The Secular Trends in Male:Female Ratio at Birth in Postwar Industrialized Countries

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Finnish investigators [Vartiainen et al. Environmental Chemicals and Changes in Sex Ratio: Analysis Over 250 Years in Finland. Environ Health Perspect 107:813–815 (1999)] presented the sex ratio of all newborn babies from 1751 to 1997 in order to evaluate whether Finnish long-term data are compatible with the hypothesis that the decrease in the ratio of male to female births after World War I and World War II in industrial countries is caused by environmental factors. They found an increase in the proportion of males from 1751 to 1920, which was interrupted by peaks in male births during World War I and World War II and followed by a decrease thereafter, similar to the trends in many other countries. The turning point of male proportion, however, preceded the period of industrialization and introduction of pesticides and hormonal drugs. Thus, a causal association between these environmental exposures and this decrease is unlikely. In addition, none of the various family parameters (e.g., paternal age, maternal age, age difference in parents, birth order) could explain the historical time trends. Vartiainen et al. concluded that at present it is unknown how these historical trends could be mediated. The postwar secular decline of the male:female ratio at birth is not an isolated phenomenon and parallels the decline of perinatal morbidity and mortality, congenital anomalies, and various constitutional diseases. This parallelism indicates a common etiology and may be caused by reduction of conceptopathology, as a correlate to increasing socioeconomic development. An inverted dose response or the dose–response fallacy due to vanishing male conceptuses explains the low sex ratios before World War I and World War II in newborns from black parents and from the lowest socioeconomic classes. *Key words*: neural tube defects, ovopathy, primary sex ratios, secondary sex ratios, socioeconomic patterning, tertiary sex ratios, vanishing male conceptuses. *Environ Health Perspect* 109:749–752 (2001). [Online 13 July 2001]
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The decrease in the male:female sex ratio at birth, or the secondary sex ratio (SSR), generally found in post-World War II industrialized countries, such as the United States (*1,2*), Canada (*1*), Denmark (*1,3,4*), Germany (*5*), The Netherlands (*1,4,5*), and Finland (*6*), is a subject of continuing debate. The main hypothesis is that environmental chemical contaminants are responsible for this decrease. Fluctuation of the SSR has been promoted as a possible sentinel health indicator (*4,7*). However, current chemical pollution was virtually absent during the 18th and 19th centuries, which were characterized by a continuing increase of the SSR (*1,2,5*), as stressed by Vartiainen et al. (*6*). Environmental chemicals, therefore, do not explain the increasing SSRs before World War I and World War II or the decreasing ones afterward. In addition, environmental chemicals are unlikely to account for the increasing SSRs found among neonates born to black parents in the United States (*3*), nonmetropolitan areas of Italy (*8*), or low socioeconomic classes (*9,10*), compared to the simultaneously decreasing SSRs among those born to white parents in metropolitan areas or the upper classes.

In this paper we focus on the maturation of the oocyte and liquefaction of the cervical mucus in animal and human reproduction. We also offer a unifying concept that explains the fluctuations in sex determination at conception, that is, the primary sex ratio (PSR), and the shorter male life expectancy at every age from conception onward. Male-biased loss of pathologic conceptuses entails reversal of the secondary sex ratio (SSR) at birth; male-biased loss of children and adults affects the decline of the tertiary sex ratio during life, causing the increasing "gender gap."

Unifying hypothesis on sex determination. The intricate connections between either equal proportions of each sex and optimal conceptions at the core of the fertile window of the menstrual cycle, or between disproportionate rates of male-biased and pathologic conceptuses outside of this window are due to periovulatory hormone variation, which simultaneously modulates cervical liquefaction and oocyte maturation.

The cervical liquefaction plays a pivotal role in the migration of the spermatocytes (*11*), whereas developmental competence of the human oocyte is acquired during follicle formation and meiotic progression (*12*). Before midcycle, both liquefaction of the mucus plug and maturation of the oocyte are modulated by estrogens. Concurrence of both facilitates equal access and fertilization of optimally matured oocytes by X- and Y-bearing spermatocytes and full expression of the genetic potential resulting in good embryo quality.

In contrast, nonoptimal liquefaction and maturation due to hormonal disturbances occur at the very beginning and the end of the fertile window. Because the head, length, perimeter, and area of Y-bearing spermatozoa are significantly smaller than those of X-bearing spermatozoa, and their necks and tails are shorter (*13*), differential migration of the Y-bearing spermatozoa (*14*) and preferential fertilization of nonoptimally matured oocytes are likely. The pleiotropic nature of experimentally induced aging of the oocyte in animals before or after ovulation [i.e. overripeness ovopathy (*15–17*)] depends on molecular, biochemical, and physiologic processes in the oocyte, which encompasses both nuclear and cytoplasm constituents. The teratogenic results are impossibility of fertilization, improper implantation, prenatal loss, transitory retardation in the rate of development, and a spectrum of anomalies such as deficiencies in organogenesis or differentiation in various tissues and organ systems. Thus, ovopathy entails comorbidity of a broad spectrum of mutually interrelated conditions, and the teratogenic components apparently depend on degree and pleiotropic nature of overripeness ovopathy (*18*).

Dose–response sex ratio increase and reversal as a dose–response fallacy. This male-biased loss of conceptuses and individuals can evolve in sex ratio reversal, as shown by the overrepresentation of male blastocysts or births in rabbits after a short delay in fertilization and sex ratio reversal after a prolonged delay (*19,20*). Positive and, after having surpassed a certain threshold, negative dose–response gradients are due to vanishing

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male conceptuses, in analogy with the "vanishing twins" during pregnancy, as is very well known from the epidemiology of twins. This phenomenon explains some theoretical constructions necessary for explaining the inconsistencies and controversies in epidemiologic data (*21*), namely, distortion by differential prenatal loss or an inverted dose–response gradient (*22*,*23*), or the dose–response fallacy (*24*). The unexpectedly low SSRs after extended preovulatory phases in humans (*25*) and in many other pathologic conditions can be cleared up by this fallacy (*26*), as is shown below.

We do not claim that this dose–response fallacy is an all-purpose explanation. SSR reversal will only occur in case of an extreme accumulation of conceptopathology associated with a disproportional (male-biased) pregnancy loss. Further amelioration and optimalization of the periconceptional conditions will entrain a positive dose response, which is followed by a negative one after having passed a certain threshold.

The often-seen SSR reversal below the 100:100 level (*27*) cannot be reconciled exclusively by overripeness ovopathy, but only by its combined action with deleterious sublethal X-linked genes, which in males is not compensated for by a second X-chromosome with normal genes (*28*). Both mechanisms are necessary because SSR reversal under the 100:100 level occurs only after extreme accumulation of periconceptional casualty, whereas genetic mechanisms run randomly and independently from the eliciting exogenous factors.

The "U"-shaped configuration of SSR and pathologic progeny vis-à-vis timing of ovulation. The tendencies toward disproportionate attrition and loss of conceptuses at the very beginning and very end of the fertility window versus optimal survival at the middle of the window are in line with the "U"-shaped configuration in relation to the estimated ovulation date for conceptions that are destined to end in spontaneous abortion (*29*). In addition, these tendencies explain the other well-known "U"-shaped probabilities for delivering male offspring vis-à-vis timing of insemination in various animals or estimated ovulation in humans: insemination at the time of ovulation apparently biases the SSR in favor of equal sex proportions, in contrast to a moderate increase in males before or after ovulation (for pooled data, 94:100 vs. 117:100) (*30*). The similarity of mechanisms in SSR determination in both nonhuman and human progeny fit this concept.

The close connection between either reproductive success and equal proportion of sexes or high SSRs and male-biased pathologic progeny is in line with the high SSRs found in miscarriages, stillbirths, and progeny with developmental defects. Male-biased attrition caused by inappropriate timing of ovulation or fertilization during the receptive period is shown in infants from women with irregular cycles compared to regular cycles (119:100 vs. 91:100) (*31*) and in early prenatal loss, as suggested by the gradually decreasing sex ratios in 12–15-week versus 16–19-week fetal deaths (*32*).

High-risk conditions for conceptopathology. The risk factors for nonoptimal periovulatory modulation of cervical liquefaction and oocyte maturation in humans are associated with high-risk conceptions related to compromised ovulation and/or fertilization: for example, nonoptimal maternal age and interpregnancy interval, specific seasons, endocrinologic disturbances, inadequate diet and socioeconomic status (SES), wars and other stressors, unhealthy lifestyle, and occupational burden (*33*).

Lessons about folic acid. Research has shown that folic acid deficiencies lead to neural tube defects and to developmental anomalies of the eyes, digestive tract, lungs, skeleton, and face. Wynn and Wynn (*34*) stressed the importance of women taking folic acid supplements before conception because estradiol and progesterone—both necessary for optimal maturation of the oocyte—are depressed by inadequate folate or vitamin B_{12} intake and induce long follicular phases or delayed ovulation, both of which are markers for slow down in embryonic growth and risk of congenital anomalies (*34*). The recently established 4-fold increase in maternal risk of having a child with Down syndrome, when affected by abnormal folate metabolism (*35*), has shown that pathologic conception is the culprit of meiotic nondisjunction in this continuum of pregnancy wastage.

Gradual attrition in the rate of oocyte pathology may account for the strongly divergent sex ratios in spontaneously aborted and/or terminated fetuses with neural tube defects. The sex ratios apparently depend on the site of the lesion along the neuroaxis: more males have low spinal lesions involving the sacrum, but high thoracic and cervical involvement is biased toward females (*36*,*37*). This basic concept, therefore, may help to reduce overstated genetic determinism.

Effects of inadequate diet and maternal depletion. Punnett (*38*) reported in 1902 that favorable nutritive conditions tend to produce females, and males tend to be produced in unfavorable conditions. This has received support from observations and experiments on numerous animals. Animals that receive critical (minimally adequate) levels of nutrition are barely able to ensure fertility and, if so, they produce malformed offspring; below this threshold of nutritional adequacy, animals become infertile (*34*,*39*). In rhesus monkeys and women, gonadal function, particularly the preovulatory phase, is strongly affected by caloric intake, as reflected in length of the menstrual cycle (*39*,*40*). Dieting, long-distance running, or situations that create a demand for performance and new adjustments increase the risk of longer or shorter menstrual cycles (*41*,*42*) and luteal inadequacy (*43*).

Poor nutritional status and low prepregnancy body mass index of the mother endanger the outcome of pregnancy and also increase the risk of congenital malformations (*44*,*45*). The relationship between maternal body depletion and male-biased prenatal loss or developmental pathology in the surviving fetuses is illustrated by the effect of extreme famine exposure during the Dutch Hunger Winter (December 1944–January 1945). The prevalence of central nervous system defects in children and the prevalence of schizophrenia, personality disorder (*46*), or coronary heart disease (*47*) in adults were much higher in people who were conceived during these months than in the months before and after. Male-biased mortality before and after birth is always higher in individuals with these defects (*48*,*49*).

SSR and socioeconomic status. Length of the menstrual cycle and menstrual disorders are powerfully influenced by social position (*50*,*51*). Lower SES mothers suffer more frequently from menstrual disorders, and they are more likely to have low standards of nutrition and abnormal body mass index (*51*,*52*), to smoke tobacco, and to use drugs (*53*,*54*). In addition, they often use less safe and effective methods of contraception, which may result in unplanned and unwanted pregnancies (*55*), often at a very young or an advanced maternal age, and in very short or very (unintendedly) long birth-to-conception intervals.

This accumulation of conceptopathology in the lowest SES strata suggests the highest dose exposure and explains many puzzling aspects of well-known social patterning of developmental anomalies and neonatal, infant, or adult morbidity and mortality, even when the effects of race and birth order are taken into account (*51*,*56*). This high dose exposure also elucidates the lowest SSRs in the lowest SES ranges (*9*,*10*). In our hypothesis, they are due to inverted dose response or SSR reversal. The SSR increases when the family's socioeconomic level rises from low to moderate is due to decreasing rates of conceptopathology and, hence, increasing rates of optimally matured and fertilized oocytes (i.e., less male-biased fetal loss and more male survivors). Finally, when the socioeconomic level improves further, the SSR decreases to more equal gender proportions after having reached a plateau (*9*,*10*); this is due to increased rates of optimal conceptions. Thus, improvements in nutritional standards, general health, and prenatal care are operative over only one part of the socioeconomic scale: the SSRs always reach a level beyond which they are no longer biologically meaningful (*9*). Populations in socioeconomic transition—characterized by continuous improvements in living conditions, education, and reproductive hygiene—also show always-increasing SSRs, which go hand in hand with less pregnancy wastage and increases in natural fertility and male survivors (*57–61*). These divergences between low and high SSRs, and particularly the dose–response fallacy, may help to explain the exceptions to the general SSR decrease after World War II in some countries (Italy, Spain, France, Ireland, and Australia) (*62*).

The postwar decreases of the SSRs in industrialized countries. The same line of thought accounts for the low and increasing SSRs among children from black parents in the United States (*2*) or in the (southern and poor) nonmetropolitan areas in Italy (*8*), in contrast to the decreasing SSRs among children from white parents and (northern and wealthier) metropolitan areas.

In conclusion, we agree with Vartiainen et al. (*6*) that the cause of these fluctuations of male to female births before and after World War I and World War II in industrial countries cannot be caused by the introduction of pesticides. In contrast, we suggest that the very low SSRs before World War I and World War II were caused by an accumulation of conceptopathology, inherent loss of male-biased conceptuses, and inverted dose response (*22,23*) or the dose–response fallacy (*24*); the continuous increases are caused by perennial amelioration and optimalization of the periconceptional circumstances (amelioration of nutrition and family planning, as a correlate of socioeconomic development and education). The secular decreases of the SSRs and pregnancy wastage after World War I and World War II, in whites (United States), and in northern metropolitan areas (Italy) fit in with further optimalization of the conceptions and an approach to equal gender distribution.

Similar dose–exposure effects in SSR and in the rate of developmental anomalies are consistently present in other high-risk conditions characterized by menstrual cycle abnormalities, namely, inappropriate maternal age and interpregnancy interval, specific seasons, endocrinologic disturbances, stress (and wars), inadequate lifestyle, and occupational burden, as described elsewhere (*26, 33*). In each set of data, SSR inversion only occurs in case of an extreme accumulation of conceptopathology associated with disproportional (male-biased) prenatal loss. Perennial amelioration and optimalization of the periconceptional curcumstances causes a positive dose response.

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