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## Comparing neonatal outcomes in women with preeclampsia and those with normal pregnancy

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**Abstract:** *Background:* Preeclampsia has remained an important public health problem in the developing world where it is associated with a five-fold increase in perinatal morbidity and mortality.

*Objective:* We set out to compare neonatal outcomes between women with preeclampsia and those with normal pregnancy. We also sought to evaluate factors associated with poor outcome in the neonates.

*Materials and Methods:* This was a prospective cohort study that enrolled 90 women (45 with preeclampsia and 45 with normal pregnancy) after 20 weeks gestation. Maternal socio-demographic and clinical information was obtained at enrolment and delivery using questionnaire. Neonatal anthropometric and physiologic data was obtained at delivery and used for classifying the birth weight according to the WHO classification. APGAR score was used to evaluate the presence of birth asphyxia. We defined poor outcome as the presence of at least one of low birth weight, prematurity, birth asphyxia and need for admission. SPSS version 25 was used in all analysis. Significance testing was set at  $p=0.05$ .

*Results:* The women with preeclampsia were significantly heavier at booking (BMI  $29.0 \pm 6.9$  Kg/

$m^2$  vs  $25.0 \pm 5.2$ ,  $p=0.005$ ), have higher mean booking systolic blood pressure ( $122. \pm 22.6$  mmHg vs  $111.5 \pm 12.7$  mmHg,  $p=0.003$ ) and diastolic blood pressure ( $79.8 \pm 14.3$  mmHg vs  $68.8 \pm 9.0$  mmHg,  $p<0.001$ ). Neonates of women with preeclampsia were significantly more premature (mean gestational age =  $36.8 \pm 3.2$  weeks vs  $38.7 \pm 2.0$  weeks,  $p=0.001$ ) and lighter (mean birth weight =  $2,529 \pm 817.5$ g vs  $3,079.2 \pm 527.4$ g,  $p<0.001$ ).

Overall, 22 (49.4%) of the neonates of women with preeclampsia had significantly poor outcome compared with 12 (27.4%) of the neonates of women with normal pregnancy ( $p=0.01$ ). Univariate logistic analysis showed only being a male neonate, maternal preeclampsia and admission in index pregnancy were significantly associated with poor outcome. Multivariable logistic regression showed only being a male neonate to be 3 times more likely to have a poor outcome (Wald=5.34. OR=3.2,  $p=0.02$ ).

*Conclusions:* Intrauterine exposure to preeclampsia is associated with poor neonatal outcomes especially in males

**Key words:** infant outcome, preeclampsia, Nigeria

## Introduction

Preeclampsia/eclampsia (PE/E) has remained a significant public health problem in Nigeria and the developing world where it is said to complicate about 2-10% of all pregnancies resulting in a five-fold increase in perinatal morbidity and mortality.<sup>1</sup> PE is a pregnancy-specific disorder characterized by hypertension, significant proteinuria, with or without edema.<sup>2-5</sup> Because of its unpredictability, varying clinical presentations and potential infant adverse outcomes, pregnant women with confirmed preeclampsia require intensive monitoring or hospitalization.<sup>3-5</sup>

Global estimates have shown that about 25% of the babies born to mothers with pre-eclampsia are growth restricted while a further third are likely to be born premature.<sup>2, 4-7</sup> In addition, pre-eclampsia is said to be responsible for every 1 in 4 infant deaths especially early newborn deaths.<sup>8,9</sup> PE is associated with poor infant outcomes.<sup>8,9</sup> Low birth weight, prematurity and severe birth asphyxia are some of the most prevalent problems associated with poor outcomes in these infants.<sup>8,9</sup>

The recent review of the millennium development goals (MDGs) where Nigeria was unable to attain the health related goals creates a justification for us to revisit our obstetric and neonatal practices both of which were the significant contributors to the failure of lack of progress towards addressing the high childhood and maternal mortality rates in the country.<sup>10,11</sup> Preeclampsia is a significant contributor to Nigerian's high infant and maternal mortality as well as the failure to attain the MDGs.<sup>10,11</sup> This study sought to investigate those maternal socio-demographic and clinical factors that may predict neonatal outcomes following preeclampsia in order to help change the approach to management of preeclampsia through early diagnosis and management.

We thus hypothesized that maternal socio-demographic and clinical parameters significantly influence neonatal outcome in women with preeclampsia/eclampsia. Our specific aim was first to determine neonatal outcomes in women with PE/E. Secondly, we sought to determine which maternal factors were significantly associated with poor neonatal outcome in PE/E.

## Materials and methods

### Study setting

This study was conducted between April 2017 and May 2018. We recruited participants from the 4 tertiary health facilities in Jos, capital of Plateau state namely; Jos University Teaching Hospital (JUTH), Plateau Specialist Hospital (PSSH), Bingham University Teaching Hospital (BhUTH) and Our Lady of Apostle (OLA) Hospital. These hospitals were chosen because of the availability of specialist obstetric care services. Altogether, these hospitals have an annual delivery rate of about 14,000 babies with deliveries for preeclampsia/eclampsia, accounting for about 5% of this total annual deliveries.

### Study population

This study was carried out between April 2017 and May 2018 as part of the infant outcomes study on women with preeclampsia in Jos. All the women were recruited antenatally and followed up to delivery. At delivery, all the infants had anthropometry and echocardiography done. Our sample size was 90: 45 newborns of mothers with PE/E and 45 controls matched for sex. Sample size was determined using Open Epi version 3.03a. A minimum sample size of 80 based on the estimated effect size of 20%, a power of 80% and an  $\alpha$  level of 0.05 was reached. However, 90 women (45 in each arm) were eventually enrolled and studied to account for attrition being a cohort study.<sup>12</sup> We excluded women with chronic disorders like diabetes, HIV and Sickle cell anemia in the control and exposure groups in order to avoid confounding. Ethical approval was obtained from each of the participating hospitals before commencement of the study. Written informed consent was obtained from the newborn's mothers or fathers before recruiting the newborns.

### Definition of term

Preeclampsia was defined as systolic blood pressure  $\geq$  140 mmHg or diastolic pressure  $\geq$  90 mmHg, (or increases of 30 mmHg systolic or 15 mmHg diastolic from the baseline) on at least two occasions six or more hours apart and associated proteinuria that develops from the 20<sup>th</sup> gestational week in a previously normotensive woman.

### Study design

This was a prospective cohort study comparing a sample of women with a diagnosis of pre-eclampsia/eclampsia with normotensive women for the assessment of their fetal and infant outcome.

### Study procedure

- 1. Maternal recruitment process:** At baseline, women who came for antenatal and also had a diagnosis of preeclampsia or eclampsia based on our definition as stated above were invited to participate. Those who agreed and gave informed consent were then recruited into the study. At the same time, a near age and ethnic matched woman with normal pregnancy was recruited as control for each woman recruited with PE/E. Both groups were followed up to delivery and their newborns assessed and compared. However, one woman recruited as control developed preeclampsia 4 weeks into follow up but was replaced with another control.
- 2. Maternal assessment:** Each woman who consented to the study was enrolled after obtaining an informed consent. An interviewer-administered questionnaire was used to obtain socio-demographic and relevant clinical history. In addition, standard method/protocol for weight and height (and length in case of newborn) measurements was used to obtain baseline anthropometric parameters of both

mothers and newborns<sup>13</sup> Blood pressure was measured using the JNC 7 protocol after which a unique identification number was given to each woman for ease of identification during follow up.<sup>14</sup> Clinical review of each participating pregnant woman was done at her regular antenatal visits until delivery of the baby.

3. **Neonatal assessment:** At delivery, basic anthropometric data (such as weight, length, head circumference and thoracic circumference) and physiologic parameters (eg APGAR scores) were obtained from the baby using standard methods/protocols. The newborn anthropometric measurement was then used in classifying the birth weight according to the WHO classification while APGAR score was used to evaluate the presence of birth asphyxia.<sup>15,16</sup>

#### Study outcomes

The primary outcome of interest is the presence of any adverse neonatal/infant event. This is defined as one or a combination of the following:

1. Birth asphyxia
2. Need for admission to the special care unit
3. Prematurity (a baby born before 37 completed weeks)
4. Low birth weight (baby weighing less than 2500gm).

The secondary outcome of interest is death occurring in the first 28 days of life.

#### Ethical consideration

Ethical clearance was obtained from the research and ethics committee of the Jos University Teaching Hospital and other participating hospitals (BhUTH, PSSH and OLA Hospital) before the commencement of the study.

#### Statistical analysis

Statistical analysis was done using SPSS version 25.<sup>17</sup> Mean differences in maternal age, booking weight and parity as well as infant weight and gestational age were compared between babies born following preeclamptic pregnancy and those born following normal pregnancy using a t-test. Difference in proportion of the newborns by sex as well as maternal education, fever in pregnancy, alcohol use and contraceptive use was done using 2 by 2 table cross tabulations. Spectrum of CHD was depicted using bar charts and a frequency table. Univariate analysis was done to evaluate the relationship of each of the maternal and newborn variables with newborn adverse outcome. Those that were found to be significant were then included in the multivariable logistic regression analysis to determine the predictors of poor outcome. The criterion for significance for all analyses was set at a P-value of < 0.05.

## Results

### Descriptive characteristics

Table 1 shows the maternal descriptive characteristics. There was no significant difference in age between women with preeclampsia and those with normal pregnancy (31.1± 6.3 years vs 29.3± 5.6 years; p=0.17). The women with preeclampsia were significantly heavier at baseline compared with women with normal pregnancy (mean BMI 29.0±6.9 vs 25.0±5.0; p=0.005). Mean gestational age at booking was not significantly different between the two groups (Preeclampsia= 22.0±6.3 vs Normal pregnancy=24.0±6.3; p=0.08). Mean systolic blood pressure at antenatal booking was significantly higher in women with preeclampsia compared with women without preeclampsia (122.7±22.6 mmHg vs 111.3±12.7 mmHg, p=0.03). Similarly, mean diastolic blood pressure at antenatal booking was significantly higher in women with preeclampsia compared with women without preeclampsia (79.6±14.3 mmHg vs 68.8±9 mmHg, p<0.001

**Table 1:** Maternal descriptive characteristics

Studied variable	Preeclampsia	Normal pregnancy	P value
Mean Maternal age	31.1±6.3years	29.3±5.6year	0.17
Booking BMI (Kg/m2)	29.0±6.9	25.0±5.0	0.005
Mean Weight change in pregnancy(Kg)	6.8±5.6	5.7±5.1	0.40
Mean Booking GA (Weeks)	22.0±7.3	24.9±6.3	0.08
Mean SBP at enrolment (mmHg)	122.7±22.6	111.5±12.7	0.03
Mean DBP at enrolment (mmHg)	79.6±14.3	68.8±9.0	<0.001
Mean Booking PCV (%)	34.5±4.5	35.1±3.2	0.08

### Mean neonatal studied variables

Mean infant gestational age at birth was 36.8±3.3 weeks in infants born following preeclampsia compared with 38.6±1.5 weeks in infants born following normal pregnancy (p=0.004). The infants born following preeclampsia were significantly lighter in weight compared with those born following normal pregnancy (2508.0±819 grams vs 3015.6±589grams, p=0.004). Infants born following preeclampsia had a significantly shorter mean birth length compared with those born following normal pregnancy (45.7±6.7 cm vs 56.1±1.4 cm, p=0.04). The mean 5<sup>th</sup> minute APGAR score was significantly lower in infants born following preeclampsia compared with those born following normal pregnancy (7.8±3.9 vs 8.7±1.4, p=0.01).

### Incidence of adverse outcomes

As shown in table 3, prematurity was observed in 18 (40.0%) of newborns born following preeclampsia compared with 5(11.1%) of newborns born following normal

pregnancy ( $p=0.02$ ). Low birth weight was observed in 19 (42.2%) of newborns born following preeclampsia compared with 5 (11.1%) of newborns born following normal pregnancy ( $p<0.001$ ). Fifteen (33.3%) of newborns born following preeclampsia needed admission in the neonatal unit compared with 5(11.1%) of infants born following normal pregnancy ( $p=0.01$ ). One (2.2%) of the infants born following preeclampsia had severe birth asphyxia compared with none of those born following normal pregnancy ( $p=0.01$ ). Neonatal death was observed in 6(13.3%) of infants born following preeclampsia compared with none in those born following normal pregnancy ( $p<0.001$ ). Overall, 22(48.9%) of infants born following preeclampsia had poor outcome compared with 12(26.7%) of those born following normal pregnancy ( $p=0.01$ ).

**Table 2: Mean of Neonatal Variables Studied**

Variable	PE/E	Control	p
Gestational Age (weeks)	36.8±3.3	38.6±1.5	0.004
Birth weight (kg)	2508.0±819	3015.4±559	0.004
Birth Length (cm)	45.7±6.2	56.1±3.0	0.04
Mean APGAR (1 <sup>st</sup> min)	6.6±2.1	8.61±1.9	0.16
Mean APGAR (5 <sup>th</sup> min)	7.8±3.9	8.7±1.4	0.01

**Table 3: Incidence of adverse outcomes**

Variable	Preeclampsia Freq (%)	Normal Pregnancy Freq (%)	P value
Prematurity	18(40.0)	5(11.1)	0.02
Low birth weight	19(42.2)	5(11.1)	<0.001
Need for admission	15(33.3)	5(11.1)	0.01
Severe Asphyxia	1(2.2)	0(0.0)	0.001
Neonatal deaths	6(13.3)	0(0.0)	<0.001
Poor outcome (Composite)	22(48.9)	12(26.7)	0.01

#### Predictors of adverse outcomes

Table 4 shows logistic regression coefficients of variables predicting poor outcomes. Being the newborn of a woman with preeclampsia was associated with a 4-fold increased likelihood of having poor infant outcome (OR=4.2, 95%CI=1.6-11.2). Being a male infant was associated with 3-fold increased likelihood of having poor infant outcome (OR=3.2, 95%CI=1.2-8.5) although this did not reach statistical significance.

**Table 4: Predictors of Poor Neonatal Outcomes**

Predictor variable	B	SE	Wald	OR	P value
Male sex	1.16	0.50	5.34	3.2	0.02
Preeclampsia	1.43	0.50	8.13	4.2	0.04
Maternal illness	0.51	0.71	0.53	1.67	0.47

## Discussion

In this study, we found women with preeclampsia to be slightly older though not significantly so compared with those women who had normal pregnancy. We found no significant difference in the gestational age at which the women booked their index pregnancy. However, the women with preeclampsia were significantly heavier and have higher systolic and diastolic blood pressures at booking. This is similar to what Roberts et al<sup>18</sup> reported in their multi-country study that looked at trends in the socio-demographic and clinical characteristics of women with preeclampsia and hypertension in pregnancy across Sweden, Canada, United States, Denmark, Norway and Scotland.<sup>18</sup> Advanced maternal age especially at first pregnancy has been shown to increase the risk of preeclampsia. This risk is also said to be increased in the presence of maternal obesity and overweight.<sup>19</sup> The precise mechanism for this is not very clear but theories around increased tendency towards inflammation and immune dysregulation with resultant aging of the uterine blood vessels might be prospective explanations for this heightened risk.<sup>20,21</sup>

We also found the neonates born following preeclampsia to have a significantly lower mean APGAR scores especially in the first minute. Neonates of women with preeclampsia were found with significantly lower first minute APGAR scores pointing to some possible intrauterine fetal distress.<sup>20,21</sup> First minute APGAR scores usually indicate need for resuscitation. When considering the neonatal outcomes measures, we found neonates of women with preeclampsia to have a significantly higher incidence of prematurity and low birth weight. In addition, early neonatal deaths was seen in about 6(13.3%) of those neonates (all of whom were neonates of women with preeclampsia). One of these early neonatal deaths was in a neonate with severe birth asphyxia. Pregnancy induced hypertension just like chronic hypertension has been associated with impaired fetal growth with resultant low birth weight and its associated complications.<sup>22</sup> Low birth is an important sequel of preeclampsia because of the occurrence of fetal under-nutrition as a result of utero-placental vascular insufficiency, which results in growth retardation leading to various degrees of fetal morbidity such as prematurity and mortality.<sup>21,23</sup> It is thus not surprising to see these neonates having increased incidence of low birth weight, prematurity and birth asphyxia.

Overall, those neonates born following preeclampsia have poorer outcome when the composite of prematurity, low birth weight, birth asphyxia and need for admission into the NICU were considered. In addition, frequency of admission into the neonatal intensive care unit was significantly higher in those born following preeclampsia compared with their counterparts born following normal pregnancy. Preeclampsia was the main predictor of poor outcome in this cohort of neonates with male sex also increasing the odds of having poor outcome.

### Strength of the study

The strength of this study lies in its longitudinal design, the multicenter nature of the study as well as the comparison of the outcomes with neonates of women with normal pregnancy. The use of standard definitions and study protocols in each of the recruiting hospitals help to make the data more uniform thus reducing measurement bias and confounding.

### Limitations

Being a pilot study with a small sample size, firm conclusions cannot be made even though the power and sample size used was appropriately calculated. However, the findings here make a good reference point for future large size population-based studies.

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### Conclusions

Maternal preeclampsia/eclampsia has a significant effect on infant outcomes especially the incidence of low birth weight and prematurity. Male neonates are at greatest risk of poor outcome.

Thus, the association of preeclampsia with adverse fetal outcome, increased perinatal morbidity and mortality calls for a more concerted effort towards collaborative care rather than the current practice employed by single specialty obstetric care.

### Future directions

A large-scale community-based study is being planned to further evaluate these hypotheses as a way of furthering our understanding and thus improve care for neonates of preeclamptic pregnancies

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