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Overweight and Fasting Hyperglycemia in Children Born Preterm in a Resource-Limited Country (Cameroon)

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Abstract

Introduction: The survival of more preterm babies through improved management techniques may imply an increased risk of non-communicable diseases including obesity, diabetes and other cardiovascular risk diseases with age. The prevalence of these diseases varies worldwide. The main objective of this study was to determine the rates and factors associated with overweight and diabetes in children born preterm at the Yaoundé Gyneco-Obstetrics and Pediatrics Hospital. **Methodology**: We conducted a retrospective cohort study including children aged 6 to 11 years. Data were collected from the records of premature and full-term infants hospitalized from January 1, 2008 to December 31, 2013. Patients were evaluated during outpatient consultation, where height, weight, Body mass index and blood pressure were measured together with fasting capillary blood glucose levels. The *Fisher* test and the *Chi-square* test were used to compare proportions. Relative risk (RR) was used to establish the relationship between the different variables. **Results**: We enrolled 125 children born preterm and 250 born at full-term. The mean age was 8.2 ± 1.6 years. The cumulative incidence of pathologies varied according to type: Overweight 32% in preterm versus 13.6% in full-term ($p = 0.00002$) and 2.4% with obesity, fasting hyperglycemia 73.20% in preterm versus 48% in full-term ($p < 0.001$). No cases of diabetes were registered. No factors were significantly associated with the occurrence of these diseases in our series. However, there was a positive correlation between obesity and high blood pressure ($r = 1.14$, $p = 0.000002$). **Conclusion**: Overweight was more common in children born preterm than those born full-term. No cases of diabetes were found but there was a significant incidence of pre-diabetic state.

Keywords

Overweight, Diabetes, Prematurity, Low-Income Country

1. Introduction

Prematurity, a major public health problem is the second leading cause of neonatal mortality in developing countries. In combination with intrauterine growth retardation, prematurity is now an indicator of the general health status of newborns, and a determinant key of child survival, health and development [1]. In some Western countries, the frequency of prematurity varies from 5% to 9% [2] while in Africa, it is estimated to be above 15% [3] [4]. In Cameroon, the premature birth rate was 13% in 2010 [5]. At the Yaoundé Gynaeco-Obstetric and Paediatric Hospital in 2011, 26.5% of newborns admitted to the neonatology unit were premature [6]. The newborn, regardless of birth weight and/or gestational age, is a fragile being. This fragility increases when birth occurs before term, with the potentially serious consequences in the short, medium and long term. Advances in perinatal medicine and neonatology have improved the survival of premature infants. Despite the benefits of these advances in terms of reducing mortality, premature infants are at risk of developing chronic non-communicable diseases in the long term, including obesity and diabetes, increasing subsequent cardiovascular risk [7] [8] [9]. Diabetes in children is more frequent today around the world, due to an improvement in diagnostic techniques and an increase level of knowledge on the mechanism of the onset of this disease. Many studies demonstrated the relationship between prematurity and endocrine disorders such as obesity and diabetes [7]-[13]. The frequency of these diseases is increasing in Europe and Asia, but not systematically assessed in our context. This could explain the scarcity of data on the subject in sub-Saharan Africa in general and Cameroon in particular. The main objective of this study was to determine the factors associated with the occurrence of obesity and diabetes in premature infants. This study will provide data on the extent of the problem in our context together with the associated risk factors; in order to raise attention of health personnel to look out for these diseases during the follow up of premature infants and the early management of detected cases, thus contributing to the reduction of preventable morbidity and mortality in adulthood.

2. Materials and Methods

We conducted a historical cohort study over a 6-year period from January 2008 to December 2013; including patients aged 6 - 11 years by June 2019. Were included all newborns regardless of gender and Gestational age, admitted to the neonatal unit during the study period and discharged alive. The exposure factor considered was prematurity. Thus two groups were constituted: children born prematurely and children born at full-term and admitted immediately after their respective premature and matched for age and sex. We excluded all small for gestational age, congenital malformations and incomplete records. The minimum sample size was 122 patients, using the formula for cohort study proposed by Charan and Biswas in 2013

$$\text{Sample size} = \frac{\left[Z_{\alpha}\sqrt{\left(1+\frac{1}{m}\right)p^{*}\left(1-p^{*}\right)}+Z_{\beta}\sqrt{p_{1}\left(1-p_{1}\right)/m+p_{2}\left(1-p_{2}\right)}\right]^{2}}{\left(p_{1}-p_{2}\right)^{2}} \quad [14]$$

As part of the procedure, after obtaining the research authorizations requested from the competent authorities, we went through the neonatal admission registers where we listed the names of the patients to be included in the study. Then we searched for files and incomplete files or files that did not have a telephone number at this stage were excluded. The parents were then contacted by phone to take appointments for a consultation. After obtaining the informed consent of the parents, the consultation was done, during which parameters such as the height, weight, and abdominal circumference were taken; the right arm Blood pressure was taken after at least 5-minutes rest (three times). Concomitantly, fasting capillary blood glucose levels was performed. Patients with high blood pressure were reviewed 15 days after for re-assessment. Normal cases continued the usual follow-up according to a schedule proposed to them and pathological cases were referred to the appropriate specialist for optimal follow-up.

Diabetes was defined as a fasting capillary blood glucose > 1.26 g/l while fasting hyperglycemia was defined as fasting capillary blood glucose was between 1.1 - 1.26 g/l. Obesity was define as a BMI/age > 3z-score. We defined pre-high blood pressure as a blood pressure between 90^{th} - 95^{th} percentile of blood pressure according to the sex, height and age after three measurements. High blood pressure was defined as blood pressure greater than 95^{th} percentile.

The data were analyzed with the Epi-Info® software version 3.5.4. For the comparison of the means in the different groups, the *Annova* test was used when the distribution was symmetric and the *Kruskal Wallis* test when it was not. The relative risk (RR) with its 95% confidence interval was used to establish the strength of the association between the different variables. The *Pearson* correlation test was used to assess the positive or negative correlation between two quantitative variables. The p value was calculated by the *Fisher* test when the number of variables was less than 5 and the *Chi-square* test was used in the other cases to compare the proportions. The significance threshold was defined for $p < 0.05$.

Ethical considerations

The ethical clearances of the Institutional Ethics and Research Committee of the Faculty of Medicine of the University of Yaoundé 1 and the Gynaeco-Obstetrics and Paediatric Hospital of Yaoundé were obtained before the start of the study. The data collected were kept strictly confidential and used only for the purposes of the study.

3. Results

We enrolled 125 children born preterm and 250 term born patients matched by age and gender.

3.1. Sociodemographic Data

The mean age of premature infants was 8.2 ± 1.6 years with extremes of 6 - 11 years. There was a slight female predominance, with a sex ratio of 0.98. The exposed and non-exposed children were comparable for age ($p = 0.98$) and sex ($p = 0.6$). The mean age of the mothers was 28.38 ± 6.32 with extremes ranging from 17 to 43 years. The majority was single, primiparous and employed (Table 1).

3.2. Neonatal Profile of the Children

Most of the preterm children (60%) were born at a gestational age above 32 weeks, and 65.6% had birth weight between 1000 and 2000 g. The mean gestational age of exposed children was 33.26 ± 2.18 with extremes ranging from 28 and 36 weeks, and an average birth weight of 1940 g ± 456 (Table 2). The main

Table 1. Distribution by maternal socio-demographic data.

Variables	Preterm infants (n = 125) Number (%)	Term born (n = 250) Number (%)
Age		
<20 years	16 (12.80)	24 (9.60)
20 - 40 years	105 (84.0)	219 (87.60)
>40 years old	4 (3.20)	7 (2.80)
Marital status		
Married	50 (40.0)	97 (38.80)
Single	73 (58.40)	153 (61.20)
Divorced	2 (1.60)	0 (0)
Profession		
Employment	53 (42.40)	99 (39.60)
Unemployed	47 (37.60)	84 (33.60)
Student	25 (20.0)	67 (26.80)
Level of education		
Not in school	1 (0.80)	0 (0)
Primary school	11 (8.80)	17 (6.80)
Secondary school	69 (55.20)	126 (50.40)
Superior	44 (35.20)	107 (42.80)
Parity		
Primiparous	54 (43.20)	130 (52.0)
Pauciparous	43 (34.40)	67 (26.80)
Multiparous	28 (22.40)	53 (21.20)

Table 2. Distribution of the population by birth history.

Variables	Preterm infants (N = 125) n (%)	Term born (N = 250) n (%)
Mode of delivery		
Low track	78 (62.40)	143 (57.20)
Caesarean section	47 (37.60)	107 (42.80)
Place of delivery		
HGOPY	91 (72.80)	167 (66.80)
Other hospitals	34 (27.20)	83 (33.20)
Gestational age		
<28 *SA*	1 (0.80)	-
28 - 32 *SA*	50 (40.0)	-
>32 *SA*	74 (59.20)	250 (100)
Resuscitation at birth	29 (23.20)	46 (18.40)
Birth weight in grams		
<1000	3 (2.40)	-
1000 - 2000	82 (65.60)	-
>2000	40 (32.0)	250 (100)

problems presented by the study population were, neonatal bacterial infections (104 exposed versus 148 unexposed) and neonatal asphyxia (8 exposed versus 28 unexposed). The median length of hospitalization was 9.5 (4 - 15), with extremes ranging from 1 to 45 days. Treatment received during hospitalization was mainly antibiotics, including aminosides (99 exposed versus 129 unexposed), with a median duration of antibiotics of 8 days (3 - 10) and extremes ranging from 3 to 19 days. The mean duration of use of aminoside was 7 days. Four premature infants were transfused during the hospital stay.

3.3. The Measured Parameters

Mean height at follow-up: 136.12 cm ± 14.37 cm with extremes ranging from 108 cm to 150 cm. The children had an average weight of 33.28 Kg ± 8.28 Kg with extremes ranging from 19 to 61 Kg. The mean BMI was 17.99 Kg/m^2 ± 3.24 Kg/m^2 with extremes ranging from 10.71 to 29.59 Kg/m^2. Overweight was found in 40 (32%) children born preterm against 20 (8.0%) in children born at term. Fasting hyperglycemia was found in 91 (72.80%) preterm children against 68 (27.2%) in controls (Table 3).

3.4. Incidence of the Different Pathologies in the Two Study Populations

We found no cases of diabetes. Patients had hypertension as co-morbidity in 17.60% of cases (Table 4). Overall, these pathologies were found mainly in former premature infants.

Table 3. Parameters measured in the study.

Parameters	Preterm infants (N = 125) n (%)	Born at term (N = 250) n (%)
Abdominal Circumference		
<50 cm	2 (1.60)	12 (4.80)
≥50 cm	123 (98.40)	238 (95.20)
Fasting blood glucose		
<110 mg/dl	34 (27.20)	182 (72.80)
110- < 126 mg/dl	91 (72.80)	68 (27.20)
Systolic Blood Pressure		
<90th percentile	53 (42.40)	39 (15.60)
>90th percentile	72 (47.60)	211 (84.40)
Diastolic Blood Pressure		
<90th percentile	86 (68.80)	227 (90.80)
>90th percentile	39 (31.20)	23 (9.20)
BMI/age (Z-Score)		
>3	3 (2.40)	0 (0)
>2	37 (29.60)	20 (8.0)
Between −2 and 2	81 (64.80)	225 (90.0)
<−2	3 (3.40)	5 (2.0)
<−3	1 (0.80)	0 (0)

Table 4. Distribution of pathologies in the two groups.

	Preterm infants N = 125 n (%)	Term born N = 250 n (%)	p-Value
Fasting hyperglycemia	91 (72.80)	68 (27.20)	$p < 0.001$
Overweight	40 (32)	20 (8.0)	$p = 0.00002$
High blood pressure	22 (17.60)	5 (2.00)	$p < 0.001$

There was a strong correlation between the increase in body mass index and increase in systolic blood pressure, as well as with diastolic blood pressure with a Pearson correlation coefficient of 1.41 (Figure 1 and Figure 2).

3.5. Factors Associated with Obesity and Diabetes

The use of aminoglycosides and blood transfusion were associated with the occurrence of fasting hyperglycemia and overweight (Table 5), but did not remain statistically significant after the logistic regression. Therefore, prematurity alone could explain the high incidence of these diseases in the studied population.

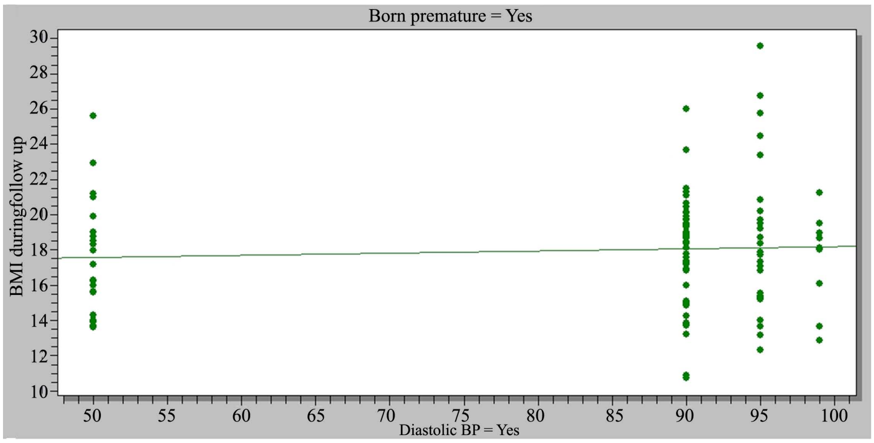

Figure 1. Correlation between BMI and diastolic Blood pressure.

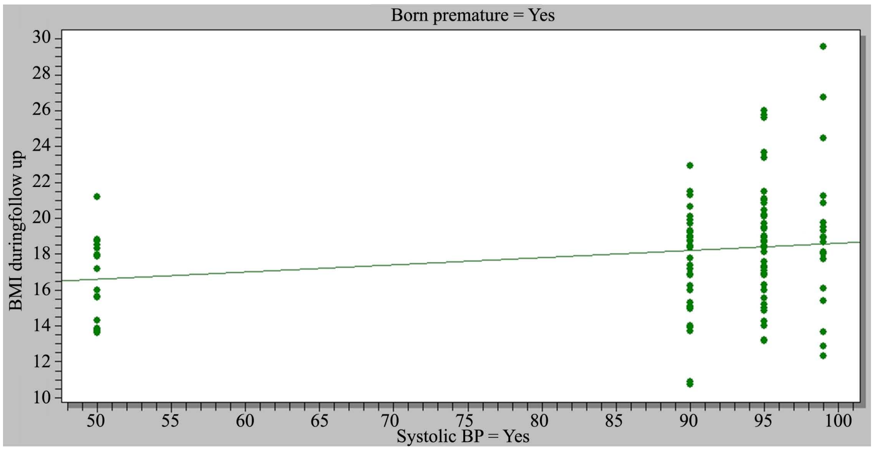

Figure 2. Correlation between BMI and systolic blood pressure.

Table 5. Treatment associated with overweight and fasting hyperglycemia.

Variables (treatment)	Preterm Infants (N = 125) Fasting hyperglycemia/overweight			Term born (N = 250) Fasting hyperglycemia/overweight		
	Yes n (%)	No n (%)	p	Yes n (%)	No n (%)	p
Aminophylline Yes/No	28 (46.7)/32 (53.3)	35 (53.8)/30 (46.2)	0.42	-	-	-
Blood Transfusion Yes/No	4 (7.7)/48 (92.3)	0 (0)/60 (100)	**0.04**	2 (1.2)/165 (98.8)	0 (0)/61 (100)	0,53
Umbilical catheter Yes/No	13 (21.7)/47 (78.3)	16 (24.6)/49 (75.4)	0.69	1 (0.5)/182 (99.5)	0 (0)/67 (100)	0.36
Oxygen Yes/No	9 (15)/51 (85)	11 (16.9)/54 (83.1)	0.76	8 (4.4)/175 (95.6)	2 (3)/65 (97)	0.62
AntiH2 Yes/No	22 (36.7)/38 (63.3)	26 (40)/39 (60)	0.7	10 (5.5)/173 (94.5)	3 (4.5)/64 (95.5)	0.52
Aminosides Yes/No	52 (86.7)/8 (13.3)	47 (72.3)/18 (27.7)	**0.04**	95 (51.9)/88 (48.1)	31 (46.3)/36 (53.7)	0.43

*Note that only the treatment received during hospitalization had some factors associated with those diseases on the bivariate analysis.

4. Discussion

Of the 125 patients enrolled in our series, 63 were female, giving a slight female predominance with a sex ratio of 0.98. The average age was 8.2 years with extremes ranging from 6 to 11 years. These findings are different from those of Kaze in Cameroon in 2017 and Grancher in France in 2014 [15] [16] who found a clear predominance of the male sex.

The mothers had an average age of 28.38 years, had mainly a secondary level of education, were mostly primiparous and single. High Blood pressure was the main maternal pathology associated with prematurity. These findings are similar to those of Grancher *et al.* in France who had also found primiparity, an average age of 29.5 years and hypertension as the main associated pathology to prematurity [16]. Bowers *et al.*, on the other hand, found that a higher level of education was associated with prematurity.

Most of the patients (60%) were born at a gestational age above 32 weeks, and 65.6% had birth weight between 1000 and 2000 g. These findings are similar to those of Grancher *et al.* in 2014 in France in terms of weight but different for gestational age. In fact they found that the majority of children in their series were born between 28 and 32 weeks of gestation. This difference could be explained by the higher mortality of premature babies born before 30 weeks of gestation in our context [6] [15].

In our series, we had no cases of diabetes. On the other hand, we had 91 (72.80%) children born preterm with fasting hyperglycemia, reflecting a pre-diabetic condition. These results are different from those of the other authors in the literature [8] [9] [10] [11] who found diabetes in their series. Crump *et al.* found that gestational age at birth was inversely associated with both type 1 and type 2 diabetes risks, and the risk increased with age. However, they stated that this association was only partially explained by shared genetic or environmental factors in families. This difference could be explained by the relatively longer time to assess the occurrence of diabetes in children born preterm, than ours. In fact, in our study we evaluated children aged 6 to 11 years old while the other studies evaluated the risk of diabetes in children aged 15 years and over. We can also justify this difference by the high morbidity and mortality of very premature babies in our context, who are also the most at risk of developing diabetes. Since the onset of diabetes is multifactorial, prematurity alone cannot explain it, but remains a clearly identified risk factor in many studies [9] [10] [11] [15] [16].

Fasting hyperglycemia in our series was influenced by blood transfusion and aminoglycoside use, but these could only be confounding factors. Prematurity alone would explain this fasting hyperglycemia. Many theories have been put forward to explain this: Preterm birth interrupts the development of pancreatic beta cells, which are formed predominantly in the third trimester of pregnancy, and might permanently reduce their number or function [17]. Other contributing factors may include exposure to antenatal corticosteroids and rapid catch-up growth in infancy, leading to visceral adiposity and insulin resistance [18].

Therefore, close monitoring of these patients must be done in order to detect and manage diabetes in a timely manner. The other authors also found that factors associated with the onset of diabetes in premature infants included low birth weight, a history of maternal and/or family diabetes, and excess postnatal growth [7] [8] [10] [11]. However, the rate of postnatal growth was not accessed in our series.

Weight gain in preterm infants is used as an indicator of growth and a criterion for hospital discharge [19]. Some studies have reported that "catch-up growth" and weight gain in preterm infants during the critical postnatal period is associated with better cognitive outcomes [20]. However, other studies have reported that nutritional supplements that accelerate catch-up growth increase the risk of future obesity and lead to metabolic syndrome [21]. Environmental influences may also lead to obesity and metabolic syndrome via epigenetic programming in preterm infants. Overweight was found in 40 (32%) children born preterm compared to 20 (8%) in the control group. Specifically, we had 37 (29.6%) cases of overweight and 3 (2.4%) cases of obesity among premature children. There was no gender difference. These findings correlate with those of the other authors [7] in the literature, including Tetyana *et al.* in 2013 in the USA, who had found an increase in the occurrence of obesity with age and prevalence ranging from 22% to 37% with age [10]. Ou-Yang *et al.* reported that preterm infants had a greater likelihood of childhood obesity than term infants. However, no difference of childhood obesity was found between "small for gestational age" (SGA) and "appropriate for gestational age" (AGA) among preterms and that accelerated weight gain also significantly increased the likelihood of subsequent childhood obesity among preterms [22]. We did not find any factors associated with obesity on prematurity in our series. Prematurity, probably eating habits and other risk factors for overweight/obesity could be associated with the occurrence of overweight found in our study. These findings are different from those found by Tetanya *et al.*, who found that preterm children born large for gestational age and increased gestational age were risk factors for later obesity [10]. Prematurity alone cannot explain the onset of obesity, which is known to be multifactorial.

We found a strong positive association between increased body mass index and high systolic blood pressure ($r = 1.14$, $p = 0.000002$), as well as a weaker association with high diastolic blood pressure ($r = 0.87$, $p = 0.001725$). These findings are similar to those of Bower *et al.* who reported that postnatal weight gain was positively associated with hypertension [23]. On the other hand Bonamy *et al.* found that high blood pressure was associated with low gestational age and high body mass index [24]. While Vashishta *et al.* found that low birth weight and young age at follow up was associated with a higher risk of systolic/diastolic blood pressure > 90th percentile [25]. Barker earlier reported that small fetuses with large placenta were are greater risk of developing high blood pressure in adulthood [26]. They further explained that such discordance could lead to circulatory adaptation in fetus, altered arterial structure in the child and hypertension in adulthood.

Limitation of the study

The major limitation of this study was the short study period. If we had had a longer period, we could have had some cases of diabetes.

5. Conclusion

Fasting hyperglycemia, which is a pre-diabetic condition, as well as overweight, was more common in children born preterm. Strict compliance with post-hospital follow-up of premature infants, as well as systematic screening by healthcare professionals is proceeded during routine monitoring of premature infants in order to detect these pathologies early and reduce avoidable morbidity in adulthood.

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Conflicts of Interest

The authors do not declare any conflict of interest in relation to this article.

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