5) and <4 antenatal visits (aOR 9.5, 95%CI 1.3–67.5). Significant placental lesions were placental infarction (aOR 19.5, 95%CI 2.9–130.1) and chronic villitis (aOR 35.9, 95% CI 1.2–1034.3). Our study showed that primiparous women, those with pregnancy-induced hypertensive diseases and those with <4 antenatal visits were more at risk for LBW. Significant placental lesions observed among LBW were placental infarcts and chronic villitis. Since LBW has the tendency to recur, and given that some causes such as placental infarcts are preventable, we recommend that a histological examination of the placenta should always be carried out in cases of LBW.

1. Introduction

Low birth weight (LBW) is defined as a birth weight less than 2500 g. Prevalence of LBW varies widely worldwide, ranging from approximately 7%–18% [1], with a rate of term born LBW between 1.1% and 6.1% [2–5].

LBW is associated with increased neonatal morbidities such as hypothermia, neonatal sepsis, respiratory, gastro-intestinal, hematologic, metabolic disorders as well as increased perinatal mortality [4–6].

Although the diagnosis of LBW is easy at delivery, its risk factors are not all known. These risk factors include hypertensive diseases of pregnancy, maternal anemia, severe maternal malnutrition, maternal cardiac and respiratory diseases, myomatous uterus, maternal alcohol and tobacco consumption, urinary tract infections, maternal infestations such as malaria, congenital infections like rubella and cytomegalovirus, and fetal chromosomic abnormalities [1,2,4–7].

Placental causes exist as well, and include: placental infarcts, microscopic chorionic cysts, decidual arteriopathy, chronic villitis, placental hemangiomas, placenta abruptio, circumvallate placenta and umbilical cord abnormalities [8–13]. In 20–30% of cases, no

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cause is found. In some women, LBW has the tendency to recur, especially when due to placental infarcts.

No study in our country has been conducted on the placental aspects of LBW neonates. Hence, this study was aimed at identifying the sociodemographic and obstetric characteristics of women with LBW neonates, as well as the associated placental histopathological findings observed.

2. Methods

This case control study was carried out in the maternities of the University Teaching Hospital and the Central Maternity, both of Yaoundé, Cameroon, from November 1st, 2013 to April 30th, 2014. Placentas of term born LBW (<2500 g at ≥37 completed weeks) were recruited. For each case, the placenta of the neonate born at term just after the delivery of the case with birth weight between 3000 and 3500 g was recruited as control. An informed consent was obtained from each woman. This study was approved by the two institutional ethics committees. Variables recorded on a pre-established and pretested questionnaire by the principal investigator included maternal age and parity, marital status, maternal height, complications that occurred during pregnancy, gestational age at delivery (confirmed by an ultrasound scan performed before 20 weeks gestation), maternal pre-gestational body mass index, gestational weight gain (difference between the weight just before delivery and the weight just after she realized that she was pregnant, but before 10 weeks), the number of antenatal visits, the sex and birth weight of newborn, the umbilical cord length (the distance from the point of cord insertion on the placenta to the point of insertion on neonate's umbilicus), the placental weight (measured just after the cord has been clamped and sectioned) and placental histology. The membranes and the umbilical cord were not removed prior to weighing because the entire placenta had to be taken to the pathologist or to the principal investigator who were the ones to carry sampling.

Placental histological examination was obtained through the following steps; six specimens of about 15 × 15 × 5 mm each were taken immediately after the placental weight has been obtained, the first two specimens (I and II) were taken at the placental margin with the latter on the maternal surface. Secondly, the two other specimens (III and IV) were taken at the central part of the placenta with the latter on the maternal surface. Thirdly, one (V) was taken on suspicious lesions and lastly, one (VI) on the umbilical cord. All the specimens were immediately fixed in a 10% formaldehyde solution for 48 h. Thereafter, serial sections of 0.3–0.5 mm were done and fixed for 24 h following the same procedure. All specimens were progressively dehydrated (with an histokinet LEICA TP 1020) in a 70% up to 100% ethanol solution, thereafter in Xylen solution, then embedded in a 61 °C paraffin solution and kept in a refrigerator. Sections of 2–5 μm were later done (with the apparatus LEICA RM 2125 RT) and kept in Barnstead/Electrothermal and lastly put on slides. After removing paraffin solution (with heat or Xylen solution), rehydration was later done by including slides progressively in solutions of 90% down to 70% ethanol and in distilled water. Slides were stained with hematoxylin-eosin solutions. Later on, the slides were dehydrated, following the same procedure described above. Preparations were put on slides using a synthetic resin (PERTEX) and all the slides were read, without knowing the group allocation, by the same pathologist.

The necessary sample size was calculated as needing at least 23 women in each group, using the following formula: $N = 2 \times (Z\alpha + Z\beta/P_0 - P_1)^2 \times P \times (1-P)$ where $Z\alpha = 1.65$ corresponding to a type I error of 5%, $Z\beta = 0.84$ corresponding to a type II error of 20% or a power of 80%, P_0 the prevalence of placental infarcts in women with LBW (50%), P_1 the prevalence of placental infarcts in women without LBW (15%) and P is $(P_0 + P_1)/2$. Data were analyzed using Epi info 3.5.4. Data of LBW neonates were compared to those of neonates of the control group. Fisher exact test was used to compare categorical variables and t-test to compare continuous variables. We used odds ratios with their 95% confidence intervals (CIs) to present the comparison between the two groups. Multiple logistic regression analysis was undertaken to control for potential confounders. $P < 0.05$ was considered statistically significant.

3. Results

During the study period, 46 term born LBW neonates were delivered out of 1492 singleton term deliveries (3.1%). Sixteen mothers refused their placentas from being taken away for cultural reasons. The remaining 30 placentas of LBW neonates and the same number of placentas of women of the control group were examined. Demographic and obstetrical characteristics are given in Table 1.

Regarding marital status, 22 women were single in the LBW group as against 18 in the control group ($P = 0.41$). Parity 1 was more frequently observed in both groups (Table 2). Odds Ratio (OR) for LBW was 3.4 (1.2–10) for women of parity 1 compared with women of parity >1 ($P = 0.03$).

Pre-gestational body mass index (BMI) is shown in Table 3. OR for LBW was 4.9 (95%CI 1.6–15.0, $P < 0.009$) when BMI <25 (23/30 cases in the LBW group as against 12/30 cases in the control group) was compared to ≥25.

Concerning maternal diseases that could have influenced the occurrence of LBW, chronic hypertension (blood pressure ≥140/90 mm Hg diagnosed before 20 weeks gestation in known hypertensive women) was present in two women (6.7%) in the LBW group as against zero (0%) among the controls, and pre-eclampsia (blood pressure ≥140/90 mm Hg developed after 20 weeks gestation associated with proteinuria ≥300 mg/24 h) was present in eight women (26.7%) in the LBW group as against two (6.7%) among the controls. OR for LBW was 5.1 (95%CI 0.98–26.4, $P = 0.08$) in women with pre-eclampsia. Sickle cell disease (Hemoglobin SS) was present in one woman (3.3%) of the LBW group as against none (0%) among the controls. Passive tobacco consumption was present in one woman in each group while HIV positive status was present in two women in each group.

A total of 16 female fetuses (53.3%) were observed in the LBW group as against 14 (46.7%) in the control group. OR for LBW was 1.3 (95%CI 0.4–3.6, $P = 0.79$) when the fetus was a female.

OR for LBW for umbilical cord length <50 cm was 3.7 (95%CI 1.04–13.6, $P = 0.07$) while OR for LBW for placentas weighing

Table 1
Distribution of some variables in both groups.

Variables		LBW group (<2500 g)	Control group (3000–3500 g)	P value
Number of women		30	30	
Maternal age in year (range)		26.2 ± 5.5 (16–40)	26.6 ± 4.7 (16–38)	0.76
Parity (range)		1.8 ± 1.5 (1–8)	2.2 ± 1.3 (1–6)	0.27
Maternal height (cm)	Mean ± SD (range)	161.8 ± 6.6 (148–180)	163.8 ± 7.5 (150–180)	0.27
	<165	23 (76.7%)	15 (50%)	
	≥165	7 (23.3%)	15 (50%)	
Number of antenatal visits	Mean ± SD (range)	4.0 ± 1.6 (0–8)	4.9 ± 1.5 (2–8)	0.028
	<4	11 (36.7%)	4 (13.3%)	
	≥4	19 (63.3%)	26 (86.7%)	
Gestational age in week (range)		38.1 ± 1.4 (37–42)	38.6 ± 1.4 (37–42)	0.17
Gestational weight gain (kg)		8.5 ± 5.5 (0–20)	8.0 ± 5.7 (0–22)	0.73
Pre-gestational BMI (kg/m^2)		22.6 ± 3.0 (15.2–28.8)	26.8 ± 6.0 (17.7–42.6)	0.0011
Birth weight (g)		2251 ± 283.1 (1500–2490)	3216 ± 195.8 (3000–3499)	<0.0001
Umbilical cord length (cm)	Mean ± SD (range)	51.8 ± 10.8 (31–74)	63.0 ± 11.3 (44–87)	0.0002
	<50	11 (36.7%)	4 (13.3%)	
	≥50	19 (63.3%)	26 (86.7%)	
Placental weight (g)		468.3 ± 87.9 (280–750)	655.6 ± 133.5 (370–920)	<0.0001

LBW: low birth weight, BMI: body mass index.

Table 2
Distribution of parity in both groups.

Parity	LBW group N (%)	Control group N (%)
1	20 (66.7)	11 (36.7)
2	4 (13.3)	9 (30)
3	3 (10)	5 (16.7)
4	1 (3.3)	3 (10)
5	1 (3.3)	1 (3.3)
6	0 (0)	1 (3.3)
≥7	1 (3.3)	0 (0)
Total	30 (100)	30 (100)

LBW: low birth weight.

<500 g was 38.5 (95%CI 7.4–199.8, P < 0.0001) (22 cases in the LBW group as against two in the control group).

Pathological examinations of the placentas found anomalies in 25 cases (83.3%) in the LBW group as compared to 11 (36.7%) in the control group. The commonest anomalies found in the two groups were placental infarcts and placental chorangiosis (Table 4).

Placental anomalies were associated with an OR for LBW of 8.6 (95%CI 2.5–29.0, P = 0.0004). Some placentas had more than one anomaly. Multiple anomalies (≥2) were observed in 20 cases (66.7%) in the LBW group as against five (16.5%) in the controls (OR 10, 95%CI 2.9–34.0, P < 0.0001).

Among women (n = 8) with pre-eclampsia or eclampsia, the placental lesions were found only in placentas of LBW neonates. It included placental infarcts (50%), decidual arteriopathy (50%), placental chorangiosis (37.5%), perivillous fibrin deposition (25%), reduced chorionic villous vascularization (25%), chronic villitis (12.5%) and placenta abruptio (12.5%). The anomaly found in the placenta of the LBW neonate delivered by the woman with sickle cell disease was placental infarction. Placental lesions were not found in women with pre-eclampsia/eclampsia in the control group.

After adjusting for confounding factors, main risk factors for LBW were placental infarcts (aOR 19.5, 95%CI 2.9–130.1), chronic villitis (aOR 35.9, 95%CI 1.2–1034.3) and hypertensive diseases of pregnancy (aOR 18.1, 95%CI 1.02–322.5) (Table 5).

4. Discussion

Our rate of term born LBW (3.1%) was within the range of the rates found worldwide [2–5]. In our series, single, primiparous women with pre-gestational BMI <25 kg/m^2, with height <165 cm had an increased risk for LBW, as noticed by other researchers [11]. Moreover, women who had <4 antenatal visits, whose pregnancies were complicated by pre-eclampsia or eclampsia, those whose baby was a female, with a cord length <50 cm and a placental weight <500 g were also at risk of LBW, as found by some authors [1,4,7,11,12].

Some of these primiparous women were adolescents (<20 years old). Adolescence is a proven risk factor for LBW [4,5]. Adolescents are still in the growing stage and nutrients input have to be shared by both the mother and the fetus [14]. The fact that single women were more at risk of delivering LBW neonates can be explained by inadequate nutrition and poor quality antenatal care, due to lack of financial means that a husband could bring to her.

The explanation why women whose height <165 cm also were more at risk of delivering LBW neonates is not very clear. The high LBW rate observed among women with a pre-gestational BMI <25 kg/m^2 might either be constitutionally small for date or the LBW might result from severe maternal malnutrition. The fact that women who had less than four antenatal visits were at risk of LBW could be explained by the fact that some diseases, such as pre-eclampsia, malaria or anemia, could not be diagnosed and treated earlier.

Pre-eclampsia or eclampsia is known to induce maternal vascular changes which reduce the utero-placental blood flow and can lead to placental infarction, thus, explaining the LBW especially if it occurred far from term. The small placental weight associated with LBW might result from poor placental development due to maternal vascular changes. The explanation why cord length <50 cm was also a risk factor for LBW is unclear.

Concerning pathological examinations of placentas of LBW neonates. Our rate of anomalies (83.3%) was close to the rate of 80.7% observed in Thailand [15], but higher than that of 65.4% found by Salim et al. [11], and 25.2% observed by Pathak et al. [16]. This shows that the vast majority of LBW placentas from developing countries present anomalies. This high incidence in our environment might be due to the fact that some endemic diseases with known high risk of LBW, such as malaria, have a high affinity for the placenta [17]. Some cases of chronic villitis observed in our study might be due to placental malaria, as found elsewhere [18]. More studies are needed to confirm these assertions. Apart from the

Table 3
Distribution of pre-gestational body mass index in both groups.

Pre-gestational BMI (Kg/m^2)	LBW group N (%)	Control group N (%)
<20	5 (16.7)	4 (13.3)
20 to <25	18 (60)	8 (26.7)
25 to <30	7 (23.3)	10 (33.3)
30 to <35	0 (0)	6 (20)
≥35	0 (0)	2 (6.7)
Total	30 (100)	30 (100)

BMI: body mass index, LBW: low birth weight.

Table 4
Distribution of placental anomalies in both groups.

Anomalies[a]	LBW group N (%)	Control group N (%)	OR	95%CI	P
Reduced chorionic villous vascularization	9 (30)	1 (3.3)	12.4	1.4–105.7	0.012
Placental infarction	20 (66.7)	6 (20)	8	2.4–25.8	0.0006
Obliterative fetal vasculopathy	6 (20)	1 (3.3)	7.2	0.8–64.4	0.10
Chronic villitis	6 (20)	1 (3.3)	7.2	0.8–64.4	0.10
Decidual arteriopathy	9 (30)	3 (10)	3.8	0.9–16.0	0.10
Placental chorangiosis	9 (30)	4 (13.3)	2.7	0.7–10.3	0.20
Perivillous fibrin deposition	6 (20)	2 (6.7)	3.5	0.6–18.9	0.25
Placental calcifications	13 (43.3)	9 (30)	1.7	0.6–5.1	0.42
Placenta abruptio	3 (10)	0 (0)	–	–	0.12
Microscopic chorionic cysts	2 (6.7)	0 (0)	–	–	0.25
Total number of placentas with lesions	25 (83.3)	11 (36.7)	8.6	2.5–29.0	0.0004

[a] Some placentas had multiple anomalies, LBW: low birth weight, OR: odds ratio.

Table 5
Adjusted odds ratios of causes of LBW.

Variables	OR (95%CI)	aOR (95%CI)	P value
Chronic villitis	7.2 (0.8–64.4)	35.9 (1.2–1034.3)	0.036
Infarcts	8 (2.4–25.8)	19.5 (2.9–130.1)	0.002
Pre-eclampsia/eclampsia	5.1 (0.9–26.4)	18.1 (1.0–322.5)	0.048
Primiparity	3.4 (1.2–10)	14.0 (2.1–92.7)	0.006
Number of antenatal visits <4	3.7 (1.0–13.6)	9.5 (1.3–67.5)	0.02
Reduced chorionic villous vascularization	12.4 (1.4–105.7)	1.2 (0.06–25.0)	0.89
Decidual arteriopathy	3.8 (0.9–16.0)	1.7 (0.1–21.0)	0.7

OR: odds ratio, aOR: adjusted OR.

placental lesions due to malaria which is endemic in our environment, the placental pathology might be the same as that found in developed countries, except that poor pregnancy follow up might contribute to the high frequency or to the severity of some cases of LBW in our environment.

Some placentas of the control group revealed pathological findings too. The risk for LBW increased with the number of placental lesions. This means that a single lesion might not be enough to induce intra uterine growth restriction, unless it is widely spread through the whole placenta. Since 20% of placentas of LBW in our series were without any lesion, non-placental causes of LBW should be explored when placental histology is normal. This might include some constitutional (genetic) LBWs.

The placental histopathological lesions commonly observed were placental infarction (villous necrosis secondary to local obstruction of maternal uteroplacental circulation), as observed by some authors [8–11]. This anomaly induces the reduction of the exchange surface. Consequently, nutrients and oxygen transfer to the fetus are reduced, explaining the LBW. The increased coagulable state observed during pregnancy, due to the increase in almost all coagulation factors, may lead to thrombosis in the placental vessels with placental infarction.

Chronic villitis in our series was also significantly associated with LBW. This has been found elsewhere [8–10]. Chronic villitis, or inflammation of the villi characterized by the presence of lymphocytes or plasma cells infiltration, alters the diffusion of substrate from the intervillous space into the fetal circulation. The presence of maternal macrophages in the perivillous space likely amplifies the immune response [8]. This might reduce the transfer of nutrients and oxygen to the fetus, following reduction of placental blood flow [9].

Perivillous fibrin deposition was also more frequently found in placentas of LBW neonates, as found by some authors [11], though not statistically significant in our series.

Other lesions found in placentas of LBW neonates, though with limited impact on the occurrence of LBW in our study were: reduced peripheral chorionic villous vascularization (defined as the presence of two vascular lumen or less observed in more than 10 villi per focus), obliterative fetal vasculopathy or avascular villi (defined as a fetal vascular lesion affecting the large vessel of the placenta, most of the time associated with villitis of unknown etiology), decidual arteriopathy (defined as a lesion manifested as atherosis, or macrophages lining the arteriolar intima and fibrinoid necrosis, of the decidual artery in the placental bed), placental chorangiosis (which is a placental pathology characterized by an abundance of blood vessels within the chorionic villi), placenta abruptio, microscopic chorionic cysts (defined as fluid filled spaces in the placental membranes, beneath the chorionic plate or within cell islands or septa) and placental calcifications (defined as deposition of flecks of calcium along the basal plate, the septa and occasionally in the placenta substance). These lesions could have been significantly associated with LBW if our sample size were large.

Placenta praevia, circumvallate placenta and placenta diffusa were not found in the study group. This might be due to our small sample size which constitutes the major limitation of our study. Hence, more studies with larger sample size should be carried out in our environment to confirm these findings.

LBW was significantly observed in primiparous women, in women with <4 antenatal visits and in women with pregnancy-induced hypertensive diseases. The majority of placentas of LBW neonates in our study revealed the presence of histological lesions. Significant placental causes of LBW in our study were placental infarcts and chronic villitis. We recommend that a histological examination of the placenta should always be carried out in cases of LBW, and prevention of future LBWs with aspirin must be taken in order to reduce LBW prevalence, given that this has been proven elsewhere [19].

Conflicts of interest for all authors

None.

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