INTRODUCTION

Differences between male and female infants in mortality, growth, and the susceptibility to specific diseases exist during the perinatal period (fetal and neonatal), as is shown by numerous embryologic, physiologic, epidemiologic, and anthropologic observations in humans and by laboratory studies and field observations in animals.

For a cohort of individuals at a given point in life, the sex ratio (simple ratio of males to females) depends not only on the different rates of mortality between the sexes but also on the relative numbers of males and females present at birth. In humans, as in most mammalian species, slightly more males are born than females. At birth the sex ratio is approximately 1.05, representing a proportion of male births of about 51.3%. After birth the mortality of males is higher, and the sex ratio declines progressively. By the end of the first year of life, 120 males have died for every 100 females. Males continue to die at a higher rate throughout childhood and adulthood.

Males are not only more numerous and more likely to die at birth, they are also larger. Differences in the rates of growth and metabolism between males and females have been reported from the earliest embryologic period onward and may influence sexual organogenesis, the sex ratio during gestation, and relative male–female survival rates during intra-uterine and extra-uterine life.

Males are more likely to experience stillbirth, premature birth, congenital malformations, pulmonary hemorrhage, intracranial hemorrhage, respiratory distress, perinatal asphyxia, perinatal infection, cerebral palsy, and developmental delay. Sudden Infant Death Syndrome (SIDS) is more common in males. Infants are at highest risk for SIDS during the first 2–4 months of life. Besides male sex, other risk factors include maternal smoking, exposure to a suboptimal uterine environment, poor fetal growth, and prematurity.

Males also face a higher incidence of neurobehavioral and developmental difficulties during childhood. In epidemiologic surveys, attention deficit hyperactivity disorder (ADHD), characterized by poor concentration ability, motoric hyperactivity, impulsivity, and frequently learning difficulties, is four times more common in boys than in girls. The increased male susceptibility to disease depends upon the interplay of environmental risk factors with fundamental genetic, endocrinologic, immunologic, and metabolic differences between the sexes.

THE SEX RATIO DURING FETAL LIFE

Sex Ratio at Conception

Phenotypic sexual differentiation in mammals consists of a sequence of genetic and hormonal components referred to as the Jost paradigm. The genetic component, consisting of either the XX or XY chromosome complement, is determined at conception. Gonadal differentiation occurs at 6–7 weeks gestation in humans with expression of the Y chromosome-borne SRY gene, resulting in the formation of either male or female gonads. The development of male sex organs and secondary characteristics is an active process controlled by three hormones produced by the testis: Müllerian inhibiting substance (also called anti-Müllerian hormone), testosterone, and insulin-like factor 3 (INSL3). Phenotypic female characteristics develop in the absence of these three testicular hormones.

Evidence of a preponderance of male fetal losses suggests that the sex ratio is even higher around the time of conception than at birth. By assuming a constant male–female ratio of fetal loss during pregnancy, the sex ratio from the earliest point in embryonic life has been estimated to be approximately 1.1 to 1.2. However, the precise
point at which male numerical predominance develops is unknown. Several studies have shown that the ratio of Y- to X-bearing spermatozoa in humans is approximately equal; thus, the elevated sex ratio may reflect differences in rates of fertilization, implantation or early survival. The classical explanation for the sex ratio of more rapid arrival to the ovum of lighter, faster-swimming Y-bearing spermatozoa has been discounted, and postulates involving an immunologic or hormonal preference of the ovum for Y-bearing spermatozoa remain unsupported.3,12,20–24

An alternative explanation for male predominance is that it occurs after fertilization, at the time of implantation. Two days after fertilization the average number of male embryos exceeds that of female embryos. At the same time the metabolic rate, as measured by glucose and pyruvate uptake and lactate production, is higher in male embryos than female embryos. The higher metabolic rate and larger size of male embryos may confer a survival advantage (albeit temporary) on male embryos at the time of implantation. The enhanced metabolic rate of male embryos may be the result of the action of Y-chromosome-derived transcription factors acting on maternally-derived mitochondria. Higher metabolic rate (and increased temperature) may also play an epigenetic role in male sex differentiation.6,7,19,24–26

Sex Ratios and Periconceptional Influences

Male and female fetuses and infants respond differently to biological, environmental, and cultural influences. Environmental stresses including crowding, heat, and natural catastrophes have been found to alter the birth sex ratio in human populations. A sharp decline in the sex ratio at birth was reported 9 months following the 1995 Kobe earthquake and 320 days after both the 1952 London smog and the 1965 Brisbane flood. Similarly, a drop in the sex ratio to 1 was seen in New York City in 2002 following the terrorist attack on September 11, 2001. Using combined Danish registries, Hansen et al. found that severe periconceptional life events (development of cancer or myocardial infarction in her partner or older children) experienced by the mother during the first trimester result in a smaller proportion of male births. Deviations in monthly environmental temperature above the overall mean were associated with a higher birth sex ratio. Data from California support the hypothesis that the fetal death sex ratio varies positively over time with the unemployment rate. Temporary decreases in the sex ratio such as these might be due to alterations of parental hormones, altered quality of semen or an increased rate of early spontaneous abortion of males. It is notable that the peak drop of the sex ratio in New York City occurred 5 months after the September 11 attacks, making increased male fetal loss, rather than altered conception, the likely mechanism. Interestingly, the sex ratio did not change following the severe Dutch famine during the winter of 1944–45.

In contrast, the proportion of males born increased sharply after both world wars in combatant countries.13,27–37

Lower birth rank, increased parental age, and decreased frequency of coitus have been associated with a lower sex ratio. Psychological stress in one parent has been shown to favor the production of offspring of the opposite sex. Parental social status may alter the sex ratio. Parents engaged in stereotypical ‘masculine’ occupations (law, politics, natural science, medicine, business, etc.) and ‘dominant women’ were more likely to produce sons than daughters.38 James has assessed the numerous, often conflicting studies relating the sex ratio in animals and humans to various environmental, social, and disease-related circumstances and has concluded that the relative parental levels of estrogen, testosterone, and gonadotropin at the time of conception contribute to the determination of fetal sex. Others have argued that the birth sex ratio is influenced by the quality of the ovum at different times in the menstrual cycle.1,24,26,39–44

Sex Ratio and Fetal Loss

The results of chromosomal analyses to determine the sex ratio in spontaneous abortions have varied. Several of these studies have found a predominance of female tissue. After carefully excluding maternal contamination of tissue and androgenetic 46,XX hydatidiform moles, Hassold et al. estimated the sex ratio for genetically normal spontaneous abortions to be approximately 1.30. The study also noted an overall male predominance among spontaneously aborted fetuses with various trisomies, with the sex ratio lowest for trisomy 9 and highest for trisomy 21.45

Manipulation of the Sex Ratio

Attempts at selecting the sex of an infant by controlling the frequency, timing or position of coitus or insemination in relation to ovulation have a long history of use but have never been shown to be effective. Modern laboratory techniques have been applied to the question of sex selection in an effort to control the expression of serious X-linked diseases. These techniques have attempted to take advantage of potentially differing physical, antigenic, and biochemical properties that might allow separation of X- and Y-containing spermatozoa. Flow cytometry cell sorting uses fluorescence in-situ hybridization (FISH) to label X- and Y-containing chromosomes, which are then separated by flow cytometry. The technique is advertised to be a highly effective method of sex selection; but several commentators have worried about potential damage to genetic material subjected to fluorochrome staining, laser, and a high voltage electromagnetic field.46–49

Pre-conceptional sex selection for reasons of parental choice (as opposed to the elimination of genetic disease) is ethically controversial. Nevertheless, post-conceptional
sex selection has been a long-standing practice in some cultures, where infanticide or, more recently, selective abortion based on prenatal ultrasonographic determination of fetal sex are the methods of selection. In Korea, the sex ratio climbs with each pregnancy, exceeding 2.0 for the fourth child. In India, where a large gap exists between the expected and actual number of females, the sex ratio for urban births is 1.1–1.2. Similar findings have been described in China where, in census data, the births of girls have not been reported because of early deaths, most likely due to infanticide. The trend toward fewer than expected females in China is now increasingly due to selective abortion after ultrasonographic sex determination. The concept of ‘missing women’ has been advanced to focus attention on the impact of such practices. It has been estimated that there are now 40–50 million missing women in India alone, and perhaps 100 million missing women worldwide.50–54

Sex Ratio and Length of Gestation

Male infants are more likely to deliver prematurely. In an analysis involving more than 1.8 million births in six New England states, Cooperstock and Campbell found a 7.2% excess of males among white singleton preterm births (20–37 weeks gestation). Beyond 36 weeks, the proportion of males declined sharply, falling below the mean proportion of all white singleton births (51.3%) by 40 weeks gestation. Among preterm singleton black infants, the male excess was significantly smaller (2.3%). Male excess has also been reported in the birth of preterm twins less than 33 weeks gestation. Female twin pairs have a significantly longer gestation period than either male twin pairs or discordant female/male twin pairs. Mortality also has been reported to be lower in female pair twins than in either male pair or discordant twins. A ‘masculinizing’ effect of the male twin on respiratory morbidity in the female twin partner in very low birthweight (VLBW) male–female twins has been observed.55–58

SEX DIFFERENCES IN FETAL AND NEONATAL GROWTH

Fetal Growth Differences

The earliest attempts to assess the rate and range of fetal growth used cross-sectional data from live born infants to construct percentile charts for growth during the third trimester. In these charts gestational age was calculated from the last menstrual period. Lubchenco et al. provided separate growth charts for male and female newborns. In these the weight of males born at the 50th percentile exceeds that of females born at the 50th percentile by approximately 50 g at 28 weeks gestation and 100 g at term. These percentile charts have been used arbitrarily to define categorical indices of fetal growth such as small-, appropriate- and large-for-gestational age (<10th, 10th–90th, >90th percentiles, respectively). By such measures female fetuses have about a 20% greater risk for intra-uterine growth retardation (IUGR) than male fetuses.59,60

Fetal ultrasonography provides a potentially direct, longitudinal measure of fetal growth; however, standard algorithms usually have been constructed from cross-sectional data and are not adjusted for different growth rates of the sexes. In a prospective longitudinal study through the second and third trimester, Moore et al. found significantly different trajectories for male and female head growth, such that the mean biparietal diameter (BPD) for males at 28 weeks gestation was approximately equal to the mean BPD for females at 29 weeks. Pedersen et al. found that male fetuses were larger than female fetuses as early as 8 weeks of gestation. The male–female difference, expressed as the time needed for the female fetus to attain male size, ranged from 1 day at 8–12 weeks gestation to 6–7 days at term.5,61–63

Data on early fetal male–female size difference are supported by animal studies, in which evidence for size differences is present from very early in intra-uterine life, prior to gonadal differentiation. Tsunoda et al. found a size difference in mouse embryos at the blastocyst stage. Prior to implantation into foster mothers, they classified cultured embryos as ‘fast-cleaving’, ‘intermediate-cleaving’ or ‘slow-cleaving’ according to the time between fertilization and blastocyst formation. Fast-cleaving embryos were much more likely to produce males than slow-cleaving embryos. Similar results were found with bovine embryos. In human in vitro fertilization studies, larger embryos at the time of implantation were found to be much more likely to result in male births. These studies suggest that the male–female size difference is genetically rather than hormonally determined. In an article titled ‘Blastocysts prepare for the race to be male’, Mitwocch reviewed evidence in support of the hypothesis that the faster male growth rate is one of the major conditions influencing male anatomic sexual expression; slower growing embryos result in the development of an ovatextis or ovary.7–9,26,64

Neonatal Growth Differences

At birth, males are slightly larger than females. In the United States the median birthweight of term males (3530 g) exceeds that of females (3399 g) by 131 g. The respective values for recumbent length and head circumference are 49.98 cm and 35.81 cm for males and 49.23 cm and 34.71 cm for females. Revised postnatal percentile growth charts based on combined cross-sectional and longitudinal data from diverse sources have recently been published by the Centers for Disease Control. These charts show that by one year of life the male–female size difference increases, with the median weight of males exceeding that of females by almost 800 g.10
Body composition also differs during the first year of life and into childhood. Males demonstrate larger body dimensions (chest circumference, upper arm circumference, calf circumference) but females have larger measures of body fat (skinfold thickness). In VLBW premature infants the intra-uterine sex difference in growth rate carries over into extra-uterine life, with males growing larger and leaner than females. In one study of VLBW infants fed diets in which nutrient content and density were systematically varied, the growth rate of male infants exceeded that of female infants by approximately 1 g/kg/day. Subscapular skinfold thickness was measured and was greater in females than males but the difference narrowed as the daily caloric intake increased.\textsuperscript{10,65}

**EXCESS MALE MORTALITY**

**The ‘Male Disadvantage’**

In 1971 Naeye et al. analyzed 2735 consecutive autopsies involving both neonatal deaths and stillbirths and found an excessive risk of neonatal death in males. The ratio of male to female deaths overall was 1.28, which differed significantly from the sex ratio at birth for the general population (1.05). The male to female ratio in stillbirths without congenital anomalies was similar to that of the general birth population. However, among neonatal deaths the ratio of males to females was much higher (1.32). Higher male mortality was seen consistently over a wide range of causes of death, including major congenital malformations, hyaline membrane disease, pulmonary hemorrhage, intracranial hemorrhage, aspiration pneumonia, pre- and post-natal infection, and the effects of maternal diabetes and toxemia. The study also examined the effects of socioeconomic status and race on mortality and found that the highest sex ratio occurred among non-poor whites. The authors postulated that while the stillbirths were due to a failure of the maternal environment and therefore affected sexes equally, there existed an inherent ‘male disadvantage’ for survival in the neonatal period that was not related to a specific disease process. A recent study confirms the presence of a male disadvantage among VLBW infants. Other evidence has pointed to an interaction between male gender and poorer pregnancy outcomes, perhaps due in part to the larger size of male fetuses at a given gestational age. Women carrying male fetuses had higher rates of gestational diabetes melitius, fetal macrosomia, failure to progress during the first and second stages of labor, cord prolapse, nuchal cord, and true umbilical cord knots. Cesarean sections also were found more frequently with male newborns.\textsuperscript{11,13,66–68}

### Sex Ratio, Infant Mortality, and Race

In the United States the difference in survival between the sexes is modified by a survival difference between the races. Although infant mortality rates for both black and white infants continue to decline, the infant mortality rate of black infants remains more than double that of white infants, and the relative gap between the races appears to be growing. In 1980 the infant mortality rates for black and white males were 25.9 (per 1000) and 12.3, respectively, a ratio of 2.1. By 2004 the rate for black males had fallen to 13.8 compared to 5.7 for white males, a ratio of 2.4. Infant mortality rates for white and black males are about 23% higher than for white and black females, but the trend toward higher relative mortality in black females compared to white females over time is similar. The excess overall mortality for black infants is related largely to a downward shift in the birthweight distribution and the much greater risk of death for lower birthweight infants regardless of race and sex (see Table 1.1)\textsuperscript{4,69}

Within a given birthweight category the effect of birthweight on survival is contrary to the overall effect: that is, the group with the lowest mean birthweight (black females) has historically had the highest survival rate, while the group with highest mean birthweight (white males) has had the lowest. However, it appears that this hierarchy of birthweight-specific survival may be changing, perhaps due to improved care of extremely low birthweight infants. In New York City white females now have birthweight-specific survival rates which exceed those of black females

### TABLE 1.1 United States Birthweight-specific Survival Rates by Gender for Newborns with Birthweight <1500 g During The First 28 Days of Life, 2004\textsuperscript{69}

<table>
<thead>
<tr>
<th>Birthweight (g)</th>
<th>Females</th>
<th></th>
<th>Males</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths</td>
<td>Births</td>
<td>% survival</td>
<td>Deaths</td>
</tr>
<tr>
<td>499 or less</td>
<td>2729</td>
<td>3382</td>
<td>19.3</td>
<td>3019</td>
</tr>
<tr>
<td>500–749</td>
<td>2003</td>
<td>5762</td>
<td>65.2</td>
<td>2781</td>
</tr>
<tr>
<td>750–999</td>
<td>537</td>
<td>5904</td>
<td>90.9</td>
<td>895</td>
</tr>
<tr>
<td>1000–1249</td>
<td>314</td>
<td>6981</td>
<td>95.5</td>
<td>383</td>
</tr>
<tr>
<td>1250–1499</td>
<td>225</td>
<td>8346</td>
<td>97.3</td>
<td>300</td>
</tr>
<tr>
<td>Total &lt;1500</td>
<td>5807</td>
<td>30375</td>
<td>80.9</td>
<td>7379</td>
</tr>
</tbody>
</table>
in essentially all categories (see Table 1.2). These changing relationships raise complex and disturbing questions about differential access to healthcare and the influence of a host of socioeconomic factors and toxic exposures on neonatal and infant mortality.\textsuperscript{70}

**Interaction of Growth and Mortality**

An intriguing hypothesis discussed by Clarke and Mittwoch postulates a connection between the increased rates of growth, metabolism, and mortality in males compared to females. In vitro populations of fibroblasts cannot divide indefinitely; a so-called species-specific ‘growth crisis’ related to the rate of chromosomal alterations occurs when the number of generations reaches a critical threshold. The authors also note that within a species, lower caloric intake and lower metabolic rates have been associated with increased longevity. Thus, decreased longevity and increased susceptibility to disease from embryonic life onward may be the price males pay for enjoying a higher basal metabolic rate and a faster rate of growth that, initially, may have provided a survival advantage at the time of implantation and contributed to male phenotypic expression.\textsuperscript{6,7 – 9,18,19,25}

**THE EFFECT OF GENDER ON THE INCIDENCE AND SEVERITY OF DISEASES IN INFANCY AND CHILDHOOD**

**Early Metabolic Programming**

There has been a lot of interest recently in the developmental origins of adult disease, or ‘metabolic programming’. Nutritional and metabolic exposures at critical times during early development may have long-term effects on the health of the adult. Experience during early life may be predictive of different health outcomes such as body size, body composition, and risk of diseases such as obesity, diabetes, hypertension, stroke, and cardiovascular disease. (For example, infants born to mothers with type 2 diabetes have a higher risk of developing diabetes in later life.) Two factors that appear to be implicated are fetal and postnatal growth rate. As stated previously, there are differences in the allocation of energy between male and female infants. Male newborns are heavier at birth than females at the same gestational age, with greater lean mass in males and greater fat mass in females. Skinfold thickness to birthweight and tricipital skinfold thickness to body weight ratios increase significantly with increased maternal weight gain in 1st and 2nd trimesters of gestation in the female fetus but not in the male fetus.\textsuperscript{71 – 74}

Chronic hypertension has become an increasing problem because of the rising incidence of obesity, diabetes, and renal disease. Reports have shown an association with low birthweight and the development of adult hypertension. A recent meta-analysis found no significant gender differences in the association between low birthweight and high blood pressure. However, in a rabbit model of maternal hypertension the female offspring exhibited increased risk for the development of hypertension. This finding was thought to be related to changes in the growth and development of renal sympathetic nerves during fetal life which may contribute to the development of hypertension in the adult animal. In another study using a rat model with placental insufficiency and growth restricted offspring, both male and female offspring were hypertensive for the first 10 weeks of life. The male offspring remained hypertensive after puberty. This may be related to the interaction of the sex

<table>
<thead>
<tr>
<th>Birthweight (g)</th>
<th>Black non-Hispanic</th>
<th>White non-Hispanic</th>
<th>Puerto Rican</th>
<th>Other Hispanic</th>
<th>Asian or Pacific Islander</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–499</td>
<td>952.4</td>
<td>777.8</td>
<td>1000.0</td>
<td>866.7</td>
<td>1000.0</td>
<td>901.2</td>
</tr>
<tr>
<td>500–749</td>
<td>500.0</td>
<td>571.4</td>
<td>437.5</td>
<td>529.4</td>
<td>700.0</td>
<td>519.8</td>
</tr>
<tr>
<td>750–999</td>
<td>111.1</td>
<td>155.6</td>
<td>280.0</td>
<td>214.3</td>
<td>200.0</td>
<td>164.0</td>
</tr>
<tr>
<td>1000–1499</td>
<td>37.7</td>
<td>60.6</td>
<td>12.8</td>
<td>28.3</td>
<td>68.2</td>
<td>40.5</td>
</tr>
<tr>
<td>1500–2499</td>
<td>5.7</td>
<td>14.1</td>
<td>6.9</td>
<td>8.7</td>
<td>5.0</td>
<td>8.6</td>
</tr>
<tr>
<td>2500+</td>
<td>8.3</td>
<td>3.6</td>
<td>4.7</td>
<td>3.8</td>
<td>2.8</td>
<td>4.9</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–499</td>
<td>931.0</td>
<td>666.7</td>
<td>1000.0</td>
<td>875.0</td>
<td>1000.0</td>
<td>884.1</td>
</tr>
<tr>
<td>500–749</td>
<td>398.2</td>
<td>281.3</td>
<td>310.3</td>
<td>321.4</td>
<td>687.5</td>
<td>381.8</td>
</tr>
<tr>
<td>750–999</td>
<td>142.9</td>
<td>28.6</td>
<td>117.6</td>
<td>46.5</td>
<td>76.9</td>
<td>76.9</td>
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<tr>
<td>1000–1499</td>
<td>13.3</td>
<td>17.5</td>
<td>37.0</td>
<td>34.1</td>
<td>87.0</td>
<td>26.4</td>
</tr>
<tr>
<td>1500–2499</td>
<td>5.9</td>
<td>3.6</td>
<td>12.7</td>
<td>5.0</td>
<td>4.2</td>
<td>5.7</td>
</tr>
<tr>
<td>2500+</td>
<td>7.0</td>
<td>2.0</td>
<td>5.0</td>
<td>2.6</td>
<td>3.2</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Rates are per 1000 live births. Number of births = 125,563.
Data compiled by NYC Department of Health.
hormones with other regulatory pathways such as the renin-angiotensin system during fetal and postnatal life. After puberty estrogen may provide protection in the female from the hypertension. Adverse effects can be passed transgenerationally from mother to daughter and then to her offspring. In rat studies, exposure to maternal protein restriction during pregnancy and postnatally produced female offspring (F1 generation) with increased insulin sensitivity. Her offspring, the F2 generation, showed altered glucose and insulin metabolism in both males and females.\(^75\)\(^-\)\(^81\)

**Postnatal Effects of Changes in the Intra-Uterine Environment**

**MATERNAL DIABETES**
Abnormal intra-uterine environments have been found to affect male and female fetuses and newborn infants differently. In a retrospective review of singleton term births born to mothers with pregnancies complicated by diabetes, male infants had a higher incidence of hypoglycemia. This observation may be explained by higher levels of human chorionic gonadotropins (HCG) found in the fetuses of mothers with diabetes. Elevated HCG levels cause Leydig cell hyperplasia, resulting in higher levels of testosterone, which in turn produce hyperplasia of the pancreatic beta islet cells and increased insulin secretion. With the abrupt cessation of the transplacental glucose supply at birth, increased insulin in males raises the probability of hypoglycemia.\(^82\)

A similar explanation may account for the higher incidence of respiratory distress syndrome (RDS) in male offspring of diabetic compared to non-diabetic mothers of comparable gestational ages. Higher levels of androgens have been described in both cord blood and amniotic fluid in such infants. This increased level of testosterone may in turn block the production of surfactant, exposing the male infant to a higher risk for RDS. Studies in the chick show that androgens block glucocorticoid regulation of lung maturation.\(^83\)\(^,\)\(^84\)

**Susceptibility and Response to Acidemia and Hyponxia**
In a Swedish study, male fetuses demonstrated more frequent and more severe episodes of acidemia following a protracted course of abnormal fetal heart tracings indicative of fetal distress. On follow-up evaluations at 4 years of age, these same male children had a higher incidence of neurodevelopmental problems. An in vitro study of the effect of hypoxia on hippocampal neuronal cells demonstrated increased vulnerability of male cells and of female cells primed with testosterone. This finding was postulated to account for some of the gender differences in neuropsychiatric diseases related to hippocampal integrity. Studies in the hypoxic-ischemic neonatal rat model have shown gender-specific differences in caspase-dependent apoptosis that may also help explain gender differences in outcome following hypoxic-ischemic insults in the human neonate.\(^85\)\(^-\)\(^87\)

**Alloimmunization, Hyperbilirubinemia**
Male fetuses have been shown to be more severely affected by alloimmunization of fetal red blood cells to D antigen. Male fetuses required a greater number of intra-uterine transfusions and these were performed at a lower gestational age. The odds ratio for the male developing hydrops fetalis was 13.1. Male newborns also may have higher levels of hyperbilirubinemia: in a study of 840 low birthweight infants, mean peak bilirubin was significantly higher (by 0.8 mg/dl) in males in a regression model controlling for race, birthweight, gestational age, intraventricular hemorrhage, and sepsis.\(^88\)\(^,\)\(^89\)

**Effects of Maternal Smoking**
Maternal smoking during pregnancy reduces fetal growth for both sexes but affects male infants disproportionately. At birth, males born to mothers with a history of heavy cigarette smoking had an 8.2% reduction in weight and a 12% reduction in fat accretion compared to 4.8% and 2%, respectively, in females. In males, head circumference was also significantly smaller, with fall-off in head growth noted as early as the second trimester. Since male fetuses have a higher rate of growth than females, factors limiting growth may have a greater impact on males. Male fetuses may be more sensitive to the direct effect of the toxic byproducts of cigarette smoke in regard to cell replication, changes in the hormonal milieu, and fetoplacental circulation.\(^90\)

**Effects of Drugs of Abuse**
Drugs of abuse such as heroine and cocaine have been shown to interfere with fetal growth. Significant decreases in birth size have been observed in infants with in utero cocaine exposure as measured by urine toxicology at birth or by analysis of cocaine content in hair or meconium. Several of these studies, using regression models to control for the effects of demographic and other risk factors, found an independent effect of sex on birth size. Although no gender specific effect of cocaine was reported, a re-examination of the original data shows that relatively larger decrements in birth size, particularly of head circumference, are observed in cocaine exposed males (D.A. Bateman, unpublished data). Similar findings of interference with growth have been described in infants born to mothers with heroin addiction. Many of these infants are premature and also exhibit growth retardation. Cell size and cell number have been found to be decreased in autopsy studies compared to infants of mothers with similar socioeconomic status and nutrition.\(^191\)\(^-\)\(^93\)

Several studies have been reported on the neurobehavioral development of children exposed to drugs of abuse in utero. Children exposed in utero to cocaine demonstrated a higher incidence of neurobehavioral difficulties such as hyperactivity and language and developmental delays. When the effects were stratified by sex, male children showed a significantly higher incidence of developmental difficulties. The male
children also scored significantly lower on the Bayley Scales of Infant Development. In one study, school age behavior was altered in males but not in females. Boys with persistent intra-uterine cocaine exposure had more problems with central processing, motor skills, and handling abstract concepts than controls or exposed girls. Similar neurodevelopmental and behavioral difficulties were described in children who were born to mothers on methadone maintenance during pregnancy, with male children affected more than female children. These findings correlated with the exposure to methadone, the quality of mothering and the rearing environment. Male children appeared to be more vulnerable to the interaction of adverse effects of intra-uterine exposure to drugs of abuse, opioids, and environmental factors.94–98

Congenital Anomalies and Gender

The incidence of certain congenital anomalies varies with the sex of the infant and survival. The incidence of trisomy 18, for example, is higher among male than female stillbirths, but among live born infants with trisomy 18, females outnumber males three to one. Down syndrome, on the other hand, is more common in males among both live born and stillborn infants. Isolated anomalies of multifactorial inheritance that have an unequal sex distribution include pyloric stenosis, clubfoot, and cleft lip (more common in males) and cleft palate alone, meningomyelocele, anencephaly, and congenital hip dislocation (more common in females). Isolated diaphragmatic hernias, especially postero-lateral types, occur more frequently in male infants. Congenital diaphragmatic hernias that occur in conjunction with chromosomal anomalies are more common in female infants. A treatment choice for infants with congenital diaphragmatic hernia with severe respiratory decompensation is extracorporeal membrane oxygenation (ECMO). A group of infants treated with ECMO were evaluated for neurocognitive development at 31 months of age. These infants exhibited an increased incidence of developmental difficulties, especially the male children, again illustrating the increased long-term vulnerability of the male child. 45,99–102

### Table 1.3 The Gender Ratio Observed for Specific Types of CHD, Described as Male/Female Ratio of Incidence

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Samánek et al.</th>
<th>Calzolari et al.</th>
<th>Samánek et al.</th>
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PDA, Patent ductus arteriosus; ASD, atrial septal defect; VSD, ventricular septal defect; CoA, coarctation of the aorta; HLHS, hypoplastic left heart syndrome; TOF, tetralogy of Fallot; DORV, double-outlet right ventricle; TGA, transposition of the great arteries. From Miller-Hance and Tacy, 2004; used by permission.

Asthma and Gender in Children

Asthma is nearly twice as common in male children (11.4% vs. 6.9%) and male asthmatic children suffer more frequent attacks during the preschool period. Predictors of childhood asthma have included male gender, low birthweight, and neonatal respiratory distress due to various etiologies. When controlled for birthweight, prematurity, and neonatal respiratory distress, a significant association was found between male gender and preschool asthma. Possible etiologies entertained for the higher incidence of asthma in the male child have been the presence of smaller airways relative to lung size and diminished lung function. 103,108,109

Gender and Diseases of Premature Birth

**Effects on Mortality**

Infants with birthweight less than 1000g and gestational age less than 28 weeks continue to contribute disproportionately to infant morbidity and mortality. This is compounded by the recent increase in the incidence of multiple births (by 20%) as a result of in vitro fertilization. Mortality is on the decline for extremely premature infants, but major morbidity, especially in those with birthweights <750 g, remains unchanged. The incidence of neonatal complications such
as chronic lung disease, necrotizing enterocolitis, intraventricular hemorrhages, and poor postnatal growth may even have risen.\textsuperscript{111}

Table 1.1 displays the neonatal survival rate (during the first 28 days of life) according to birthweight category and gender for all VLBW babies (<1500 g) born in the United States in 2004. Both gender and race-ethnicity play significant roles in mortality, morbidity, and neurodevelopmental outcome. The white premature male has the highest rate of mortality (see Table 1.2). Significant predictors of mortality in premature infants are low gestational age (<28 weeks, especially 23–26 weeks), intraventricular hemorrhage, Apgar score <3, and male gender. Recently, the National Institute of Child Health and Human Development Neonatal Research Network has published separate graphic estimates for risk of mortality stratified by gender and birthweight (see Figure 1.1).

Tyson and co-workers have used the NICHD data set to construct predictive equations for mortality prior to NICU discharge and disability at 18–22 months corrected age, based on expected birthweight, gestational age, gender, plurality, and maternal receipt of antenatal corticosteroids. For example, a 24-week singleton male infant with an expected birthweight of 650 g whose mother received antenatal corticosteroids has a predicted mortality of 45% with a 77% probability of death or severe disability. For females with similar characteristics, the probability of mortality and death or severe disability are 34% and 62%, respectively. It should be emphasized that these equations are still in the investigational stage and have not been verified with broad population-based data.\textsuperscript{66,69,111–113}

**Apgar Score**

The Apgar score, a tool used to assess well-being at 1 and 5 minutes after birth, incorporates five elements: respiratory effort, heart rate, reflex irritability, muscle tone, and color. In the preterm infant, the Apgar score is directly related to birthweight and gestational age. Among premature infants, Apgar scores are significantly higher at 1 and 5 minutes in females. In addition, male premature infants frequently require more vigorous resuscitation. Higher Apgar scores in the preterm female infant may be related to the higher catecholamine levels found in female infants at birth, resulting in a more normal pressor response and improved cardiovascular stability.\textsuperscript{114}

**Cerebral Blood Flow**

Cerebral blood flow is lower in preterm female infants. This is of particular interest in that it may contribute to the better survival and neurodevelopmental outcome seen in premature females. The reason for these differences is unknown, but may be related to differences in mean arterial blood pressure, cardiac output, and/or sex hormonal influences.
Gender-related differences in cerebral blood flow distribution persist through childhood and adulthood, although the patterns change and the significance of the differences is unknown. Improved developmental outcome in males treated in the early perinatal period with indomethacin, which results in decreased cerebral blood flow, has been noted.\textsuperscript{115–117}

**Respiratory Distress Syndrome**

Respiratory distress syndrome (RDS), or respiratory insufficiency of prematurity, is one of the major complications seen in premature low birthweight infants. The incidence of RDS in premature infants between 500–1500 g ranges from 50 to 80%. Infants with lower birthweights and gestational ages have a higher incidence of RDS. The relative risk for developing RDS and its complications is 1.7 for male premature infants compared to female infants of the same gestational age. Gender differences in specific measures of airway function have been demonstrated.\textsuperscript{118–120}

Antenatal steroid administration to women in premature labor has been shown to induce fetal lung maturation and decrease the incidence and severity of RDS in the premature newborn. Usually, either betamethasone or dexamethasone is administered within 24 hours of delivery to women who are in premature labor at less than 32 weeks gestation. The administration of antenatal steroids was found to be more effective in preventing or ameliorating RDS in the female premature infant than in the male. After steroid administration, the incidence of RDS in the male was 29.1% and in the female 8.6%. In premature sheep, pulmonary function measured by compliance, conductance, lung volume and PaO\textsubscript{2} showed greater improvement in females than in males after antenatal steroid administration. The pharmacologic and physiologic response to antenatal steroids may be related to the presence of an endogenous inhibitor of surfactant production in the lung in the male infant. Dehydrotestosterone has been shown to inhibit fetal pulmonary surfactant production. A lag in the production of surfactant has been demonstrated in the rabbit fetus. An increase in the incidence of RDS has been described in preterm male twin pairs compared to preterm female twin pairs; male twins, although heavier, showed the same blunted response to antenatal administration of betamethasone. An increased incidence of RDS also has been noted in girls of unlike-sex preterm twins compared to girl-girl twins. A transchorionic paracrine effect on the female twin has been proposed to account for this observation.\textsuperscript{58,118,119,121–125}

Surfactant production, reflecting the maturity of the fetal lung, can be evaluated by measuring the L/S (lecithin/sphingomyelin) ratio in amniotic fluid. The L/S ratio for white male fetuses is the lowest (most immature) when compared with white female, black female or black male fetuses. The data suggest a relative delay in surfactant production, which may be genetically determined in white males.

The response of the fetal lung to various hormones such as glucocorticoids and androgens may be influenced by genetic factors controlling development.\textsuperscript{83}

Chronic lung disease (CLD) is a complication seen in small premature infants in association with RDS and its treatment modalities (especially mechanical ventilation and supplemental oxygen) and with other complications of prematurity including infection and the presence of a patent ductus arteriosus (PDA). The incidence of CLD varies with gestational age, birthweight, and length of ventilatory therapy. Male gender is also a risk factor for the development of CLD. This is consistent with the increased incidence and severity of RDS in male infants. Male preterm infants also are more likely to experience episodes of apnea and bradycardia and to develop anemia and electrolyte disturbances during the neonatal period. Interestingly, a prospective cohort study from Holland of prematurely born infants with and without CLD found a higher prevalence of asthma and respiratory symptoms in young adult women compared to men.\textsuperscript{126,127}

**Septicemia**

Septicemia is another common complication in low birthweight premature infants. Its incidence is inversely proportional to gestational age and birthweight. The risk of septicemia is 48% higher in male premature infants. Septicemia is associated with increased mortality as well as serious morbidity including severe intraventricular hemorrhage, CLD, and prolonged ventilatory treatment. The reason for the greater male susceptibility to infection is not known.\textsuperscript{128}

**Neurobehavior and Pain Perception**

Gender differences in socio-emotional behavior, well documented in human adults, may have antecedents in the earliest days of life. Neonatal imitation, considered the earliest form of communicative exchange, differed between male and female infants at 3–96 hours of life. In response to an index finger gesture, female infants had a higher number of fine motor movements and specific imitative gestures, faster response, and higher heart rate response than male infants. Early neurobehavioral gender differences on the Newborn Behavioral Assessment Scale (Brazelton Exam) also have been documented. In one study, female infants scored higher than male infants in areas of auditory orientation, alertness, and state regulation. Males had higher irritability scores. In serial assessments of predominant mood during the first two years of life, boys were reported more often to be in happy-excited moods, whereas girls were more often in a quiet-calm mood. Analysis of cord blood sex hormones including androstenedione, estrone, and progesterone showed small but significant associations and interactions between mood and cord hormone levels.\textsuperscript{129–131}

Multiple adult studies have shown gender differences in pain perception but little information is available on
whether or not these differences are present in the neonatal period. Interpretation of neonatal studies has been made more difficult because of the use of different instruments to evaluate pain. Biological differences have been described in responses to pain in males and females. Pain thresholds and tolerance are lower in women. Shorter latency time to cry and facial reactions have been described in male newborn infants. In addition, female infants of all gestational ages expressed more facial features of pain than males during capillary stick and 1 minute post procedure. These findings may reflect early developmental differences in pain perception among male and female infants.  

**Prognosis**

The long-term prognosis of low birthweight premature infants is guarded. The smaller, sicker, and more premature the infant is, the higher the incidence of long-term morbidity. A 2-year follow up of low birthweight infants demonstrated that cerebral palsy, sensorineural hearing loss, visual disorders, and developmental delays were related to the severity of illness during the neonatal period. In the same study, male children showed poorer development of language and personal skills than female children, irrespective of neonatal morbidity. In another study from Holland the prevalence of handicaps at 5 years of age was three times greater in boys than girls (21% vs. 7%, odds ratio 3.2). This did not change when adjusted for gestational age and birthweight. A critical review of follow-up studies in school-aged children born at less than 1500g demonstrated age-appropriate IQ scores but with a large variability. There was a greater need for special education for these children for learning difficulties, motor incoordination, and behavior problems. In studies where gender was examined, the outcome for females was generally better than that of males.  

The results of several multi-center follow-up studies of extremely low birthweight (ELBW, <1000m) infants have been published recently, showing that approximately one-third to one-half of surviving ELBW infants demonstrate major developmental handicaps by 18–22 months corrected age. Data from the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network, involving at least 12 centers and collected over an 8-year period, showed that more than half of surviving ELBW children had neurodevelopmental impairment (NDI), consisting of one or more of the following: cerebral palsy, Bayley Mental Developmental Index score (MDI) <70, Bayley Physical Developmental Index Score (PDI) <70, blindness or deafness. Only 21% of infants tested were considered to be unimpaired. Disability occurred in males 1.5–2 times more frequently than in females. In studies out of Cleveland, rates of NDI in ELBW and VLBW cohorts examined over two decades were approximately 30%. Intact survival was noted in half of the infants examined at 20 months corrected age; however, males were half as likely as females to survive intact. Table 1.4 summarizes the gender-specific outcome differences observed in several large follow-up studies.  

Hack *et al.* have pointed out the poor predictive validity of Bayley scores for cognitive function of ELBW infants at school age. Nevertheless, neurodevelopmental problems persist through early school age and even into young adulthood. The EPICure study used a battery of standardized tests to identify neurologic and developmental disability at 6 years of age in infants born ≤25 weeks gestational age. Overall, 41% of infants tested had serious impairment (>2 SD below comparison mean score); the rates in boys and girls were 49% and 32% respectively. Hack *et al.* followed a cohort of VLBW survivors born in 1977–9 into young adulthood and found higher rates of neurosensory impairment, lower IQ, and lower academic achievement scores and subnormal height compared to controls. Although many of the male–female differences seen in younger cohorts were not observed, VLBW men (but not women) were significantly less likely than normal-birthweight controls to be enrolled in educational programs after high school. A follow-up study of 8-year-old Finnish children of normal and low birthweight demonstrated that the boys had poorer linguistic and motor skills than the girls. Multivariate logistic regression analyses showed that lower birthweight, young maternal age, more than four children in a family, reconstructed family, hearing impairment, and male gender were the most important determinants of poor speech and language abilities with and without adjustment for neonatal risk factors.  

Several studies have examined whether or not data gathered during the perinatal period might be predictive of long-term outcome, in order to identify at-risk children with special needs. In addition to gestational age and birthweight, significant perinatal predictors of poor neurodevelopmental outcome include neonatal sepsis, non-white race, and male gender. Low socioeconomic status and male gender were predictors of educational handicaps. The strongest child-related risk factor in all models tested was male gender. Male children were more than twice as likely to use special education services for learning problems. A male child was six times more likely to be referred for special services for emotional disorders. The NICHD neonatal network is currently evaluating the validity of a predictive model for survival and survival without profound neurodevelopmental impairment, using risk factors at or before birth for infants born at 23–25 weeks gestation.  

**SUMMARY**

In the fetal and neonatal periods and during infancy, males and females differ in at least three fundamental ways. First,
males are more numerous; and their numerical superiority appears to be derived at conception or shortly thereafter. Second, males are larger than females and have higher metabolic rates. This difference also is apparent from very early fetal life, from the blastocyst stage, when the increased cell number and metabolism in males may, in fact, influence phenotypic sexual expression. Third, males have a higher mortality rate than females, are more susceptible to most diseases of infancy, and suffer disproportionately from their long-term consequences. This has been termed the ‘male disadvantage’. Each of these three major differences appears to involve the interplay of genetic, hormonal, metabolic, and perhaps evolutionary influences that are not yet well understood.

References
CHAPTER 1 · The Effects of Gender in Neonatal Medicine


