


 COMMENTARY

# The human prenatal sex ratio: A major surprise

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Two remarkably consistent and poorly understood features of human biology are the slightly male-biased sex ratio at birth and the female survival advantage throughout life. These patterns appear across geography and time wherever reliable birth and death records are available (1, 2). The slight male bias, typically ~51.3% of live births, is so consistent (Fig. 1A) that when birth sex ratios deviate much from it, suspicions are aroused of sex-specific abortion or infanticide (3, 4). Putting together the birth sex ratio bias and the female survival advantage (5), we expect a monotonically declining sex ratio from birth to death, which is exactly what we find across cultures and across historical epochs (Fig. 1B). By age 100 y, there are three to four women for every surviving man, and by the extraordinary age of 110 y, 95% of the survivors are women. Note, however, that until later life the sex ratio does not stray far from 50:50, an observation that would gladden the heart of evolutionary biologist, Sir Ronald Fisher, who argued that natural selection should favor equal parental expenditure—a delightfully vague phrase—in males and females (6). Fisher assumed, as have many since then, that the human sex ratio at conception is even more male-biased than the sex ratio at birth, and there were some good reasons to assume this. First, males are less likely than females to survive from birth to age 5 y in all countries with reliable records (5). Therefore, extrapolating backward suggests a more male-biased sex ratio in utero. Second, male babies born at very low body weight are less likely to survive than females born at the same weight (7). Finally, up to 70% of babies spontaneously aborted early in gestation are male (8). Thus, given this evidence that males are more susceptible to death—that is more frail—both before and after birth, the question wasn't so much whether the sex ratio at conception was male-biased, but exactly how dramatic that bias was. Therefore, it comes as something of a surprise when, in by far the most comprehensive analysis of prenatal sex ratios ever performed, Orzack et al. (9) report in PNAS

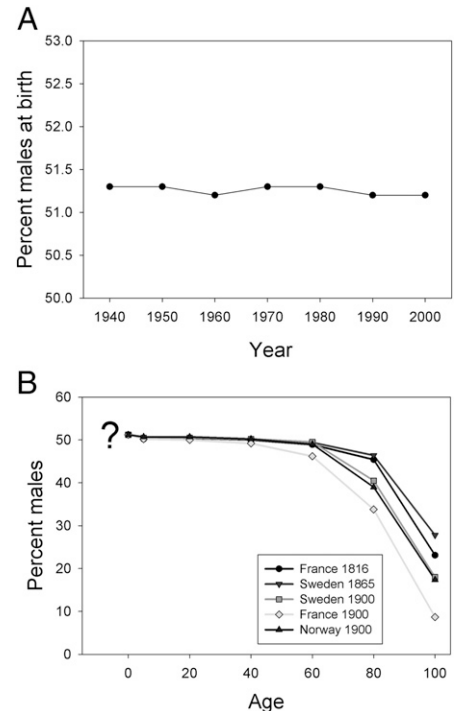
that the sex ratio at conception is not significantly different from 50:50.

Taking advantage of the spread of assisted reproductive technologies (ART) and recent advances in prenatal genetic testing, Orzack et al. (9) karyotyped, either by fluorescence in situ hybridization or array comparative genomic hybridization, nearly 140,000 3- to 6-d-old embryos created by ART and found that 50.2% were male. This result is not statistically different from the 50:50 expectation of simple Mendelian segregation of X and Y chromosomes. Karyotypic abnormalities were found in more than 60% of these embryos, and in accord with evidence from spontaneous abortions, statistically more male than female embryos were abnormal. However, it is worth considering the magnitude of the effect. Statistical significance isn't necessarily biological significance. Abnormal embryos were 50.9% male and normal embryos were 49.3% male.

Several possible critiques of this surprising conclusion immediately spring to mind. Fertilization in a dish is not the same as natural fertilization in any number of ways that might affect the sex ratio, for example. Or there could be massive sex-biased mortality of embryos before 3–6 d postconception. Orzack et al. (9) defuse the most serious of these objections fairly convincingly by noting that birth sex ratio of babies conceived by ART does not differ from those naturally conceived, nor does the method of ART—in vitro versus in vivo fertilization, for example—affect birth sex ratio.

A conundrum remains though. If the sex ratio at conception is 50% male, and male embryos are more likely to harbor major genetic anomalies as well as more likely to be spontaneously aborted, then how does the sex ratio rise to its consistent ~51% male by birth? The answer has to be greater female mortality at some gestational stage. Where is the evidence for that?

Orzack et al. (9) investigated the entire trajectory of sex ratio throughout gestation using assembled data on fetal sex from 39 studies of abortions induced between 2- and



**Fig. 1.** (A) Stability of the sex ratio at birth in the United States over 60 y (13–17). (B) Percent males from birth to age 100 y in diverse historical populations with excellent birth and death records. Data from birth cohort life tables from ref. 5. The question mark denotes that before Orzack, et al. (9), little was known about sex ratio during most of gestational life.

20-wk gestational age for reasons unrelated to fetal health, chorionic villus sampling for fetal sex data between gestational weeks 6 and 12, amniocentesis results for data between gestational weeks 10 and 20, and fetal deaths versus live births from gestational week 18 to natural birth. In sum, these studies indicate male-biased deaths in utero until week 2, then female-biased deaths over the next 4 mo, then little bias for a while, before switching again to male-biased deaths roughly 5 wk before the end of gestation. This appears to be an altogether more chaotic process than is easily explainable by any hypothesis about in utero selection. Again,

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according to these data, the bias is at no point very great. In utero sex ratios at no time during gestation fall below 47% or rise above 53% male.

Human birth sex ratios have been an object of fascination and study since at least the 17th century. Seemingly no end of hypotheses have arisen concerning how behavior, such as coital timing or frequency, or the environment—from war to fasting to depression to earthquakes to terrorism to environmental pollutants—affect birth sex ratio (10, 11). Again, these effects are small. The commonplace theory that birth sex ratios rose in belligerent countries after World War I is based on a rise from 51.4% male births during the war to 51.7% male births immediately afterward (12). A number of the environmental hypotheses assume that stressful conditions lead to preferential in utero culling of what were assumed to be frail male fetuses from an initially heavily male-biased sex ratio at conception. Certainly, abundant evidence supports a frail male scenario from birth onward, if “frail”

is taken to mean more susceptible to dying (1). However, the extensive evidence presented by Orzack et al. (9) on the trajectory of fetal sex ratios throughout gestation offer no support for a particularly frail male fetus except near the end of pregnancy. If the sex

ratio at or near conception is indeed a Mendelian 50:50, as these extensive data indicate, but is a slightly male-biased 51.3% at birth, then if anything, during much of gestation female fetuses turn out to be the (slightly) frailer sex.

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