Increase in male fetal deaths in Japan and congenital anomalies of the kidney and urinary tract

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A B S T R A C T

The male to female (M/F) fetal death ratio in Japan from the mid 1970s to 2005s has consistently increased while total fetal deaths have declined. Public health records and other evidence were reviewed to assess the recent trends in infant renal failure, the congenital anomalies of the kidney and urinary tract (CAKUT), and the sex ratio of these disorders. The M/F infant death rate caused by renal failure has increased from 0.75 to 3.0 over the past 3 decades. There has been an increase in CAKUT as a cause for fetal and infant deaths, and renal hypoplasia and dysplasia were male predominant. The increase in the M/F deaths ratio caused by infant renal failure, as well as increased male predominant CAKUT suggests that the Wolffian duct regression might have affected the initial development of the kidney and male genital tract thus contributing to male fetal deaths.

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1. Introduction

Over the past 50 years, the Vital Statistics of Japan revealed the M/F fetal death ratio increased from 1.29 in 1955 to 1.37 in 1975, 2.05 in 1995, 2.17 in 2000 [1] and 2.29 in 2005. However, the factors to affect this trend or related trends occurring in Japanese fetuses have not been studied. If this increase in the M/F ratio of fetal deaths directly affects the sex ratio at births, then the underlying factors for this prenatal sex-dependent phenomenon must be carefully examined. So far, the possible causes for changes in the sex ratio at birth discussed were time of exposure to hormones, parental age, in vitro fertilization, stress, maternal illness, child birth order, maternal hormone level, unusual environmental exposures, and obesity [2,3]. The trend of increasing male fetal deaths requires explanation today. In this report we investigated evidence that congenital anomalies of the kidney and urinary tract (CAKUT) and other related information, because the trend in the CAKUT and the male fetal deaths might have some associations with each other. In addition, it is also important to investigate postnatal data on infant death to explain the prenatal trend of increasing M/F ratio of fetal deaths. Infant death is defined as the number of infant deaths (1 year of age or younger) per 1000 live births. Fetal death is defined as the number of fetal deaths (after 12 weeks of gestation) per 1000 live births and deaths. Preterm birth refers to the birth of a baby of less than 37 weeks gestational age. Premature birth, commonly used as a synonym for preterm birth, refers to the birth of a premature infant weighing 500–2499 g.

2. Role of the Wolffian duct in the kidney and male genital tract formation

It is well-known that the development of the urinary and genital systems is intimately interwoven. The renal system is formed in three sequences: from the pronephros to the mesonephros, and then to the metanephros (permanent kidney). The mesonephric duct also known as the Wolffian duct connects the mesonephros to the cloaca and serves as the anlage for certain male reproductive organs. The ureteric bud develops from the Wolffian duct and gives rise to the ureter, and that later develops into the adult kidney. It is widely known androgen play a vital role in Wolffian duct development [4], but the mechanisms that underline this are unknown. If development of the Wolffian duct is hindered, the genesis of the male genital tract as well as initial kidney development could be disturbed. That could be one of the causes of various CAKUT. CAKUT is a family of diseases with a diverse anatomical spectrum including kidney anomalies, and various types of urinary obstructions. CAKUT occur in 1 out of 500 newborns, and constitute approxi...
3. Increases in the M/F infant death ratio due to renal failure

Due to improvements in obstetric care, fetal, neonatal, and infant deaths rates have declined significantly over the past decades in Japan. Fetal deaths rate decreased from 46.8 in 1980 to 29.1 in 2005 per 1000 total births [6]. Infant deaths rate decreased from 7.5 in 1980, 2.8 in 2005 per 1000 live births [6]. As shown in Fig. 1, the M/F ratio of fetal deaths has increased from 1.29 in 1955 to 2.29 in 2005. On the other hand, M/F ratio of infant death (due to various causes) has not shown significant changes during the last decades. The ratio is between 1.1 and 1.4. However, as shown in Fig. 2, the M/F ratio of infant deaths due to renal failure shows entirely different trend.

![Fig. 1. M/F ratio of fetal deaths and infant deaths in Japan. This figure shows the changes in the male to female (M/F) ratio of fetal deaths and infant deaths in Japan. The data is from the Vital Statistics of Japan. The graph is an update of the graph shown by Mizuno [1].](image)

Among the various causes of infant deaths, congenital anomalies comprise the highest proportion (34.7%) in 2005 [7]. This fact suggests that infant deaths due to abnormal prenatal developmental has become an important problem. Deterioration of fetal renal development could also results in infant deaths due to renal failure. According to the Vital Statistics of Japan, the death rate from renal failure in infants aged 0–4 years decreased from 1.4 in 1985 to 0.3 in 2005 in males (per 100,000), and from 1.7 in 1985 to 0.1 in 2005 in females (per 100,000) [8]. However, as shown in Fig. 2, the M/F death ratio resulting from renal failure increased from 0.8 to 3.0. Currently, the male infant renal failure death rate exceeds that of females. In contrast, the M/F renal failure death ratio among other age groups (5–9, 10–14, and 15–20 years) has not shown significant changes during the same period [8]. Although deaths resulting from renal failure are categorized as postnatal outcomes, prenatal deaths resulting from renal anomalies might show a similar trend, because kidney genesis occurs early in gestation.

Since this evidence is based on national-level statistics which represents one of the adverse health outcomes of approximately of 32 million births over the past 25 years (e.g., 1.57 million births in 1980, and 1.06 million births in 2005) in Japan, the causes of this rising sex-dependent phenomenon deserve attention. Furthermore, there is a similarity between the trend in renal failure-related infant deaths and fetal deaths (Figs. 1 and 2). As noted in a previous study, the M/F ratio of fetal death has increased more than doubled, and we found that the earlier the gestation, the higher the M/F ratio. The M/F fetal death ratio at 12–16 weeks of gestation was as high as 10.01 in 1996, compared to only 2.52 in 1975 [1]. Survival of male fetuses especially early in gestation appears to have threatened over the past decades, suggesting a possible disturbance in male genesis by unknown extraneous factors. It is possible that in both trends, increasing M/F death ratio resulting from renal failure and the M/F fetal death ratio are associated.

4. Known causes of CAKUT cannot explain the rising sex-dependent trend

Between 1979 and 1986, four Japan nationwide surveys looked at infants and young children with pediatric chronic end-stage renal diseases (ESRD). The surveys (for children under 15 years), which started again from 1998 [9,10], demonstrated that cystic or hereditary anomalies or CAKUT comprise 48–65% of the ESRD causal diseases, and these are increasing. Furthermore, renal hypoplasia and dysplasia are major diseases causing CAKUT today in contrast to focal segmental glomerulosclerosis decades ago. Known and suspected causes of CAKUT are failure of ureteric bud activity such as ectopic budding of the initial ureter [11], failure of an interaction between the epithelium of the ureteric bud and the mesenchyme of the metanephric blastema [12], and failure of nephrons to develop: thus preventing formation of collecting ducts. These defects sometimes cause involution of the kidney and disruption of fetal urinary flow. Furthermore, recent biogenetic studies have revealed that renal development is regulated by many forms of genes encoding transcription and growth factors [13,14]. However, Hiraoka et al. revealed that the genes identified until date cannot account for the predominance of males with CAKUT. Furthermore, ultrasound screening of 4000 apparently healthy Japanese neonates demonstrated that congenitally small kidneys with diminished function were found only in boys at a much higher incidence than that suggested previously [15]. It is possible that an altered hormonal environment of the uterus, which might suppress the development of the Wolffian duct, may better explain the increasing male CAKUT predominance.

![Fig. 2. M/F ratio of deaths rate due to infant renal failure. Left vertical axis shows male to female (M/F) ratio of death rate due to infant renal failure. Right vertical axis shows death rate of renal failure of male infant and female infant, respectively (per 100,000). Data is from the Vital Statistics of Japan.](image)
5. Fetal deaths caused by CAKUT (from the Vital Statistics of Japan)

More evidence suggests that there has been an increase in CAKUT over several decades in Japan. An investigation into the causes of the fetal deaths, as reported in the Vital Statistics of Japan from the 1980s to 2000 [16] revealed that fetal deaths by CAKUT, coded under the International Classification of Diseases (ICD) (753, congenital anomalies of the urinary system which includes kidney anomalies) have been increasing. The number of the deaths due to CAKUT has increased 10 times over the past two decades.

In the past decade, renal agenesis and dysgenesis (coded 753.0) accounted for about half of these deaths. Whether this reflected a true increase or resulted from a change in detection or reporting practices is unknown. The prevalence of ultrasonography might explain some of these increases; however, during the same periods, the number of fetal deaths reported for other congenital anomalies, such as those of the cardiovascular, respiratory, and skeletal-muscular systems has not shown significant changes.

6. Infant deaths caused by CAKUT and renal agenesis/dysgenesis

A close examination of the causes of infant deaths (below 1 year of age) in the Vital Statistics shows a similar trend [16]. Comparing the data between 1969–1973 and 1989–1993 shows that the percentage of the congenital anomalies as causes of infant deaths had increased twofold: from 18.7% in 1969–1973 to 35.1% in 1989–1993. Furthermore, the percentage of renal agenesis/dysgenesis among congenital anomalies of the urinary system increased ninefold from 1% in 1969–1973 to 2% in 1989–1993. Among them, the percentage of renal agenesis/dysgenesis was higher in boys [15].

Besides data from the Vital Statistics, a report on Japan’s mass screening for early detection of CAKUT in infancy from 1994 to 2001 showed that of the 2700 screened 1-month-old infants, 4.1% (112) had abnormalities in the first screening, and 0.67% (18) had CAKUT on further examination [17]. Another screening of 5700 1-month-old infants yielded 3.5% (198) positive cases of CAKUT [18]. The latter study demonstrated that the incidence of CAKUT, which often causes childhood chronic renal failure in Japan, is increasing.

7. Male predominance of CAKUT

Among various reports on CAKUT, male predominance in cases of renal hypoplasia and dysplasia deserves further attention. Table 1 shows reports from 1997 to 2005 in Japan. Eighty four percent of intermittent hydronephrosis were found in boys [19], male predominance was also shown in vesicoureteral reflux [19] in 2005. M/F ratios of 2.15 for hydronephrosis, and 3.25 for hydroureter were reported for children under 20 [20]. Furthermore almost all of the hypoplastic kidneys with vesicoureteral reflux (VUR) were found in boys in 2003 [21]. The M/F ratio for renal dysplasia and hypoplasia in the pediatric end-stage renal failure was between 1.3 and 5.99 (1998–2002) [9,10], all of the intermittent hydronephrosis were boys [22], and all of the congenital small kidney were boys in 1997 [23]; thus showing marked male predominance. Male predominance in CAKUT has also been reported in other countries. Yeung et al. [24] showed that mild reflux associated with normal kidneys affected mostly females and a proportion of males, whereas severe reflux combined with kidney damage, mostly fetal in origin was almost exclusively a male disorder.

8. Neonatal surgery for hydronephrosis and low birth weight infants (LBW)

An increase in CAKUT as a cause of pediatric chronic end-stage renal failure, as well as fetal and infant deaths seems to have occurred over the past decades in Japan. And its male predominance is shown. Moreover, CAKUT is known to predispose to various types of pediatric nephropathy such as hydronephrosis. According to a national survey on neonatal surgery [25], the number of the surgical procedures performed due to hydronephrosis increased 1.6 times from 1998 to 2003. Of them, ureteropelvic junction obstruction now comprises 62.7% (increased by 9% from 1998 to 2003), and VUR comprises 10.8%. Although hydronephrosis is one of the most sensitive developmental responses elicited by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in mice, and is produced by maternal doses of TCDD too low to cause palatal clefting [26], its trend in human newborns has not been given attention from the perspective of the effects of endocrine disruptive chemicals (EDCs) on the developing fetuses.

Further evidence that might suggest an increase in infants with kidney malfunction in Japan is found in low birth weight (LBW) trends. Multiple animal models have suggested an association between LBW and congenital nephron deficit [27]. Furthermore, in humans, Silver et al. [28] noted that intrauterine growth restriction appears to be associated with a decrease in fetal renal volume, because renal volume is a possible proxy for nephron number. Moreover, Hiraoka [21] noted that infants with CAKUT often show varying degrees of a reduced number of nephrons at births. In
Thus, the percentage of LBW infants (less than 2500 g) in Japan has increased from 5.1% in 1975 to 8.6% in 2000, and 9.6% in 2005, almost doubling in the last three decades. Moreover, the percentage of ELBW (extreme low birth weight) less than 1000 g has increased from 0.1 in 1980 to 0.3 in 2006. Such increases in the overall LBW infants may have been due to a relative increase in survivors of premature babies because of the recent advances in neonatal care such as neonatal surgery. The numbers of the neonatal surgical procedures performed each year in Japan has increased 5.6 times (662 in 1969 to 3709 in 2003) in the last four decades [25]. Male infants exceed the female infants (male 57%, female 42%) in 2003. The percentage of LBW in them has increased from 19% in 1973 to 33% in 2003, and their survival rate after surgery increased from 49% in 1973 to 72% in 2003. Therefore, most of the neonates who have undergone surgery could survive in Japan today. Consequently, there is an increase in premature babies with several complications. As LBW has been shown to lead to a low nephron endowment with subsequent glomerular hyperfiltration, additional renal disease can therefore be expected to have a more severe course [29]. Thus, the increases in LBW in Japan over the past decades might suggest the possibility that kidney function in Japanese newborns has been deteriorating incrementally. And as shown in Table 1, male predominance is noted.

Additional evidence which might suggest an increase in male infants with kidney malfunction as well as endocrine malfunction in Japan might be found in the data on dwarfism. Dwarfism, any types of marked human smallness, usually results from a combination of genetic factors and endocrine malfunction. However, it can also be caused by acquired condition such as kidney disease. LBW infants tend to lose water and electrolyte into the urine and lose body fluid and have a high risk of developing dwarfism in later life. The reports on the children’s specific chronic diseases [16] revealed that 7363 males and 3747 females (less than 20 years old) have submitted an application for growth hormone treatment to stimulate growth in 2004. Today, more males are suffering from short stature in Japan. As pituitary dwarfism comprise the major part of dwarfism in Japan, there is a possibility that male are the target of endocrine disruption. Moreover, the rising LBW infants might have contributed to this trend.

9. Conclusion

The trend of increasing male fetal deaths in Japan between the mid 1970s to 2005 is unexplained. Based on national-level statistics for over 32 million births in the past decades, the present study showed evidence of an increasing M/F ratio in infants deaths with renal failure, suggesting an association of this trend with the increasing M/F fetal death ratio. Both trends are embryologically connected to each other by the Wolffian duct. EDCs might have played a role in these trends, because an altered hormonal environment of the uterus could affect the Wolffian duct development. Although much research has been devoted to exploring the causes of CAKUT, known genetic causes identified until date do not seem to account for the increasing predominance of males with such anomalies.

Conflict of interest

None.

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References


