Original Article

Comparison of Outcomes in Early and Late-Onset Preeclampsia in Two District Hospitals in Abuja

Faith U. Otalike[1], Joseph A.M. Otubu[2], Fidelis S. Bakut[1]

[1]Department of Obstetrics and Gynecology, Garki Hospital, Abuja
[2]Center for Reproductive Health Research, Abuja

ABSTRACT

Introduction: Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality. Early and late-onset preeclampsia represents two distinct phenotypes having specific pathophysiology and differing clinical outcomes. Early onset preeclampsia (EOPE) is known for its life-threatening manifestations. Late-onset preeclampsia (LOPE) is more prevalent in developing countries and evolving research has revealed its association with worse outcomes. This study aimed at comparing outcomes in EOPE and LOPE in two district hospitals in Abuja. **Materials and methods:** A prospective cohort study involving 120 women diagnosed with preeclampsia using the revised International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria. Participants were stratified into EOPE and LOPE depending on gestational age at diagnosis. Maternal and perinatal outcomes were noted throughout pregnancy, delivery and during the immediate post-partum period. **Results:** Maternal outcomes such as progression to severe hypertension, eclampsia, abruptio placentae, acute kidney injury and mode of delivery were comparable in EOPE and LOPE ($P>0.05$). There was a statistically significant risk for stillbirth, low APGAR score, neonatal admission, preterm complications, and overall perinatal mortality in EOPE while the risk for small for gestational age infants was higher in LOPE ($P<0.05$). The case fatality rate was 1.7%. **Conclusion**: Preeclampsia, irrespective of its time of onset, portends adverse maternal and perinatal complications. Its diagnosis at any time should prompt heightened surveillance and timely institution of management to optimize outcomes.

Keywords: Outcomes, early onset, late onset, preeclampsia, ISSHP

Corresponding Author:

Faith U. Otalike
Department of Obstetrics and Gynecology,
Area 3, Tafawa Balewa way
Garki, Abuja
Nigeria
Email:
faithemagboron@gmail.com
Tel: +2348065968517

INTRODUCTION

Globally, preeclampsia is a major contributor to maternal and perinatal morbidity and mortality.[1] It is estimated to complicate 2% to 10% of pregnancies accounting for over 70,000 maternal deaths and over half a million fetal and neonatal deaths annually.[1-4]The International Society for the Study of hypertension in Pregnancy (ISSHP) in 2014 defined preeclampsia as systolic blood pressure at greater than or equal to 140mmHg and/or diastolic blood pressure greater than or equal to 90 mmHg on at least two occasions measured four hours apart in

previously normotensive women accompanied by one or more new-onset conditions at or after 20 weeks' gestation. These conditions include proteinuria, evidence of maternal organ dysfunction or uteroplacental dysfunction.[5] In the past, proteinuria was a *sine qua non*-condition in characterising preeclampsia but has been removed in recent guidelines. [4,5]

Preeclampsia has two distinct phenotypes; early onset preeclampsia which occurs before 34 weeks' gestation and late-onset preeclampsia at or after 34 weeks.[6,7] EOPE is believed to be due to defective trophoblastic invasion in pregnancy while LOPE is as a result of maternal predisposition to inflammation or vascular problems.[8,9,10] This distinction is a better indicator of disease significance, is relevant for research and has been embraced in the recent recommendations by ISSHP.[4,5,8] Literature is replete with documented adverse outcomes often credited to EOPE.[6,8,11,12]. On the other hand, LOPE prevails in developing countries and emerging literature has revealed that it is not completely benign, being associated with poor clinical outcomes[7,13–16]. This lends clinical relevance, especially in low-resource settings. [2,7] In Nigeria, where preeclampsia ranks amongst the top three leading causes of maternal and perinatal morbidity and mortality, [17–21] there is a dearth of information on early and late-onset preeclampsia and clinical outcomes. The study was carried out to compare maternal and perinatal outcomes in EOPE and LOPE contribute to prior existing knowledge on this subject.

MATERIALS AND METHODS

Study area

The study was conducted among pregnant women who accessed care in two district hospitals within the Federal Capital Territory (FCT). The FCT is in the North central geo-political region of Nigeria, occupying a land area of 7,315 square kilometers with a population of 1,406,239 of which 673,067 are females.[22] Abuja falls within latitude 8.25^0 and 9.2^0 north of the equator and longitude 6.45^0 and 7.35^0 east of the Greenwich meridian. The FCT has ten district hospitals that offer secondary health care services. The study was carried out in Nyanya General Hospital, located on the outskirts of Abuja and Garki Hospital which is in the city Centre.

Study design

The study was a prospective cohort study carried out from April 2020 to September 2020. The inclusion criteria comprised consenting pregnant women who were sure of their last menstrual period or had done an early ultrasound scan. Women who had preexisting diabetes, hypertension, renal or liver disease, seizure disorder, multiple pregnancies and autoimmune disorders were excluded.

Sample size determination

The sample size was determined using the formula for cohort studies:[23]

$$n = \frac{\{Z\alpha \sqrt{(1 + 1/m)\, p^* (1-p^*)} + Z\beta\sqrt{p1\,(1-p1)/m + p2\,(1-p2)}\}^2}{(p1 - p2)^2}$$

where n was the desired sample size, Zα standard normal deviate corresponded to a 95% confidence level, Zβ was the standard normal deviate for the power of the study at 80%, p1 and p2 were the estimated proportion of outcomes for EOPE and LOPE from a previous Nigerian study [24] (at 52.2% and 32.5% respectively). To accommodate for ten percent attrition rate, a total of one hundred and twenty subjects were recruited.

Data collection

The antenatal clinic and wards, labour wards, and accident and emergency units of the hospitals were the portals of recruitment of potential participants who accessed care before 20 weeks' gestation. The blood pressure, weight, height, and dipstick urinalysis were recorded at the initial visit. In subsequent visits, at blood pressure values at or above 140/90mmHg, history was taken for symptoms suggestive of preeclampsia and an examination was carried out. The blood pressure was also re-checked, and dipstick urinalysis reviewed. If the repeated blood pressure remained elevated, other tests were requested including a full blood count, liver enzymes, serum electrolytes and creatinine. The participants were recruited into the study only after the diagnosis of preeclampsia had been made using the revised ISSHP criteria.[4] The aim of the study was explained and consent was

confirmed following which a pretested semi-structured questionnaire was completed with sections; section A for socio-demographic data, B for obstetric and relevant medical history and C for maternal and perinatal outcomes.

Participants were enrolled into EOPE or LOPE category using 34 weeks' gestation as the cut-off and were followed up for maternal and perinatal outcomes in the antepartum, intrapartum and up to a week post postpartum. Maternal outcomes of interest were progression to severe hypertension, eclampsia, acute kidney injury, abruptio placentae, mode of delivery and maternal mortality. Perinatal outcomes assessed were stillbirth, APGAR scores at birth, birth weight at delivery, neonatal intensive care unit (NICU) admission, complications of prematurity (respiratory distress syndrome, neonatal sepsis, neonatal jaundice) and perinatal mortality. Birth weights of the neonates were measured with the electronic Seca model 724 weighing scale and a neonatal anthropometric chart developed for Nigerian infants was employed to identify small for gestational age neonates.[27] The APGAR scores were interpreted using labour ward standard protocols.

Blood pressure determination

Blood pressure was obtained with the patient seated, legs uncrossed and with her back supported. The arm was supported on an armrest and at the level of the right atrium. Measurement was with an appropriately sized cuff, whose length is 1.5 times the upper arm circumference. Blood pressure was taken manually using the mercury sphygmomanometer (Accoson, England) and measured values were documented in mmHg with the first audible sound (Korotkoff I) the systolic pressure and the disappearance of sound (Korotkoff V) as the diastolic pressure. However, Korotkoff IV (abrupt muffling) was used if sounds remained audible on deflation.

Procedure for dipstick urinalysis

Random spot samples were taken after instructing participants on clean catch midstream urine collection. This involved cleaning the vulva with clean water. While standing astride, the participant parted the labia. An initial first stream of urine passed into the toilet, following which 10- 15 mls of mid-stream urine was allowed to drip into an already labelled wide-mouthed urine bottle. The urinary dipstick strip (combistik 10® by Dream Future Innovation, Korea) was immersed completely in the sample of urine for a short period and then extracted. The strip was left to stand for a few seconds and the result was deduced based on the concentration of protein detected by pluses. Two plus on dipstick urinalysis was considered significant.

Data analysis

The findings were analyzed using IBM Statistical Package for Social Sciences version 23.0 for windows. Categorical variables were summarized using frequencies and percentages, while the mean and standard deviation was used for continuous variables. Statistical significance was set at $P<0.05$.

RESULTS

There were 1309 deliveries during the period of study. A hundred and twenty women were diagnosed with preeclampsia using the ISSHP criteria of which, LOPE accounted for 70% (84) compared to 30% (36) who had EOPE. This is depicted in Figure 5.1.

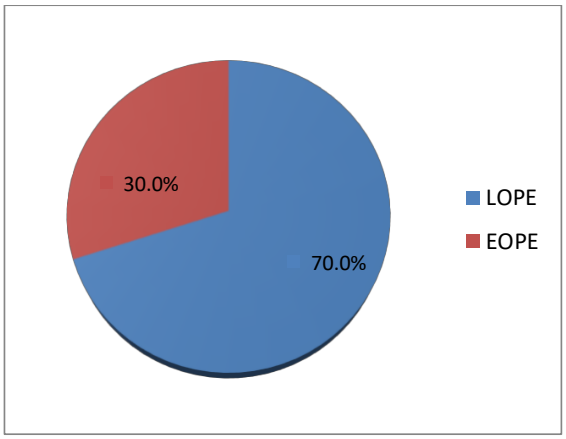

Figure 1: Pie chart illustrating the proportion of women with early (EOPE) and late onset (LOPE) preeclampsia

Maternal and perinatal outcomes of early and late-onset preeclampsia were compared in Table 5.1. Maternal outcomes were progression to severe hypertension, eclampsia, abruptio placentae, acute kidney injury and mode of delivery. These were similar in both groups. Additionally, maternal mortality did not differ between EOPE and LOPE *(P>0.05)*. Perinatal outcomes were stillbirth, APGAR score at 5 minutes, birth weight at delivery, NICU admissions and prematurity complications. Compared to late-onset preeclampsia, neonates delivered to mothers who had early-onset

preeclampsia had poorer 5-minute APGAR scores and NICU admissions. Perinatal mortality was also significant *(P<0.05)* in these neonates. Maternal and perinatal outcomes were compared with the gestational age range in Table 2.

Table 1: Maternal/Perinatal outcomes of EOPE and LOPE patients

	EOPE (*N*=36) (%)	**LOPE (*N*=84) (%)**	***P* value (χ^2)**
Maternal outcomes:			
Progression to severe HTN	30 (83.3)	74 (88.1)	0.332
Eclampsia	5 (13.9)	6 (7.1)	0.187
Abruptio placenta	4 (11.1)	11 (13.1)	0.512
Acute kidney Injury	2 (5.6)	1 (1.2)	0.214
Mode of delivery:			
VD	14 (38.9)	28 (33.3)	0.559
Caesarean Section	22 (61.1)	56 (66.7)	0.177
Maternal mortality	1 (2.8)	1 (1.2)	0.512
Perinatal Outcomes:			
Stillbirth	15 (41.7)	6 (7.1)	0.001
APGAR score at 5min <7	6 (16.7)	5 (6.0)	0.010
Birth Weight: SGA	4 (11.1)	16 (19.0)	0.007
NICU admission	21 (61.1)	34 (40.5)	0.030
Prematurity complications:			
Respiratory distress	12 (33.3)	20 (23.8)	0.195
Neonatal Jaundice	13 (36.1)	10 (11.9)	0.002
Neonatal sepsis	10 (27.5)	6 (7.1)	0.004
Perinatal mortality	17 (47.2)	8 (9.5)	0.001

Abbreviations: SGA- Small for gestational age, HTN-Hypertension, VD-Vaginal delivery

Table 2: Maternal/perinatal outcomes of EOPE and LOPE patients by gestational age at diagnosis

	Gestational age (weeks)				***P* value**
	G1 *N*=4 (%)	**G2 *N*=32 (%)**	**G3 *N*=27 (%)**	**G4 *N*=57 (%)**	
Maternal outcomes:					
Progression to severe HTN	4 (3.8)	26 (25.0)	23 (22.2)	51 (49.0)	0.600
Eclampsia,	0 (0.0)	5 (45.4)	4 (36.4)	2 (18.2)	0.148
Abruptio placentae	1 (6.7)	3 (20.0)	6 (40.0)	5 (33.3)	0.271
Acute kidney Injury	0 (0.0)	2 (66.7)	0 (0.0)	1 (33.3)	-
Mode of delivery;					
VD	4 (9.5)	10 (23.8)	8 (19.1)	20 (47.6)	0.043
Caesarean Section	0 (0.0)	22 (28.2)	19 (24.4)	37 (47.4)	0.001
Perinatal outcomes:					
Stillbirth	3 (14.3)	12 (57.1)	2 (9.5)	4 (19.1)	0.001
Perinatal death	4 (16.0)	13 (52.0)	3 (12.0)	5 (20.0)	0.001
Apgar at 5min <7	1 (9.1)	5 (45.4)	3 (27.3)	2 (18.2)	0.364
Birth weight: SGA	0 (0.0)	4 (20.0)	11 (55.0)	5 (25.0)	0.001
NICU Admission	1 (1.8)	20 (36.3)	16 (29.0)	18 (32.7)	0.017
Prematurity complications:					
	1 (3.1)	11 (34.4)	9 (28.1)	11 (34.4)	0.366
Respiratory distress	0 (0.0)	13 (56.6)	5 (21.7)	5 (21.7)	0.002
Neonatal jaundice	1 (6.3)	9 (56.3)	3 (18.7)	3 (18.7)	0.001
Neonatal sepsis					

Abbreviations: G1- Gestational age 20- < 28 weeks; G2- 28-33+6 weeks, G3- 34 -36+ 6 weeks, G4– ≥37weeks SGA-Small for gestational age, HTN- Hypertension, VD-Vaginal delivery

Infants delivered to women who had developed preeclampsia between 28 weeks to <34weeks gestation generally had poorer perinatal outcomes compared with the other gestational age spectrum.

DISCUSSION

This study revealed that maternal outcomes between early and late-onset preeclampsia were comparable *(P*>0.05). This finding contrasts with several studies that associate EOPE with grave maternal complications. [6,8,11,12]. In this study, over 80% of cases in each group had presented with or rapidly progressed to severe hypertension while on admission while other maternal complications such as eclampsia, abruptio placentae and acute kidney injury were recorded. In either EOPE or LOPE, over two-thirds of cases had caesarean delivery which was primarily motivated by the disease severity at presentation. Additionally, two maternal deaths occurred within the study period, one in each group giving a case fatality rate of 1.7%.

In terms of perinatal outcomes, the stillbirth rate in EOPE was significantly higher compared to LOPE (41.7% versus 7.1%). Furthermore, all neonatal survivors (61.1%) delivered to mothers with early onset preeclampsia were admitted into intensive care unlike in late-onset preeclampsia. The neonates in the early onset category were at significant risk of neonatal jaundice and sepsis (*P< 0.05*) which are recognized problems of prematurity. However, the only striking observation was that there was a significant risk of having a small for gestational age neonate in LOPE (*P<0.05)*. This sharply contrasts with studies done in South Africa and Reunion Island where infants delivered to mothers with early onset preeclampsia were more likely to be small for gestational age. [14,25]

Additionally, clinical outcomes were evaluated across specific the gestational age ranges. Generally, a substantial percentage of the women (86%) had presented with severe features or had deteriorated a few hours into admission precluding further pregnancy prolongation even in those remote from term. Maternal complications such as eclampsia and acute kidney injury had occurred at a higher frequency between 28weeks to <34weeks which was like a Nigerian study[26]. Although the highest number of

cases of abruptio placentae had occurred after 34 weeks but before term, women presenting with preeclampsia at term were more likely to present with severe hypertension (49%) compared to earlier gestations. Consequently, women at term had significant caesarean delivery risk in view of disease severity, unfavourable Bishop score, failed induction of labour as well as other obstetric indications.

Furthermore, regarding perinatal outcomes, the stillbirth rate was highest at a gestational age between 28 weeks to<34weeks. The neonatal salvage rate was zero before 28 weeks, increasing to 59% in infants delivered before 34weeks and it was over 90% at term. Infants delivered remote from term (28weeks to <34 weeks) were often admitted and managed for preterm complications such as neonatal jaundice and neonatal sepsis. They had also suffered respiratory distress with comparable frequency to term neonates (34.4%). This was because there were no neonatal survivors before 28 weeks to make comparisons. The high caesarean delivery rate recorded after 37 weeks may have accounted for respiratory morbidity in the term neonates.

Some limitations of the study were that long-term maternal and perinatal outcomes were not determined. A longer study period and a larger sample size would have allowed for more robust deductions to be made from the study.

CONCLUSION

The study revealed that early onset and late-onset preeclampsia are associated with adverse maternal and perinatal outcomes. Notably observed was that perinatal outcomes were disproportionately poorer in the former, which may have been because of preterm delivery that typically characterizes early-onset preeclampsia. Maternal complications occurred with comparable frequency in both entities

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