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Original Article

Does aggressive and expectant management of severe preeclampsia affect the neurologic development of the infant?

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Abstract: Objective: To compare and evaluate the influences of expectant and aggressive management of severe preeclampsia on the first year neurologic development of the infants in pregnancies between 27 and 34 weeks of pregnancy. Methods: Seventy women with severe preeclampsia between 27 and 34 weeks of gestation were included in the study. 37 patients were managed aggressively (Group 1) and 33 patients were managed expectantly (Group 2). Glucocorticoids, magnesium sulfate infusion and antihypertensive drugs were administered to each group. After glucocorticoid administration was completed Group 1 was delivered either by cesarean section or vaginal delivery. In Group 2 magnesium sulfate infusion was stopped after glucocorticoid administration was completed. Antihypertensive drugs were given, bed rest and intensive fetal monitorization were continued in this group. Results: The average weeks of gestation, one minute and five minute apgar scores and hospitalization time in intensive care unit were similar in both groups ($P > 0.05$). Three neonatal complications in Group 2 and five in Group 1 were detected according to the Denver Developmental Screening Test-II and one pathologic case was detected in both groups following neurologic examination. Neonatal mortality was seen in seven patients in Group 1 and one in Group 2. There were no significant differences between groups in terms of neonatal mortality and morbidity and maternal morbidity ($P > 0.05$). The average latency period was 3.45 ± 5.48 days in Group 2 and none in Group 1. Conclusion: There was no significant difference in the first year neurological development of infants whose mothers underwent either expectant and aggressive management for severe preeclampsia.

Keywords: Severe preeclampsia, aggressive management, expectant management, neurologic development

Introduction

Hypertensive diseases are the most commonly seen medical complications in pregnancy and have incidence between 5-10% [1]. The actual incidence of preeclampsia is not known but is approximately 5-8% [2, 3].

Maternal and perinatal morbidities significantly increased with severe preeclampsia [3, 4]. Severe preeclampsia is related to increased maternal mortality (0.2%) and morbidities (5%) such as seizures, pulmonary edema, acute renal and liver failure, disseminated intravascular coagulopathy (DIC), and stroke. These complications are most commonly seen before 32 weeks gestational age or in patients who have other systemic illness [5].

In severe preeclampsia, maternal and fetal conditions generally worsen and only delivery can stop this progression. Early diagnosis and appropriate management can improve maternal and fetal conditions. Delivery should be planned for pregnant women who develop the disease after 34 weeks of gestation because of

increased morbidity and mortality of women and increased risk to the fetus (intrauterin growth restriction (IUGR), hypoxemia, and death). Delivery must be considered immediately in the event of eclampsia, multiorgan dysfunction, severe IUGR (< 5 percentile), ablatio placenta and non-reassuring non-stress test (NST) [6, 7].

If both maternal and fetal conditions are stable, there is no consensus on the management of severe preeclamptic women before 34 weeks of gestation. In these patients, some authors accept birth as definitive treatment independent from the gestational age, whereas others suggest delivery if maternal and fetal indications present [6, 7].

Labor is always acceptable for the mother, but it may not always be ideal for the fetus. Our aim in this study was to compare expectant and aggressive management of pregnant women with severe preeclampsia between 27 and 34 weeks of gestation, and to evaluate the influence of these on the first year of neurologic development in the infants.

Materials and methods

This is a prospective cohort study and was conducted by examining hospitalized patients in Zeynep Kamil Women and Children Diseases, Education and Research Hospital, Department of Obstetrics and Gynecology, between January 1, 2010, and January 1, 2012. The study group consisted of 70 pregnant women with severe preeclampsia between 27-34 weeks of gestation. Multiple pregnancies were excluded from the study. All patients were followed up in the hospital. Complete blood count (CBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, creatinine, lactate dehydrogenase (LDH), uric acid, total protein and albumin, protein in spot urine, and 24-hour urine protein levels were measured. Severe preeclampsia signs were determined as: systolic blood pressure ≥ 160 mmHg; diastolic blood pressure ≥ 110 mmHg; ≥ 5 gram proteinuria in 24 hour urine collection; oliguria (≤ 500 mL/24 hour diuresis); severe IUGR; central nervous system dysfunction or symptoms of liver capsule distension; hepatocellular damage (serum transaminase levels rising 2 times above normal values); and thrombocytopenia (< 100000/mm^3).

Thirty-three women were assigned to expectant management and 37 women were assigned to aggressive management. Both expectant and agressive management groups received 12 mg betamethasone and a second 12 mg dose was administered 24 hours later. Magnesium sulfate infusion and antihypertensive therapy were started for both groups. After bethamethasone therapy was completed, the aggressive management group (n = 37) were delivered either by cesarean (C/S) or vaginal delivery with induction. In the expectant management group (n = 33), magnesium sulfate infusion was stopped, antihypertensive drugs were completed, and bed rest and intensive fetal monitarization were continued.

Fetal cardiotocography was evaluated every 6 hours and ultrasound was performed once a week for fetal monitoring. CBC, AST, ALT, LDH, urea, creatinine, uric acid, total protein, and albumin analysis were performed daily. Indications for termination of pregnancy were: reaching 34 weeks gestation, and fetal distress and maternal indications (hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, renal morbidity, uncontrolled hypertension, prodromal symptoms, and antepartum hemorrhage.

Renal morbidity was determined as deterioration of renal function (elevation of urea and creatinine, electrolyte imbalance) and oliguria or anuria. Liver morbidity was determined as elevation of liver enzymes, prolongation of bleeding time, and hypoalbuminemia. All patients who were diagnosed as having HELLP syndrome were managed aggressively. Fetal distress was diagnosed when repetitive late decelerations and decreased variability in NST occurred. IUGR was not an indication for delivery per se but was handled as a supporting factor of other indications to terminate the pregnancy.

Type of delivery, indication for birth, birth weight, 1st and 5th minute apgar scores, neonatal intensive care requirement and hospitalization time in intensive care unit, complications and managements of all patients were recorded. Infants were evaluated using the Denver Developmental Screening Test-II by a child development specialist and their neurologic examination was performed by a neurologist at 12 months.

Table 1. Evaluation of maternal demographic features, pregnancy week, birth weight and APGAR scores

		Expectant Management (Mean ± SD)	Aggressive Management (Mean ± SD)	*P* value
*Average week of gestation		31.09 ± 2.53	30.64 ± 2.31	0.447
***Gravida		2.28 ± 1.50	2.06 ± 1.56	0.435
***Parity		0.92 ± 1.27	0.59 ± 1.58	0.208
*Body Mass Index (BMI)		31.22 ± 5.02	31.70 ± 3.19	0.633
***APGAR scores	1st min	5.73 ± 1.86	72 ± 1.52	0.813
	5th min	7.30 ± 1.74	7.33 ± 1.39	0.836
		n (%)	n (%)	
**Birth weight (gr)	< 1000	7 (25)	7 (13.3)	0.449
	1000-1500	9 (32.1)	12 (40)	
	1500-2000	8 (28.6)	12 (40)	
	> 2000	4 (14.3)	2 (6.7)	

*Student's t-test, **Chi-Square test, ***Mann-Whitney U test.

The Denver Developmental Screening Test-II (DDST-II) [8-10] is a development scale. DDST-II assesses a child's development in 4 general areas, 1. personal-social; 2. language; 3. fine motor-adaptive; and 4. gross motor abilities of the infant. Screening with this scale produces 3 scores: normal, suspect, and untestable (these children refuse participation in some items that 95% of age-matched children could pass).

Statistical analysis

Statistical evaluation of the study data was made with Statistical Package for the Social Sciences (SPSS) for Windows 2008 Statistical Software (Utah, USA). Student's t-test, Mann-Whitney U test were used for comparison of parameters. For comparing qualitative data, Chi-square test, Yates's continuity correction and Fisher's exact tests were used. A value of $P < 0.05$ was considered statistically significant.

Results

The mean age of the patients was 27.61 ± 5.50 years. The mean pregnancy week of patients was 30.86 ± 2.41. The average latency period was 3.45 ± 5.48 days.

The patients' average weeks of gestation were 31.09 ± 2.53 in the expectant management group and 30.64 ± 2.31 in the aggressive management group. There was no statistically significant difference bewteen the average weeks of gestation of both groups ($P > 0.05$). Birth weight of neonates in both groups showed no statistically significant difference ($P > 0.05$). Apgar scores (1-5 minute) were not significanty different relative to the management groups ($P > 0.05$) (**Table 1**).

Birth weights of 5 (15.1%) newborns in the expectant management group and 4 (10.8%) in the aggressive management group could not be measured because of the need for neonatal resuscitation.

Five women were diagnosed as having HELLP syndrome and all were in the aggressive management group, which was statistically significant ($P < 0.05$). Fetal distress, IUGR, uncontrolled hypertension, renal morbidity, prodromal symptoms, and antepartum hemorrhage were not statistically significantly different between the management groups ($P > 0.05$) (**Table 2**).

The hospitalization time in the neonatal intensive care unit, respiratory distress, sepsis and intracranial hemorrhage, and surfactant requirement were not statistically significantly different according to the management groups ($P > 0.05$). The neonatal mortality ratio in the aggressive management group was more than the expectant management group, but it was not statistically significant ($P > 0.05$) (**Table 3**).

The DDST-II results and neurologic examination findings were not statistically significantly different between the management groups ($P > 0.05$) (**Table 4**). Maternal renal and liver morbidities were not statistically significantly different between the management groups ($P > 0.05$) (**Table 5**).

Discussion

Preeclampsia is one of the most important reasons for maternal and perinatal mortality and morbidity. Maternal and perinatal mortality and morbidity increase in severe forms of preeclampsia and delivery is the only treatment. Fetal lung development is supposed to be completed after 34 weeks of gestation; therefore, some physicians share a common idea about

Table 2. Indications of Delivery and Pregnancy Termination According to Management Groups

	Expectant Management n (%)	Aggressive Management n (%)	*p*
*HELLP syndrome	0 (0.0)	5 (13.5)	0.056
**Fetal Distress	9 (27.3)	16 (43.2)	*0.253*
*IUGR	4 (12.1)	3 (8.1)	*0.699*
**Uncontrolled Hipertension	16 (48.5)	12 (32.4)	*0.261*
*Renal morbidity	2 (6.1)	1 (2.7)	*0.599*
*Prodromal symptom	4 (12.1)	3 (8.1)	*0.699*
*Antepartum hemorrhage	1 (3)	3 (8.1)	*0.616*

*Fisher's Exact Test. **Yates Continuity Correction Test. $p < 0.05$. IUGR: Intrauterin Growth Restriction.

Table 3. Evaluation of fetal parameters

	Expectant Management (Mean ± SD) n (%)	Aggressive Management (Mean ± SD) n (%)	*P* value
*Fetal hospitalization period (day)	23.58 ± 20.85	32.29 ± 33.71	0.182
**Neonatal mortality	1 (3)	7 (18.9)	0.058
***RDS	5 (15.2)	8 (21.6)	0.699
***Sepsis	5 (15.2)	7 (18.9)	0.920
**Intracranial hemorrhage	0 (0)	1 (2.7)	1.00
**Surfactant requirement	3 (9.1)	5 (13.5)	0.714

*Mann-Whitney U test, **Fisher's exact test, ***Yates test. RDS: respiratory distress syndrome.

delivery in severe preeclampsia after this week. However, early termination of pregnancy in severe preeclampsia for decreasing maternal mortality and morbidity can cause increased perinatal mortality and morbidity [1-3].

In the past, it was believed that the neonates who were born from severe preeclamptic pregnancies had low mortality and morbidity compared with neonates born from normotensive women at the same gestational week. It was believed that pulmonary and neurologic maturation were increased due to in-utero stress. However, in recent years, case- control studies have not shown increased lung and neurologic maturation in neonates born from preeclamptic pregnancies [11-13].

Advances in maternal and neonatal monitorization remove most physicians from the idea of delivering severe preeclamptic pregnancies immediately. Improvement in neonatal outcomes after corticosteroid prophylaxis has led many physicians to wait for the use of corticosteroids. Termination of pregnancy after prophylaxis or expectant approach is still a matter of debate. Gestational age, fetal and maternal status direct the management.

Odendaal et al evaluated 58 severe preeclamptic women between 28-34 weeks of gestation in a randomized prospective study and the average latency period was 7.1 days [14]. In another randomized prospective study of Sibai et al, 95 pregnant women between 28-32 weeks of gestation were examined and the average latency period was 15.4 days; delivery week and birth weight were significantly increased in the expectant group [15]. The latency period between hospitalization and delivery was different between the studies. In a non-randomized study by Odendaal et al, the authors reviewed 129 preeclamptic women < 34 weeks of gestation, the latency period was 11 days [16], was 9.5 days in a retrospective study by Olah et al [17], and 14 days in the study of Visser et al [18]. Hall et al reported on 340 women between 24-34 weeks of gestation who presented with early-onset severe preeclampsia and managed with expectant management and found that pregnancies were prolonged 11 days before delivery [19, 20]. Haddad et al performed a prospective observational study of 239 women with severe preeclampsia and the prolongation time of pregnancy was classified according to gestational weeks; prolongation time was 6 days below 29 weeks, 4 days between 29-31 weeks, and 4 days between 32-33 weeks [21].

In our study the latency period ranged between 1-28 days and the average latency period was 3.45 days. The latency period in our study was calculated from post corticosteroid administration as in the studies of Sibai [15] and Haddad

Table 4. Neurologic evaluation of the ınfants

		Expectant Management n (%)	Aggressive Management n (%)	*P* value
Denver II test	Normal	29 (90.6)	25 (83.3)	0.467
	Suspect	3 (9.1)	5 (17.2)	
Neurologic examination	Normal	27 (96.4)	24 (96)	
	Suspect	1 (3.6)	1 (4)	1.000

Fisher's exact test.

Table 5. Evaluation of maternal parameters

		Expectant Management n (%)	Aggressive Management n (%)	*P* value
Maternal morbidity	Renal	0 (0)	2 (5.4)	0.49
	Liver	1 (3)	5 (13.5)	0.20

Fisher's exact test.

[21]. In some studies it was determined as the time between hospitalization and delivery [14-20].

When deciding the type of delivery, it was suggested that maternal and fetal conditions, weeks of gestation, and Bishop's cervical score should be considered [1]. In a study of Sarsam et al, severe preeclamptic women between 24-34 weeks of gestation were evaluated. In the expectant management group there were 27 C/S and 12 vaginal births, and in the aggressive management group there were 27 C/S and 12 vaginal deliveries [22]. In our study, the number of C/S were higher than in the literature. Most of our patients had low Bishop's scores and were < 34 weeks of gestation; these may be the cause of the high percentage of CS in our study. When maternal and fetal deterioration or complications occur in severe preeclampsia, maternal and fetal morbidity and mortality are high. As a result, the majority of physicians hesitate to wait for vaginal birth because of complications both for fetus and mother. Thus C/S was preferred for terminating the pregnancy as quickly as possible. However, this does not imply that we advocate the termination of severe preeclampsia by cesarean section; vaginal delivery may be an option for severe preeclampsia under appropriate conditions.

Sarsman et al conducted a study with 74 severe preeclamptic women and they compared one minute Apgar scores, which were 5.05 in the expectant management group and 3.56 in the aggressive management group; a statistically significant difference was determined between the two groups [22]. In our study, a statistically significant difference was not determined in the 1st and 5th minute Apgar scores of the neonates.

Odendaal et al observed that fewer neonates needed ventilation in the expectant management group than in the aggressive management group, they also determined that neonatal complications were reduced in the expectant management group [14]. Sibai et al found shorter hospitalization time in the intensive care unit and fewer neonatal complications in their study [15]. Sarsman et al detected significant differences between the expectant and aggressive management groups in terms of RDS. In the aggressive management group, 10 fetal deaths occurred and two (20.5%) were related with RDS; in the expectant management group, 4 fetal deaths occurred and two were related with RDS [22]. In our study, when other fetal parameters were evaluated, no significant differences were determined between the groups in terms of neonatal intensive care unit admission rate and duration of hospitalization in the neonatal intensive care unit. Neonatal mortality was seen in 7 patients in the aggressive management group and 1 in the expectant management group; however, the difference did not reach statistical significance. Relative to surfactant requirement, respiratory distress syndrome, sepsis, and intracranial hemorrage, there were no significant differences between the groups.

The main parameter of our study was neurologic morbidity of neonates. For this purpose, the DDSTest-II and neurologic examinations were performed when the infants completed the first year. According to these parameters, no significant difference was determined between the expectant and aggressive management groups.

When maternal outcomes were analyzed, maternal mortality, pulmonary edema, eclampsia, neurologic morbidity, postpartum hemorrhage, and hypertensive seizures were not

observed in our study, and there was no requirement for the intensive care unit. Only two patients developed renal morbidity in the aggressive management group but renal failure did not develop in these patients and there was no requirement for dialysis. Liver morbidity was observed in 1 patient in the expectant management group and 5 in the aggressive management group. No severe maternal morbidity developed in either group and there was no statistically significant difference between the groups.

Conclusion

To the best of our knowledge, there were no statistically significant differences between the expectant and aggressive management groups in terms of neonatal and maternal morbidity and mortality; neonatal mortality was very close but did not reach significance ($P = 0.058$). Corticosteroid administration in the aggressive management group gave good results in terms of perinatal morbidity. In our study, we assigned severe preeclamptic women between 27-34 weeks of gestation to expectant and aggressive management groups and determined no significant difference in terms of neonatal neurologic morbidity. With reference to our study, termination of pregnancy in severe preeclampsia might be considered for pregnancies < 34 weeks of gestation after corticosteroid treatment is completed.

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Disclosure of conflict of interest

None.

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