Declines in Sex Ratio at Birth and Fetal Deaths in Japan, and in U.S. Whites but Not African Americans

Devra Lee Davis, Pamela Webster, Hillary Stainthorpe, Janice Chilton, Lovell Jones, and Rikuo Doi

Methods: Public health records from national statistical agencies were assembled to create information on sex ratio at birth and in fetal deaths in the United States (1970–2002) and Japan (1970–1999), using SPSS.

Results: Sex ratio at birth has declined significantly in Japan and in U.S. whites, but not for African Americans, for whom sex ratio remains significantly lower than that of whites. The male proportion of fetal death has increased overall in Japan and in the United States.

Conclusions: Sex ratio declines are equivalent to a shift from male to female births of 135,000 white males in the United States and 127,000 males in Japan. Known and hypothesized risk factors for reduced sex ratio at birth and in fetal deaths cannot account fully for recent trends or racial or national differences. Whether avoidable environmental or other factors—such as widespread exposure to metalloestrogens or other known or suspected endocrine-disrupting materials, changes in parental age, obesity, assisted reproduction, or nutrition—may account for some of these patterns is a matter that merits serious concern.

Key Words: African Americans, environment, fetal deaths. Japan, race, sex ratio, trends. Environ Health Perspect 115:941–946 (2007). doi:10.1289/ehp.9540 available via http://dx.doi.org/ [Online 9 April 2007]
In the first decade after a chemical plant explosion caused unusually high exposures to dioxin, of the children born to those with the highest exposures, all were female. In another study, Egeland et al. (1994) showed that men who were occupationally exposed to dioxin had altered gonadotrophin and testosterone levels; the researchers hypothesized that altered maternal hormone levels might affect the viability of Y-bearing sperm or the fetuses conceived by them. A follow-up study failed to find significant changes in sex ratio of offspring or fetal death rates in this small sample population (Schnorr et al. 2001). A recent study of men and women working in a Russian plant that manufactured the herbicide 2,4,5-trichlorophenoxyacetic acid found that only 38% of the children fathered by these exposed workers were male, whereas exposed mothers produced a normal 51% males (Ryan et al. 2002). An investigation of the effect of a variety of chemicals on the sex ratio of chemical industry workers in Japan was, in some ways, inconclusive (Okubo et al. 2000): Although researchers found that exposure to chemical materials may have affected the sex ratio of the offspring of the workers, they could not indicate with certainty which chemical materials may have been responsible. The workers’ exposure to heat, they hypothesized, may have been a co-contributor.

Maternal Exposure

Maternal exposure can also be an important determinant of sex ratio. Maternal serum exposure to polychlorinated biphenyls (PCBs) from the consumption of contaminated Great Lakes fish resulted in decreased sex ratio of offspring (Weisskopf et al. 2003). The odds of having a male child decreased by 46% for every unit increase in the natural log of serum PCB concentration. This observation adds to the growing body of evidence that exposure to certain chemicals can alter sex ratio at birth. Moreover, an increased risk of cryptorchidism among sons of female gardeners has been reported in Denmark, suggesting an association with prenatal exposure to chemicals used in farming and gardening (Weidner et al. 1998). There is some evidence that dose and combinations of exposures can have differing impacts on sex ratio (Axelrod et al. 2001). One small study found that mothers with the highest levels of exposure to PCBs gave birth to proportionally more males than females, whereas those with the lowest exposure did not (Sharpe and Skakkebaek 1993).

Results

Our data show distinct and unexplained trends in sex ratio in Japan and in the United States. Since 1970, sex ratio (SR) has declined significantly in U.S. whites and Japanese. But in African Americans, SR has increased modestly over time, while remaining lower than that of whites.

Figure 1 shows the male proportion of live births in Japan from 1949 to 1999. In years before 1970, sex ratio fluctuated greatly from year to year, but since 1970 sex ratio has declined fairly steadily with less yearly fluctuation. For 1970–1999, the regression coefficient is $-9.91 \times 10^{-5}$ with an $R^2$ of 0.70. Over the study period of 1970–1999, SR for Japan declined significantly ($p < 0.01$) from 0.5172 to 0.5135. This is equivalent to a decline of 37 males per 10,000 births. If the 1970 male proportion had remained constant, this would correspond to a shift from male to female births of approximately 127,000 over these three decades.

In Japan, fetal death rates are typically more than twice those of the United States, and range to as much as five times as large. For example, in 1999 Japan reported 31.6 deaths per 1,000, whereas the 1999 U.S. fetal mortality rate for all races was 6.7 per 1,000. Figure 2 shows the male proportion of fetal deaths. For 1972–1999, the rate of increase is $4.27 \times 10^{-3}$, nearly seven times greater than that of the proceeding 72 years. The proportion of fetal deaths that are male has gone from just over half to nearly two-thirds, a figure that held throughout the 1990s. Male fetuses in Japan, then, are clearly at greater risk of dying than are female fetuses. Although fetal death rates have generally fallen, from around 100 per 1,000 in 1960 to 32 per 1,000 in 1999, the proportion of fetal deaths that are male has declined significantly ($p < 0.01$) from 0.5172 to 0.5135. This is equivalent to a decline of 37 males per 10,000 births.

Materials and Methods

We conducted separate analyses for the United States and Japan. For Japan, we examined sex ratio at births and of fetal deaths from 1949 to 1999. We relied on national statistics provided by the Japanese Vital Statistics Bureau (Japan Statistical Yearbook 2000), which are published yearly, but are not available for the postwar years 1944–1946.

For the United States, we examined trends in sex ratio overall, for African Americans, and for whites, from vital statistics data (Martin et al. 2003) from 1970 to 2002. Last, we calculated the U.S. sex ratio of all fetal deaths, using fetal death data files for 1983–1995 (National Center for Health Statistics 2003). We examined trends in the male proportion of live births, and from these we calculated simple linear regressions. We calculated the male proportion of fetal deaths by dividing the number of male fetal deaths by the sum of male and female fetal deaths. If the number of male fetal deaths is greater than that of females, the proportion of male deaths will be greater than that of females. We examined only deaths after 20 weeks gestation because most deaths before that time are of unknown sex. Where sex was unknown, that case was excluded from analysis. Mother’s race was used to calculate proportions by race.

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Fetal death rates have declined for all races since 1970, falling roughly in half from 14 to 6.6 per 1,000 in 2000. Although all races have experienced declines in fetal mortality, there are racial disparities in levels of infant mortality. For all years, U.S. African Americans have a higher fetal mortality rate and a higher male proportion of fetal deaths than U.S. whites. In 2000, the fetal mortality rate for African-American mothers was 12.4 per 1,000, compared with a rate for white mothers of 5.6 deaths per 1,000 (Minino et al. 2002).

Discussion

Previous reports have indicated that in several industrial countries, including the Netherlands, Denmark, Finland (Moller 1996; Vartiainen et al. 1999), Canada (Allan et al. 1997), and the United States, the proportion of males born declined significantly from 1970 to 1990, ranging from an annual drop of 0.001 for the United States (Davis et al. 1998) to 0.003 for the Netherlands (Van Der Pal-de Bruin et al. 1997). In some Latin American countries (Feitosa and Krieger 1992), the male proportion has fallen by about one male birth per 1,000 live births since the 1970s. Such declining patterns are not evident in some longer term trends. An independent jointpoint analysis by the U.S. Centers for Disease Control and Prevention reported that the trend for whites and Mexicans mirrored the overall downward trend for the last 30 years, but trends for African-American and Chinese mothers rose, and trends for other groups were stable (Mathews and Hamilton 2005) One analysis in Finland (Vartiainen et al. 1999) found that male proportion had increased from 1751 to 1920, and decreased afterward, except for peaks during and after World War I and World War II. Another analysis found parallels between the postwar secular decline of the male:female ratio at birth and the decline of perinatal morbidity and mortality, congenital anomalies, and various constitutional diseases (Jongbloet et al. 2001). Not paternal nor maternal age, nor difference in age of parents, nor birth order can explain these varying time trends (Vartiainen et al. 1999).

The continuing trends in declining sex ratio for U.S. whites and for Japanese that we report here are consistent with those reported recently in other industrial countries, and remain unexplained. Among the explanations suggested for these declines in sex ratio are prenatal exposures to endocrine-disrupting environmental pollutants at a critical stage of sexual differentiation. Researchers theorize that the same chemicals that reduce the sex ratio in the offspring of male workers (Jongbloet et al. 2001) may cause similar effects in populations that are chronically exposed to low levels of these same pollutants.

Not only are fewer males born to some highly exposed cohorts of workers, but surviving male fetuses also appear more susceptible to detrimental effects of toxic exposures than females (Del Rio Gomez et al. 2002; James 1998b; Toppari et al. 1996). Garry et al. (1996) have shown that both reduced SR and higher rates of male birth defects are associated with paternal occupation as a pesticide applicator.

How workplace exposures may contribute to reduced sex ratio in offspring has yet to be explained. Fetal development of male characteristics is a complex process largely determined by the hormonal cascade controlled by the SRY gene. Without the proper hormonal cues, even genetically male fetuses will develop along the default female pathway. Sex ratios at birth may be an “important tool” for the investigation of endocrine disruption and a marker of endocrine disruption of one or both parents at the time of conception (Sharpe and Skakebecke 1993).

A growing body of evidence indicates that several exogenous factors may be functioning to impair male development. Male reproductive disorders including reduced sperm count...
and quality, testicular cancer, cryptorchidism (undescended testes), and hypospadias (displacement of the urinary opening toward the scrotum) have been increasing in industrial countries (Del Rio Gomez et al. 2002; Toppari et al. 1996; Weidner et al. 1998). Each of these disorders represents a mild degree of feminization and may have a shared etiologic origin in prenatal exposure to xenosterogenic endocrine disruptors. Thus, declining sex ratio may be a manifestation of further increased phenotypic feminization of XY fetuses. Evidence that changes in sex ratio could represent a complete phenotypic feminization of genetically male fetuses is provided by observations in animal populations and should be explored further in humans.

Whatever their causes, trends in the sex ratio of fetal death can have important impacts on trends in SR. With respect to the different sex ratio trends in U.S. African Americans and whites, it is important to consider that fetal loss is more common with male fetuses, as indicated by the male dominance in sex ratio of fetal deaths in all populations studied. Improvements in obstetric care for the general population may account for increases in SR that occurred before 1970 in many countries. If fetal deaths in Japan are recorded at 12 weeks and in the United States at 20 weeks, this could account for why the death rates differ so much. But the increasing proportion of males in fetal deaths in the United States and Japan is noteworthy.

In the United States, quality of and access to prenatal obstetric care for African Americans historically has lagged behind those of whites. To the extent that improvements in obstetric care lead to reductions in fetal deaths that occur disproportionately in African-American males, then these advances in care could affect sex ratio at birth. It is possible that improvements in prenatal care may reduce male fetal death rates, with a time lag in the African-American population, as advances have reached this population at a later point in time. The effect of any exposure causing a decline in SR would be more clearly reflected in the white population than the African-American population, because for African Americans recent changes in SR are subject to the confounding effect of drops in the male fetal death rate, as a result of improved prenatal care. As male fetal loss rates decline because of better obstetric care for U.S. African Americans, more male fetuses are expected to survive to birth, leading to an increase in SR. For all years, U.S. African Americans have a lower SR than U.S. whites. Both worldwide and within the United States, sex ratios vary by a few males per 100 females when one examines different racial and ethnic groups. In the United States, this difference could be partly the result of differences in fetal death rates combined with sex ratio of fetal deaths. African Americans have a higher fetal death rate and a higher male proportion of fetal deaths. Combined, these factors could account for reductions in SR for U.S. African Americans compared with U.S. whites by eliminating a larger proportion of male fetuses between conception and birth. Thus, the slight increase in SR for U.S. African Americans since 1970 may be the result of relatively recent advances in prenatal care.

Racial differences in sex ratio in the United States may seem puzzling, though it is possible that what is “normative” varies slightly among groups of different racial heritage. Among the reasons why sex ratio in African Americans could be consistently lower than that of whites are factors that contribute to prenatal mortality differences. Some studies have found that greater rates of early onset puberty and premature menarche in young African-American women (e.g., James 2006) whereas others have reported greater exposures to hair care and other personal care products that are contaminated with hormones (e.g., Paulozzi 1999). Whether these factors contribute to a more estrogenic prenatal environment and thereby to a lower proportion of male births, and to greater rates of breast cancer in young African-American women < 35 years of age, are topics that merit serious research.

One other possibility deserves mention. Among African-American young women, obesity is nearly 50% higher than among their white counterparts. Among non-Hispanic white adults 20–74 years of age, 46.8% of women are overweight or obese (body mass index ≥ 25.0). Among non-Hispanic African Americans in the same age group the percentage is 68.3 (Herman-Giddens et al. 1997). In the United States, several observers have speculated that the rise of obesity, while reflecting suburban sprawl, increasing television watching, and inactivity patterns of children, may also be attributed to increased consumption of growth-stimulating and endocrine-disrupting agents in the food supply (Tiwary 1998).

Many developed countries where sex ratio has declined have also seen substantial increases in average body weight and obesity (Centers for Disease Control and Prevention 2002). Moreover, it appears that increased body weight is correlated with a lower sex ratio. At least one study in Africa found that obesity was independently related to a low sex ratio at birth (Andersson and Bergstrom 1998). A declining sex ratio for a population has generally been diagnosed as an indicator of worsening female advantage (Jayarat and Subramanian 2004). Additional research regarding the role of societal factors in the alteration of sex ratio is needed.

One particular aspect of Japanese culture that may be involved in earlier changes in sex ratio in Japan we do not analyze here. According to one widely held superstition, called Hinoe-uma, females born in certain years are believed to be stronger than males and will ultimately kill their husbands. Based on this belief, every 60 years when Hinoe-uma occurs, female babies have been killed by midwives or sometimes even by their family immediately after birth. This is believed to have resulted in a rise in sex ratio in 1906 and again in 1966 (Itoh and Brando 1987).

Regarding changes in SR in Japan, Mizuno (2000) hypothesized that the increase in sex ratio of fetal death in Japan may be affecting the overall rate. Our data suggest that the steady decline in Japanese fetal death rates may be mitigating the impact of Japan’s greatly elevated sex ratio of fetal deaths on SR. Had fetal death rates remained constant, it is likely that SR would have declined even further than it has. Why the sex ratio of fetal deaths in Japan has risen so dramatically since 1970 requires explanation. One possibility we believe merits evaluation is the body burden of mercury or other metalloestrogens, to which male fetuses may be more susceptible. Bioaccumulation of methylmercury can occur in tuna, haddock, and other large fish, an important part of the Japanese diet (Iso et al. 2006). Recent research suggests that a host of prenatal effects occur at intake levels 5–10 times lower than that of adults (Iso et al. 2006). Past research has documented that when severe and widespread methylmercury pollution was experienced in Minamata City, Japan, there was an extreme reduction in the sex ratio at birth of fetal Minamata disease patients, especially in the period of worst pollution and at the worst polluted area (Doi et al. 1987, 2001). The authors also noted that a characteristic seasonal pattern of the birth of male and female fetal Minamata disease patients coincides with the seasonal patterns of the fish catch in Minamata and the outbreak of Minamata disease patients. Lately, Sakamoto et al. (2001) confirmed this independently of Doi et al. (1987, 2001) with the same data, and they also described an increase in male stillborn fetuses.

Strikingly, the severity of birth defects and impairment of sex ratio in Minamata was increased most in those with the highest levels of mercury (Sakamoto et al. 2001). We hypothesize that the decline in sex ratio in industrial countries may be caused partly by prenatal exposure to metalloestrogens and other endocrine-disrupting chemicals at a critical stage of prenatal development, or paternal exposures that take place before conception that select against expression of the Y chromosome, or some combination of these factors that selectively increase male fetal death rates. Workplace studies and experimental
that altered gene expression can be affected by
findings support this hypothesis. Recent
could influence sex.
timing of meiosis in the ovary and testes and
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