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Original research article

Maternal and foetal morbidity in women with pre-eclampsia at varying gestational ages and its correlation with placental pathology

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Abstract

Objective: We examined the effects of early- and late-onset preeclampsia on maternal and perinatal outcomes as well as compared pathological changes of placenta in these two groups.

Results: Compared with the late-onset group, the early-onset group had higher rates of C-section (35.29%), Placental Abruption (31.37%), HELLP Syndrome (15.68%) and Disseminated Intravascular Coagulation (7.84%), stillbirths (29.41%), FGR (13.7%), abnormal Apgar score (35.29%), NICU admissions (33.3%) and neonatal death (5.88%). The placental pathological changes observed in patients with hypertensive disorders of pregnancy like retroplacental hematoma, infarction, calcification, decidual arteriopathy, atherosis were more frequently associated with early onset PE as compared to late onset PE that has an adverse influence on perinatal outcome even after correcting gestational age.

Conclusion: Present study concluded that the women suffering from hypertensive disorders of pregnancy and particularly those who were diagnosed with early onset pre-eclampsia bears the major brunt of the disease and its complications in the form of fetomaternal morbidity & mortality.

Keywords: Early-onset preeclampsia, late onset preeclampsia, maternal outcome, perinatal outcome, placental pathological changes.

Introduction

Preeclampsia is new-onset hypertension and either proteinuria or end-organ dysfunction after 20 weeks of gestation in previously normotensive women[1]. It involves multiple organ systems complicating 2–10% of pregnancies[2] and represents one of the most common causes of maternal mortality and severe maternal morbidity. The concept of early and late onset preeclampsia occurring before and after 34 weeks of gestation respectively has recently gained attention and it is widely accepted that these two entities have different etiologies and should be regarded as different forms of the disease[3]. Early-onset PE is commonly associated with abnormal uterine artery Doppler, foetal growth restriction, and adverse maternal and neonatal outcomes where as late-onset PE is mostly associated with normal or slight increased uterine resistance index, a low rate of foetal involvement, and more favourable perinatal outcomes[4].

Early-onset PE and FGR are placenta-mediated diseases that share important similarities as demonstrated by Crispi *et al*.[5]

According to some investigators early onset pre-eclampsia and late onset preeclampsia share some risk factors[6], including older maternal age, Hispanic race, Native American race, smoking, unmarried status, and male foetus. Several risk factors were more strongly associated with early-onset preeclampsia than late-onset disease, including black race, chronic hypertension, and congenital anomalies. In contrast, younger maternal age, nulliparity and diabetes mellitus were more strongly associated with late-onset preeclampsia than with early-onset disease. In addition, early-onset preeclampsia was significantly associated with a high risk for foetal death, but late-onset preeclampsia was not.

The pathological changes of preeclampsia provide evidence of reduced oxygen delivery and exposure to oxidative and likely endoplasmic reticular stress. Histological changes in the placenta with preterm preeclampsia and with FGR are those of reduced perfusion including accelerated villus branching, large and numerous syncytial knots, and small sclerotic villi. It is suggested that most of these findings are related to low oxygenation secondary to reduced perfusion[7]. In the great majority of pre-eclamptic cases, the

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placenta shows the effect of low uteroplacental flow. The placenta is smaller on an average than the placenta from uncomplicated pregnancy and infarcts are more numerous, larger and often centrally located.Some investigators have also found that histopathological lesions of placenta differ, depending on when in gestation the diagnosis of pre-eclampsia is established. In Late onset preeclampsia which accounts for the vast majority of preeclampsia cases absolute uteroplacental ischemia appears to be less relevant in the pathogenesis as compared with early onset pre-eclampsia. Evidence in support of this view includes the recent observation that more than half of patients with late onset pre-eclampsia do not have placental histological lesions consistent with maternal under perfusion.

Our prospective study was an attempt to evaluate the effects of early onset and late onset pre-eclampsia on maternal and perinatal outcomes and we tried to correlate the pathological changes of placenta of women with early onset and late onset pre-eclampsia in an effort to support the hypothesis that pre-eclampsia is more than one disease.

Material and Methods

A prospective observational comparative study of 204 cases was done in Dr. Baba Saheb Ambedkar Medical College and Hospital, New Delhi, India after approval from hospital ethical and research committee. Out of 204, 102 normotensive women were control, 51 women had early onset pre-eclampsia and 51 had late onset pre-eclampsia.

Reasoning for selecting sample size:

The study by Krielessi V *et al.*[8]observed that in Group A (severe hypertension), preterm delivery was more than Group B (mild hypertension) (67.27% in Group A vs 38.18% in Group B). Significantly lower placental weight were found in pregnancies complicated with severe hypertension and remained significantly lower after correction for gestational age (Group A =354.62 ± 122.33 versus Group B= 427 ±137.67). Taking these values as reference, the minimum required sample size with 80% power of study and 5% level of significance was 51 patients in each study group by comparing placental weight between two groups. So sample size taken was 51 for early onset pre-eclampsia and 51 for late onset pre-eclampsia and 102 for controls.

Pregnant women ≥20 weeks of gestation with pre-eclampsia (defined according to American College of Obstetrics and Gynecology criteria[1] and normotensive pregnant women with term gestation were included in study. Patients with medical conditions like Chronic hypertension, Renal Disorders Heart Diseases as well as twin Pregnancy, Placenta Previa, Premature Rupture of Membranes (PROM), smoking, Gestational diabetes mellitus, eclampsia, HELLP Syndrome, congenital malformations were excluded. Patients who presented with preeclampsia but the exact timing of onset of hypertension were not known were also excluded.

Demographic profile including age, gravidity was noted. Complete general physical, systemic and obstetric examination was done. All patients were admitted, PIH profile (CBC, Peripheral smear for haemolysis, BT, CT, CRT, PT with INR, LFT, KFT, GCT, Urine routine & microscopic examination), ophthalmoscopic examination was done and managed according to recent ACOG guidelines[9]. women with pre-eclampsia without severe features at or beyond 37 0/7 weeks of gestation were delivered and those less than 37 0/7 weeks of gestation with no indication for delivery were managed expectantly with maternal with serial assessment of maternal symptoms and foetal movement (daily by DFMC), serial measurements of BP and assessment of CBC with Platelet Counts, LFT, KFT (weekly), USG to assess foetal growth and antenatal testing to assess foetal status were done. In case of evidence of foetal growth restriction, umbilical artery Doppler velocimetry was done.

In women with preeclampsia with severe features at or beyond 34 0/7 weeks of gestation, and in those with unstable maternal or foetal conditions irrespective of gestational age, delivery soon after maternal stabilization was done. Women with severe preeclampsia at less than 34 0/7 weeks of gestation pregnancy received corticosteroids. The goal of hypertension treatment was to lower BP to prevent cerebrovascular and cardiac complications while maintaining uteroplacental blood flow(i.e. BP was maintained around 140/90 mm Hg).The mode of the delivery was determined by foetal gestational age, foetal presentation, cervical status and maternal and foetal conditions. After delivery maternal complications were noted in the form of severity of preeclampsia (BP mmHg), mode of delivery (spontaneous, induction, preterm or caesarean), intrapartum and postpartum complications in form of placental abruption, postpartum haemorrhage and DIC.

Patients were examined for signs and symptoms of impending eclampsia, pulmonary edema, renal failure & HELLP and were managed according to guidelines. All newborn babies were evaluated at birth for any complications. In all cases foetal outcome was observed in form of APGAR score at 1min, at 5min, birth weight, FGR, meconium staining, signs of prematurity, congenital anomalies, respiratory distress & NICU stay. Newborns< 2.5 kilograms were classified as low birth weight. Newborn with APGAR score < 7 at 1 minute and 5 minutes were defined as having birth asphyxia.

After delivery placenta was collected and washed under running tap water. It was left to drain of blood for at least 2hrs and labelled with name of the mother and Identification Number & examined for:

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1. Size
2. Placental Weight: It was calculated after umbilical cord, membranes and non-adherent blood clots have been removed. Placenta weighing 90th percentile for estimated gestational age was LGA or Hyperplasia.
3. Insertion of Umbilical Cord and abnormalities in umbilical cord viz. knots (either true or false) and cord twisting.
4. Thickness of placenta: by inserting needle in centre of placenta.
5. Condition of Membranes.
6. Presence of Infarction, Retroplacental Hematoma and Calcification.

The placentae were weighed without umbilical cord. Fetoplacental weight ratio was calculated. All placentae were fixed in 10% formalin solution and sent to Pathology Department for macroscopic and microscopic examination. In all cases the placenta was sliced into 2cm thick coronal sections. The samples were examined macroscopically for umbilical vessel abnormalities and calcifications. Representative specimens were taken from the cord insertion, full thickness of macroscopically normal placenta, peripheral part of placenta, placental membranes and from abnormal areas. After 24hrs of embedment in paraffin, histological sections were taken by microtome (4µm). All samples were stained with Hematoxylin and Eosin. The biopsy specimen was examined by routine light microscopy (original magnification X 40). A pathologist was blinded to all clinical data except of gestational age (in order to assess the villous maturation) reviewed all histological samples with regard to presence or absence of following aspects:

A. Vascular lesions

1. **Decidual arteriopathy:** Decidual spiral arterioles with narrow calibres and residual medial smooth muscles cells beyond 20 weeks of gestation.
2. **Atherosis:** An accumulation of foamy lipid-filled macrophages with mural fibrinoid necrosis (vessel walls replaced by acellular bright pink amorphous material) of decidual arterioles.
3. **Infarction:** Ischemic villous necrosis.

B. Hyperplasia

Increased placental weight, increased cytotrophoblast cells.

C. Inflammatory lesions

1. **Umbilical vasculitis:** Presence of neutrophils.
2. **Chorionic plate vasculitis:** Neutrophilic inflammation of chorionic plate vessels.
3. **Acute chorioamnionitis:** Neutrophils in the chorion of the membrane roll with or without extension into the chorioamniotic mesoderm and amnion.

D. Villous hypovascularity

Analysis of hyalinized villi

E. Others

1. **Stromal fibrosis:** Collagen fibres within core of villi.
2. **Fibrinoid necrosis:** Condition where villous stroma is replaced with fibrinoid stroma.
3. **Placental calcification:** Assessed on gross examination.
4. **Syncytial knots:** Representative of characteristic deformation of terminal villi indicative of uteroplacental insufficiency.

Statistical analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality rejected then non parametric test was used. Statistical tests applied as follows

1. Quantitative variables were compared using unpaired t-test/Mann-Whitney Test (when the data sets were not normally distributed.) between the two groups and Anova/Kruskal Wallis test (for non-parametric data) between three groups.
2. Qualitative variables were compared using Chi-Square test/Fisher's exact test.

A p value of<0.05 is considered statistically significant. The data is entered in MS EXCEL spreadsheet and analysis is done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

A total of 204 pregnant women (102 in control, 51 in early onset pre-eclampsia and 51 women in late onset pre-eclampsia group) were followed until discharge after delivery.

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Table 1: Baseline demographic characteristics and caesarean section rates in control, early- and late-onset preeclampsia groups

Characteristic	Control N=102	Early onset N=51	Late onset N=51	P value
Age< 20 years	17	9(17.64%)	2(3.92%)	<0.0513
Primigravida	48	29(56.6%)	30(59.14%)	<0.05
Multigravida	54	22(43.13%)	21(44.32%)	<0.05
Caesarean section	22(21.56%)	18(35.9%)	8(15.6%)	<0.0542

Values are expressed as number (%). P-value < 0.05-statistically significant

Table 1 showed that incidence of early onset pre-eclampsia (in cases<20 years of age) was 17.64% while the incidence of late onset pre-eclampsia was 3.92%. Both early onset and late onset PE were seen more often in primigravida as compared to multigravida. In our study we came across caesarean section in 18(35.29%) of early onset PE as compared to 8(15.68%) of late onset PE.

Table 2: Maternal complications in control, early-and late-onset preeclampsia groups

Complications	Control N=102	Early onset N=51	Late onset N=51	P value
Placental abruption	01(0.98%)	16(31.37%)	06(11.76%)	P<0.0589
HELLP syndrome	00	08(15.68%)	02(3.92%)	-
DIC	00	04(7.84%)	00	-

Values are expressed as number (%). P-value < 0.05-statistically significant

Table 2 showed that incidence of Placental Abruption, HELLP Syndrome and Disseminated Intravascular Coagulation was highest in Early Onset PE.

Table 3: Perinatal outcome parameters in control, with early-and late-onset preeclampsia group

Parameters	Control N=102	Early onset N=51	Late onset N=51	P value
Stillbirth	01(0.98%)	15(29.41%)	01(1.96%)	P<0.0534
FGR	04(3.92%)	07(13.7%)	03(5.88%)	P,0.0523
Apgar score <7	13(12.74%)	18(35.29%)	08(15.56%)	
NICU admissions	13 (12.74%)	17(33.33%)	08(15.56%)	P<0.056
Neonatal deaths	02(1.96%)	03 (5.88 %)	01(1.96%)	P<0.0590

Values are expressed as number (%). P-value<0.05-statistically significant

Table 3 showed that stillbirths, FGR, Apgar score, NICU admissions and neonatal deaths were statistically significant more in early onset group.

Table 4: Placental characteristicsin control, with early onset and late-onset preeclampsia group

Characteristics	Control N=102	Early onset N=51	Late onset N=51	P value
Mean birth weight in gm	2513.9 ± 624.4	1978.1 ± 690.5	2190.5 ± 795.6	P<0.059
Mean placental weight in gm	444.9 ± 91.	365.6 ± 114.3	419.6 ± 119.9	P<0.057
Mean F/P Weight Ratio	5.55 ± 1.12	5.36 ± 1.15	5.41 ± 1.9	P<0.0527
Thickness of placenta Mean±2SD	1.62 ± 0.50	1.58. ± 0.58	1.58. ± 0.58	P<0.057
Retroplacental hematoma	03(2.94%)	20(39.21%)	08(15.68%)	P<0.0014
Infarction of placenta	07(6.8%)	33(64.7%)	12(23.52%)	P<0.0012
Calcification of placenta	13(12.57%)	31(60.8%)	13(25.49%)	P<0.0145

Values are expressed as mean±SD or number (%). P-value < 0.05-statistically significant4
F/P Weight Ratio: Fetoplacental Weight Ratio

Table 4 showed that mean birth weight, placental weight and mean F/P weight ratio was less in early onset PE as compared to late onset PE and normotensives and it was statistically significant. Although the mean diameter of placenta was reduced in early onset group but it was not statistically significant.
Our study showed incidence of markedly thinning of placenta (≤1.5 cm) was more in early onset PE with P value < 0.0571. Retroplacental hematoma, infarction and calcifications all three were more often seen in early onset group.

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Table 5: Placental histopathological variables in control, with early- and late-onset preeclampsia group

Variable	Control (N=102)	Early onset (N=51)	Late onset(N=51)	P value
Decidual arteriopathy	5 (4.90%)	9(17.64%)	3(5.88%)	< 0.05
Atherosis	2(1.96%)	7(13.72%)	4(7.8%)	<0.05
Excessive syncytial knots	3(2.94%)	10(19.60%)	13(5.88%)	<0.05

Values are expressed as number (%). P-value<0.05-statistically significant

Table 5 showed that placental pathological changes observed in patients with hypertensive disorders of pregnancy like retroplacental hematoma, infarction, calcification, decidual arteriopathy, atherosis were more frequently associated with early onset PE as compared to late onset PE that has an adverse influence on perinatal outcome even after correcting gestational age.

Discussion

Preeclampsia is a hypertensive disorder specific to pregnancy and one of the leading causes of maternal and perinatal morbidity and mortality. Although the diagnostic criteria for early and late onset PE are the same it is suggested by many authors that the pathophysiology of both differs. Etiopathogenesis of early onset PE focuses on the placenta and the utero placental circulation[10], late onset PE, on the other hand is mainly influenced by maternal factors.

Our study showed that women with preeclampsia were more prone for planned as well as emergency Caesarean sections, most common indication being foetal distress. Among normotensive control group 22 out of 102 (21.56%) underwent Caesarean section while among early pre-eclamptic group 18 out of 51 (35.29%) had Caesarean section (p value < 0.05). In our study the mean gestational age of delivery in early onset PE was found to be less (35 weeks and 3 days) as compared to late onset PE (36 weeks and 5 days) and the cause for termination of pregnancy before 37 weeks in early onset PE (either by Cesarean section or by vaginal route) was foetal distress or poor BISHOP's Score. Similar types of results were observed by YücesoyG *et al*.[11] which showed Caesarean section rate to be 48.3% in chronic hypertensive women while 63.8% in severe preeclamptic patients. Ebeigbe PN *et al*.[12]also showed increased (35.40%) incidences of Caesarean sections in early preeclamptic Nigerian women.

The incidence of maternal complications like placental Abruption (31.37%), HELLP Syndrome (15.6%) and Disseminated Intravascular Coagulation (7.8%) was highest in Early Onset PE. This is again supported by Yücesoy G *et al*.[11], who showed the early-onset group had a twofold increase in maternal complications and a significantly increased incidence of renal failure and HELLP syndrome. (p-value <0.05). Gaugler-Senden IP *et al*.[13] also concluded that HELLP Syndrome was being the one of the most common complication encountered in early onset pre-eclamptic women.

In our study foetal morbidity was also high in terms of FGR (P value < 0.0523), abnormal APGAR score at birth (P value<0.543) more NICU admissions (P value<0.0567)) and more neonatal deaths (P value<0.0590) in women with early onset than those presenting as late onset pre-eclampsia. These results are consistent with those of other studies[14, 15, 16].One contributing reason to stillbirth in women with early onset may be insufficient placentation and incomplete trophoblast invasion of spiral arteries, which results in decreased blood flow to the foetus resulting in foetal distress. Decreased uteroplacental perfusion may be the reason for the higher stillbirth rate seen in the early onset group. The neonatal death rate was higher in the early onset group than in late onset group. NICU admissions were significantly more common in babies born to mothers with early onset PE. 17 patients out of 102 (33.33%) in the early onset group versus 8 out of 51 (15.68%) in the late onset group were admitted in NICU, a difference that was statistically significant. This result is similar with those of most previous studies. Gestational age at birth was the most important factor contributing to neonatal outcomes. The greater number of adverse perinatal outcomes in the early onset group might have been due to prematurity itself rather than preeclampsia. Adverse perinatal outcomes in early onset group are explained by the difference in mean birth weighs which was 1.9 kg and 2.1 kg in the early and late groups, respectively. Normally a placenta weighs from 400 to 800gm which correlated with the mean placental weight of normotensive term patients in our study (444.9±91.7 gm). There was a reduction of placental weight in the both types i.e. women presenting with early onset PE or with late onset PE was but the reduction was more significant in those presenting as early onset PE. Similar observations were recorded Phadungkiatwattana P *et al*.[17]our study noted that there was reduction in the fetoplacental weight ratio in the hypertensive group more among those presented with early onset pre-eclampsia as compared to the normotensive control group (p-value < 0.05)Similar results with reduction of F:P weight ratio in early onset PE were obtained by Phadungkiatwattana P *et al*.[17]our study depicted incidence of retroplacental hematoma in 39.21% of Early Onset PE and 15.68% of Late Onset PE (P value <0.05) similar to Harsh Mohan *et al.*[18] who reported incidence of 20% (p-value<0.05) of retroplacental hematoma in women with pre-eclampsia who presented before the gestational age of 30 weeks.

Our study showed infarction of placenta in 33 (64.70%) of Early Onset PE and 12 (23.52%) of late Onset PE (p-value <0.0012) and calcification of placenta in 31 (60.78%) of Early Onset PE and 13(25.49%) of Late Onset PE with significant p-value (≤0.0145). Decidual Arteriopathy was seen in 9 (17.64%), Atherosis in 7 (13.72%) and Syncytial knots in 10 (19.60%) of Early Onset PE which was comparable to study done by van der *et al*.[19], which showed increased decidual arteriopathy (18%) in early onset preeclampsia and

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Stark MW,*et al*.[20]who showed increased incidences of syncytial knots (24%) and acute atherosis (18%) among women suffering from early onset pre-eclampsia. So we concluded that early- and late-onset preeclampsia placentas showed histopathological differences. These findings support that early-and late-onset preeclampsia are different subclasses of disease.

Conclusion

Early onset pre-eclampsia and late onset pre-eclampsia adversely influences the placental weight and fetoplacental weight ratio. The placental pathological changes like retroplacental hematoma, infarction, calcification, decidual arteriopathy, atherosis were more frequently associated with early onset as compared to late onset that has an adverse influence on perinatal outcome even after correcting gestational age.

And hence there are two subsets of preeclampsia viz. early onset & late onset with significantly different etiopathogenesis correlated in terms of abnormal histopathology of placenta and an adverse impact on perinatal outcome as well. From present study, it can also be concluded that the early onset pre-eclampsia bears the major brunt of the disease and its complications in the form of fetomaternal morbidity & mortality.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References

1. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. American College of Obstetricians and Gynecologists and others. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. ObstetGynecol2013;122:1122-312.
2. Berg CJ, Chang J, Callaghan WM, Whitehead SJ. Pregnancy-related mortality in the United States, 1991-1997, Obstetrics & Gynecology 2003;101(2):289-296.
3. Vatten LJ, SkjaervenR. Is pre-eclampsia more than one disease? BJOG 2004;111(4):298-302.
4. Ness RB, Sibai BM. Shared and disparate components of the pathophysiologies of foetal growth restriction and preeclampsia. Am J Obstet Gynecol 2006;195:40-49.
5. Crispi F, Domínguez C, Llurba E, Martín-Galla´n P, Cabero L, Grataco´s E. Placental angiogenic growth factors and uterine artery Doppler findings for characterization of different subsets in preeclampsia and in isolated intrauterine growth restriction. Am J Obstet Gynecol 2006;195:201-207.
6. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ 2005;330:565.
7. Roberts JM, Escudero C. The placenta in preeclampsia. Pregnancy Hypertens. 2012;2(2):72-83.
8. Krielessi V, Papantoniou N, Papageorgiou I, Chatzipapas I, Manios E, Zakopoulos N *et al*. Placental Pathology and Blood Pressure's Level in Women with Hypertensive Disorders in Pregnancy. Obstetrics and Gynecology International 2012;2012:e684083.
9. National High Blood Pressure Education Programme Working Group. Report of the National High Blood Pressure Education Programme Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol. 1997;177:1003-10.
10. Ogge G, Chaiworapongsa T, Romero R *et al*. Placental lesions associated with maternal underperfusion are more frequent in early-onset than in late-onset preeclampsia. J Perinat Med 2011;39:641-652.al.
11. Yücesoy G *et al*. Maternal and perinatal outcome in pregnancies complicated with hypertensive disorder of pregnancy: a sevenyear experience of a tertiary care centre. Arch Gynecol Obstet 2005;273(1):43-9.
12. Ebeigbe PN, Aziken ME. Early onset pregnancy-induced hypertension/eclampsia in Benin City, Nigeria. Niger J Clin Pract 2010;13(4):388-93.
13. Gaugler-Senden IP *et al*. Perinatal outcome of preeclampsia with an onset before 24 weeks' gestation. Audit in a tertiary referral center. Eur J ObstetGynecolReprod Biol. 2006;128(1-2):216-21.
14. Li XL, Guo PL, Xue Y, Gou WL, Tong M, Chen Q. An analysis of the differences between early and late preeclampsia with severe hypertension. Pregnancy Hypertens2016;6:47-52.
15. Madazli R, Yuksel MA, Imamoglu M, Tuten A, Oncul M, Aydin B *et al*. Comparison of clinical and perinatal outcomes in early-and late-onset preeclampsia. Arch GynecolObstet2014;290:53-7.
16. Lisonkova S, Joseph KS. Incidence of preeclampsia: risk factors and outcomes associated with early-versus lateonset disease. Am J ObstetGynecol 2013;209(544):e1-12.
17. Phadungkiatwattana P, Puttasiri S. Birth Weight/Placental Weight Ratio: Does the Association Differ Between Early-and Late-Onset Pre-eclampsia? Austin J Obstet Gynecol. 2018; 5(2):10-98.
18. Mohan Harsh, Sodhi S, Mohan PS *et al*. Foetal correlation with placental pathology in toxaemia of pregnancy. J Obstet and Gynecol India 1989;39:170-175.
19. Van der Merwe JL, Hall DR, Wright C, Schubert P, Grové D. Are early and late preeclampsia distinct subclasses of the disease-what does the placenta reveal? Hypertens Pregnancy 2010;29:457-467.
20. Stark MW, Clark L, Craver RD. Histologic differences in placentas of preeclamptic/eclamptic gestations by birth weight, placental weight and time of onset. Pediatr Dev Pathol. 2014;17(3):181-9.