# Sex differences in outcomes of very low birthweight infants: the newborn male disadvantage

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## Abstract

***Objective*—To determine the differences in short term outcome of very low birthweight infants attributable to sex.**

***Methods*—Boys and girls weighing 501–1500 g admitted to the 12 centres of the National Institute of Child Health and Human Development Neonatal Research Network were compared. Maternal information and perinatal data were collected from hospital records. Infant outcome was recorded at discharge, at 120 days of age if the infant was still in hospital, or at death. Best obstetric estimate based on the last menstrual period, standard obstetric factors, and ultrasound were used to assign gestational age in completed weeks. Data were collected on a cohort that included 3356 boys and 3382 girls, representing all inborn births from 1 May 1991 to 31 December 1993.**

***Results*—Mortality for boys was 22% and that for girls 15%. The prenatal and perinatal data indicate few differences between the sex groups, except that boys were less likely to have been exposed to antenatal steroids (odds ratio (OR) = 0.80) and were less stable after birth, as reflected in a higher percentage with lower Apgar scores at one and five minutes and the need for physical and pharmacological assistance. In particular, boys were more likely to have been intubated (OR = 1.16) and to have received resuscitation medication (OR = 1.40). Boys had a higher risk (OR > 1.00) for most adverse neonatal outcomes. Although pulmonary morbidity predominated, intracranial haemorrhage and urinary tract infection were also more common.**

***Conclusions*—Relative differences in short term morbidity and mortality persist between the sexes.**

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Keywords: very low birthweight infants; neonatal outcome; sex; mortality

The "male disadvantage" with respect to neonatal mortality has been recognised for more than two decades.[1] In 1986, Brothwood *et al*[2] confirmed the "relative vulnerability of boys to perinatal mortality and morbidity" described in earlier reports. They observed a higher mortality and more postnatal complications in very low birthweight boys than in girls. More boys were depressed at birth as evidenced by their Apgar scores, had respiratory distress syndrome or lung related injuries and disabilities, and were generally less stable than girls after birth. Of note, more girls in this cohort were delivered by caesarean section but the finding was not analysed or interpreted further. Towards the end of the presurfactant era, Hoffman and Bennett[3] reiterated the favourable influence of the female sex on survival and short and long term outcomes for extremely low birthweight babies. They reported a benefit for caesarean section but did not clarify the issue with respect to sex or other confounders contributing to the incidence of abdominal delivery. The effect of sex on survival has been reported for even the tiniest infants independent of such physical signs of immaturity as fused eyelids.[4] In a multivariate logistic regression analysis of infants at the threshold of viability, girls, small for gestational age infants, and infants whose mothers had received antenatal steroids had a reduced risk of death. Girls had an advantage in survival of nearly a 100 g increase in birth weight.[5] Although the introduction of surfactant has indisputably lowered mortality and morbidity in very low birthweight infants, sex differences have persisted[5–9] with a female advantage.

To determine the differences in short term outcome of very low birthweight infants attributable to sex, we compared boys and girls weighing 501–1500 g admitted to the 12 centres of the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network.

## Methods

### PATIENTS

The cohort included 3356 boys and 3382 girls, representing all inborn live births or transfers (10%) by 14 days of age from 1 May 1991 to 31 December 1993 in the birthweight range 501–1500 g at participating centres in the NICHD Neonatal Research Network. Data were collected on standardised forms, entered into local databases, and transmitted weekly to the Biostatistics Coordinating Center at the George Washington University. Maternal information (table 1) and perinatal data (table 2) were collected from hospital records. Infant outcome (table 3) was tabulated at discharge, at 120 days of age if the infant was still in hospital, or at death. Best obstetric estimate based on the last menstrual period, standard obstetric factors, and ultrasound were used to assign gestational age in completed weeks.

*Table 1 Maternal information*

| *Maternal information* | *Boys (n=3356)* | *Girls (n=3382)* | *OR (boys/girls) (95% CI)* |
|---|---|---|---|
| Married | 34 (14–67) | 33 (13–68) | 1.05 (0.95 to 1.17) |
| ⩽18 years of age | 10 (4–14) | 9 (5–15) | 1.07 (0.91 to 1.27) |
| ⩾35 years of age | 8 (5–9) | 8 (3–20) | 0.96 (0.80 to 1.15) |
| Prenatal care* | 86 (80–98) | 87 (81–96) | 0.94 (0.82 to 1.09) |
| Antepartum haemorrhage | 17 (4–31) | 14 (1–26) | 1.31 (1.14 to 1.50) |
| Antenatal steroids | 20 (1–35) | 24 (1–43) | 0.80 (0.71 to 0.90) |
| Antenatal antibiotics | 33 (20–43) | 34 (22–45) | 0.98 (0.88 to 1.09) |
| Race | | | |
| Black | 54 (6–87) | 55 (7–87) | 0.94 (0.85 to 1.04) |
| White | 31 (11–66) | 31 (11–73) | |
| Hispanic | 13 (0–48) | 11 (0–45) | |
| Other | 2 (0–18) | 2 (0–16) | |
| ROM ⩾1 hour | 51 (38–59) | 54 (38–61) | 0.88 (0.88 to 0.98) |
| ROM ⩾24 hours | 26 (18–33) | 27 (22–37) | 0.96 (0.85 to 1.07) |

Based on 6186 mothers; inborn infants born between 1 May 1991 and 31 December 1993 with birth weights from 501 to 1500 g. Data are presented as percentages with centre ranges in parentheses.
*Defined as at least one prenatal visit.
ROM, Rupture of membranes.

*Table 2 Perinatal information*

| *Perinatal data* | *Boys (n=3356)* | *Girls (n=3382)* | *OR (boys/girls) (95% CI)* |
|---|---|---|---|
| Multiple birth | 21 (11–28) | 20 (12–29) | 1.06 (0.94 to 1.20) |
| Birth weight (g)* | | | |
| 501–750 | 20 (11–24) | 21 (17–25) | |
| 751–1000 | 24 (21–26) | 23 (19–27) | |
| 1001–1250 | 27 (22–30) | 25 (20–28) | |
| 1251–1500 | 29 (22–39) | 31 (28–37) | |
| Gestational age (weeks) | | | |
| 19–23 | 8 (4–10) | 6 (3–8) | 1.28 (1.06 to 1.55) |
| 24–27 | 39 (28–48) | 35 (32–40) | 1.20 (1.08 to 1.32) |
| 28–31 | 42 (37–50) | 45 (39–48) | 0.91 (0.83 to 1.00) |
| 32–40† | 10 (6–16) | 14 (11–20) | 0.71 (0.62 to 0.83) |
| Mode of delivery‡ | | | |
| Vaginal vertex | 44 (33–50) | 42 (28–49) | 1.06 (0.96 to 1.17) |
| Vaginal breech | 7 (4–13) | 7 (5–11) | |
| Caesarean section | 49 (40–61) | 51 (45–65) | |
| Delivery room resuscitation | | | |
| Endotracheal intubation | 67 (52–78) | 63 (47–77) | 1.16 (1.05 to 1.29) |
| Resuscitation medication | 9 (2–19) | 6 (3–22) | 1.40 (1.17 to 1.68) |
| Apgar ⩽3 at 1 min | 38 (29–51) | 34 (25–41) | 1.21 (1.09 to 1.34) |
| Apgar ⩽3 at 5 min | 13 (8–21) | 10 (5–16) | 1.35 (1.16 to 1.58) |

Data are presented as percentages with centre ranges in parentheses.
*$\chi^2 = 8.3$; $p = 0.04$.
†Includes intrauterine growth retarded infants.
‡$\chi^2 = 1.43$; $p = 0.49$.

DESIGN

The characteristics of the maternal and neonatal cohorts are summarised by prevalence or incidence as appropriate. Analyses were used to assess the relation of selected risk factors to mortality and to compare these relations between boys and girls. Differences between boys and girls were evaluated by univariate and multivariate estimates of odds ratios (OR) and 95% confidence intervals (CI). Separate logistic regression models were fitted for boys and girls to estimate the relation between mortality and gestational age (weeks), birth weight (per 50 g), race, use of antenatal steroids, use of antenatal antibiotics, mother's age (per year), and delivery by caesarean section. Data are summarised as estimated OR and 95% CI. In addition, the observed and predicted (from the logistic model) number of deaths are compared for the multivariate and univariate (birthweight) models. The comparison is performed by estimating the probability of death from the models and then breaking the distributions into deciles.

## Results

Overall, the mortality for boys was 22% and that for girls 15%. Table 1 and table 2 summarise maternal and perinatal data for the study population, and indicate few differences between the sex groups, except that mothers of male infants had more antepartum haemorrhage, and boys were more premature (< 27 weeks gestational age), less likely to have been exposed to antenatal steroids (OR = 0.80), and less stable after birth, as reflected in a higher percentage with lower Apgar scores at one and five minutes and the need for physical and pharmacological assistance. In particular, they were more likely to have been intubated (OR = 1.16) and to have received resuscitation medication (OR = 1.40).

Table 3 presents the neonatal outcomes for the study population, and indicates that boys had a higher risk (OR > 1.00) for most adverse outcomes. Pulmonary morbidity predominated. Notably, there were no sex differences for septicaemia, but urinary tract infections were more common in boys. Mortality differences were noted as early as day 3 and continued through the follow up period. Average hospital stays for male survivors were about one week shorter than for female survivors.

Table 4 summarises the results from the univariate and multivariate analyses, which were run separately for boys and girls. The univariate analyses identified similar significant covariates for both sexes, with two exceptions. For girls, each year of increase in the mother's age conferred a 2% decrease in risk of mortality, while the use of antibiotics was associated with a 17% reduction in risk of death. In the multivariate analysis, black race, each 50 g increase in birth weight, each additional week of gestation, administration of antenatal steroids, administration of antenatal antibiotics, and delivery by caesarean section were associated with reductions in risk of mortality for both boys and girls. For girls, mother's age was also significantly related to risk. The change in the estimated OR for race are due to the difference in birth weight and gestational age distributions between the black and non-black cohorts. In these cohorts, a larger percentage of black neonates had birth weights between 1100 and 1500 g. This was observed for both sexes.

Table 5 classifies each baby into deciles of risk, based on their estimated probability of dying, using a multivariate model and a univariate model based on birth weight and sex. Those classified in the upper 10% of risk of dying have an observed mortality of 81.3% for boys and 66.4% for girls. The gradient of risk between the highest and lowest deciles is a factor of 22.0 (81.3/3.7) for boys and 27.7 (66.4/2.4) for girls. Thus, a boy whose estimated probability of dying places him in the highest decile risk is 22 times more likely to die than one who is in the lowest decile. The gradient for mortality is different between the sexes. For boys, the risk is 4.8% in the first two deciles, increases to 6.6% for the next two deciles, and rises consistently over the last six deciles. For girls, the percentage mortality in the lowest two deciles is 2.6%, rises to 5.0% for the next two deciles, increases gradually over the next three deciles, and then has a more substantial increase over the last three deciles. Note that classification of each

neonate based on birth weight alone results in very similar risk of death (gradients of 22.3 for boys and 18.3 for girls). The additional variables, although indicating a strong statistical relation to the risk of death, do not substantially increase the ability to classify events.

## Discussion

For over two decades, the male disadvantage with respect to neonatal mortality has been chronicled.[1–9] Despite technological advances in newborn care, including the widespread introduction and improvement in mechanical ventilation, use of antenatal steroids, and more recently surfactant therapy, the male disadvantage has persisted. However, in most instances the absolute differences are small. Pulmonary disease and its complications remain predominant as contributing causes of early death, while other morbidities, such as intracranial haemorrhage, appear to be important contributing causes of long term disabilities in surviving boys. Whether this natural selection represents a process biased against boys (an early culling of less adaptable or fit progenitors) or an affirmative action for girls (an early sparing of that segment of the population most important for birthing and nurturing the next generation) is a matter of speculation or bias. Regardless, nature is still compensating for male attrition in the newborn period through the conception of slightly more boys.[10]

Although sex differences with respect to maternal information, perinatal data, and infant outcome were the focus of this analysis, the protective factors for the two sexes were very similar (table 4). Using estimates of OR, indicating the level of risk for each of the variables "adjusted" for the other factors in the model, caesarean section, increased birth weight, antenatal steroids, and black race decreased the risk of mortality. Of note, caesarean section occurred with equal frequency among boys and girls. The association of a lower level of risk of death with caesarean section should not be interpreted as suggesting that caesarean section confers protection against mortality in very low birthweight infants, because the indications for caesarean section, including condition of the fetus, could not be taken into consideration in this analysis. Moreover, caesarean section could reflect obstetric opinion about the viability of the fetus, based on diagnostic factors or estimates of size and maturity. Similarly, vaginal delivery should not be considered as disadvantageous per se because other management factors associated with the decision to deliver vaginally could not be excluded as contributing causes. Thus a recommendation about mode of delivery for very low birthweight infants cannot be supported by the data in this study. Finally, if severity of illness, rather than risk factors had been our focus, and there had been an adjustment for severity of illness, then boys and girls may have fared comparably,[11] and the shorter median hospital stay for male survivors may reflect the fact that once the sickest infants had died, the remaining ones were less severely ill. Furthermore, table 4 should not be construed as a prescription for individual case decision making. The estimates are based on a model (logistic) and the cohort available to the 12 clinical centres during the period 1 May 1991 to 31 December 1993. For individual case decision making, elucidation of specific biological incapacities contributing to the observed morbidities and death is required, so that diagnostic tests with sufficient positive and negative predictive accuracy may encourage specific treatments for selected individuals.

*Table 3 Comparison of short term outcome in very low birthweight boys and girls*

| | *Boys (n=3356)* | *Girls (n=3382)* | *OR (boys/girls) (95% CI)* |
|---|---|---|---|
| Pulmonary | | | |
| RDS (% of population) | 65 (52–73) | 56 (40–68) | 1.41 (1.28 to 1.56) |
| Oxygen administration | 90 (82–97) | 87 (77–95) | 1.32 (1.14 to 1.54) |
| Ventilator support | 78 (71–85) | 72 (61–89) | 1.34 (1.20 to 1.50) |
| Umbilical artery catheter | 62 (53–76) | 58 (42–75) | 1.22 (1.10 to 1.35) |
| Surfactants (% of RDS) | 72 (45–86) | 66 (44–86) | 1.33 (1.10 to 1.60) |
| Pneumothorax | 7 (5–11) | 5 (3–9) | 1.33 (1.09 to 1.62) |
| Among 28 day survivors (n=5660) | | | |
| $O_2$ at 28 days (% of 28 day survival) | 41 (23–59) | 32 (21–49) | 1.45 (1.30 to 1.62) |
| Ventilator support for 28 days | 22 (10–32) | 18 (11–28) | 1.26 (1.11 to 1.44) |
| Among $O_2$ at 28 days | | | |
| Steroids (%)* | 42 (25–64) | 37 (16–56) | 1.21 (1.01 to 1.46) |
| CLD (%) | 21 (6–51) | 16 (3–48) | 1.39 (1.18 to 1.64) |
| Central nervous system | | | |
| Seizures | 5 (1–10) | 4 (0–8) | 1.30 (1.03 to 1.65) |
| Intraventricular haemorrhage† | | | |
| None | 63 | 68 | 0.80 |
| Grade I | 17 (7–32) | 16 (7–38) | |
| Grade II | 7 (3–13) | 5 (1–10) | |
| Grade III | 7 (2–10) | 6 (3–8) | |
| Grade IV | 6 (3–9) | 5 (2–11) | |
| PVL‡ | 7 (3–24) | 7 (4–22) | 0.96 (0.76 to 1.22) |
| Gastrointestinal tract/nutrition | | | |
| NEC ⩾ stage II | 6 (2–8) | 5 (3–8) | 1.19 (0.96 to 1.48) |
| Parenteral nutrition | 86 (66–100) | 84 (61–100) | 1.20 (1.04 to 1.39) |
| Central venous catheter | 26 (14–57) | 24 (8–52) | 1.07 (0.96 to 1.20) |
| Bacterial infection | | | |
| Septicaemia§ | 22 (9–31) | 21 (9–28) | 1.07 (0.96 to 1.21) |
| Meningitis¶ | 2 (0–9) | 3 (1–6) | 0.91 (0.67 to 1.24) |
| Urinary tract infection** | 5 (2–9) | 3 (0–6) | 1.78 (1.38 to 2.29) |
| Cardiovascular | | | |
| Symptomatic PDA | 30 (19–5) | 27 (16–50) | 1.18 (1.06 to 1.31) |
| Mortality | | | |
| Died by day 3 | 13 (10–20) | 9 (3–16) | |
| Died by day 7 | 15 (11–22) | 10 (5–17) | |
| Died by day 14 | 17 (13–24) | 12 (7–17) | |
| Died by day 28 | 19 (15–30) | 13 (9–19) | |
| Died before discharge | 22 (16–32) | 15 (11–22) | 1.53 (1.35 to 1.73) |
| Length of stay (median days) | | | |
| Survivors | 56 (48–70) | 62 (55–72) | |
| Deaths | 2 (2–15) | 2 (1–5) | |

Data are presented as percentages with centre ranges in parentheses.
*Postnatal steroids for bronchopulmonary dysplasia.
†Most severe grade in infants who had an ultrasound (n=5822).
‡Periventricular leucomalacia; of infants who had an ultrasound after 2 weeks (n=4077).
§A positive culture in the presence of compatible clinical signs of septiacaemia.
¶A positive culture of cerebrospinal fluid or pathogens in brain tissue in the presence of compatible clinical signs of meningitis or encephalitis.
**Bacteria present in urine from catheterised or suprapubic specimens only in the presence of compatible clinical signs of cystitis or pyelonephritis.
RDS, Respiratory distress syndrome; CLD, chronic lung disease; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus.

*Table 4 Mortality prediction. Estimated odds ratio of mortality from univariate and multivariate analysis results*

| | *Boys (710/3256)* | | *Girls (507/3309)* | |
|---|---|---|---|---|
| *Factor* | *Univariate* | *Multivariate* | *Univariate* | *Multivariate* |
| Caesarean section | 0.48† | 0.64† (0.52 to 0.79) | 0.49† | 0.66† (0.52 to 0.83) |
| Birth weight (per 50 g) | 0.77† | 0.82† (0.79 to 0.84) | 0.78† | 0.81† (0.78 to 0.84) |
| Antenatal steroids | 0.38† | 0.47† (0.35 to 0.63) | 0.42† | 0.54† (0.40 to 0.72) |
| Mother's age (per year) | 1.00 | | 0.98† | 0.97† (0.96 to 0.99) |
| Use of antibiotics | 0.95 | 0.78* (0.63 to 0.96) | 0.83* | 0.72† (0.57 to 0.91) |
| Race (black) | 1.13 | 0.79* (0.64 to 0.96) | 1.01 | 0.67† (0.53 to 0.84) |
| Gestational age | 0.62† | 0.88† (0.83 to 0.94) | 0.65† | 0.90† (0.85 to 0.96) |

*p<0.5.
†p<0.0001.

*Table 5 Distribution of deaths by decile of estimated risk. Based on multivariate and univariate models*

| | *Boys* | | *Girls* | |
|---|---|---|---|---|
| *Deciles* | *Multivariate* | *Weight* | *Multivariate* | *Weight* |
| 1 (= lowest risk) | 12 (3.7)* | 12 (3.6) | 8 (2.4) | 12 (3.6) |
| 2 | 19 (5.8) | 20 (6.1) | 9 (2.7) | 8 (2.4) |
| 3 | 25 (7.7) | 27 (8.1) | 16 (4.8) | 13 (3.9) |
| 4 | 18 (5.5) | 25 (7.5) | 17 (5.1) | 18 (5.4) |
| 5 | 28 (8.6) | 26 (7.9) | 24 (7.3) | 27 (7.9) |
| 6 | 43 (13.2) | 43 (13.4) | 21 (6.3) | 22 (6.6) |
| 7 | 53 (16.3) | 52 (16.0) | 31 (9.4) | 35 (10.5) |
| 8 | 95 (29.1) | 111 (33.3) | 63 (19.0) | 62 (18.7) |
| 9 | 155 (47.5) | 164 (49.5) | 99 (30.0) | 106 (32.0) |
| 10 | 262 (81.3) | 230 (80.1) | 219 (66.4) | 204 (65.8) |

*Observed number of deaths (probability of dying in the decile).

Table 5 allows the reader to evaluate how well mortality can be predicted from this model. For example, if this model is used to help predict outcome, female babies whose estimated probability of death categorises them in the lowest decile, are observed to have a 2.4% mortality, whereas those in the highest decile have a 66.4% mortality. Thus, even in the highest decile, there is misclassification, and thus we clearly do not know, or have not measured, all the factors that are related to mortality.

Despite overall decreases in mortality and decreases or no change in morbidities among very low birthweight infants of both sexes, relative differences persist between the sexes. The biological mechanisms contributing to the male disadvantage or female advantage have not been elucidated. Until science can rationalise the male and female circumstances, nature's intent will remain obscure.

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