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Prognosis of the very low birthweight baby in relation to gender

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SUMMARY The effects of gender on mortality and morbidity of all neonates weighing <1500 g admitted to King's College Hospital Neonatal Intensive Care Unit during 1980–82 (n=271) were examined. Very low birthweight boys had a significantly higher mortality and more postnatal complications than girls. The higher incidence of respiratory distress syndrome and pulmonary interstitial emphysema in boys was associated with increased mortality in the first year. Surviving boys had significantly more problems, including lower Apgar scores at five minutes, more frequent apnoeic attacks and bradycardic episodes, transient tachypnoea, neonatal anaemia, and lower blood calcium and phosphate concentrations. Surviving children were followed up at 1 and 2 years of age. Development of boys at 1 year was significantly delayed compared with girls in all fields save locomotor. Although at 2 years some of the differences had diminished, those in language and personal social skills were more pronounced. More than twice as many boys as girls had major neurodevelopmental disorders.

The relative vulnerability of boys to perinatal mortality and morbidity has been documented in perinatal studies.[1 2] In particular, a greater incidence of problems in pregnancy and complications of delivery, birth asphyxia and neurological signs in the neonatal period,[3 4] a higher incidence of infections, including those occurring after prolonged rupture of membranes,[5] and congenital malformations[6] have been reported in boys. Hyaline membrane disease[7] and transient symptomatic hypoglycaemia have been found more often in preterm boys. In general, prospective studies of socioemotional and intellectual development repeatedly found boys to have more aggressive and hyperactive behaviour than girls.[8] It has been noted that girls begin to speak earlier than boys.[9] There is also a tendency for boys to be among the low scorers in verbal tests while there is no sex difference in the group of high scorers.[8] In one study very low birthweight boys had lower intelligence quotient (IQ) scores than girls at 3 years,[10] but most reports on the effects of gender on behaviour have centred on older children and have reported little or no difference. Only a few studies have investigated differential development in boys and girls in infancy.

This study examines (a) whether gender differences reported for the general neonatal population in regard to mortality and morbidity are apparent in a high risk very low birthweight population, and (b) whether gender differences in early developmental progress can be partly explained by differences in perinatal and postnatal morbidity.

Patients and methods

The sample consisted of 271 neonates of birth weight <1500 g, cared for in the Neonatal Intensive Care Unit of King's College Hospital between January 1980 and December 1982 inclusive. The 141 boys and 130 girls were born to mothers in the hospital catchment area or were referred in utero before birth or shortly after birth for intensive care. The social class of the parents of study infants was predominantly social class IIIb (Registrar General Classification of Occupations, 1980).

All survivors were assessed in the first two years by one of us (MB). One infant was assessed at another London teaching hospital at the age of 1 and 2 years using different developmental tests. Six children were not available for assessment at 1 year at our hospital. Five had moved, information about their clinical and developmental state at 1 year being given to us by their health visitors or general practitioners. One infant was assessed at home but was too unwell with a respiratory tract infection to complete the developmental assessment, and the family then moved abroad. These six children were all assessed at 2 years. By this time a further child's

family had moved abroad. He had been assessed as normal by us at 1 year and was reported to be normal at 2.

A list of 74 variables, including demographic information and data on pregnancy, delivery, and neonatal course, were collected prospectively and recorded on standard forms.

Development was assessed at 1 year using Knobloch and Pasamanick's development screening test.[11] This assessment, like the Griffiths' scales, is adapted from Gesell's developmental scales[12] and is highly correlated with the Griffiths' test at one year (A. Stewart. Personal communication, 1985). It assesses the following areas: adaptive functioning, gross and fine motor abilities, verbal skills, and personal social skills.

At 2 years the Griffiths' scales were used,[13] which assessed the locomotor, personal social, hearing and speech, eye and hand coordination, and performance skills. Both assessments allow for general developmental quotients and subquotients to be calculated. A full clinical and neurological examination was also carried out at 1 and 2 years.

Results

Sex differences in mortality and morbidity.

The total study sample (n=271)

The mean (SD) birth weight for boys was 1116·5 (229·7) g and for girls was 1169·2 (223·4) g. These did not differ significantly. Altogether, 105 (74%) boys and 92 (71%) girls were white. A number of significant sex differences were found in the total population of newborns (survivors plus deaths). The mean age of the mothers of boys (25·5 (SD 5·4) years) was nearly two years younger than that of girls (27·3 (5·9) years) (p=0·009), and more girls were born by caesarian section (Table 1).

The state of boys after delivery as judged by the mean Apgar score at one minute was poorer than that of girls, (4·7 (SD 2·7) *v* 5·4 (2·8); p=0·05) and remained lower at five minutes (7·1 (2·3) *v* 7·9 (2·1); p=0·001), and they had a higher incidence of hypothermia (Table 1). Recurrent episodes of bradycardia occurred more often in boys, and more boys experienced respiratory distress syndrome, pulmonary interstitial emphysema, and pneumothorax. Pneumonia and intraventricular haemorrhage occurred more often in boys. The greater severity of respiratory disease in boys was additionally reflected in the increased need for ventilation and higher ventilating pressures.

Boys required blood transfusions for anaemia more often than girls and more of them had umbilical arterial catheters inserted. No significant differences in the other variables mentioned above were found.

Non-survivors (n=83)

The overall sample was split into survivors and those

Table 1 *Percentage of boys and girls positive for neonatal variables and significant diffferences for boys* v *girls in these variables by* χ^2 test

Variable	*All infants*				*Survivors*				*Non-survivors*			
	Boys (n=141)	*Girls (n=130)*	χ^2	*p Value*	*Boys (n=83)*	*Girls (n=105)*	χ^2	*p Value*	*Boys (n=58)*	*Girls (n=25)*	χ^2	*p Value*
Multiple births	17·7	23·1	1·20	NS	12·0	25·7	5·47	<0·05	25·9	12·0	1·98	NS
Non-white race	25·5	29·2	0·47	NS	25·3	22·9	0·15	NS	25·9	56·1	6·98	<0·01
Previous miscarriage	40·4	38·5	0·11	NS	48·2	35·2	3·2	NS	29·3	52·0	3·9	<0·05
Pre-eclampsia	22·0	25·4	0·43	NS	18·1	30·5	3·8	NS	27·6	4·0	5·97	<0·05
Type of delivery	39·0	53·1	5·40	<0·05	43·4	59·0	4·56	<0·05	67·2	72·0	0·18	NS
Hypothermia	56·0	34·0	12·50	<0·001	41·0	28·6	3·17	NS	77·6	60·0	2·69	NS
Apnoea	47·5	37·7	2·67	NS	59·0	36·2	9·73	<0·01	31·0	44·0	1·29	NS
Bradycardia	52·5	36·9	6·62	<0·05	51·8	35·2	5·21	<0·05	53·4	44·0	0·62	NS
Respiratory distress syndrome	57·4	40·8	7·53	<0·01	45·8	40·0	0·63	NS	74·1	44·0	6·98	<0·01
Transient tachypnoea	10·6	7·7	0·70	NS	16·9	7·6	3·84	<0·05	1·7	8·0	1·98	NS
Pulmonary interstitial emphysema	36·9	14·6	17·30	<0·001	24·1	13·3	3·63	NS	55·2	20·0	8·75	<0·01
Pneumothorax	20·6	10·8	4·86	<0·05	10·8	7·6	0·59	NS	34·5	24·0	0·89	NS
Pneumonia	30·5	22·3	2·33	NS	31·3	18·1	4·46	<0·05	29·3	40·0	0·91	NS
Intraventricular haemorrhage	34·8	23·8	3·87	<0·05	25·3	21·9	0·30	NS	48·0	32·0	1·88	NS
Necrotising enterocolitis	15·6	22·3	1·99	NS	19·3	21·0	0·08	NS	10·3	28·0	4·12	<0·05
Oxygen given	83·7	64·6	12·96	<0·001	74·7	58·1	5·65	<0·05	96·6	92·0	0·79	NS
Ventilated	70·9	48·5	14·24	<0·001	56·6	40·0	5·14	<0·05	91·4	84·0	0·98	NS
Ventilating pressure >20 cmH_2O	33·3	14·6	12·86	<0·001	18·1	7·6	4·72	<0·05	55·2	44·0	0·87	NS
Unbilical arterial catheter	54·1	34·7	9·82	<0·01	41·0	31·4	1·84	NS	76·0	20·8	3·55	NS
Blood transfusion	70·4	43·4	20·30	<0·001	65·1	41·0	10·79	<0·001	77·6	52·0	5·43	<0·05
Intralipid infusion		★			34·9	21·9	3·94	<0·05		★		
Serum calcium (<1·75 mmol/l)		★			49·4	33·3	4·97	<0·05		★		
Serum phosphate (<1·3 mmol/l)		★			31·3	13·3	9·0	<0·01		★		

★Excluded because of missing values for babies that died.

who died within the first year (one boy died of sudden infant death syndrome at 16 weeks; the remainder died before leaving hospital). Perinatal and postnatal factors in surviving and non-surviving babies were analysed to examine sex differences in morbidity and mortality. The overall survival rate in 1980–82 was 69%. Boys accounted for the majority of infant deaths. While 58 out of 141 (41%) of boys died during the first year of life, the mortality of 25 out of 130 (19%) for girls was significantly lower ($\chi^2=15{\cdot}3$, $p<0{\cdot}001$).

In those who died there were no significant differences in mean gestation, maternal age, and Apgar scores. More girls were of non-white origin, however, and a history of previous miscarriage was more common in the mothers of girls (Table 1 column 3). Pre-eclampsia occurred more often in the mothers of boys.

More boys than girls who died had respiratory distress syndrome or pulmonary interstitial emphysema. More girls died of necrotising enterocolitis—the only neonatal variable that showed girls at a disadvantage relative to boys. Boys had blood transfusions for anaemia more often than girls.

The early neonatal morbidity of boys was increased relative to girls. They had lower mean Apgar scores at five minutes (7·6 (SD 2·1) *v* 8·2 (1·8); $p<0{\cdot}05$) and more episodes of apnoea and bradycardia. They also experienced transient tachypnoea and pneumonia more often than girls. They were ventilated more often, required higher ventilating pressures, and were more likely to be given oxygen. Anaemia (lowest haemoglobin 10·2 (SD 2·1) g *v* 11·6 (3·7) g) and the need for blood transfusion occurred more often in surviving boys, and they were given Intralipid infusion more often than were the girls.

Sex differences in early development. The general development quotients at 1 and 2 years and the subtests were compared for sex differences. The mean development quotients at 1 and 2 years for chronological and corrected ages are presented in Table 2. The significant differences are the same whether the development quotient is corrected for prematurity or not. The general development quotient of boys is significantly lower than that of girls at 1 and 2 years. Boys scored lower than girls at 1 year in nearly all areas of development. In particular, boys scored less in the adaptive subtests, had poorer fine motor control, and had less pre-verbal ability and their personal social skills were less well developed than those of girls. There was no significant difference between the sexes in gross motor behaviour. At 2 years the differences in verbal and personal social skills were found to have increased. No significant differences were detected in their fine motor or locomotor skills nor in the cognitive performance field.

Major neurodevelopmental sequelae. Neurodevelopmental abnormalities identified by 2 years included cerebral palsy, sensorineural hearing loss, visual disorders such as delayed visual maturation, retinopathy of prematurity, and an overall developmental delay of sufficient severity to predict mental retardation (general development quotient <70).[14] Over 11% (21 out of 188) of all infants had major neurodevelopmental disorders. Out of these 21 infants, 14 were boys ($\chi^2=4{\cdot}86$; $p=0{\cdot}028$).

We examined whether exclusion of these children affected sex differences in the development quotients reported above and found they remained essentially unaltered.

Morbidity and gender differences in psychosocial development. We wanted to determine whether boys and girls with similar morbidity factors have consistently different development quotients. We therefore tested the effect of sex on development quotients at 1 and 2 years after allowing for the effect of postnatal morbidity.

The following morbidity factors related to gender formed set 1: maternal age, multiple birth, type of delivery, Apgar score at five minutes, recurrent attacks of apnoea, recurrent episodes of bradycardia, transient tachypnoea, pneumonia, ventilation, peak ventilation pressures, treatment with oxygen, blood transfusion, Intralipid infusion, serum calcium

Table 2 *Gender differences in developmental quotients at 1 and 2 years (corrected for prematurity). Values are mean (SD)*

	Boys	*Girls*	*t*	*p Value*
Knobloch developmental scales (1 year assessment)				
n=	82	99		
General development quotient	109·01 (17·71)	115·19 (16·91)	−2·39	<0·05
Adaptive	107·65 (16·09)	113·13 (17·94)	−2·16	<0·05
Fine motor	111·08 (22·68)	117·73 (19·56)	−2·09	<0·05
Language	110·41 (24·54)	118·42 (25·40)	−2·15	<0·05
Personal social	115·87 (20·85)	123·23 (19·17)	−2·45	<0·05
Gross motor	100·02 (20·80)	103·43 (20·10)	−1·12	NS
Griffith developmental scales (2 year assessment)				
n=	81	105		
General development quotient	101·01 (17·05)	107·68 (18·28)	−2·57	<0·05
Locomotor	104·79 (25·07)	106·77 (22·83)	−0·56	NS
Personal social	103·55 (21·41)	116·91 (25·56)	−3·88	<0·001
Hearing and speech	94·88 (21·64)	107·25 (25·15)	−3·60	<0·001
Eye and hand coordination	100·44 (19·50)	105·54 (18·89)	−0·80	NS
Performance	101·36 (20·40)	101·93 (19·56)	−0·19	NS

Table 3 *Effect of sex on development quotients at 1 and 2 years after allowing for postnatal morbidity*

	Set 1: morbidity factors			*Set 2: 16 morbidity factors plus sex*			*Additional independent contribution of sex*		
	% Of variance explained	*F value*	*p value*	*% Of variance explained*	*F value*	*p value*	*% Of additional variance explained*	*F value*	*p value*
Knobloch developmental scales (1 year assessment)		df 16; 164			df 17; 163			df 1; 163	
General development quotient	22·9	3·04	<0·001	23·8	2·99	<0·001	0·9	1·84	NS
Adaptive	18·7	2·36	<0·01	19·5	2·33	<0·01	0·8	1·64	NS
Gross motor	20·6	2·66	<0·001	20·7	2·50	<0·01	0·1	0·19	NS
Fine motor	20·2	2·59	<0.01	20·9	2·54	<0·01	0·7	1·54	NS
Language	13·5	1·59	NS	14·7	1·68	NS	1·2	2·33	NS
Personal social	24·3	3·30	<0·001	25·0	3·19	<0·001	0·7	1·38	NS
Griffith developmental scales (2 year assessment)		df 16; 169			df 17; 168			df 1; 168	
General development quotient	23·2	3·18	<0·001	23·8	3·09	<0·001	0·6	1·39	NS
Performance	12·7	1·54	NS	13·2	1·50	NS	0·5	0·87	NS
Locomotor	21·3	2·85	<0·001	21·3	2·67	<0·001	0·0	0·06	NS
Eye and hand coordination	17·8	2·28	<0·01	17·9	2·16	<0·01	0·1	0·29	NS
Hearing and speech	20·3	2·69	<0·001	23·4	3·03	<0·001	3·1	6·91	<0·01
Personal social	22·6	3·08	<0·001	25·0	3·29	<0·001	2·4	5·37	<0·05

and phosphate concentrations, and lowest haemoglobin concentration. These 16 morbidity factors were entered in the regression equation first. The morbidity factors plus sex were entered next to evaluate whether the increase in the regression sum of squares (when going from 16 to 17 degrees of freedom) was significantly greater than the residual mean square.

As shown in Table 3 column 3, at 1 year there were no significant sex differences in development quotients after allowing for the effect of postnatal morbidity. Table 3 column 1 shows that the quotients are significantly predicted by the 16 morbidity factors. Now it is apparent that the lower mean development quotient in boys at 1 year (Table 2) is due to their increased neonatal morbidity. At 2 years boys still had poorer language and personal social skills than girls, irrespective of the number of problems they had had during the neonatal period (Table 3 column 3). However, the neonatal morbidity factors were still the best predictors of the development quotients at 1 and 2 years (Table 3 column 1). Of the 16 morbidity factors examined, those that had a significant independent linear association with the general development quotient at 1 year were: multiple birth ($\beta=0{\cdot}17$, $p<0{\cdot}05$), high peak ventilation pressure ($\beta=0{\cdot}19$, $p<0{\cdot}05$), and blood transfusions ($\beta=0{\cdot}23$, $p<0{\cdot}05$). At 2 years high peak ventilation pressure was the only independent predictor of the general quotient ($\beta=0{\cdot}22$, $p<0{\cdot}01$).

Discussion

The published reports on sex differences and early childhood morbidity indicate that boys are generally more vulnerable.[1–4] The present study provides additional evidence for this in a population of infants especially at risk. While it is well established that male preterm infants suffer more respiratory distress syndrome,[7] a finding replicated in our own study, we find in addition that very low birthweight boys face a cluster of problems associated with poor outcome.

Overall, we found that boys had lower Apgar scores and suffered hypothermia more often than girls. These factors are accepted as antecedents of respiratory distress syndrome. The increased need for ventilation and higher peak pressures in boys is likely to explain their increased incidence of pulmonary interstitial emphysema and pneumothorax.[15] These latter factors have been shown to be associated with a higher incidence of intraventricular haemorrhage,[16 17] a complication that we found more often in boys. The increased use of umbilical arterial catheters and blood transfusion may simply reflect that the boys were more ill than the girls and required more blood sampling. As we have also found, however, that blood transfusion is an important predictor of neurodevelopmental disorder at 2 years[18] anaemia requiring blood transfusions is possibly in itself harmful to very low birthweight babies.

The question remains why boys suffer more perinatal and neonatal insults. Different hypotheses have been put forward to explain this. They include the assumption that boys are constitutionally weaker than girls, and therefore more prone to illness, and that for a given gestational age girls are more physiologically mature than boys. For example, the female fetus has been reported as advanced in respiratory function.[7] As birth weight rather than

gestation was used as a selection criterion and boys are heavier than girls we would expect and indeed found that overall the mean gestational age of boys was one week less than that of girls. This difference was not significant in survivors and could not account for the difference we found in morbidity and development between boys and girls. In the babies who died there was also no significant difference in mean gestation.

In the period 1980–82 twice as many boys died as girls in the first year of life. Different factors seem to be associated with mortality in boys and girls—that is, boys suffer more severe respiratory problems and girls more severe necrotising enterocolitis, a finding reported previously.[7 19] Other factors associated with increased mortality were a maternal history of previous miscarriage and non-white origin in girls and maternal pre-eclampsia in boys. As girls experience less neonatal illness than boys these social and antenatal factors may become apparent as contributors to death in girls.[1]

Surviving boys did not experience respiratory distress syndrome or pulmonary interstitial emphysema more than girls, but their increased incidence of episodes of recurrent apnoea, bradycardia, transient tachypnoea, and pneumonia shows their susceptibility to respiratory illness—with increased need of ventilation.

The higher incidence of hypophosphataemia and hypocalcaemia may be another general indicator that the boys were iller than the girls, as was their requirement for additional intravenous calories by Intralipid infusion. As far as we are aware no sex differences in hypocalcaemia and hypophosphataemia have been documented in premature babies. Low ionised and total calcium concentrations in whole blood have been shown to be correlated with Apgar scores at one and five minutes in premature babies.[20] Our boys had lower Apgar scores at five minutes than girls, which might have resulted in lower calcium concentrations. This effect of asphyxia would, however, not explain more prolonged hypocalcaemia, and there are likely to be other associated factors.

We found that the very low birthweight boys had major neurodevelopmental abnormalities twice as often as girls. Increased incidence of handicap in boys has been reported previously.[21]

Our results also indicate that the differences in psychosocial development at 1 year between boys and girls were fairly small, although they reached significance. In contrast, by 2 years a more pronounced difference was apparent in language and personal social skills. Both morbidity factors and sex by itself independently contributed to these differences. A possible explanation for the differences at 2 years is that the Griffith scales might be more reliable because the greater number of items would be expected to reduce measurement error. Significant correlations, however, between the Knobloch developmental screening test and Griffith scales administered to the same children at roughly the same age have been found.

In addition to socialisation processes, constitutional factors like vulnerability to illness or neurological problems have been cited as a possible basis for early sex differences. The evidence is, however, sparse.[3] Our findings indicate a substantial contribution of neonatal complications to gender differences in development at 1 and 2 years of age in a very low birthweight infant population. In a small sample of preterm infants Siegel reported associations between perinatal complications and cognitive and language development.[22] Careful perusal of her paper shows that sex is another independent predictor of outcome. The variable sex has both genetic and socialisation components. A number of studies have reported that parents engage in different interaction patterns with boys and girls.[23] In particular, mothers have been observed to talk more to their daughters than their sons[23] and female neonates seem to be more responsive to auditory stimulation.[24] The provision of appropriate toys has a positive correlation with cognitive development in boys but not in girls, while the converse is true of the effects of maternal involvement.[22] One might speculate that the difference in personal social skills and language between boys and girls may have resulted from less verbal stimulation given by their mothers to boys, in particular between 1 and 2 years. A proper test of this hypothesis, however, requires a study that includes not only perinatal but also environmental factors.[25]

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