BIRTH WEIGHT AND PONDERAL INDEX IN PRE-ECLAMPSIA: A COMPARATIVE STUDY

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SUMMARY

Objective: To evaluate the effects of early-onset and late-onset pre-eclampsia on fetal growth.

Design: Longitudinal prospective analytical survey

Setting: Obstetrics unit of Department of Obstetrics and Gynaecology in Korle Bu Teaching Hospital.

Subjects and Methods: 11,784 nulliparous women carrying singleton pregnancy were prospectively followed up based on a schedule of antenatal care from 14-16 weeks gestation till delivery. Exclusion criteria included obesity (BMI>30.0), underweight (BMI<18.5), chronic hypertension, diabetes mellitus, chronic renal disease, connective tissue diseases, hyperthyroidism, hypothyroidism, cardiac disease, HIV/AIDS, anaemia (Hb<10.0 g/dL), malaria during the index pregnancy, alcohol abuse and cigarette smoking. The selected women were observed for onset of pre-eclampsia, timing of delivery, and baby's birth weight and crown-heel length for each baby were entered into a register. The ponderal index of each baby at birth was also computed.

Results: The incidence of pre-eclampsia in the 11,784 women was 7.03%. The babies delivered by mothers who had early-onset (<37 weeks gestation) pre-elampsia, were of significantly lower birth weights (p=0.003 to p=0.02) and ponderal indices (p=0.002 to p=0.02) at all gestational ages of delivery compared with babies of mothers who did not have pre-eclampsia. However, in late-onset ($\geq$37 weeks) pre-eclampsia, the birth weights and ponderal indice at all gestational ages were comparable to non-pre-eclamptics.

Conclusion: These results support the hypothesis that pre-eclampsia is an aetiologically heterogenous disorder that occurs in at least two subsets: a late-onset pre-eclampsia with normal fetal growth denoting normal placental function and an early-onset type with fetal growth restriction implying placental dysfunction.

Keywords: Pre-eclampsia: early-onset, late-onset, birth weight, ponderal index.

INTRODUCTION

Preeclampsia remains one of the leading causes of maternal and neonatal morbidity and mortality worldwide[1,2,3,4,5]. Multiple strategies have been proposed for the prevention of pre-eclampsia with mixed results[1,6,7].

While the prevention of pre-eclampsia continues to elude us, meticulous medical management of the mother and surveillance of the fetus will contribute to an overall lowering of its contribution to perinatal and maternal morbidity and mortality.

Fetal growth restriction is closely related to perinatal morbidity and mortality[8,9]. In a normal pregnancy, the trophoblasts invade and break down the thick-walled spiral arteries so that the vessels become thin-walled and dilated at first in the decidual segment and later in the myometrium. The effect is to allow blood flow into the intervillous space to increase. Pre-eclampsia is widely known to cause fetal growth restriction[10,11]. This is believed to be due to shallow invasion by fetal trophoblasts in maternal spiral arteries in early pregnancy, which may cause occlusion of the vessels[12,13].

Clinical studies have suggested that in pre-eclampsia, fetal growth restriction often precedes the development of hypertension and proteinuria[14,15]. However, casual observation reveals that not all pre-eclamptic women deliver small babies. Some studies in Europe have shown that some cases of late-onset pre-eclampsia (at 37 or more weeks' gestation) may be associated with normal birth weight or large for gestational age babies[14,16]. Such studies are lacking in the West African subregion.

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The objective of this prospective study was to evaluate the effects of early-onset and late-onset pre-eclampsia on fetal growth.

MATERIALS AND METHOD

Nulliparous women, carrying a singleton pregnancy, were prospectively followed up based on a schedule of antenatal care from 14-16 weeks gestation till delivery during the period 1st January 1996 to 31st December 2003 at the Korle Bu Teaching Hospital, (KBTH).

At the KBTH, patients at the antenatal clinic are usually seen every four weeks till 28 weeks, then fortnightly till 36 weeks, thereafter weekly till delivery. At each visit, among other clinical assessments, the blood pressure and weight are taken and a urine sample tested for protein and glucose.

All patients in this study had ultrasound scan at the first visit (14-16 weeks) for confirmation of gestational age. All patients who developed significant medical or obstetric problems including pre-eclampsia were admitted to the wards. Those with pre-eclampsia stayed in the ward till delivery.

Immediately after delivery, the birth weight to the nearest 10g and crown-heel length to the nearest 1cm were measured by the midwife. Data on maternal age **and** attainment of formal education were also collected. The onset of pre-eclampsia, timing of delivery, baby's birth weight and crown-heel length for each patient were entered into a register.

The ponderal index [100 (weight in g)/(length in cm)^3] of each baby at birth was also computed.
Pre-eclampsia in this study is defined as increased blood pressure (hypertension) after 20 weeks' gestation with proteinuria. Preterm delivery is defined as delivery before 37 completed weeks' gestation.

Hypertension is defined as persistent and consistent increased blood pressure on at least two occasions of 140/90mmHg or higher, or increase in systolic blood pressure of at least 30mmHg and increase in diastolic blood pressure of at least 15mmHg from the woman's average levels before 20 weeks' gestation. Proteinuria is defined as excretion of 0.3g or more per day, usually equivalent to at least 1+ on a urine reagent strip testing.

Patients whose ultrasound scan dating at the first visit did not agree with the last menstrual period date were excluded from the study. Also excluded from the study were women who were obese (booking body mass index more than 30.0) or underweight (booking body mass index less than 18.5) and women with chronic hypertension, diabetes mellitus, chronic renal disease, connective tissue diseases, hyperthyroidism, hypothroidism, cardiac disease, HIV/AIDS or anaemia (Hb less than 10.0g/dL). Also excluded were women who had malaria during the index pregnancy, abused alcohol or smoked cigarettes or who attended for antenatal care at the Korle Bu Teaching Hospital, but delivered at other health facilities.

All cases of pre-eclampsia were delivered at or before 40 completed weeks' gestation. Severe pre-eclampsia is likely to result in a preterm delivery.

Pre-eclamptic babies born preterm were compared with non-pre-eclamptic babies born preterm and term pre-eclamptic babies were compared with term non-pre-eclamptic babies.

The data collected were analysed with a computer using the Epi Info version 6 software package. Categorical variables were analysed with the chi-square test, and continuous variables compared using the student's t test. A p-value of less than 0.05 was interpreted as statistically significant. The odds ratio (OR) was also estimated for association of pre-eclampsia and formal educational attainment.

RESULTS

The total number of nulliparous women carrying singleton pregnancies studied was 11,784. Of these women, 828 (7.03%) developed pre-eclampsia. Early-onset pre-eclampsia occurred in 447 cases (3.79%) and late-onset in 381 cases (3.23%).

Table 1 Maternal Age and No. of Pre-eclampsia

Age (years)	Total No	No. of early-onset pre-eclampsia (%)	No. of late-onset pre-eclampsia (%)	Total No. of pre-eclampsia (%)
< 20	2082	132 (6.34)	93 (4.47)	225 (10.81)
20-35	8961	264 (2.94)	213 (2.38)	477 (5.32)
>35	741	51 (6.86)	75 (10.12)	126(17.00)
Total	**11784**	**447 (3.79)**	**381 (3.23)**	**828 (7.03)**

The maternal age distribution is shown in Table 1. Pre-eclampsia occurred significantly more frequently in women above 35 years compared with those between 20-35 years (P=0.01), and also in those below 20 years (P=0.02). Significantly, a

greater proportion of women above 35 years developed late-onset pre-eclampsia (P=0.02). Comparing early-onset and late-onset pre-eclampsia in the various age groups (Tables 2i and 2ii) revealed that both conditions were significantly more common in the age groups less than 20 years and above 35 years than in the age group 20-35 years.

Table 2(i) Maternal age and pre-eclampsia (less than 20 years V/S 20-35years)

Age (Years)	Yes	No	Total
Panel A: Early and Late Onset Pre-eclampsia			
< 20	225	1857	2082
20-35	447	8484	8961
Total	**702**	**10341**	**11043**
OR = 2.16, 95% CI = 1.82 – 2.55			
P= 0.01			
Panel B: Early Onset Pre-eclampsia			
< 20	132	1950	2082
20-35	264	8697	8961
Total	**396**	**10647**	**11043**
OR = 2.33, 95% CI = 1.99 – 2.78			
P= 0.001			
Panel C: Late Onset Pre-eclampsia			
< 20	93	1989	2082
20-35	213	8748	8961
Total	**306**	**10737**	**11043**
OR = 1.92, 95% CI = 1.49 – 2.48			
P= 0.02			

Table 2(ii) Maternal age and pre-eclampsia (over 35years V/S 20-35years)

Age (Years)	Yes	No	Total
Panel A: Early and Late Onset Pre-Eclampsia			
>35	126	615	741
20-35	447	8484	8961
Total	**603**	**9099**	**9702**
OR = 3.64, 95% CI = 3.02 – 4.25			
P= 0.001			
Panel B: Early Onset Pre-eclampsia			
>35	51	690	741
20-35	264	8697	961
Total	315	9387	9702
OR = 2.43, 95% CI = 1.76 – 3.09			
P= 0.001			
Panel C: Late Onset Pre-Eclampsia			
>35	75	666	741
20-35	213	48	8961
Total	**288**	**9414**	**9702**
OR = 4.63, 95% CI = 4.12 – 5.14			
P= 0.0001			

Table 3 shows formal educational attainment. The number of women who had not attended school at all and developed pre-eclampsia was only 9 out of the total of 239. There was no significant difference between those who had not attained tertiary education (≤ 12 years of schooling) and those who had attained tertiary education in the occurrence of pre-eclampsia. However late-onset pre-eclampsia occurred significantly more often among those who had more than 12 years of formal education (P=0.003) as shown in Table 4.

Table 3 Formal educational attainment and number of pre-eclampsia

Educational attainment (Years)	Total No.	No. of Early Onset PE (%)	No. of Late Onset PE (%)	Total PE (%)
0	239	6(2.51)	3 (1.26)	9(3.77)
< 9	5425	234(4.31)	204 (3.76)	438(8.07)
10-12	4263	144 (3.38)	93 (2.18)	237(5.56)
> 12	1857	63 (3.39)	81 (4.36)	144(7.75)
Total	**11784**	**447(3.79)**	**381(3.79)**	**828(7.03)**

Table 4 Educational attainment and pre-eclampsia

School Years	Yes	No	Total
Panel A: Total pre-eclampsia			
≤12	684	9243	9924
> 12	144	1713	1857
Total	**828**	**10956**	**11784**
OR = 0.88, 95% CI + 0.73 1.07			
P= 0.18			
Panel B: Early onset pre-eclampsia			
≤ 12	384	9543	9927
> 12	63	1794	1857
Total	**447**	**11337**	**11784**
OR = 1.15, 95% CI = 0.87 – 1.52			
P= 0.32			
Panel C: Late onset pre-eclampsia			
≤ 12	300	9627	9927
> 12	81	1776	1857
Total	**381**	**11403**	**11784**
OR = 0.68, 95% CI = 0.53 – 0.86			
P= 0.003			

Because higher education is associated with later maternal age at the first birth, the relationship between total, early-onset and late-onset pre-eclampsia and education were examined in the age groups ≤ 35 years and > 35 years (Table 5). Early-onset pre-eclampsia occurred more significantly in those who had not had tertiary education, while the late-onset pre-eclampsia was more significant in those who had attained tertiary education. The male to female sex ratio at birth was 1:0.99, compared with a ratio of 1:0.98 in total delivery at the Korle-Bu Teaching Hospital over the same period. Women who had early-onset pre-eclampsia delivered significantly lighter babies than non pre-

eclamptics (Table 6). However, the babies of those who developed late-onset pre-eclampsia, were of comparable weight to the babies of non pre-eclamptics.

Table 5 Formal education attainment

School Years	Yes	No	Total
Panel A: Early onset pre-eclampsia (Age ≤ 35 years)			
≤ 12	349	6585	6934
> 12	47	987	1034
Total	**396**	**7572**	**7968**
OR = 1.11, 95% CI = 0.81 – 1.54			
P= 0.50			
Panel B: Early onset pre eclampsia (Age > 35 years)			
≤ 12	32	278	310
> 12	19	78	97
Total	**51**	**356**	**407**
OR = 0.47, 95% CI = 0.24 – 0.92			
P= 0.03			
Panel C Late onset pre-eclampsia (Age ≤ 35 years)			
≤ 12	249	1028	1277
> 12	57	741	798
Total	**306**	**1769**	**2075**
OR = 3.15, 95% CI = 2.30 – 4.31			
P= 0.02			
Panel D Late onset pre-eclampsia (Age > 35 years)			
≤ 12	59	208	267
> 12	16	51	67
Total	**75**	**259**	**334**
OR = 0.90, 95% CI = 0.46 – 1.79			
P= 0.47			

Table 6 Mean birthweight of babies

G A (Weeks) at De-livery	Non-Pre-eclamptics N	BWgt	Early onset Pre-eclampsia N	BWgt	Late onset Pre-eclampsia N	BWgt
30 - 32	156	1548	30	1012* (p=0.02)		
33 - 36	2637	2317	358	1672 (p=0.002)		
37 - 40	8991	3296	59	2115 (p=0.003)	381	3447 p=0.06)

G A = Gestational Age BW = Birthweight
*By definition No. woman with late-onset pre-eclampsia delivered before 37 completed weeks

The mean ponderal indices of the babies at each gestational age of delivery are shown in Table 7. The mean ponderal indices of the babies delivered by women who had early-onset pre-eclampsia were significantly lower than the babies of non-pre-eclamptic mothers at each gestational age. The babies of late-onset pre-eclampsia mothers had slightly higher ponderal index compared to those of non-pre-eclamptics.

Table 7 Mean ponderal index of babies

G A (weeks) at de-livery	Non-Preeclampsia N	Ponderal Index	Early-Onset Preeclampsia N	Ponderal Index	Late-Onset Preeclampsia N	Ponderal Index
30-32	156	2.55	30 (P=0.002)	1.79		
33-36	2637	2.81	358 (P=0.02)	2.21		
37-40	8991	3.02	59 (P=0.002)	2.29	381 (P=0.48)	3.07

DISCUSSION

The incidence of 7.03% of preeclampsia in this study is comparable with the commonly cited incidence of 5-10%[17,18,19,20]. There was no significant difference between the incidence of early-onset preeclampsia (3.79%) and late-onset preeclampsia (3.23%) in this study. This is quite different from a Norwegian study which revealed an incidence of 0.5% for early-onset preeclampsia as against 3.3% for late-onset preeclampsia[19].

Nulliparous women more than 35 years of age or less than 20 years were significantly more likely to develop preeclampsia than those between 20-35 years old. This finding is in agreement with other studies which showed a 2-9 fold increase in the incidence of preeclampsia in nulliparae over 40 years and a 2-3 fold increased incidence in those less than 20 years compared with the 20-40 years age group[20,21,22].

Socio-economically advantaged women have been shown to have a lower incidence of preeclampsia, even after racial factors are controlled[23], although another study found the converse to be true[24]. In this study, it was only the incidence of late-onset preeclampsia that was significantly higher among women who had attained tertiary formal education than in women who had not gone beyond the secondary level.

Many factors that influence birth weight like multiple pregnancies, maternal obesity and under weight, intercurrent chronic medical conditions in

pregnancy, anaemia, cigarette smoking, alcohol and other substance abuse were excluded in this study.

Although male babies tend to be slightly heavier at birth than females[25], a separate analysis was not done on the basis of sex in this study because the number of male babies was about the same as that of females.

The mean birth weight and the ponderal indices of babies delivered by mothers who had early-onset pre-eclampsia were lower than those of non-pre-eclamptics across all gestational ages. These findings agree with other studies[10,11,14,16] and support the hypothesis of placental hypoperfusion caused by shallow invasion of fetal trophoblast in early pregnancy leading to fetal growth restriction in preeclampsia[15,26,27].

Nulliparous women who developed late-onset pre-eclampsia delivered babies whose birth weights were comparable to or higher than those of non-pre-eclamptics. The ponderal indices of the babies of women who developed late-onset pre-eclampsia were also similar to those of non-pre-eclampsitics. Consistent with this study, recent evidence indicates that in most cases of late-onset pre-eclampsia, the newborn has normal weight[16,19] and more infants than expected are large for gestational age[14].

Thus our results do not support the widely accepted hypothesis that placental dysfunction is necessary in the development of pre-eclampsia. It is generally believed that pre-eclampsia may be caused by products released by the ischaemic placenta: the products, in turn, cause endothelial activation, which results in hypertension and proteinuria[28].

Decreased perfusion of the feto-placental unit would decrease fetal size, even before the appearance of the defining criteria of pre-eclampsia (hypertension and proteinuria)[10,15].

Our finding of excess of large neonates in late-onset pre-eclampsia rather suggests that placental dysfunction is absent or plays only a minor role in late-onset pre-eclamptic pregnancies. The excess of large for gestational age infants in this study could be explained by the demonstration of increased cardiac output in late-onset pre-eclamptic pregnancies[29].

CONCLUSION

These results suggest that preeclampsia is an aetiologically heterogenous disorder, that occurs in at least two subsets, one of late-onset with normal fetal growth (normal placental function) and another of early-onset with fetal growth restriction (placental dysfunction).This being the case, it is unlikely that a single treatment or preventive measure would be effective for both. It is therefore important to study the two subtypes separately to examine whether the subsets differ in severity or have different risk determinants.

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