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Severe pre-eclampsia and infants of very low birth weight

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SUMMARY The effect of severe pre-eclampsia on the outcome of infants of very low birth weight was studied in a prospective case control study of 35 pairs of infants of comparable gestation. Significantly more infants were delivered before the onset of labour and by caesarean section in the group with pre-eclampsia. These babies tended to be smaller and had a higher incidence of hyaline membrane disease, patent ductus arteriosus, pulmonary air leak, and hypotension. They also required more intensive treatment with oxygen and mechanical ventilation. The significant difference in birth weight was still apparent at 2 years of age. Although the mean psychomotor developmental index and the incidence of specific neurodevelopmental impairments were not significantly different between the two groups, survivors in the group born to pre-eclamptic mothers had a significantly lower mean mental developmental index, and significantly more of these children had one or more impairments compared with the control group at 2 years of age.

Pre-eclampsia occurring in the second trimester or early in the third trimester differs from late onset disease not only in its serious maternal morbidity but in its high perinatal mortality and morbidity.[1 2] In severe pre-eclampsia neonatal outcome has been reported to be influenced by both the disease and the administration of antihypertensive and anticonvulsant drugs to the mother.[3] The aim of this study was to determine the effects of severe pre-eclampsia and its treatment on the neonatal course and long term outcome of very low birthweight (VLBW, <1500 g) infants.

Patients and methods

At this centre a perinatal database is established prospectively from admission for all VLBW infants. In the four years before this study 71 (17%) of 413 VLBW infants were born to mothers with severe pre-eclampsia. In this birthweight group comparison of the infants born to mothers with and without pre-eclampsia showed a significant difference in gestational age because significantly more infants in the pre-eclamptic group were small for gestational age. We therefore undertook a prospective case control study to define more clearly the effects of severe pre-eclampsia. Thirty five VLBW infants born to mothers with severe pre-eclampsia from 1982 to 1984 were compared with 35 infants born at about the same time to normotensive mothers and matched for gestation, sex, and survival. All the VLBW survivors had clinical, neurological, and psychological assessments at 2 years of age corrected for prematurity.

Severe maternal pre-eclampsia was diagnosed when the mother had a resting blood pressure of over 140/90 mm Hg, persistent proteinuria without urinary tract infection, and generalised oedema before 32 weeks of gestation. Babies were considered small for gestational age when the birth weight was below the 10th centile based on intrauterine growth charts derived from a Melbourne population.[4] Hyaline membrane disease was diagnosed when all the following criteria were present: respiratory distress not attributable to other causes; retraction and poor air entry during spontaneous respiratory efforts; chest *x*-ray films showing diffuse fine granular infiltrates persisting at least until the third day; fractional inspired oxygen (FiO_2) greater than 0·3 to maintain an arterial oxygen tension of over 8·0 kPa beginning during the first 12 hours and lasting at least three days; and a maximum FiO_2 requirement greater than 0·4. Patent ductus arteriosus was diagnosed if there was a precordial systolic or continuous murmur or echocardiographic evidence of a left to right shunt or both. Neurological impairment at follow up was defined as cerebral palsy of any type or severity,

developmental delay with a mental developmental index more than two standard deviations below the mean on the Bayley scales of infant development, blindness, or sensorineural deafness.

Statistical analysis was by the χ^2, Fisher's exact, and paired *t* tests as appropriate.

Results

Table 1 shows the significant differences in maternal and obstetric factors between the 35 infants born to mothers with severe pre-eclampsia and the 35 matched controls. Though none of the mothers in the control group had complications associated with pre-eclampsia such as generalised oedema, disseminated intravascular coagulation, renal failure, neurological symptoms, or liver dysfunction, significantly more had chorioamnionitis and antepartum haemorrhage. Significantly more infants of mothers with severe pre-eclampsia were delivered before the onset of labour and by caesarean section. Caesarean section was carried out for maternal indications in 25 cases and for fetal distress in seven. The range of drugs given to the mothers before delivery was appreciably different in the two groups. The mothers with pre-eclampsia were given methyldopa (17 mothers), magnesium (14), hydralazine (10), chlormethiazole (nine), β blockers (eight), anticonvulsants (six), diazepam (five), and diuretics (three). The control mothers did not receive these drugs. Salbutamol was used in nine control mothers in an effort to stop their preterm labour but was not given to those with pre-eclampsia. Betamethasone was given to one mother with pre-eclampsia and two in the control group.

The infants in the two groups were appropriately matched for gestational age (mean 28·9 (SD 2·0) weeks *v* 28·2 (2·0) weeks), male to female ratio (15:20 *v* 17:18) and two year survival (77% *v* 80%). Table 2 shows the significant differences in neonatal

Table 1 *Significant differences in maternal and obstetric variables*

	Pre-eclampsia group (n = 35)	*Control group (n = 35)*	*P*
Mean (SD) maximum blood pressure (mm Hg):			
Systolic	178 (28)	126 (13)	<0·00025
Diastolic	114 (12)	77 (8)	<0·00025
No (%) with:			
Proteinuria	35 (100)	1 (3)	<0·00025
Oedema	35 (100)	0	<0·00025
Disseminated intravascular coagulation	6 (17)	0	<0·02
Renal failure	5 (14)	0	<0·02
Neurological deficit	5 (14)	0	<0·02
Liver dysfunction	3 (9)	0	<0·05
Fever	0	7 (20)	<0·0125
Membranes ruptured >24 h	0	9 (26)	<0·0125
Antepartum haemorrhage	1 (3)	10 (29)	<0·0125
Presence of labour	5 (14)	31 (89)	<0·0125
Caesarean section	32 (91)	10 (29)	<0·00025

Table 2 *Significant differences in neonatal factors*

	Pre-eclampsia group (n = 35)	*Control group (n = 35)*	*P*
Mean (SD) birth weight (g)	920 (187)	1067 (159)	<0·0005
Mean (SD) birth weight centile	28 (22)	49 (23)	<0·0005
Mean (SD) birth length centile	26 (25)	43 (23)	<0·0005
Data on admission (means (SD)):			
Packed cell volume	0·51 (0·08)	0·46 (0·09)	<0·02
White cell count ($\times 10^9$/l)	16·8 (11·9)	19·1 (9·4)	<0·0125
Platelet count ($\times 10^9$/l)	132 (53)	246 (89)	<0·02
Systolic blood pressure (mm Hg)	41 (13)	45 (14)	<0·05
Neonatal events:			
No (%) with white cell count $<6\times 10^9$/l	12 (34)	3 (9)	<0·0125
No (%) with platelets $<150\times 10^9$/l	14 (40)	5 (14)	<0·0125
Mean (SD) volume expansion, day 1 (ml)	17 (16)	14 (15)	<0·05
No (%) with hypotonia	9 (26)	2 (6)	<0·05
No (%) with feed intolerance	5 (14)	0	<0·05
Mean (SD) age meconium passed (days)	4·9 (6·8)	2·6 (2·3)	<0·0005
No (%) with hyaline membrane disease	29 (83)	15 (43)	<0·0005
No (%) with patent ductus arteriosus	22 (63)	11 (31)	<0·05
No (%) with pulmonary air leak	14 (40)	7 (20)	<0·05
Mean (SD) length of hospital stay (days)	65 (85)	40 (51)	<0·05
Respiratory treatment:			
Mean (SD) duration of oxygen treatment (days)	48 (77)	21 (31)	<0·02
Mean (SD) maximum FiO_2	0·70 (0·28)	0·57 (0·32)	<0·02
No (%) given mechanical ventilation	30 (86)	23 (66)	<0·05
Mean (SD) duration of ventilation (days)	30 (34)	17 (26)	<0·02
Mean (SD) maximum peak pressure (kPa)	2·55 (1·37)	1·67 (1·47)	<0·05
Mean (SD) maximum rate (beats/min)	47 (15)	37 (11)	<0·0025

characteristics and problems. Infants of mothers with severe pre-eclampsia fell within lower birthweight and length centiles. This intrauterine growth retardation was associated with a higher packed cell volume at birth. Other haematological abnormalities included leucopenia and thrombocytopenia (no infants in the pre-eclampsia group had septic complications.). The systolic blood pressure on admission was lower in the pre-eclampsia group, who also required a higher volume of blood or colloid in the 24 hours after birth to maintain normal blood pressure. In the first week after birth hypotonia feed intolerance with abdominal distension and delay in passage of meconium were also more common in this group.

Cardiorespiratory disorders of hyaline membrane disease, patent ductus arteriosus, and pulmonary air leak were more common in the pre-eclampsia group, as was use of mechanical ventilation (Table 2). In this group 29 (97%) of 30 ventilated infants had hyaline membrane disease, compared with 15 (65%) of 23 infants in the control group. They required longer and more intensive oxygen treatment and mechanical ventilation and spent longer in hospital than the control group. When only those infants ventilated for hyaline membrane disease were compared the pre-eclampsia group had similar requirements for oxygen support (FiO_2 0·80 (0·20) *v* 0·81 (0·25)) but needed significantly longer periods of treatment with oxygen (60 (84) days *v* 28 (31) days, $p<0·05$) and mechanical ventilation (36 (35) days *v* 24 (30) days, $p<0·05$), greater maximum peak pressure (3·04 (0·981) kPa *v* 2·65 (0·981) kPa, $p<0·05$), and greater maximum ventilator rate (50 (14) beats/min *v* 40 (12) beats/min, $p<0·05$).

There were no significant differences between the two groups in head circumference centile at birth; Apgar scores at one and five minutes; admission temperature, arterial blood pressure, pH, and ratio of arterial oxygen tension to FiO_2; persistent pulmonary hypertension and haemorrhagic pulmonary oedema; periventricular haemorrhage, leucomalacia, and posthaemorrhagic hydrocephalus; seizures and hypocalcaemia; hyperbilirubinaemia; necrotising enterocolitis; renal failure; and retinopathy of prematurity.

At the two year assessment no significant differences in centiles of height and head circumference were found, but weight centiles remained significantly lower in the pre-eclampsia group (Table 3). The mean psychomotor developmental index on the Bayley scales of infant development was similar in the two groups. Survivors in the pre-eclampsia group, however, had a significantly lower mean mental developmental index. Furthermore, six (22%) of 27 survivors in this group compared with one (4%) of 26 survivors in the control group had one or more impairments ($p<0·05$). The incidence of specific impairments, however, was not significantly different between the groups. Of the six impaired survivors in the pre-eclampsia group, four had hemiplegia secondary to neonatal intraventricular haemorrhage or intracerebral haemorrhage or both, one had severe developmental delay due to periventricular haemorrhage in utero, and one had spastic diplegia and sensorineural deafness associated with normal findings on cerebral ultrasonography. Four of these six impaired survivors were small for gestational age at birth. The single impaired survivor in the control group was not small for gestational age at birth but had spastic quadriplegia and severe developmental delay due to meningitis. At two years the growth of the survivors who had impairment was no different from that of those who were neurodevelopmentally normal.

Table 3 *Comparison of outcome in survivors. Data expressed as mean (SD) and number (per cent)*

	Pre-eclampsia group (n = 27)	*Control group (n = 26)*
Growth centiles:		
Mean (SD) weight	16 (19)	28 (30)*
Mean (SD) height	17 (20)	27 (27)
Mean (SD) head circumference	42 (21)	46 (31)
Bayley scores:		
Mean (SD) mental developmental index	94 (25)	106 (21)*
Mean (SD) psychomotor developmental index	89 (22)	93 (15)
No (%) of survivors with one or more impairments:	6 (22)	1 (4)*
Type of impairment:		
No (%) with cerebral palsy	4 (15)	1 (4)
No (%) with developmental delay	3 (11)	1 (4)
No (%) with blindness	1 (4)	0 (0)
No (%) with sensorineural deafness	1 (4)	1 (4)

*$p<0·05$.

Discussion

Three case control studies have previously been reported, each concerning 22 to 29 infants born to mothers with severe pre-eclampsia.[1-3] Two of these studies were carried out in groups with a mean gestation of 32 weeks[1 3] compared with a mean of 29 weeks for the 35 infants in our study. The remaining study reported on 29 infants with a mean gestation of 28 weeks,[2] but because pregnancies complicated by severe pre-eclampsia were treated conservatively the neonatal survival rate was only 28% (eight survivors) compared with the two year survival rate of 77% in the present study. Severe early pre-eclampsia is usually associated with progressive

deterioration in both mother and baby. When it is managed conservatively the unfavourable intrauterine conditions cause all the stillbirths and most of the neonatal deaths.[1–3]

The incidence of small for gestational age infants reported in mothers with severe pre-eclampsia has ranged from 20% to 80%.[1–6] Cumulative data from these studies showed that 226 (28%) of 817 infants reported on were small for gestational age. This compares with 15 (43%) of 35 infants in the present study.

The aetiology of pre-eclampsia is unknown. Abnormalities noted in the mothers in this study showed clinically that the disease affects several systems. Severe vasoconstriction probably leads to ischaemic changes in various organs, endothelial damage, and deposition of platelets and fibrin thrombi. This vasoconstriction may result from the presence of a circulating vasoconstricting substance or the absence of a normally present vasodilator.[8 9] Because this effect on vascular tone is found in fetal plasma at birth[9] the incidence of patent ductus arteriosus in the pre-eclampsia group may be related to the maternal disease. Neonatal thrombocytopenia and leucopenia have been reported in pre-eclampsia.[10 11] A highly significant correlation between maternal and neonatal platelet counts strongly supports a common pathological process.[3] Neonatal hypotonia, feed intolerance, and delayed passage of meconium have also been reported in infants of mothers with severe pre-eclampsia.[3] These problems were thought to be associated with treatment of the mother with magnesium sulphate,[12 13] which was used in 40% of our mothers with pre-eclampsia. Furthermore, the mothers of five of the nine hypotonic infants were treated with intravenous diazepam just before delivery. The increased incidence of hypotension in the pre-eclampsia group may well reflect the variety of antihypertensive drugs given to the mothers.[14]

The severity of uteroplacental insufficiency affecting the fetus in severe maternal pre-eclampsia was reflected in the rate of intrauterine growth retardation (43%) and the high packed cell volume at birth in our study. Two previous studies reported significantly lower Apgar scores at one and five minutes in infants born to mothers with pre-eclampsia compared with control infants, and this was attributed to severe uteroplacental insufficiency.[3 7] No difference in Apgar scores was found in the present study, in which the caesarean rate was 91% (32/35) in mothers with severe pre-eclampsia. The arterial pH on admission was also similar in the pre-eclampsia and control groups, suggesting that timely delivery of the compromised fetuses could have prevented the development of severe birth asphyxia.

The present study showed that VLBW infants born to mothers with severe pre-eclampsia of early onset had a significantly higher incidence of hyaline membrane disease than the control infants. They also had a significantly higher incidence of associated cardiorespiratory disorders, such as patent ductus arteriosus and pulmonary air leak, and significantly higher requirements for and a longer duration of treatment with oxygen and mechanical ventilation. One previous study reported an identical incidence of severe respiratory disease,[3] and another reported a higher incidence of hyaline membrane disease[7] in the pre-eclampsia group compared with the control group, though the difference did not reach significance. It has also been reported that the incidence of hyaline membrane disease, including both mild and severe forms, was significantly lower in preterm infants born after pregnancies complicated by pre-eclampsia compared with those born after uncomplicated pregnancies.[15] The incidence of severe disease in that study, however, which used a similar definition of hyaline membrane disease to that in our study, did not differ significantly between the two groups; the incidence of severe disease was higher in the pre-eclampsia group after caesarean section compared with the uncomplicated group. One difference between that study[15] and the present one was in the incidence of caesarean section in the pre-eclampsia group (33% compared with 91% in the present study); most sections were performed before the onset of labour. It has been shown that, compared with preterm infants born vaginally, those born by caesarean section, particularly before the onset of labour, have a much greater risk of severe hyaline membrane disease.[16] That labour has a beneficial effect on neonatal lung function is beyond doubt.[17] It seems to have a central role both in initiating the absorption of fetal lung liquid and in promoting surfactant secretion, though how these effects are mediated remains uncertain. A recent study showed that preterm infants born by caesarean section to mothers with pre-eclampsia of early onset had a higher, though not significantly different, incidence of hyaline membrane disease than control infants, and no evidence was found of a raised fetal serum cortisol concentration, which had been implicated in the induction of fetal pulmonary maturation in pregnancies complicated by pre-eclampsia.[18]

The fetal growth rate of infants born after pregnancies complicated by severe pre-eclampsia was affected by adverse maternal and placental factors. Once released from the intrauterine environment, infants whose growth deviates from the norm at birth show a strong tendency to revert towards the mean.[19] By 2 years of age growth in

height and head circumference was normal but weight was not in the pre-eclampsia group. We previously reported that the early growth rate in extremely preterm infants small for gestational age was higher than that in those who were the appropriate weight for gestation,[20] and others have shown that growth catches up by the age of 3 years.[21]

Maternal hypertension is associated with a significant developmental delay in gross motor, fine motor, and visual motor functions in early childhood.[22] Epidemiological studies have also shown that the incidences of pre-eclampsia and intrauterine growth retardation are significantly increased in children with cerebral palsy compared with the normal population.[23] Although our case control study did not show a difference in the psychomotor developmental index or incidence of specific impairments between the two groups, the mental developmental index was significantly lower and more children had one or more impairments in the pre-eclampsia group. Four of the six impaired survivors in this group had neonatal periventricular haemorrhages to explain their impairments, but the origin of the impairment in the remaining two survivors was antepartum.

The timing of delivery in women who develop severe pre-eclampsia during the second trimester is difficult. The potential benefit of increased fetal maturity from delaying delivery must be balanced against the risk of fetal hypoxia and sudden intrauterine death or severe growth restriction, which includes retardation of head growth.[7] Progressive deterioration in maternal wellbeing may also expose the mother to severe morbidity or even death. As a result the obstetrician is often forced to deliver the infant despite fetal immaturity. Our observations indicate that VLBW infants born to mothers with severe pre-eclampsia have significantly more neonatal morbidity than those of a similar gestational age born to normotensive mothers. It is, therefore, important to anticipate and manage these neonatal problems appropriately, as they compound those of very preterm birth, for which these infants are already at risk.

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