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Proximate causes of the variation of the human sex ratio at birth

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ABSTRACT

There is evidence that the human sex ratio (proportion males at birth) is the result of two processes. First, the sexes of zygotes (from which the primary sex ratio would be calculated) are thought to be partially controlled by the hormone levels of both parents around the time of conception. Second, this primary sex ratio is apparently modified downwards by male-sex-selective spontaneous abortion caused by high levels of maternal stress-induced adrenal androgens, thus yielding the sex ratio at birth (the secondary sex ratio). Since maternal stress is one cause of spontaneous abortion (and of other forms of reproductive sub-optimality), and since some forms of pharmacological treatment of maternal stress are deleterious to the foetus, best practice would suggest non-pharmacological treatment (e.g. psychotherapy, hypnosis or massage) for pregnant women who have a previous history of spontaneous abortion, preterm birth or low-birth-weight infants.

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1. Introduction

The human sex ratio (proportion male at birth) varies with a great number of variables [1]. This variation (e.g. with such demographic variables as maternal age, paternal age, birth order, race, season and time) is very small in magnitude with respect to most variables, and would never have been detected if there had not been huge quantities of data available from national systems of birth registration (dating from 1837 in England & Wales). These data have proved a magnet to statisticians and probability theorists [2,3]. Thus evidence has been adduced that p (the probability that a birth is male) not only shows Lexis variation *across* women, but also shows Poisson variation *within* women [3,4]. This latter (Poisson) variation apparently occurs not only across a woman's reproductive life, but also within her individual cycles. However, though all this variation has been demonstrated, its likely proximate causes have eluded identification until the past half-century. Here I present a synopsis of recent theorising on this. Research in this area has focussed on two major endocrine axes [5]. These are first, the hypothalamic-pituitary-gonadal (HPG) axis and sex steroids, especially testosterone in men, and oestrogen in women. The second axis is the hypothalamic-pituitary-adrenal (HPA) axis and maternal adrenal androgens. I suggest that the variation of the human sex ratio at birth has evolved as the result of two processes acting in sequence which respectively depend on these two axes. In temporal order, these processes are 1) the selection of the sexes of the zygotes at conception, and 2) the modification of the resulting primary sex ratio during pregnancy by male-sex-selective spontaneous abortion. These processes will now be described in turn.

2. The hormonal control of the sex of the zygote at conception (primary sex ratio)

A major determinant of the sexes of mammalian zygotes must be chance. However the established non-random variation of the human sex ratio at birth also mandates a search for other proximate determinants (causes). Accordingly, I have suggested that the sex of a zygote is partially controlled by the hormone levels of both parents around the time of conception. *Ex hypothesi*, the formation of male zygotes is associated with high levels of testosterone (in either parent), and with high levels of oestrogen (in the mother). Female zygotes are *ex hypothesi* associated with high levels of gonadotrophins (in either parent) and (perhaps) high levels of progesterone in the mother. I have cited data to support these claims [6–9]. The plausibility of this hypothesising has been augmented overall by the recent demonstration [10] that testosterone in men and oestrogen in women satisfy the definition of 'condition' specified in the influential and well-supported evolutionary hypothesis of Trivers & Willard [11] (henceforth TW). This argument may be spelled out in the form of four propositions viz

a. TW hypothesised that women who score high on a heritable agent that is positively associated with fertility have a higher probability of bearing sons
b. The TW argument is equally applicable to fathers as mothers.
c. I hypothesised that high levels of testosterone in men and of oestrogen in women are associated with higher probabilities of bearing sons.

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d. There is good evidence that high levels of testosterone in men and of oestrogen in women are heritable and positively associated with fertility [10].

Thus, these two hypotheses (mine and theirs) support one another. This is important because most of the hormonal evidence originally adduced to support my hypothesis was observational: it was not experimental and hence it was not decisive in identifying causal direction. (It is now clearer that hormone levels partially directly determine the sex of zygotes, rather than that both have a common cause).

Ethical considerations restrict direct experimentation on human pregnancies. And though (or perhaps because?) stockbreeders have a financial interest in controlling the sex of their animals, there is little relevant published experimental work aimed at understanding offspring sex ratio variation of non-human mammals. In short, the variation of the human sex ratio at birth is usually minuscule, and it can only be directly studied via observational (correlational) data. So it is not surprising that its proximate causes are only now being identified.

3. The modification of the primary sex ratio by hormonally-driven male-sex-selective spontaneous abortion to yield the secondary sex ratio

Here I present evidence for three propositions viz

A. When pregnant women are stressed, they are at additional risk of spontaneous abortion—especially of male foetuses.
B. Stressed women release high levels of adrenal androgens.
C. High levels of maternal adrenal androgens are, at least partially, responsible for male-sex-selective spontaneous abortions and other forms of reproductive sub-optimality (preterm birth, low birth weight and foetal growth retardation).

The evidence for these three propositions will now be given in order.

A. *Maternal stress and reproductive sub-optimality*
For centuries it had been suspected that when pregnant women are exposed to physical or psychological stressors, there are consequent adverse effects on the foetus. A recent review of population-based studies concluded that maternal stress is a risk factor for, and a potential cause of, spontaneous miscarriage, stillbirth, low birth weight, preterm birth, intrauterine growth retardation and infant mortality [12]. Catalano and his colleagues, using time series analysis, have shown that stress-related public phenomena cause pregnant women to abort—and particularly to abort frail male foetuses [13]. The stressors studied by these workers included the labour market [14], terrorist activity [15], and an earthquake [16]. Others have documented male-biassed abortion in pregnant women exposed to famine [17] and in pregnant women exposed to (reports of) public shootings, riots and bombings in the US [18] and to public bereavement in the US and Britain following the deaths of President Kennedy, and of Princess Diana [19,20].
I shall now give grounds for suggesting that stressed women produce high levels of maternal adrenal androgens.
B. *Stress and adrenal androgens in women*
The major sources of androgens in women are the ovaries in healthy women and the adrenals in stressed women. It seems reasonable to suppose that the main sources of the maternal androgens that cause various forms of reproductive sub-optimality are the adrenals [21]. These react to stress of many sorts e.g. infectious disease, psychotic disorder, surgical trauma, and strenuous exercise [22]. For instance, high androgen levels have been reported in women who are chronically stressed [23], chronically fatigued [24], chronically depressed [25] or exposed to fearful stimuli during pregnancy [26]. Thus there can be no reasonable doubt that stressed women produce high levels of adrenal androgens including testosterone. I shall now give grounds for supposing that high levels of these androgens cause various forms of reproductive sub-optimality.
C. *Maternal adrenal androgens, spontaneous abortion and other forms of reproductive sub-optimality*
High androgen levels in pregnant women are reportedly associated with foetal growth restriction *in utero* [27] and with spontaneous abortion [28]. The latter authors reported that in their data set (571 women who each had had 3^{+} spontaneous abortions) the free androgen index was a more powerful predictor of a subsequent spontaneous abortion than advanced maternal age or than the number of prior spontaneous abortions. Moreover the experimental administration of testosterone to pregnant ewes reportedly had similar adverse effects on their pregnancies [29–31]. The sheep is now regarded as a standard model for human pregnancy [32]. So this experimental work is strong evidence that high maternal androgen levels are, at least partially, a cause, rather than a consequence, of human spontaneous abortions.

4. Two possible roles for evolution in the variation of sex ratio at birth

It is relatively easy to propose evolutionary hypotheses to account for adaptive biological phenomena, but it is difficult to test them [33]. So one may ask whether evolution has played a role in the variation of human sex ratio at birth. It has been proposed that this variation evolved in response to two different contingencies that presumably were of most relevance at different periods of evolutionary time [10]. In temporal order, these were

A. Extreme operational sex ratios in small breeding populations and the attendant danger of extinction: and
B. The greater variance of reproductive success in males than females in many species, including man.

It is interesting to consider the hypothesised evolutionary responses to these two contingencies in the context of one another here. This is so because it may yield an explanation for the occasional failures of the hypothesis of Trivers & Willard [11]. Meanwhile, it should be noted here that (since it made an adaptive prediction), the relative success of that hypothesis constitutes evidence that some sex ratio variation at birth *does* have evolutionary precursors.

A. *The danger of extreme operational sex ratios in small breeding populations*
Over evolutionary time, most human breeding populations were small. Under such conditions, there is the danger that, as a consequence of chance (genetic drift) or warfare, the sex ratio of a breeding population will become so biassed as to endanger its continued survival. If the operational sex ratio is biassed, the members of the majority sex are in what demographers call a 'marriage squeeze'. They may be expected to suffer psychological and physiological stress as a consequence of the difficulty of finding and keeping a mate. I have adduced evidence that (under some circumstances, and possibly as an evolutionary response to this contingency) stress causes people to produce offspring of a sex opposite to their own [10]. Whether this phenomenon has an evolutionary explanation or not, it certainly provides a potential escape from the danger of extinction posed by a highly biassed operational sex ratio in a small breeding population. More recently, Song [34] has adduced evidence for adaptive intergenerational sex ratio adjustment in contemporary China.
B. *The greater variance of reproductive success in males than females*
A few men have large numbers of children, and an appreciable proportion of men have no children: in contrast, most women

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