

Saint Paul's Hospital Millennium Medical College

Department of Obstetrics and Gynecology



**St. Paul's Hospital
Millennium Medical College**

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**Perinatal outcomes of twin pregnancies complicated with preeclampsia at
a tertiary Hospital in Ethiopia: retrospective case–control study**

**Final thesis submitted to Saint Paul's Hospital Millennium Medical
College, department of obstetrics and gynecology, as partial fulfillment of
specialty certificate in Obstetrics and Gynecology**

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List of Abbreviations

ANC	antenatal care
ART	artificial reproductive technology
BP	blood pressure
BPP	biophysical profile
CBC	complete blood count
CI	confidence interval
C/S	cesarean section
DIC	disseminated intravascular coagulation
DZ	dizygotic
Eg	example
GA	gestational age
GOT	glutamic oxaloacetic transaminase
GPT	serum glutamic pyruvic transaminase
HPCP	hypertensive disorder of pregnancy
HDP	hypertensive disorder of pregnancy
IRB	institutional review board
IUGR	intrauterine growth restriction
MZ	monozygotic
PE	preeclampsia
OR	Odd ratio
RDS	respiratory distress syndrome
SPHMMC	St. Paul's Hospital Millennium Medical College
SPSS	statistical package for social sciences
WHO	World health Organization

Abstract

Background: Preeclampsia accounts for 10 to 15 % maternal deaths globally, corresponding to 50,000 annual maternal deaths. Twin pregnancy is a known risk factor for preeclampsia and it is also associated with increased adverse perinatal and maternal outcomes. Three-fold greater perinatal mortality is seen in twin pregnancy in comparison to singleton pregnancies. Prematurity being main contributor of this greater risk of perinatal mortality, 50% of twin pregnancies deliver before 37 weeks. Inadequate data exists regarding the clinical characteristics and perinatal outcomes of twin pregnancies with PE.

OBJECTIVE: To compare perinatal outcomes of twin pregnancies complicated with preeclampsia (PE) and those without hypertension in a teaching Hospital in Ethiopia.

Methodology: A facility based case-control retrospective study was conducted from December 1/2018 – April 30/2019 at St.Paul's Hospital Millennium Medical College(SPHMMC). Data was collected by reviewing medical records, and delivery and NICU registry books. In this study, perinatal outcomes of 63 cases of twin pregnancies complicated with preeclampsia (PE) were compared with 110 normotensive twin pregnancies. Eligible cases were selected based on the inclusion and exclusion criteria among mothers who received care at the hospital from September 2016 to August 2018. Structured questionnaire was used to retrieve data from medical records. Statistical test of association was done using Chi square for categorical data; strength of association with OR and 95% CI .Those variables with P-value of <0.2 on univariate analysis were entered into multivariable logistic regression analysis and adjusted OR was calculated.

Results: This study showed that twin gestations complicated with preeclampsia was associated with significantly increased magnitude of preterm birth(61.9% in the preeclampsia group Vs 33.6% in the group without hypertension) with AOR= 2.58and 95thCI(1.34-5.4). Though the AOR for END (2.98), RDS (1.47), and IUGR (1.8) was also increased in the preeclamptic twin gestations, it was not statistically significant.

Conclusions: Twin pregnancies complicated with PE were associated with significantly increased rate of preterm birth in our study. Unlike previous study, this study showed no statistically significant association of preeclampsia and of adverse perinatal outcomes, namely RDS, early neonatal death, IUGR, and low Apgar. We recommend a well-designed analytic study to be conducted that may come out with far stronger evidence.

1. Introduction

1.1 Background

Preeclampsia (PE) is a common and severe form of hypertensive disorder complicating pregnancy (HDCP) and remains a leading direct cause of maternal and neonatal mortality and morbidity.(2,3).It is estimated to account for about 40 to 60 % of maternal deaths in developing countries. The prevalence of hypertensive disorders of pregnancy is high in Ethiopia and it accounts for 19% maternal deaths in Ethiopia.(4).The International Society for the Study of Hypertension in Pregnancy defines preeclampsia as hypertension of at least 140/90 mmHg on two separate occasions at least 4 hours apart accompanied by significant proteinuria of at least 0.3 g in a 24-hour collection of urine (or 0.30 mg/mmol protein/creatinine ratio), arising de novo after the 20th week of gestation in a previously normotensive woman and resolving completely by the 6th postpartum week.(5)

Although defined by hypertension and proteinuria, preeclampsia involves multiple organ systems (e.g.renal, liver, brain, vascular, coagulation, placenta)that may define different pathophysiological phenotypes.¹²The exact pathophysiology of PE remains to be elucidated.(6)Nevertheless it is widely acknowledged that PE is a syndrome that may arise by different pathophysiological pathways in which impaired placentation, maternal constitution and abnormal circulatory and immunological adaptation to pregnancy may play a role.(7)In preeclampsia , while the definitive treatment is delivery of the fetus and placenta, expectant management with close observation may be appropriate in carefully selected patients, especially before 34 weeks of gestation.(3)

Due to inherent biological factors, twin pregnancies have increased rates of obstetric and perinatal complications such as preeclampsia, post- partum hemorrhage and preterm birth, which are known risk factors for maternal and perinatal mortalit(6).The prevalence of preeclampsia is increased in twin pregnancy. Preeclampsia occurs in 6 to 31 percent of twin pregnancies. The

incidence of PE in twin pregnancy is increased three-fold in comparison to singleton pregnancy.(2).Placental weight is speculated as a possible cause of this difference in incidence of PE in twin and singleton pregnancies but it is not yet scientifically proved.(8)

It is acknowledged that PE increases the risk of adverse maternal–neonatal outcomes mainly from data of singleton pregnancies. Recently, multiple studies have focused on the incidence and risk factors of twin pregnancies with PE, but inadequate data exists regarding the clinical characteristics and perinatal outcomes of twin pregnancies with PE.(2)

1.2 STATEMENT OF PROBLEM

Preeclampsia / Eclampsia is one of the leading causes of maternal and perinatal morbidity and mortality worldwide.(9) Preeclampsia is a pregnancy specific disorder with an overall incidence rate of 5 to 8%. It accounts for 50.000 maternal deaths worldwide each year and it is the second most common cause of stillbirth and early neonatal death in developing countries.(10)

Preeclampsia is estimated to account for 40 to 60% of maternal deaths in developing countries. The prevalence of hypertensive disorder of pregnancy is high in Ethiopia. It ranges from 1.2 % to 18.25%. It accounts for 19 % of maternal mortality in Ethiopia. In a recent systematic review and meta-analysis done by Berhe et al in Ethiopia, the prevalence of preeclampsia / Eclampsia alone is reported to be 5.47%.(4) Preeclampsia/eclampsia is identified as one of the major cause of maternal mortality and it is worked up on for improvement as the main component of quality health services in Ethiopia.(9)

Twin pregnancy is a known risk factor for preeclampsia. In a recent retrospective study done in 2016 by Grum et al , it was reported that clinicians should give special attention to primigravity and twin pregnancy to promptly diagnose and treat preeclampsia. The adjusted OR was reported 2.68 and 8.22 for primigravida and twin pregnancy respectively in the study.(9)The incidence rate of preeclampsia is increased threefold in twin pregnancy, which is 9.5% compared to that of

2-3% for singleton pregnancy. In singleton pregnancy 25 to 30% of the cases deliver preterm (preterm PE). Francisco et al found that the incidence rate of preterm PE to be 9 times higher in twin pregnancy compared to that of singleton pregnancy. The incidence of fetal and maternal short-term and long-term consequences of preeclampsia is higher in preterm preeclampsia than in term preeclampsia.(11)

Increased mortality and morbidity as a result of preeclampsia is always a terror to the mother and the fetus. In a retrospective study done in Ethiopia in 2013, which studied maternal perinatal outcomes in pregnancies complicated with hypertension, the rate of perinatal mortality was found to be 120.37 per 1000 live births. In addition, the rate of preterm birth was reported as 30.5 percent. Severe preeclampsia was the most common among all hypertensive disorders in pregnancy.(12)

Though twin pregnancy is a known risk factor for preeclampsia with increased adverse maternal and perinatal outcome, the explanation for the cause and effect relationship of twin pregnancy on preeclampsia remains enigmatic.(2) Neither the chorionicity nor zygosity of the pregnancies is found to alter this increased risk of preeclampsia in different studies.(8,13) Placental weight is speculated as a possible cause of the difference in the incidence of preeclampsia in twin pregnancy and singleton pregnancy but it is not yet scientifically proved.(8)

Inadequate data exist regarding the clinical characteristics and perinatal outcomes of twin pregnancies with PE. A recent retrospective cohort study done in China in 2016 on characteristics of perinatal and neonatal outcome of twin pregnancies with preeclampsia reported increased adverse perinatal outcome. In the study, 143 cases of twin pregnancies with preeclampsia were compared to 356 cases of singleton pregnancies complicated by preeclampsia. The frequency of preterm birth was reported 81% in the twin preeclamptic arm as compared to 68.66% in the normotensive arm. The results of the study showed two-fold increased rate of adverse perinatal outcome. The rates of indicated preterm birth and IUGR were also increased.(2)

1.3 Significance of study

Preeclampsia accounts for 50,000 maternal deaths worldwide each year and it is the second most common cause of stillbirth and early neonatal death in developing countries.(10)Preeclampsia/eclampsia remains one of the commonest causes of perinatal mortality and morbidity in developing countries, mainly due to high rate of preterm birth associated with it.(12)In singleton pregnancy with preeclampsia, 25 to 30 % of cases deliver preterm. Twin pregnancy has 3 fold increased incidence rate of preeclampsia and it is associated with increased adverse perinatal outcomes. The incidence rate of preterm preeclampsia (delivery before 37 weeks in preeclampsia) in twin pregnancy is reported to be increased up to nine folds of that of singleton pregnancy in one study.(11)

Though the incidence of preeclampsia in twin pregnancy has been well studied, inadequate data exists on the perinatal outcome.² It is not studied but preeclampsia is reported as one of the top five causes of perinatal mortality in the monthly perinatal reports at SPHMMC. As one of the biggest referral Hospitals in Ethiopia, SPHMMC receives quite high number of referrals of twin pregnancies. Sealing the knowledge gap regarding the impact of preeclampsia in twin pregnancy on perinatal outcomes at SPHMMC statistically as compared to the normotensive ones was the main goal of this study.

2. Literature Review

Hypertensive disorders, including gestational hypertension(GH) and pre-eclampsia (PE), are among the most common medical complications of pregnancy, with a reported incidence ranging from 5% to 10%.(14)Hypertensive pregnancy disorders cover a spectrum of conditions, including preeclampsia/eclampsia, gestational hypertension, chronic hypertension, and preeclampsia superimposed on chronic hypertension.(7) It is the most common medical problem in pregnancy and one of the top three leading cause of maternal mortality globally.(2,15) Hypertensive disorders of pregnancy (HDP) account for nearly 18% of all maternal deaths

worldwide, with an estimated 62 000–77 000 deaths per year. The mortality is 20 percent in the developed countries, 25% in South America, and 10% in African countries.(6,16)

Preeclampsia occurs in 2 to 8 percent of pregnancies and is more common in primigravidas as compared to multigravida.(3,7) It is common in developing countries with a prevalence of 2.3% of all pregnancies. A study done in Ethiopia in 112 Hospitals and 685 health centers showed that 1.2% of all institutional deliveries were complicated by preeclampsia/eclampsia.(17)

A recent cross-sectional study which was done by the WHO in 29 countries in Latin America, Africa, Asia, and Middle East showed that mothers with preeclampsia were 8 times more likely to have maternal near-miss. The study was implemented at 357 health facilities. The near-miss was 60 times more likely in eclampsia cases. The prevalence of preeclampsia was 2.16% and there were 8542 mothers included in the study who suffered from hypertensive disorders of pregnancy.(6) Women with gestational hypertension or mild pre-eclampsia constitute about 75% of women with hypertensive disorders of pregnancy at term.(18)

The incidence of hypertension in pregnancy in general and preeclampsia specifically is increasing worldwide. In the developed world it has increased by 40 percent from 1991 to 1999. ¹Preeclampsia is also common cause of perinatal morbidity and mortality. The morbidities and mortalities are more due to indicated preterm births as delivery of the placenta remains the only definitive management of preeclampsia.(3,16,19)

Although most obstetricians worry more about the risk of maternal death in women whose pregnancies are complicated by hypertensive disorders, the risk of perinatal death is more daunting. For instance, the risk of maternal death is less than 1% in severe preeclampsia and whereas that of perinatal death is about 13%. The situation is even worse in eclampsia where the risks of maternal and perinatal deaths occur in about 5% and 28% respectively.(20)

The prevalence of HDP in Ethiopia ranges from 1.2 to 18.25 %. In a recent systematic review done in 2018 by Berhe et al , the pooled prevalence of preeclampsia /eclampsia alone was

5.47%.(4)Preeclampsia/eclampsia is identified as one of the major causes of maternal mortality in Ethiopia.(9)

Due to inherent biological factors, twin pregnancies have increased rates of obstetric and perinatal complications such as preeclampsia, post-partum hemorrhage and preterm birth, which are known risk factors for maternal and perinatal mortality. Eclampsia, placental abruption, and postpartum hemorrhage are more common in twin gestation when compared to that of singleton. The overall perinatal complications is also increased in twin pregnancy.(6)

Preeclampsia occurs in 6 to 31 percent of twin pregnancies.(8)The incidence of PE in twin pregnancy is increased three fold. (2) The range of relative risk of gestational hypertension, preeclampsia and eclampsia for twin compared to singleton gestations is 1.2 to 2.7, 2.8 to 4.4 and 3.4 to 5.1 respectively. Parity, African-American ethnicity, and young maternal age are all factors that increase the relative risk of acquiring hypertensive disease to 4.0, 1.8 and 1.5 in mothers of twin gestations.(15)Twin pregnancy is a known as a risk factor for preeclampsia but the exact reason why it is more seen in twin pregnancies is still not yet known. Neither the chronicity nor zygosity of the pregnancies alters this increased risk.(8,13)Placental weight is speculated as a possible cause of this difference in incidence of PE in twin and singleton pregnancies but it is not yet scientifically proved.(8)

In a retrospective comparative study that was done in 1976 at Leeds Maternity Hospital, there were 125 cases of preeclampsia-eclampsia in the DZ group which was 18.5 % Vs 17.5% - 62 cases of preeclampsia/eclampsia in the MZ group. The conclusion of the study was that zygosity doesn't affect the incidence of PE in twin pregnancies.(21) Similarly, a cohort study done in London in 2001 , in which 666 twin pregnancies were studied , concluded that chorionicity has no effect in the incidence of preeclampsia in twin pregnancies.The occurrence of preeclampsia in both groups was comparable (9.3% in the monochoronic group and 7.5% in the dichorionic ones).(8). A mini review which included 8 articles aimed at studying risk factors in twin pregnancy that predispose for preeclampsia. It didn't find chorionicity as a significant factor associated with the occurrence of preeclampsia in twin pregnancy.(13)

In a cohort study done in USA , which included 86 765 deliveries from 2000 to 2009, including 3244 twins, preterm severe preeclampsia was more common in twin pregnancies (2.4% vs 0.4%, $P<0.001$, relative risk 5.70 (95% confidence interval 4.47 to 7.26)), compared to singleton.(23). A retrospective study done by Blickstein et al in Israel in 1992 in which 25 mild and 19 severe preeclampsia cases in twin pregnancies (12.5%) were compared to 44 matched for gestational age controls, showed that preeclampsia was associated with increased rate of CS delivery, low Apgar score , and lower mean GA at Delivery.(22). Similarly, the ESPRIT (Evaluation of Sonographic Predictors of Restricted growth in Twins) study done in Ireland found that in twin gestations, gestational hypertension independently confers an increased risk for emergency caesarean delivery, birth weight discordance and NICU admission.(24). A recent study done in China by Yuan et al on the perinatal outcome of twin gestations with PE concluded that twin pregnancies with PE were associated with worse perinatal outcome. Significant increases were observed in the frequencies of preterm delivery (OR=2.75, $P<0.001$), iatrogenic preterm birth (OR=3.52, $P<0.001$), and IUGR (OR=2.94, $P=0.001$) in the preeclampsia (PE) group, and the PE group had more than a 2-fold risk of adverse neonatal outcomes. The comparison on the discordance of intertwin weight was not significantly different.(2)

Retrospective cohort study in 2002 through December 2011 was done found that significant risk factors associated with developing a hypertensive disorder in a twin pregnancy were primiparity (adjusted odds ratio [aOR]: 1.77; 95% confidence interval [CI]: 1.21–2.61), pregestational high body mass index (aOR 1.35, 95%CI: 1.08–1.70), family history of hypertension (aOR: 1.50; 95%CI: 1.02–2.17) and previous history of GH or PE (a OR 8.85; 95%CI: 2.70–29.0).(14)

3. Objectives

3.1 General Objectives

- To compare perinatal outcomes of twin pregnancies complicated with preeclampsia to twin pregnancies with no hypertension in a teaching Hospital in Ethiopia

3.2 Specific Objectives

1. To compare the magnitude of preterm birth between twin pregnancies with PE and those without hypertension
2. To compare the magnitude of IUGR between twin pregnancies with PE and those without hypertension
3. To compare the rate of adverse neonatal outcomes(stillbirth , early neonatal death, low APGAR score, and NICU admission for RDS) in twin gestations between women with PE and those without hypertension

4. Methodology

4.1 Study Area

The study was conducted in the obstetric unit of Saint Paul's Hospital Millennium Medical College (SPHMMC) in Addis Ababa, Ethiopia. SPHMMC is a referral teaching Hospital with an obstetric unit that attends around 750 to 850 deliveries per month, which is the highest delivery service in Ethiopia. Most of the obstetric population is high risk clients, including twin pregnancy and preeclampsia, referred from different catchment health centers, non-catchment health centers, and Hospitals

4.2 study period

From December 1, 2018 to April 30, 2019

4.3 Study design

A facility-based retrospective case-control study done from December 1, 2018 to April 30, 2019

4.4 Study Populations

All pregnant women who gave birth at SPHMMC from Sep 2016 to August 2018

4.5 study subjects

Women with twin pregnancies who gave birth at SPHMMC

4.5 SAMPLE SIZE AND SAMPLING PROCEDURE

Determination of the sample size was according to the report in the previous retrospective study done in China. The rate of preterm birth was 81 % in the preclamptic twin gestations and 68.66 percent in the normotensive group .Using a margin of error of 5% ($\alpha= 0.05$) , power of 80% and confidence interval of 95% (standard value of 1.96), the OR for frequency of preterm birth was 2.75.²

Using a controls/ cases ratio of 2, open Epi online sample size calculation for Unmatched Case-Controls studies (Fleiss) was used to calculate the sample size. Sample size –Cases (P1)=73, Sample Size- controls(P2=146) was planned. Unfortunately, dueto very strict inclusion and exclusion criteria (mainly GA), 63 preeclampsia cases were finally analyzed against 110 normotensive cases with a controls / cases ratio of 1.8

4.6 Inclusion and Exclusion Criteria

Inclusion Criteria

Case

- Twin pregnancy with confirmed chorionocity ,GA> 28
- Diagnosis of preeclampsia
- Live co-twin with no congenital anomaly
- Delivery at labor ward at SPHMMC
- ANC follow up at SPHMMC or catchment health center

Control

- Twin pregnancy with confirmed chorionocity GA > 28 wks
- No hypertension
- Delivery at labor ward at SPHMMC
- Live co-twin and no congenital anomaly
- ANC booked at SPHMMC or catchment H.C

Exclusion Criteria

- Gestational hypertension
- Chronic hypertension
- Unknown GA
- Eclampsia
- Concurrent medical &obstetric illness
- Higher order pregnancy
- Chronic hypertension with superimposed preeclampsia

4.7 VARIABLES

Independent variables

- Age in years
- Gestational age
- Parity
- Mode of delivery
- ANC status
- Chronicity
- EFW
- EFW discordance $\geq 20\%$

Dependent variables

- Stillbirth
- Early neonatal death
- IUGR
- Preterm birth
- Low Apgar score
- NICU admission for RDS

4.8 Data collection

Delivery registry was used to identify twin deliveries and using a structured questionnaire in English language, data was collected by reviewing maternal charts and NICU registry. The questionnaire included socio-demographic data and obstetrics characteristics (parity, ANC status, mode of delivery, delivery outcomes, .etc). Data was collected by year-II residents. Completeness and consistency of the data was checked daily by the principal investigator

4.9 DATA QUALITY ASSURANCES

Data was collected by year-II residents. Completeness and consistency of the data was checked daily by the principal investigator

4.10 DATA PROCESSING AND ANALYSIS

Data collected by reviewing maternal records was verified and entered into a data management system using Epi Info TM 7, and later analyzed using SPSS version 23.

Statistical test of association was done using Chi square for categorical data; strength of association with OR and 95% CI. Those variables with P-value of <0.2 on univariate analysis were entered into multivariable logistic regression analysis and adjusted OR was calculated.

4.11 ETHICAL CONSIDERATION

Ethical clearance & permission letter was obtained from the Institutional Review Board (IRB) of St. Paul's hospital millennium medical college (SPHMMC). A written informed consent was not necessary for this retrospective study, and patient anonymity was preserved.

4.12 Dissemination of results

Results of the study were submitted to the SPHMMC Obstetrics and Gynecology department. A copy of the final result will be disseminated to the SPHMMC research office and other concerned bodies. An attempt will be made to publish the study in peer-reviewed journals.

4.13 Operational Definitions

Preeclampsia: blood pressure measurement of greater or equal to 140/90 for the first time in pregnancy after 20 weeks of gestation at two occasions at least 4 hours apart in the presence of proteinuria – 24 hours urine protein of 300mg/dl or single urine dipstick +1 and above, or presence of severity features in the absence of proteinuria .

Severity features of preeclampsia: Single BP measurement of 160/100 and above, platelet count less than 100,000, GPT and GOT elevated at least twice the normal upper normal, creatinine of 1.2 mg/dl and above, epigastric pain, headache, blurring of vision, and pulmonary edema

Early USG: USG that dates up to AGA of 24 weeks.

Indicated preterm birth: any iatrogenic birth at gestational age less than 37 weeks and above 28 weeks of gestation either for maternal or fetal indications.

Normotensive(Without hypertension); No record of any degree or type of hypertension in pregnancy

Stillbirth: any in utero death at GA greater than 28 weeks of gestation

Preterm birth: any birth before GA of 37 weeks of gestation and greater than 28 weeks of gestation

HELLP syndrome: elevated transaminases (GPT and GPT elevated two times the upper normal), and platelet count less than 100, 000 with LDH level greater than 600

GA calculation: The gestational age was calculated using the last menstruation period (LMP) or confirmed by early ultrasound (up to 23 weeks USG).

Normotensive; No record of any degree or type of hypertension in pregnancy

The determination of twin chorionicity was clinically based on an ultrasound evaluation, including the gestational sac number at early pregnancy, the placental number, the fetal sex, “T” sign or “I” sign and it was confirmed by a placenta examination after delivery

Intrauterine growth restriction (IUGR) was defined as at least one fetus with a birth weight less than the 5th percentile for the gestational age

5. Results

A total of 423 twin pregnancies were retrieved in the Hospital information system at labor ward from September 2016 to August 2018. One hundred and seven out of the total were complicated with preeclampsia, which represents 25.3%. Statistically significant difference was found in the magnitude of preterm birth and mean EFW between twin gestations complicated with preeclampsia and those twin gestations without hypertension.

The frequency of preterm birth was 61.9% in the PE group which was statistically different from that observed in the normotensive ones (33.6%) at p-value of <0.0001. However in the subgroup analysis, percentage of delivery at GA less than 34 weeks of gestation out of the total frequency of preterm birth observed in each group was not statistically different between the two groups (20.51% in PE group and 27% in the normotensive group, p-value 0.56).

A difference of 160 grams was found in the mean EFW between both groups at p-value of 0.003 (EFW PE group=2120.35 vs EFW of 2282 gms in the normotensive group). However, there was no statistically different distribution of EFW discordance $\geq 20\%$ between the two groups (13.3% in the normotensive group Vs 11.32% in the preeclamptic group, p value= 0.76).

The cesarean delivery rate was 75.81% in the PE group, and 59.63 % in the non-preeclamptic group respectively and that was not statistically significant (p-value=0.072). The distribution of primigravida cases was 28.57% in the PE group, which was not statistically different from that of normotensive group (37.9%) with p-value of 0.24. In both groups 65% of the cases had their ANC booked at SPHMMC. The distribution of chorionicity in both groups was similar. Ninety two percent in the PE group and 90% in the normotensive group (without hypertension) group were dichorionic twins.

Table 1: Baseline characteristics of twin gestations with PE and normotensive groups

Variables	Normotensive Twin pregnancy (n=110)	Twin pregnancy with preeclampsia (n=63)	p*
Maternal age, mean $\pm$ SD	26.90 $\pm$ 4.20	28.27 $\pm$ 4.62	0.049
Estimated Fetal Weight, mean $\pm$ SD	2282 $\pm$ 434.49	2120.35 $\pm$ 436.25	0.003
Gestational age at delivery			
< 34 weeks	10 (9.09)	8 (12.70)	0.001
34 weeks- 36 ⁺ 6 days weeks	27 (24.55)	31 (49.20)	
$\geq$ 37 weeks	73 (66.36)	24 (38.10)	
Mode of delivery			
Spontaneous vaginal delivery	41 (37.62)	13 (20.97)	0.072
Cesarean section	65 (59.63)	47 (75.81)	
Instrumental	3 (2.75)	2 (3.22)	
Gravidity, n(%)			
Primigravida	41 (37.96)	18 (28.57)	0.245
Multigravida	67 (62.04)	45 (71.43)	
ANC Status, n (%)			
Booked at SPHMMC	72 (65.45)	41 (65.08)	0.960
Booked at Catchment HC	38 (34.55)	22 (34.92)	
Chorionicity, n%			
Dichorionic	99 (90.00)	58 (92.06)	0.788
Monochorionic	11 (10.00)	5 (5.94)	
Discordance of EFW $\geq$ 20%, n(%)	12 (13.33)	6 (11.32)	0.726

* p- Value is reported for tests of association

Gestational age calculation, CS done in labor, CS or instrumental delivery done for Non-Reassuring Fetal Heart Rate Pattern (NRFHRP), and dexamethasone treatment were analyzed as cofounders. Except for the distribution of CS or instrumental delivery for NRFHRP, the difference in the distribution of these variables was significantly different and finally.

While 28.44 % the group without hypertension lacked early USG for accurate GA dating, 48.39 % in the preeclamptic group lacked the same mile stone for more reliable GA dating. This was a significant finding with p value= <0.012 . Out of the CS deliveries, 62.1% in the normotensive group and 22.92% in the preeclamptic group, CS delivery was done in labor (p value = <0.0001). Again, it was a significant finding. Nine cases in the twin with PE group received dexamethasone treatment representing 14.3% which was statistically different from that of without hypertension group(0.09%) with a p value =0.001.

Table 2: Distribution of potential cofounders in twin complicated with PE and normotensive

Variables	Normotensive Twin pregnancy (n=110)	Twin pregnancy with preeclampsia (n=63)	p*
GA Calculation			
Both reliable LNMP and early US	17 (15.6)	3 (4.84)	0.012
Early US	61 (55.96)	29 (46.77)	
Only reliable LNMP	31 (28.44)	30 (48.39)	
CS done in labor, n(%)	41(62.12)	11(22.92)	<0.0001
CS or instrumental done for NRFHRP	4(6.35)	0(0.00)	0.128
Dexametasone treatment, n%	1(0.09)	9 (14.30)	0.001

Multivariable logistic regression analysis showed that the adjusted Odds Ratio (AOR) for of preterm birth was significantly increased (AOR=2.58 with 95th CI(1.24 – 5.35) at p-value of 0.01). This is a very significant finding. There were 5 early neonatal death (END) in the group of twin pregnancy with preeclampsia (PE) and only 1 early neonatal death in the normotensive group (without hypertension). The AOR for early neonatal death was 2.98 with 95th CI (0.16 – 55.59) and p-value of 0.46, which was not statistically significant finding.

Similarly, there was no significant finding in the AOR for respiratory distress syndrome (AOR=1.47, p-value 0.519), IUGR (AOR=1.85, p-value=0.44), low Apgar score (AOR=0.96, p value=0.933). For the reason there was only one observation of stillbirth, stillbirth was excluded from the analysis. There was no statistically significant finding in the comparison of association of rate of low birth weight (LBW), very low birth weight (VLBW).

Table 3: Selected perinatal outcomes in twin pregnancy with preeclampsia compared with normotensive group adjusted for potential covariates

Perinatal outcome	Normotensive	Preeclampsia	COR (95 th % CI)	AOR (95 th % CI)	p*
RDS, n(%)	19 (16.52)	22 (30.14)	2.05 (0.85 - 4.98)	1.47(0.45 - 4.770)	0.519
IUGR, n(%)	7 (6.54)	7 (10.77)	1.44 (0.42 – 4.92)	1.85(0.38 – 9.01)	0.444
LowApgarScore, n(%)	16 (14.41)	13 (20.00)	1.31 (0.54 – 3.14)	0.96(0.33 – 2.76)	0.933
LBW, n(%)	123 (80.39)	78 (85.71)	1.44 (0.69 – 3.03)	0.99(0.43 – 2.30)	0.989
VLBW, n(%)	14 (12.17)	7 (11.11)	1.40 (0.50 – 3.97)	0.33(0.06 –1.79)	0.201
Preterm delivery, n(%)	37 (33.64)	39 (61.91)	3.21 (1.68-6.11)	2.58(1.24 – 5.35)	0.011
END, n(%)	1 (0.93)	5 (7.81)	7.25 (0.79 – 66.41)	2.98(0.16 -55.59)	0.465

* p- Value is reported for tests of AOR

6. Discussion

In this study twin pregnancies with PE were associated with statistically significant increased magnitude of preterm birth and a lower estimated fetal weight. Preterm delivery(GA less than 37 weeks) was significantly higher in the PE group(61.91% Vs 33.64%, p value less than 0.001) compared to the group without hypertension. This is less than the frequency of 81.8% preterm delivery in twin gestations complicated with preeclampsia that was observed in a similar retrospective case-control study done by *Yuan et al* in 2016 in Chinese population.(2) .

Multivariable logistic regression analysis also showed a significant increase in the adjusted OR of preterm birth for potential covariates. Both the crude and adjusted OR of preterm delivery was significantly increased, COR =3.21(95th % CI 1.68-6.11) and AOR=2.58(95th CI 1.24-5.35) respectively with p value of 0.011.Likewise, *Yuan et al* found an OR of 2.75 for preterm birth with 95th CI (1.69-4.47) in his study.(2). Similarly Blickstein et al from reported that preeclampsia in twin gestation was associated with increased rate of preterm birth. He found that the mean GA at delivery was 34.8 ± 3.5 in the severe preeclampsia cases compared to 36.2 ± 2.8 in the controls in his study.(22)

In this study, increased AOR was also observed for early neonatal death and RDS without any statistical significance, 2.98 (95th CI 0.61-55.59, p value=0.46) and 1.47 (95th CI 0.45-4.77, p value=0.519) respectively. There was no statistically significant difference in the frequency of adverse neonatal outcome (RDS, END, and Low Apgar score). Contrary to our finding, the rate of low Apgar score was reported to be increased in a study done by Blickstein et al. In that study, the rate of low Apgar score was 4%, 7.9%, and 3.4% in the mild PE, severe PE, and control groups respectively.(22)Similarly, Yuan *et al* also found 2 fold increased OR of adverse neonatal outcome.

There was observation of increased AOR for IUGR in our study but without statistical significance at a value of 1.8 with 95thCI (0.38-9.01, p value=0.44), which contradicts an earlier report of an increase in the IUGR rate in the PE group(OR 2.94 95th CI 1.56-5.53, p value=0.001) by Yuan et al(2).

6.1 Limitation of the study

Being a retrospective case-control study with a small sample size, the results of this study is not strong and stands prone to bias. Prospective cohort study would have been the ideal study design but for the reason that large number of our patients wouldn't meet the strict inclusion and Exclusion criteria unless the time period to enroll study subjects with the desired sample size was going to be prolonged. And that was not going to be feasible with the time limitation we had to conduct the study.

In addition, 48.39 % in the preeclampsia group and nearly 28.39 % of the cases in those without hypertension group lacked early USG for accurate dating. Missed data in EFW is another limitation of this study. Inadequate literature review in the topic of research is additional limitation. The reason behind that is limited data exists regarding the perinatal outcomes of twin pregnancies complicated with preeclampsia. Finally, factors like maternal nutritional status, BMI, smoking behavior, and use of drugs were not controlled as medical records lacked all these data.

6.2 Conclusion

In conclusion, findings of this study showed that twin pregnancies complicated with PE is associated with significantly increased magnitude of preterm birth. Unlike previous studies, this study showed no statistically significant increase in rate of IUGR and adverse neonatal outcomes - RDS, early neonatal death, and low Apgar score.

6.3 Recommendation

Case-control retrospective in nature with no desired sample size, this study provides results that are not strong and prone to bias. However, the statistically significant finding of increased odds ratio of preterm birth associated with preeclampsia in twin gestation is comparable to the previous studies on similar topic of research. It can be beneficial in terms of accessing local data in this perspective about preeclampsia in twin pregnancies and boosting the existing fact of inadequate data regarding perinatal outcomes of twin pregnancies complicated with preeclampsia. We recommend conduction of further similar well designed analytic study, which may come with stronger evidence.

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8. Annexes

8.1 Annex I : Questionnaire

Serial number MRN-----

Date of admission ----- time of admission -----

Date of diagnosis time of diagnosis

Date of decision of delivery time of decision of delivery Date of delivery time Date of discharge

1. Diagnosis of preeclampsia plus twin pregnancy or twin pregnancy without preeclampsia to delivery interval day hour & minute

2. Time interval between decision of termination to delivery interval _ day _ hour & minute

3. Age in years

4. Address a) Addis Ababa (0)

b) Out of Addis Ababa (1)

5. Educational status

a) Illiterate (0)

b) Can read & write (1)

c) Elementary school (2)

d) high school (3)

e) tertiary school (4)

f) vocational school (5)

6. Occupation

a) Unemployed(0)

b) House wife(1)

c) Student (2)

d) daily laborer (3)

e) merchant(small/large scale) (4)

f) Government/ private employee (5)

g) Farmer (6)

7. Marital status

a) Single (0) b) Widowed (1) c) divorced (2) d) Married (3)

8. Gravidity 9. Parity.....

10. History of previous pregnancy complicated by hypertension yes (0) no (1)

11. History of hypertension yes (0) no (1)

12. Family history of hypertension during pregnancy yes (0) no (1)

13. History of DM yes (0) no (1)

14. Twin gestation yes (0) no (1)

15. ANC status a. Booked at SPHMMC (0) b) booked at SPHMMC catchment health center (1)

16. Referral status a. Referred at time of diagnosis preeclampsia and twin pregnancy or twin pregnancy (0)

b. Not referred (1)

17. Diagnosis on referral

18. Place from which patient was referred

a. Catchment health center (0) b) Not referred (1)

19. Medication given before referral

20. Presenting symptom

21. LMP ----- (reliable/unreliable)

a. Early U/S date & gestational age at that time

- b. Gestational age at first diagnosis of twin pregnancy with preeclampsia or twin gestation without preeclampsia Unknown (U)
22. Gestational age at termination or delivery of pregnancy Unknown (U)
23. Blood pressure evidence of preeclampsia (either BP $\geq$ 140/90 mmHg at 2 occasions 4hrs apart or a single record of 160/110 mmHg)
- a. Yes (0) b. No (1)
24. albumin: qualitative quantitative
- a. neg (0) b. Pos (1) c. Not done (2)
25. platelet count /mm³
- a. less than or equal to 100,000 (0) b. More than or equal to 100,000 (2) c. Not done (3)
26. SGOT /UL
- a. With in normal limit (0) c. More than or equal to 2 times elevation (2)
- b. Less than 2 times elevation (1) d. Not done (3)
27. SGPT /UL
- a. With in normal limit (0) c. More than or equal to 2 times elevation (2)
- b. Less than 2 times elevation (1) d. Not done (3)
28. Creatinine mg/dl
29. Headache a) yes (0) b) no (1)
30. Blurry of vision a) yes (0) b) no (1)
31. Epigastric pain a) yes (0) b) no (1)
32. Cough/shortness of breath a) yes (0) b) no (1)
29. LDH
- a. Less than 600 (0) b. More than 600 (1) c. Not done (2)
30. Diagnosis on admission
- Antihypertensives used; maximum dose used
- a) Hydralazin
- b) Methyldopa
- c) Nifedipine
- d) Propranolol
- e) Other
- Dose and duration of magnesium sulphate
31. Dexamethasone number of doses
- a. 4 doses (0) c. Didn't take dexamethasone (2)
- b. Less than 4 doses (1) d. Not applicable (3)
32. Option of management used
- a) Immediate termination (0)
- b) Delayed termination (1)
- c) Spontaneous onset of labor (2)
33. Reason for immediate termination
34. Reason for delaying delivery
35. If delivery was delayed; reason for termination of pregnancy
36. If labor was induced: method of induction
37. EFW in grams twin A twin B
37. Mode of delivery: a) SVD (0) b) C/S (1)
- (c) Vacuum (2) d) forceps (3)
- e) Destructive (5) f) c/s for 2nd twin(6)
38. Indication for C/S, or instrumental delivery
39. Anesthesia a) GA (0) b) spinal (1) c) epidural (2) d) not applicable (3) e) GA after failed spinal (4)
40. Place of delivery: a) labor ward (0) b) EGOPD (1)
41. Maternal complication
42. Duration of stay at NICU day hr& min

43. Perinatal outcome
 - a) Alive (0)
 - b) stillbirth: cause (1)
 - c) ENND: cause (2)
 - d) unknown (3)
44. 1st minute Apgar score
45. 5th minute APGAR score
46. GA at birth a) less 37 weeks (0) b) greater than 37 weeks (1)
46. Birth weight in grams
47. Neonatal complication that needed referral to NICU
48. Duration of stay in NICU day hr min
49. Admission to delivery interval day hour & minute
50. Diagnosis to admission interval day hour & minute
51. Diagnosis to start of intervention interval day hour & minute
52. Admission to discharge interval day hour & minute
53. Incision to delivery interval day hour & minute
54. Delivery to discharge interval day hour & minute
55. Perinatal outcome of twin B
 - e) Alive (0)
 - f) stillbirth: cause (1)
 - g) ENND: cause (2)
 - h) unknown (3)
56. 1st minute APGAR score
57. 5th minute APGAR score
58. Birth weight in grams
59. IUGR a) yes (0) b) no (1)
59. Neonatal complication that needed referral to NICU
60. Duration of stay in NICU day hr min
61. GA at start of intervention
62. Placentation (chorionicity) a) DCDA b) DCMA(1) c) MCMA(3)
62. Final diagnosis
 - a. twin pregnancy with Partial HELLP syndrome (0)
 - b. twin pregnancy with preeclampsia with severity features (1)
 - c. twin pregnancy with Complete HELLP syndrome (2)
 - d. twin pregnancy with preeclampsia without severity features (3)
 - e. twin pregnancy with Eclampsia (5)
 - f. normotensive twin pregnancy (4)

9. Declaration

I, the undersigned declare that this thesis is my original work in partial fulfillment of the requirement for the post graduate study in obstetrics and gynecology. I also declare that it has never been presented in this or any other university and that all resources and materials used in the thesis have been duly acknowledged.

Resident's Name: Dr. Abraham Fessehaye

Signature-----

Date of submission: May 16, 2019

This thesis has been submitted for examination with my approval as an advisor

Advisors Name: Dr.WondimuGudu, MD, MPH, FMM fellow

Assistant professor of Obstetrics and Gynecology

Signature-----

DATE-----