

# Maternal and perinatal outcomes in women undergoing expectant management of early-onset pre-eclampsia: A retrospective cohort study

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**Background.** Expectant management of early-onset pre-eclampsia, with the aim of improving perinatal outcomes, may increase the risk of maternal morbidity.

**Objective.** To study the maternal and perinatal outcomes and their association with various risk factors in women undergoing expectant management for early-onset pre-eclampsia.

**Methods.** A retrospective cohort study was carried out in a tertiary centre in south India between April 2014 and June 2015. We studied 201 women with singleton pregnancies with pre-eclampsia diagnosed between 28 and 34 weeks' gestation. Demographic data, medication and treatment details, and delivery data were extracted from maternal charts. The primary outcomes were: (i) composite maternal outcomes, defined as the development of any of eclampsia, abruptio placentae, pulmonary oedema or renal failure; and (ii) perinatal mortality. Logistic regression was used to assess the independent association risk factors with primary outcomes, after adjusting for other variables.

**Results.** Sixty-nine women (34.3%) had one or more of the composite adverse maternal outcomes, and there were 74 (36.8%) cases of perinatal mortality. The presence of imminent symptoms (odds ratio (OR)=2.35) and multiparity (OR=2.31) were associated with composite adverse maternal outcomes, whereas low birth weight and breech vaginal delivery were associated with perinatal mortality. Perinatal mortality was higher in women with pre-eclampsia diagnosed between 28 and 30 weeks. Gestational age at diagnosis was not found to be associated with composite adverse maternal outcomes or perinatal morbidity.

**Conclusion.** Expectant management in early-onset pre-eclampsia can be safely considered without increasing maternal risk, after thorough counselling about outcomes, based on the available neonatal facilities in low-resource settings.

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Pre-eclampsia affects 5 - 7% of pregnancies, and early-onset pre-eclampsia developing remote from term (<34 weeks) affects 25%.<sup>[1,2]</sup> Pre-eclampsia remote from term is associated with a higher degree of perinatal and maternal morbidity, and also mortality. These women may be at risk of developing cardiovascular diseases later in life.

Expectant management is advocated for a select group of patients with early-onset pre-eclampsia, in a hospital with adequate maternal and neonatal surveillance.<sup>[3]</sup> The objective of expectant management is to improve the perinatal outcome in terms of neonatal survival, and with lower morbidity. However, prolongation of pregnancy may increase the risk of maternal morbidity, which includes placental abruption, renal failure, pulmonary oedema and eclampsia.<sup>[4]</sup>

There is inadequate literature regarding the outcome of expectant management in developing countries with limited health resources, where the fetus is considered salvageable at a gestation of 28 - 30 weeks or even later. The MEXPRE study,<sup>[5]</sup> conducted in eight centres across Latin America, suggested no neonatal benefits with expectant management of severe pre-eclampsia from 28 - 34 weeks, but found an increase in the risk of abruptio placentae and small-for-gestational-age infants. Other studies also reported increased risk of poor perinatal outcomes in women with pre-eclampsia remote from term who received expectant management at <30

weeks' gestation.<sup>[6-8]</sup> We aimed to study the maternal and perinatal outcomes of women undergoing expectant management of early-onset pre-eclampsia, and the risk factors associated with adverse maternal and perinatal outcomes.

## Methods

This was a retrospective cohort study conducted in the Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India, from April 2014 to June 2015. This is a teaching hospital that manages about 15 000 deliveries annually, and receives high-risk mothers from all the surrounding districts. We included women with singleton pregnancies who were admitted with a diagnosis of pre-eclampsia between 28 and 34 weeks' gestation, according to the American College of Obstetrics and Gynecologists' 2013 criteria,<sup>[9]</sup> identified from the medical records. Women who delivered within the first 24 hours or had intrauterine fetal demise at admission were excluded from the study. The study was approved by the Institute Ethics Committee (Human Studies) (ref. no. JIP/IEC/2015/523).

We collected maternal demographic details, gestational age at diagnosis, systolic and diastolic blood pressure recordings and various laboratory parameters on admission. Data regarding

duration of expectant management, gestational age at delivery, magnesium sulphate prophylaxis, whether antihypertensive medication was required, use of corticosteroid therapy and mode of delivery were also retrieved. In addition, complications such as eclampsia, abruptio placentae, pulmonary oedema, renal failure and incidence of postpartum haemorrhage were also noted. Neonatal data included birth weight, Apgar scores at 1 minute and 5 minutes, condition at discharge (including death) and presence of any complications in the neonatal period.

## Outcomes

Primary outcomes were: (a) composite adverse maternal outcome, defined as development of one of the following complications: (i) eclampsia (new-onset seizures or coma in pregnancy); (ii) abruptio placentae (clinical/ultrasound findings suggestive of premature separation of placenta); (iii) pulmonary oedema (clinical/radiological); (iv) acute renal failure (urine output <500 mL/day, serum creatinine >1.2 mg/dL); and (b) perinatal mortality (PNM), which included stillbirth and early neonatal death (death up to 7 days after delivery).

Secondary outcomes were neonatal morbidity, such as hypoxic ischaemic encephalopathy (cord pH <7, and moderate or severe encephalopathy), need for ventilator support, necrotising enterocolitis (clinical/radiographic findings of pneumoperitoneum/portal air) and intraventricular haemorrhage grade III/IV (haemorrhage with ventricular dilatation or parenchymal haemorrhage).

## Sample size

Sample size was calculated using the nMaster2.0 software (CMC Vellore, India), with a 20.4 % incidence of maternal complications in women with early-onset pre-eclampsia,<sup>[8]</sup> and the risk of maternal complications and perinatal mortality was expected to be two times higher in women who were diagnosed at 28 - <32 weeks' gestation than at 32 - <34 weeks. Using a two-sided  $\alpha$  error of 5% and power of 80%, 179 women were calculated as necessary for the study. We included 201 women who received expectant management for pre-eclampsia.

## Statistical analysis

Data analysis was done using Stata version 13.1 (Statacorp, USA). Data are presented as mean (standard deviation) or as a percentage with range, as appropriate. Associations of categorical variables such as parity and intrauterine growth restriction with a primary outcome were assessed using the  $\chi^2$  test. Association of continuous variables such as gestational age at diagnosis and blood pressure with primary outcomes were compared using Student's *t*-test. Multivariate logistic regression was performed to assess the independent association of gestational age at diagnosis with primary outcomes, after adjusting for other variables. A *p*-value <0.05 was considered significant.

## Results

From April 2014 to June 2015, of the 17 602 deliveries in the hospital, 610 (3.46%) were complicated by pre-eclampsia. Of these, 257 fulfilled the inclusion criteria of pre-eclampsia diagnosed at <34 weeks. We excluded 49 women from the study who delivered within 24 hours of admission. The main indications for delivery included intrauterine fetal demise (*n*=10), eclampsia (*n*=5), non-

reassuring cardiotocography (*n*=8), abruptio placentae (*n*=8) and uncontrolled hypertension (*n*=18). Of the remaining 208 cases who received expectant management, we were able to retrieve the files and collect the data of 201 patients for inclusion in the study. The characteristics of women at the time of diagnosis of early-onset pre-eclampsia are shown in Table 1.

The median duration of expectant management overall was 11 days (range 2 - 48 days). The median duration of expectant management was 8 days in women diagnosed with pre-eclampsia at 28 - <30 weeks and 32- <34 weeks, compared with 18 days in women diagnosed at 30 - <32 weeks. The mean (standard deviation) gestational age at delivery was 33.6 (2.7) weeks, and labour was induced in 19.9% (*n*=40) of patients. Caesarean section was performed in 56 (27.8%) women, with pre-labour caesarean section in 14 (25%) cases.

Table 2 shows the various maternal and perinatal complications in the study population, based on the gestational age at diagnosis of pre-eclampsia. Of the 201 women included in the study, 69 (34.3%) had one or more of the composite adverse maternal outcomes. No maternal death occurred in the study. The incidence of adverse maternal outcomes was higher in women who were diagnosed at 32 - <34 weeks' gestation, compared with earlier gestational age at diagnosis. More women with severe pre-eclampsia at admission had adverse maternal outcomes than those without it (48 (47.5%) v. 21 (21.0%), *p*<0.001). More women developed abruptio placentae (14 (13.2%) v. 4 (4.2%)) and renal failure (27 (25.5%) v. 12 (12.6%)) in the group who were diagnosed at 32 - 34 weeks, compared with earlier gestational age. Logistic regression analysis showed that gestational age at diagnosis of pre-eclampsia was not associated with adverse maternal outcomes, after adjusting for other variables. However, multiparity (odds ratio (OR)=2.31) and presence of imminent symptoms (OR=2.35) were independently associated with adverse maternal outcomes.

Perinatal mortality (PNM) occurred in 74 (36.8%) cases in the study. PNM was significantly higher in those who were diagnosed at 28 - <30 weeks' gestation (22/32; 68.8%) compared with others (at 30.1 - <32 weeks 26/63 (41.3%), and at 32.1 - <34 weeks 26/106 (24.5%) (*p*<0.001). The incidence of PNM was found to be similar

**Table 1. Characteristics of the study population (N=201)**

Characteristic	n (%)*
Age (years), mean (SD)	25.6 (4.6)
Nulliparous	108 (53.7)
Gestational age at admission (weeks)	
28 - <30	32 (15.9)
30 - <32	63 (31.3)
32 - <34	106 (52.7)
Anaemia	103 (41.3)
Severe anaemia	17 (8.46)
Imminent eclampsia symptoms	94 (46.7)
Systolic BP (mm Hg), mean (SD)	156.8 (13.5)
Diastolic BP (mm Hg) mean (SD)	101.4 (9.7)
No. of antihypertensives given	
0	5 (2.5)
1	122 (60.7)
2	74 (36.8)
Prophylactic magnesium sulphate	110 (54.7)

SD = standard deviation; BP = blood pressure.  
\*Unless otherwise indicated.

**Table 2. Maternal and perinatal complications in the study population based on gestational age at diagnosis of pre-eclampsia (N=201)**

Complication	28 - <30 weeks	30 - <32 weeks	32 - <34 weeks	Total
	(n=32)	(n=63)	(n=106)	
Abruptio placentae	1 (3.1)	3 (4.8)	14 (13.2)	18 (8.9)
Acute renal failure	6 (18.8)	6 (9.5)	27 (25.5)	39 (19.4)
Pulmonary oedema	0 (0)	1 (1.6)	1 (0.9)	2 (1.0)
Eclampsia	2 (6.3)	5 (8.2)	7 (6.6)	14 (7.0)
Stillbirth	20 (62.5)	18 (28.6)	14 (13.2)	52 (25.9)
Neonatal death*	2 (16.7)	8 (17.8)	12 (13.0)	22 (14.8)
NICU admission*	9 (75.0)	32 (71.1)	60 (65.2)	101 (67.8)
HIE*	1 (8.3)	2 (4.4)	3 (3.3)	6 (4.0)
NEC*	0 (0)	1 (2.2)	2 (2.2)	3 (1.5)

NICU = neonatal intensive care unit; HIE = hypoxic ischaemic encephalopathy; NEC = necrotising enterocolitis.

\*Of all live-born babies.

in those with and without severe features of pre-eclampsia at the time of admission (40 (39.6%) v. 34 (34%);  $p=0.410$ ). On adjusting for other variables in the model, birth weight (OR=0.78) and assisted breech vaginal delivery (OR=7.43) were independently associated with PNM. Each 100 g increase in birth weight decreased the odds of perinatal mortality by 22%. Model testing the interaction with gestational age at diagnosis and intrauterine growth restriction with PNM did not show any significance (likelihood ratio test  $p=0.068$ ). Each 100 g increase in birth weight decreased the odds of PNM by 22%.

## Discussion

Composite maternal morbidity occurred in 34.3% of cases, and poor perinatal outcomes occurred in 36.8%. Gestational age at diagnosis of pre-eclampsia was not associated with composite adverse maternal outcomes or with PNM, after adjusting for other variables in the multivariate model. However, the presence of imminent symptoms and multiparity were associated with composite adverse maternal outcomes, whereas lower birth weight and assisted breech vaginal delivery were associated with PNM. Significantly higher PNM rates were observed in women diagnosed with pre-eclampsia at  $\leq 30$  weeks' gestation, compared with those who were diagnosed after 30 weeks.

There were no maternal deaths in the study, which is consistent with results from other studies. In 2007, a review published by Sibai and Barton<sup>[3]</sup> found that among 1 677 women in their study, only one maternal death occurred during expectant management following diagnosis of pre-eclampsia at 24 weeks' gestation. However, the reported maternal morbidity, especially abruptio placentae and renal failure, in our study was higher than that in the available literature, which indicates a need for frequent and aggressive monitoring in those women considered for expectant management. Being a tertiary referral centre, a higher proportion of pre-eclamptic women with increased risk are referred from the peripheral health facilities than in the other studies, which might account for the higher rates in the study. Women with severe features of pre-eclampsia at admission were found to have higher rates of adverse maternal outcomes in the study. Haemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome complicated 32% of the cases, which was higher than the 4 - 8% found in other studies. The rate of renal failure (19.9%) was also higher in the present study compared with others that have reported 3 - 6%.<sup>[3,7,8]</sup> Mooney *et al.*<sup>[10]</sup> reported that maternal morbidity was higher in women with expectant management,

and deterioration of the maternal condition was the indication for delivery in the majority of women, whether by induction of labour or caesarean section. In a study in Japan, the incidence of pulmonary oedema was significantly higher (20% v. 0%) in those who underwent expectant management compared with immediate delivery in women developing pre-eclampsia at <32 weeks' gestation.<sup>[11]</sup> As noted earlier, abruptio placentae is an unpredictable complication, which may not be noted to occur with uncontrolled blood pressure, amount or worsening of proteinuria, low platelets or any other signs or symptoms suggestive of deterioration. It could lead to other complications, such as renal failure or coagulopathy. For these reasons, expectant management should only be attempted in settings with facilities which have intensive/frequent monitoring, as in high dependency/intensive care units, or transfusion facilities, under a team experienced in managing these complications, for prompt intervention to reduce maternal morbidity.<sup>[12,13]</sup>

The perinatal mortality rate in our study (36.8%) was similar to that in a study in Egypt,<sup>[7]</sup> but much higher than in other studies on expectant management of pre-eclampsia from developed nations. The stillbirth (62.5%) and neonatal mortality (16.7%) rates were highest in those who had pre-eclampsia diagnosed at an earlier gestational age, similarly to the Egyptian study.<sup>[7]</sup> Swamy *et al.*<sup>[8]</sup> also observed higher gestational age at diagnosis to be associated with reduced incidence of complications such as respiratory distress syndrome and perinatal mortality. In the MEXPRE Latin-American study,<sup>[5]</sup> 60% of the perinatal deaths (15 of 25) occurred in patients with a gestational age of 28 - 29 weeks, and only 2 (8%) in the cohort with the gestational age of 32 - 33 weeks. We considered the lower limit of salvageability of the fetus to be 28 weeks, as in most developing nations, and observed that the perinatal mortality rate was higher when pre-eclampsia was diagnosed between 28 and 30 weeks. The gestational age at which the fetus is considered salvageable varies widely between developing and developed nations. The lower limit of neonatal survival is between 28 and 32 weeks' gestation in the former, whereas it is 24 weeks or even lower in most developed nations. Perinatal morbidity and mortality rates in developing countries may be higher than those at <24 weeks in developed countries, even when the fetus is delivered at 30 - <32 weeks' gestation, owing to a lack of resources and the inaccessibility of advanced neonatal facilities.

Our study had some limitations. Being a retrospective study limited to analysing records, we could not gather information

regarding certain variables, such as body mass index, which may have had an impact on the primary outcomes. In our study population, we observed adverse maternal outcomes to occur more commonly in women with pre-eclampsia diagnosed at 32 - <34 weeks' gestation than at either <32 or >34. This could be due to lesser representation of patients with gestational age <30 weeks in the study, and the fact that most women (62.5%) in this group delivered earlier due to intrauterine demise. We used robust statistical analysis to adjust for the possible factors contributing to the outcomes, using multivariate regression analysis, and also assessed the effect of the interaction of intrauterine growth restriction with gestational age at diagnosis, and the outcomes, which might be considered a strength of the study.

## Conclusion

Pregnancies in which pre-eclampsia was diagnosed at a gestational age <30 weeks had a higher incidence of perinatal mortality, consistent with the limited availability of advanced neonatal care facilities in low-resource settings. Expectant management in such women should only be considered after thorough counselling, in centres with advanced neonatal facilities, and where optimal maternal intense/frequent monitoring can be provided. Future prospective studies that examine these outcomes in women with early-onset pre-eclampsia against a comparator group of women without pre-eclampsia are required to confirm and to quantify the risk to these women.

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