Fetal and neonatal outcome in patients with severe pre-eclampsia before 34 weeks

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Summary

Delivery was delayed until 34 weeks in 129 patients with severe pre-eclampsia, unless the maternal or fetal conditions necessitated earlier delivery. No patient developed eclampsia although all sedation was terminated from 24 hours after admission until labour started, unless there was a sudden change in the patient's clinical condition. Of the 14 fetuses that died *in utero*, only 4 weighed more than 1 000 g at delivery. Three of these 4 had already died by the time of the mothers' admission. Abruptio placentae was the cause of 36% of intra-uterine deaths. The perinatal mortality rate was 223/1 000. Survival rates for liveborn babies were 47%, 78% and 82% for birth weights of 750 - 999 g, 1 000 - 1 249 g and 1 250 - 1 499 g respectively. No neonate died when the birth weight was 1 500 g or more.

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Treatment of severe pre-eclampsia in early pregnancy necessitates careful assessment of both the maternal and fetal conditions. In developed countries with adequate facilities for intensive neonatal care and with a low neonatal mortality rate from hyaline membrane disease, the decision about when to deliver the fetus may not be difficult since most of the newborns will survive in any case.[1] Plasma volume expansion controlled by pulmonary wedge pressure monitoring may also help to prolong the pregnancy until the fetus is viable.[2] In a developing country, however, where newborns are still lost because of hyaline membrane disease or necrotising enterocolitis and where neonatal intensive care beds are limited, the treatment of severe pre-eclampsia of early onset is more difficult and unfortunately also less successful.

A study was carried out to determine whether a conservative approach to the treatment of severe pre-eclampsia before 34 weeks' gestation is beneficial to the fetus.

Patients and methods

All patients with severe pre-eclampsia were admitted to the labour ward and carefully evaluated. Initial drug therapy consisted mainly of magnesium sulphate to prevent eclampsia and dihydrallazine to control blood pressure. Magnesium sulphate was administered when signs of imminent eclampsia such as visual disturbances, headaches, nausea and vomiting or epigastric pain were present. Dihydrallazine was given when the blood pressure remained at ⩾160/110 mmHg after half an hour of bed rest. An intravenous infusion was always used, but care was taken to limit the fluids given to 1 500 - 3 000 ml/24 h. Urinary output was carefully monitored and the urine was regularly tested for proteinuria.

A non-stress test (or a stress test when indicated) was done soon after admission to assess the fetal condition. As soon as the results of the special investigations were available and when the patient's clinical condition has been observed for a few hours, the important decision whether or not to deliver her was taken by the consultant on call. If gestational age exceeded 34 weeks, the patient was delivered immediately; if it was less than 34 weeks, or if the correct gestational age was uncertain and the fetus small, a more conservative approach was taken.

On the day after admission to the labour ward the patient was transferred to the high-risk antenatal ward which has specially trained nursing personnel. A senior registrar saw the patients at least 3 times a day. If intravenous dihydrallazine was still necessary to keep the blood pressure below 160/110 mmHg, α-methyldopa was prescribed. Care was taken to control the blood pressure at between 140/90 mmHg and 150/100 mmHg. When α-methyldopa was sufficient to control the blood pressure, other drugs such as hydrallazine, prazosin or ketanserin were used. Beta-blockers were never used and diuretics only for specific indications such as cardiac failure or pulmonary oedema. Magnesium sulphate was discontinued after 24 hours.

Dexamethasone was routinely given to all patients where the gestational age was more than 27 weeks but less than 34 weeks, and repeated weekly if delivery did not intervene. Urinary output was always measured and tested for protein, and blood pressure taken 4-hourly. The patients were weighed daily. All patients were explicitly informed of the importance of the decrease or absence of fetal movements and the beginning of contractions, vaginal bleeding or abdominal pain and instructed to report these abnormalities immediately.

Further biochemical supervision consisted of weekly measurements of uric acid, urea and electrolyte levels, full blood count, and liver function tests. Where indicated, these tests were performed more frequently. Fetal surveillance consisted of non-stress tests twice or more daily. An ultrasonographic examination was done soon after admission to assess fetal size and amniotic fluid volume. Ultrasonography was also used to evaluate the fetal condition when repeated non-stress tests were non-reactive and stress tests unsuccessful as well as to assess fetal growth.

Care was taken not to deliver fetuses unnecessarily early but to try to enable patients to reach a gestational age of 34 weeks. Fetal reasons for earlier delivery were repeated late decelerations of the fetal heart rate or a non-reactive pattern with reduced long-term variability and loss of fetal tone and movements as observed during a 30-minute ultrasonographic scan. Maternal reasons for delivery were an inability to keep the blood pressure below 160/100 mmHg, a urinary output below 400 ml/24 h, biochemical tests suggesting the haemolysis, elevated liver enzymes and low platelet count (HELLP)-syndrome, or suspected abruptio placentae.

All obstetric and fetal factors were carefully weighed up before the method of delivery was decided on. If the fetus was considered to be growth-retarded and demonstrated repeated late decelerations, delivery was always by caesarean section even if the cervix was favourable for induction. Patients suspected of abruptio placentae were also delivered by caesarean section. In patients less than 28 weeks pregnant, vaginal delivery was attempted and labour was induced with prostaglandins. In borderline cases the benefit of the doubt was given to the fetus and caesarean sections were done. Perinatal mortality was defined as all intra-uterine deaths of fetuses weighing 500 g or more and all first-week neonatal deaths where the baby weighed 500 g or more. Causes of death occurring after 7 days were also noted.

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Results

The study group consisted of 129 patients (mean maternal age 26,4 ± 5,6 years; mean gravidity 2,7, and mean parity 1,4). There were 40 (31%) primigravidas. The mean gestational age at admission to the high-risk antenatal ward was 29,4 ± 4,6 weeks. The mean systolic blood pressure was 161 ± 23 mmHg and mean diastolic 106 ± 12 mmHg. The mean degree of proteinuria on admission was 2,5+.

There were 8 abortions; 3 were spontaneous intra-uterine deaths and 5 were induced, because of either an increase in severity of pre-eclampsia (4 patients) or deterioration of renal function (1 patient). These fetuses weighed between 100 g and 480 g. In the 5 patients in whom abortion was induced, blood pressure ranged between 200/130 mmHg and 170/110 mmHg and proteinuria between 3+ and 4+.

Of the 14 intra-uterine deaths 3 occurred before admission and 8 fetuses had a birth weight below 1 000 g (Table I). Five (36%) of the deaths were due to abruptio placentae. In 2 patients the pregnancy was terminated for maternal reasons. In the remaining 7 patients death was probably due to placental insufficiency. In 6 patients the fetal heart rate was not monitored because in 3 the fetus had died before admission and in the other 3 the fetus was regarded as being too small to be delivered. In the 8 patients who had the fetal heart rate monitored, 3 demonstrated non-reactive tests with decreased long-term variability, 1 a reactive test and 4 repeated late decelerations. Of those with non-reactive tests the fetus in 2 was regarded as too small to be delivered (600 g and 660 g) and abruptio placentae occurred in the other (case 7). In the latter, the non-stress test was reactive 2 days before death. In the patient with the reactive test, intra-uterine death was caused by abruptio placentae (case 5). In the 4 cases of intra-uterine death preceded by repeated late decelerations, all the fetuses were regarded as being too small to be delivered. At birth abruptio placentae was found in 3 of these patients.

The mean admission to delivery time was 11 ± 11 days. Excluding the 8 abortions, there were thus 9 patients who delivered normally after spontaneous onset of labour and 30 who delivered normally after labour had been induced. There were 82 (68%) caesarean sections.

There were 20 neonatal deaths. The diastolic blood pressure before delivery was 120 mmHg or more in 2 patients, between 110 mmHg and 115 mmHg in 2 patients, between 100 mmHg and 105 mmHg in 10 patients, between 90 mmHg and 95 mmHg in 5 patients and below 90 mmHg in 1 patient. Proteinuria of 4+ was present in 3 of these patients, 3+ in 7, 2+ in 9 and a trace in 1. Of the indications for delivery in patients who had neonatal deaths, 9 were both maternal and fetal, 7 maternal, 3 fetal, and 1 abruptio placentae. Four neonatal deaths were due to hyaline membrane disease, 4 to necrotising enterocolitis, 3 to severe neonatal asphyxia and 3 to septicaemia; other causes were pneumothorax in 2, intraventricular haemorrhage in 1 and massive pulmonary haemorrhage in 1. In 2 babies the exact cause of death was uncertain. Thirteen of the neonatal deaths occurred in the first week, 6 between 7 and 28 days and 1 after 28 days (Table II).

The overall perinatal mortality rate was 223/1 000; it was 97/1 000 when only birth weights of 1 000 g or more were considered, and 280/1 000 for all deaths excluding abortions. Table III shows that in the first week after admission the intra-uterine death rate was 13%, in the second week, 7%, and in the third week 3%. Most of the first-week neonatal deaths were in infants delivered on the first or second day of admission; the neonatal death rate for the first, second and later weeks was 19%, 18,5% and 18% respectively. The causes of neonatal death in the 7 babies delivered within 2 days of admission were severe hyaline membrane disease in 3, severe neonatal asphyxia in 1, pneumothorax 7 days after birth in 1, and necrotising enterocolitis in 1 on day 12; in the last case the cause was uncertain.

No liveborn babies with a birth weight between 500 g and 749 g survived but when the birth weight was between 750 g and 999 g, babies had a 47% chance of leaving hospital alive (Table IV). There were no neonatal deaths when the birth weight was 1 500 g or more.

Discussion

In this study only 31% of patients were primigravidas, in sharp contrast with other reported series of severe early pre-eclampsia where the incidence of primigravidas varied between 67% and 72%.[3–6] The high incidence of multigravidas is difficult to explain. Since most of the women either booked late or were referred from outside hospitals or clinics, it is difficult to assess the importance of underlying essential hypertension, the most probable reason for such a high incidence of pre-

TABLE I. INTRA-UTERINE DEATHS IN PATIENTS WITH SEVERE PRE-ECLAMPSIA

Case No.	Maternal age (yrs)	Gravidity	Blood pressure (mmHg)	Protein-uria	Non-stress test (< 2 d)	Birth weight (g)
1	22	2	170/100	4+	Non-reactive	600
2	23	1	150/100	2+	Not done	570
3	38	3	160/110	0	Not done	720
4	19	1	180/120	4+	Not done	650
5	26	2	180/110	3+	Reactive	980
6	21	2	200/120	2+	Repeated late decelerations	820
7	22	1	150/90	3+	Non-reactive	1 210
8	32	6	160/90	1+	IUD before admission	2 200
9	20	1	190/120	3+	IUD before admission	1 800
10	20	2	140/100	3+	Repeated late decelerations	1 000
11	23	3	150/100	2+	Repeated late decelerations	1 000
12	26	10	185/150	3+	IUD before admission	1 020
13	23	1	150/90	1+	Repeated late decelerations	880
14	21	2	180/120	2+	Non-reactive	660

IUD = intra-uterine death.

TABLE II. PERINATAL MORTALITY RATE IN PATIENTS WITH SEVERE PRE-ECLAMPSIA

Weight (g)	Deliveries	Intra-uterine death	Neonatal death	Perinatal mortality rate (/1 000)	Neonatal death (7-28 d)	Neonatal death (> 28 d)
500-749	9	4	4	889	1	0
750-999	19	4	6	526	2	0
1 000-1 249	22	4	2	273	2	0
1 250-1 499	17	0	1	59	1	1
1 500-1 749	12	0	0	0	0	0
1 750-1 999	12	1	0	83	0	0
2 000-2 249	7	1	0	143	0	0
2 250-2 499	5	0	0	0	0	0
> 2 500	18	0	0	0	0	0
Total	121	14	13	223	6	1

Perinatal mortality rate in babies > 1 000 g = 9/93 (97/1 000).

TABLE III. CORRELATION BETWEEN PERINATAL MORTALITY AND DURATION OF HOSPITALISATION

D	Wk	Deliveries	Intra-uterine deaths	Neonatal deaths	Intra-uterine deaths (%)	Neonatal deaths (%)	Perinatal mortality rate (/1 000)
1		10	0	3			
2		17	2	4			
3		7	0	1			
4		5	1	0			
5		8	3	1			
6		5	1	0			
7		8	3	1			
	1st	60	8	10	13	19	30
	2nd	29	2	5	7	18,5	24
	After 2nd	29	1	5	3	18	21
Total		118	11	20			

TABLE IV. SURVIVAL RATES OF LIVEBORN BABIES

Birth weight (g)	No. of liveborn infants	Neonatal deaths < 7 d	Neonatal deaths 7-28 d	Neonatal deaths > 28 d	Survival (%)
500-749	5	4	1	0	0
750-999	15	6	2	0	47
1 000-1 249	18	2	2	0	78
1 250-1 499	17	1	1	1	82
> 1 500	52	0	0	0	100
Total	107	13	6	1	81

eclampsia. In a case-control study of severe pre-eclampsia of early onset, Moore and Redman[6] found that a history of chronic hypertension or renal disease was not significantly associated with pre-eclampsia but they found significantly more patients who had had previous pre-eclampsia. The incidence of previous pre-eclampsia in the present study is unknown.

This study demonstrates that antenatal heart rate monitoring is reliable in assessing the fetal condition. In the 8 cases of intra-uterine death in which the fetal heart rate had been previously monitored, 3 demonstrated non-reactive tests and 4 repeated late decelerations. Ample warning of fetal distress was therefore given by the abnormal heart rate tracings in 7 of the 8 patients. In the other patient death was caused by abruptio placentae, and unfortunately abruptio placentae is the most common cause of false-negative stress tests at this hospital.[7] The fact that abruptio placentae was unexpectedly present in 3 of the 4 cases with repeated late decelerations before death indicates that heart rate abnormalities precede the diagnosis of severe abruptio placentae. The fact that there were proportionally more intra-uterine deaths during the first week of treatment than during the subsequent weeks demonstrates that moderate delay in delivery does not necessarily raise the intra-uterine death rate. On the other hand, bed rest and treatment of hypertension may reduce the number of intra-uterine deaths. However, a carefully conducted case-controlled study with large numbers would be necessary to confirm this.

When all intra-uterine deaths are evaluated, the question of how they could have been prevented should always be asked. Since it was policy not to deliver fetuses before 28 weeks or if they weighed less than 1 000 g (unless specific maternal indications necessitated delivery), all intra-uterine deaths of a fetus less than 1 000 g should be regarded as not preventable for the purpose of this study. If those whose fetal heart could not be heard at admission are also excluded, only 3 patients remain. The 2 newborns that weighed 1 000 g each could possibly have been saved but antenatally they were regarded as being smaller. The other fetus (weight 1 210 g) could have been saved

especially if it had been delivered when the fetal heart rate changed from reactive to non-reactive (on the day before intra-uterine death).

In this study, the perinatal mortality rate was 223/1 000; this falls to 97 if only birth weights $\geqslant$ 1 000 g are considered. Comparison with other studies is difficult because of highly selected patients and small numbers. Very few reports in the literature give the perinatal mortality rate of severe pre-eclampsia and even less deal with early onset of severe pre-eclampsia. It is even more difficult when the perinatal mortality rate for babies of different birth weights is compared. Locally, only the reports of Moodley[8] and Davey[9] could be found. Moodley gave a perinatal mortality rate of 117/1 000 for primiparas and 215 for multiparas, but his study included all cases of hypertension with proteinuria and came from a different population group. Davey's study consisted of patients with hypertension and proteinuria, and was of the same population group as ours. He expressed the perinatal mortality rate for babies $<$ 1 000 g, for those between 1 000 g and 1 499 g and continued by using increments of 500 g. In order to compare the results our perinatal mortality rate was calculated in a similar way. Only the weight groups $<$ 1 000 g, 1 000 - 1 499 g and 1 500 - 1 999 g were compared; in these groups perinatal mortality rate was 877, 329 and 71/1 000 in Davey's series and 643, 179 and 42/1 000 respectively in our group. For the weight group 2 000 - 2 499 g perinatal mortality rate in Davey's group was 3/1 000; the very small numbers in our group preclude comparison. Benedetti *et al.*[5] achieved a perinatal mortality rate of 143/1 000 for 90 patients with severe pre-eclampsia but they included all gestational ages and had only 36 deliveries before 33 weeks. Sibai *et al.* [4] found no neonatal survival in any infants with a gestational age $\leqslant$ 28 weeks. The perinatal mortality rate as calculated from their study in patients with severe pre-eclampsia and 36 weeks or less gestation was 240/1 000. Excellent results were achieved by Martin and Tupper[3] who reported a perinatal mortality rate of 71/1 000 for severe pre-eclampsia in patients $<$ 36 weeks' gestation. In a study of severe pre-eclampsia of early onset Moore and Redman[6] lost 4 of the 24 babies (2 intra-uterine and 2 neonatal deaths). In the study of Sibai *et al.*,[4] there were 28 stillbirths and 15 neonatal deaths, in contrast with the 2 intra-uterine deaths and 13 neonatal deaths found by Benedetti *et al.*[5]

In our study, there are equal numbers of stillbirths and early neonatal deaths but when all neonatal deaths are included, they exceed the stillbirths. It is extremely difficult in severe pre-eclampsia, to decide exactly when to deliver the fetus; with delivery too early the newborn infant may die from complications of prematurity, but if delivery is postponed, intra-uterine death may result. Apart from the fetal condition, it may be mandatory to deliver for maternal reasons. Each unit must try to achieve a balance between the number of intra-uterine and neonatal deaths without adding unnecessary risks to the mother.

Abruptio placentae is a major cause of intra-uterine death (36% of intra-uterine deaths in our study). In other studies the incidence of abruptio placentae varied between 5,6% and 8,3%.[4,10] Although it is difficult to reduce the intra-uterine death rate from abruptio placentae, frequent heart rate monitoring may pinpoint the fetus at risk because late decelerations may appear before the clinical picture of abruptio placentae develops.

The mean admission to delivery time was 11 $\pm$ 11 days; 60 patients were delivered within a week, 29 during the second week and 29 after 2 weeks in hospital. There was no increase in the number of intra-uterine deaths with the length of hospitalisation. The incidence of neonatal deaths in these three periods was 19%, 18,5% and 18% respectively. Although neonatal mortality did not improve with duration of hospitalisation, the gain of 1 or 2 weeks before delivery could have been of great benefit to the more mature babies. The fact that more than a week was gained in 58 patients and that the administration of glucocorticosteroids is not an absolute safeguard against hyaline membrane disease make it unlikely that similar results would have been obtained if delivery had been postponed for only 48 hours. There were 4 neonatal deaths due to hyaline membrane disease, of which 3 took place when delivery occurred within the first day or two. These 3 newborns probably did not benefit from corticosteroid administration since they were delivered too soon.

When severe pre-eclampsia is encountered in early pregnancy, it is absolutely vital for the baby to be delivered at the optimum time. If the maternal condition remains stable and if the gestational age is less than about 34 weeks, valuable time can be acquired by allowing corticosteroids to improve fetal lung maturity and to ensure further intra-uterine development. Frequent heart rate monitoring is in most cases a reliable indicator of fetal distress. As 47% of newborns who weighed between 750 g and 999 g survived, all fetuses with an estimated birth weight of 750 g or more should be delivered in our unit if there are indications of fetal distress or abruptio placentae. Clinical estimation of the correct gestational age in patients unbooked or booked late, where the fetus is growth-retarded, or where the date of the last menstrual period is unknown, can be very misleading. Ultrasonographic estimation of the fetal weight is therefore helpful.

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