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ORIGINAL ARTICLE

Maternal and Perinatal Outcome During Expectant Management of Severe Pre-Eclampsia Between 24 and 34 Weeks of Gestation

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Abstract
Objective To determine the maternal and perinatal outcome after expectant management of severe pre-eclampsia between 24 and 34 weeks of gestation.
Method The maternal and fetal status was monitored by an intensive, non-invasive method among 94 women with severe pre-eclampsia between 24 and 34 weeks of gestation who were scheduled for expectant management in the OICU at a tertiary care center. Pregnancy prolongation and maternal and perinatal morbidity and mortality were analyzed by the Student '*t*' test and the Mann–Whitney U test.
Results The days of pregnancy prolongation and perinatal mortality were significantly higher among those managed at <30 weeks. Increasing gestational age correlated with a reduction of RDS. Maternal morbidities were significantly higher among those managed at <28 weeks. But, there was no maternal mortality.
Conclusion Expectant management of severe pre-eclampsia at 30–34 weeks in a tertiary care center of a developing country is associated with good perinatal outcome and risk reduction for the mother.

Keywords Early severe pre-eclampsia · Expectant management · Perinatal outcome · Maternal morbidity

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Introduction

Pre-eclampsia is an important health issue that has to be dealt with especially in developing countries where the incidence and rates of adverse outcomes are higher. The incidence of pre-eclampsia is reported as 7.6 % and severe pre-eclampsia as 3.3 %. Pre-eclampsia alone accounts for 12–18 % of maternal mortality. The highest maternal mortality rate due to pre-eclampsia reported in developing country is 0.4 %. Besides, it is associated with a fivefold increase in perinatal mortality [1].

The course of early severe pre-eclampsia is associated with a progressive deterioration of the maternal condition. Delivery remains the only definite treatment. There is a broad agreement to terminate the pregnancy when maternal or fetal conditions are altered or once 34 weeks of gestation is reached. Delivery at an earlier gestational age, however, is associated with an increased risk of adverse neonatal outcome [2]. In addition, fetal lung maturity is not accelerated by pre-eclampsia alone, and neonatal outcome remains closely dependent on the use of corticosteroid for fetal lung maturity enhancement [3]. The results of these

findings have led to a policy of expectant management to improve neonatal outcome. Expectant management, on the other hand, may worsen maternal condition [4, 5]. One randomized trial has shown an improvement of perinatal outcome without deterioration of maternal condition. This study, however, had a limited sample size [6]. This study was undertaken to determine maternal and perinatal outcomes after expectant management of singleton pregnancies with severe pre-eclampsia between 24 and 34 weeks of gestation at a tertiary care center.

Materials and Methods

From August 1, 2005 to July 31, 2006, 94 women admitted to this tertiary care institution with severe pre-eclampsia between 24 and 34 weeks of gestation were given an expectant line of management, provided both mother and fetus remained stable at the end of 24 h of admission. The diagnosis of severe pre-eclampsia was made according to the American College of Obstetrics and Gynecology (ACOG) criteria [7].

Pregnancies with unstable conditions for either the mother or the fetus during the first 24 h after admission, particularly women with eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count), severe uncontrolled hypertension (defined as difficulty to stabilize systolic blood pressure <160 mmHg and diastolic blood pressure <110 mmHg despite maximum doses of combined antihypertensive therapy—methyldopa with nifedipine or atenolol), abruptio placenta, abnormal fetal heart rate monitoring, severe oligamnios (defined as amniotic fluid index <5 cm), or reverse end diastolic flow in the umbilical artery, were excluded. Also, women with other medical illnesses like diabetes mellitus, cardiac disease, respiratory disease, epilepsy, renal disease, and obstetric complications like bad obstetric history, multiple gestation, preterm premature rupture of membrane, placenta praevia, and congenital anomalies of the fetus which would affect the feto-maternal outcome were excluded.

The study design was an observational study. Recruited women were admitted to an obstetric intensive care unit in the labor room for intensive, non-invasive monitoring of the maternal and fetal status. Gestational age was determined by means of the last menstrual period, obstetric ultrasonography (USG), or both. Betamethasone to enhance fetal lung maturity was immediately started, 12 mg intramuscular, two doses 24 h apart. Antihypertensive drugs were administered to keep the systolic blood pressure at 130–150 mmHg and the diastolic blood pressure at 80–100 mmHg. We used three oral antihypertensive agents in a stepwise approach (methyldopa 500 mg QID, nifedipine 20 mg TID, and atenolol 50 mg BD). Nitroglycerine drip (2–20 μg/kg/h) was reserved to control hypertensive peaks as well as resistant cases, along with oral antihypertensive agents. Magnesium sulfate was given to women who developed eclampsia, while prophylaxis with this agent was considered only when the patient developed imminent signs of eclampsia according to the discretion of the managing clinician. A full blood count, renal function tests, liver function tests, urine routine examination, fundoscopy, and coagulation profile were obtained. Fetal condition at entry was assessed by means of USG for the estimation of fetal growth, and amniotic fluid volume, non-stress test, and the study of the umbilical artery Doppler waveform were done in IUGR cases (defined as estimated fetal weight <10th percentile).

Maternal monitoring included blood pressure measurements every four hours and a clinical evaluation of symptoms twice daily and according to the patient's condition. Blood tests included hemoglobin, packed cell volume, platelet count, liver enzymes, urea, creatinine, and uric acid. These tests were performed biweekly. Urine albumin, 24-h urine volume, and maternal weight were assessed every day. Daily fetal movement count, biweekly non-stress test, weekly USG and umbilical artery Doppler in case of IUGR were used for antepartum fetal surveillance. Failure to control blood pressure or the development of major maternal or fetal complications was an indication for delivery. Women reaching a minimum gestation of 34 weeks without complications delivered electively. Fetal viability was set at 28 weeks of gestation with a minimum weight of 1,000 g.

Fetal indications for delivery during expectant management were abnormal fetal heart rate monitoring (repeated late decelerations, prolonged deceleration >3 min, short term variability <5 beats per minutes over 60 min), severe IUGR (estimated fetal weight <5th percentile), or severe oligamnios (amniotic fluid index <5 cm). Maternal indications for delivery during expectant management were eclampsia, HELLP syndrome [classified into complete and partial varieties (Memphis classification). Complete HELLP syndrome was defined by the presence of all three of the following criteria: Hemolysis (characteristic peripheral blood smear–schistocytes, burr cells, and serum lactate dehydrogenase ≥600 U/l or serum total bilirubin ≥1.2 mg/dl), elevated liver enzymes (serum aspartate aminotransferase ≥70 μ/l), and low platelet count (<100,000 cells/μl). Partial HELLP was defined by the presence of one or two of the above mentioned three criteria], abruptio placentae (premature separation of normally situated placenta after 28 weeks of gestation), disseminated intravascular coagulation [the presence of three or more of the following criteria: low platelets (<100,000 cells/μl), low fibrinogen (<300 mg/dl), positive D-dimers (≥50 mg/dl), prolonged prothrombin (≥14 s),

Table 1 Clinical characteristics of study population

Total number of cases recruited ($n = 94$)	
Age (years)	18–38 (23)
Gravidity	
Primigravida	48 (51.06 %)
Multigravida	46 (48.94 %)
Previous pre-eclampsia	10 (21.73 %)
Family history of pre-eclampsia	5 (5.31 %)
Gestational age at admission (weeks)	24–34 (32)

Table 2 Days gained at each entry gestation in the study

Gestational age (weeks)	Number ($n = 94$)	Mean	Median	SD	Range
24–28	10	11.3	11.5	6.86	3–23
28.1–30	12	13.33	14.5	8.139	1–24
30.1–32	15	7.4	5	4.881	1–17
32.1–34	57	4.772	4	3.148	1–14

and partial thromboplastin (≥40 s) times], pulmonary edema (diagnosed on the basis of clinical findings and chest radiograph), acute renal failure [diagnosed in the presence of oliguria (<0.5 ml/kg/h that does not resolve with fluid intake) in association with elevated serum creatinine >1.4 mg/dl], severe uncontrolled hypertension, persistent headaches or visual disturbances, persistent epigastric pain, or right upper quadrant tenderness.

The main outcome of the study was the maternal and perinatal outcome after expectant management of severe pre-eclampsia between 24 and 34 weeks of gestation. Major maternal complications included maternal death, eclampsia, HELLP syndrome, abruptio placenta, DIC, pulmonary edema, acute renal failure, and loss of vision. Major perinatal complications included fetal and neonatal death, respiratory distress syndrome (RDS), necrotising enterocolitis, intraventricular hemorrhage, sepsis, convulsions, and hyperbilirubinemia. The secondary outcome was days of pregnancy prolongation defined as full days gained since admission. Maternal outcome and pregnancy prolongation were analyzed according to the gestational age at admission, and perinatal outcome was analyzed according to the gestational age at delivery, which was divided into 4 groups—24–28, 28.1–30, 30.1–32, and 32.1–34 weeks.

Statistical Analysis

Data are presented as median with range, mean with standard deviation, or percentage as appropriate. The difference in mean was analyzed by the Student '*t*' test. Test of proportion was used to compare two sets of values and the Mann–Whitney U test was used to analyze quantitative observations. A p value <0.05 was considered significant.

Results

During the study period, 2805 women delivered in the study hospital. While 231 (8.23 %) women with any form (mild or severe, early or late onset) of pre-eclampsia were managed, 123 (4.38 %) were admitted for severe pre-eclampsia between 24 and 34 weeks of gestation. Among them, 94 (3.35 %) were given expectant management. Overall, in our study population, 23.57 % of women were not eligible for expectant management. The clinical characteristics of the study population are as shown in Table 1.

The median number of days of pregnancy prolongation was 5 (1–24). The days gained were significantly higher among those who had expectant management between 28.1 and 30 weeks (14 days) compared with the other two groups—30.1–32 weeks (5 days) and 32.1–34 weeks (4 days) as shown in Table 2.

Maternal outcomes are summarized in Table 3. There were no instances of maternal death, cerebrovascular accident, or severe acute renal failure among the 94 women. All three HELLP syndrome cases were of the partial HELLP variety and were in the antepartum period. One woman had DIC following abruptio placenta. Both the cases of pulmonary edema had spontaneous resolution over a period of 1 week. One case of loss of vision was due to retinal edema and the other was cortical blindness due to cerebral edema. Both of them regained their vision in 3 days time. Eclampsia did not result in any residual

Table 3 Maternal complications according to gestational age at admission

Gestational age (weeks)	Abruption/premature separation of placenta *n* (%)	HELLP *n* (%)	Pulmonary edema *N* (%)	Loss of vision *N* (%)	Eclampsia *n* (%)	DIC *N* (%)
24–28 ($n = 10$)	4	1	1	0	2	0
28.1–30 ($n = 12$)	4	0	0	0	0	0
30.1–32 ($n = 15$)	6	3	0	2	0	1
32.1–34 ($n = 57$)	6	0	1	0	0	0
Total ($n = 94$)	20 (21.27 %)	4 (4.26 %)	2 (2.13 %)	2 (2.13 %)	2 (2.13 %)	1 (1.06 %)

Table 4 Perinatal morbidity according to gestational age at delivery

Gestational age (Weeks)	IUGR *n* (%)	Apgar at 5′ < 7 *n* (%)	NICU admission *n* (%)	NICU stay
24–28 ($n = 6$)	1 (16.66)	0		
28.1–30 ($n = 5$)	3 (60)	1 (100)	1 (100)	14
30.1–32 ($n = 14$)	7 (50)	6 (60)	9 (64.29)	16 (4–21)
32.1–34 ($n = 69$)	27 (39.13)	6 (9.37)	42 (60.87)	8.5 (2–25)

Table 5 Perinatal mortality according to gestational age at delivery

Gestational age (weeks)	Abortion (*n*)	IUD (*n*)	Still birth (*n*)	Neonatal death (*n*)	Perinatal mortality *n* (%)
24-28 ($n = 6$)	6				
28.1–30 ($n = 5$)		1	3	1	4 (80)
30.1–32 ($n = 14$)		1	3	4	4 (28.57)
32.1–34 ($n = 69$)		1	4	0	5 (7.25)

neurologic deficit. None of them required adult intensive care admission.

Overall, the rate of IUGR was 40.42 %. Seventy-five (79.78 %) babies were born alive, with 13 (17.33 %) of these infants having an Apgar score <7 at 5 min. The total NICU admission required among 75 liveborn infants was 52 (69.33 %). They stayed in the NICU for a median number of 12 days. There was no statistically significant difference among different gestational age groups regarding the rate of IUGR, NICU admission, or NICU stay. This has been documented in Table 4.

As Table 5 depicts, there were 13 perinatal deaths for a total perinatal mortality of 13.88 % (4.91/1,000 live births); 8.07 % of the total perinatal mortality (60.89/1,000 live births) was contributed by severe pre-eclampsia in women between 24 and 34 weeks of gestation who were given expectant management. The median gestational age of the liveborn babies was 32 weeks and the median birth weight was 1,450 g (1,000–1,800 g). The median gestational age of 19 abortions and perinatal deaths was 29 weeks (25–33 weeks) and the median birth weight was 800 g (400–1,500 g). None of the babies survived in the gestational age group of below 30 weeks. All six pregnancies (6.38 %) were terminated prior to viability. In these cases, a combination of complications (absent end diastolic velocity in the umbilical artery, severe growth restriction, loss of blood pressure control, eclampsia, HELLP syndrome, and premature separation of placenta) developed during the expectant management. In the gestational age group of 28.1–30 weeks, four out of five pregnancies were terminated in view of the development of a combination of complications (abruptio placenta, loss of blood pressure control, and absent end diastolic velocity in the umbilical artery). Fourteen of 19 deaths had a birth weight below 1,000 g (400–1,000 g). The majority (75 %) of the deaths above 1,000 g were due to abruptio placenta. The causes of the deaths were non-viable pregnancy, abruptio placenta, severe IUGR, and prematurity. Neonatal survival was 93.34 %. All five neonatal deaths were of infants weighing ≤1,000 g. The median gestation age of these infants was 30 weeks (28–31 weeks). All were late neonatal deaths (8–28 days). The causes of deaths were RDS and pneumonia.

Discussion

Recent studies have suggested that fetal lung maturity, as well as fetal neurologic and physical development, was not accelerated in pregnancies complicated by pre-eclampsia [8]. In addition, neonatal mortality is closely dependent on the gestational age at delivery and on the use of corticosteroid treatment to enhance fetal lung maturity [9]. These studies have highlighted the need of expectant management to improve perinatal outcome in women with early onset severe pre-eclampsia. The goal of delivery of a live mature newborn infant in optimal condition, however, must not be achieved at the expense of maternal safety.

This study was undertaken to determine pregnancy prolongation and perinatal and maternal outcomes after expectant management of singleton pregnancy with severe pre-eclampsia between 24 and 34 weeks of gestation. Our hospital is a major referral center, and the relatively high prevalence of severe pre-eclampsia (4.38 %) in our population may therefore be related to referral bias. In this study, pregnancies were prolonged by a median number of 5 days with a significantly greater period gained at earlier gestations. The days of pregnancy prolongation observed in this study are in agreement with the results of recent trials [10–12]. Two prospective randomized controlled trials comparing expectant management with interventionist management have been published [5, 6]. The first study that included 38 patients found a mean pregnancy prolongation of 7.1 days in the group of women who were given expectant management [5]. In a larger randomized controlled trial in which 95 patients were included, the mean pregnancy prolongation was 15 days [6].

The rate of maternal complications is similar to those reported in a previous study [10]. Severe maternal

complications observed were less frequent than severe perinatal ones. There were, however, no instances of maternal deaths, cerebrovascular accidents, or severe acute renal failure necessitating dialysis in our study. On the whole, major complications resolved quickly without the need for adult intensive care admission, which is a reassuring finding. Despite the use of magnesium sulfate and careful control of blood pressure, we had two cases of eclampsia. The control of blood pressure was carefully applied with only six women (6.38 %) having loss of blood pressure control as an indication for delivery. The rate of eclampsia was slightly higher compared to other studies [11]. It is important to note, however, that in the MAGPIE trial, magnesium sulfate was not associated with a significantly decreased rate of eclampsia in the subgroup of women included from countries with a low perinatal mortality. Also, they could achieve 58 % reduction in the eclampsia rate with magnesium sulfate prophylaxis [12].

Neonatal morbidity was clearly related to the gestational age at the onset of expectant management and this is in agreement with previous studies [9, 13]. Increasing gestational age correlated with a reduction of respiratory distress syndrome [9, 14]. In addition, neonatal outcome was excellent during expectant management at 32–34 weeks. The sample size, however, is too low for valid conclusions. A much larger number of patients at 32–34 weeks need to be studied before the benefits or safety of expectant management can be stated with certainty.

Regarding perinatal and neonatal mortality rates, our results are not in agreement with results of the trial which was undertaken in a developed country [15]. Our observed perinatal and neonatal mortality rates were 13.83 and 6.49 %, respectively, which are acceptable in a developing country setup. It reflects both the socioeconomic status of the population and the standard of the neonatal intensive care unit. 73.68 % of perinatal deaths were with a birth weight <1,000 g and gestational age <30 weeks. In contrast to one recent study [14] which did not have instances of perinatal deaths in women expectantly managed at 30 or more weeks of gestation, we had nine fetal deaths in women expectantly managed at 30 or more weeks, more than half of which were caused by abruptio placenta. We could not salvage most of these fetuses mainly because of non-affordability of the patients as well as the limitation of the neonatal intensive care unit.

The excellent perinatal outcome obtained in women on expectant management at 30 weeks or more is certainly related to improvements in neonatal care, to corticosteroid treatment to enhance fetal lung maturity, and also to pregnancy prolongation. Some physicians would regard the delivery at 30 weeks or more after corticosteroid treatment to be in the best interests of both the mother and the fetus. Our study does not answer this question as we have not compared expectant management with interventionist management. Also, the sample size does not have enough statistical power for any valid conclusion. In addition, one study [6] has shown that expectant management after corticosteroid treatment in women with severe pre-eclampsia after 30 weeks of gestation improved perinatal outcome with a minimal risk for the mother, even if that study had a limited sample size.

Conclusion

Close and frequent observation of maternal and fetal status during expectant management of severe pre-eclampsia at 30–34 weeks in a tertiary care center, in a developing country, is associated with a good perinatal outcome and a reduced risk for the mother. In view of poor perinatal outcome and high maternal complications, pregnancy termination, rather than expectant management, should be considered in women with severe pre-eclampsia at <30 weeks of gestation.

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