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Offspring sex ratios at birth as markers of paternal endocrine disruption

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Abstract

There is good evidence that paternal (and maternal) hormone levels at the time of conception are associated with offspring sex ratios (proportions male) at birth. The mechanisms underlying this association (pre- or postzygotic) are not of primary relevance here. When people are exposed to endocrine-disrupting agents, these agents may have different hormonal effects on men and women. So, if endocrine disruption is to be revealed by offspring sex ratios, it is necessary to categorize the sexes of subsequent offspring by the four possible parental mating classes, viz. exposed/unexposed mothers/fathers. In general, substantially altered sex ratios may reveal endocrine disruption, but the tiny (admittedly significant) secular meanderings of national live birth sex ratios across the 20th Century (and before) are not now readily interpretable.

Keywords: Endocrine disruption; Estrogen; Gonadotropins; Sex ratios at birth; Testosterone

1. Introduction

I will argue that under some limited specifiable circumstances, the human sex ratio—that is the proportion of boys at birth—can be a useful marker of endocrine disruption or endocrine modification to one or both parents around the time of conception. The claim is that an unusual sex ratio at birth is provisional evidence that something was unusual about the hormone levels of one or both parents at the time of conception. Ex hypothesi, high levels of estrogen and testosterone (in either parent) are associated with subsequent births of sons and high levels of gonadotropins and progesterone with daughters.

Later I shall indicate some of the limitations of offspring sex ratios as markers of parental endocrine disruption. However, it is worth remarking here that—if sex ratios were accepted as valid markers—they have two great advantages over other criteria of endocrine disruption such as sperm counts and hormone assays: sex ratios are noninvasive and are readily referable to the distant past. People can usually remember the sexes of their children—even those who were born a long time ago—and in most cases no embarrassment or pain is involved in eliciting this information.

2. Materials and methods

The papers cited below are almost all in journals held in the Library of the Royal Society of Medicine, London. The following deliberations were occasioned by almost daily visits to this library over the past 25 years.

3. Results and discussion

There are huge numbers of scientific papers on human sex ratio at birth, how it varies, and what causes this variation. Since there are very large numbers of human births with the sexes accurately recorded, the topic has

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attracted the attention of mathematical statisticians. They have used the data to illustrate increasingly complex methods of analysis, but the scientific yield of this labor across the second half of the 20th Century was minimal. There is statistically significant variation of sex ratio with such readily available variables as birth order, maternal age, paternal age, social class, and race—but it is tiny (James, 1987) and uninformative with regard to the causes of the variation. However, in contrast, studies of sex ratios of offspring of selected groups of parents have been informative. The sex ratios of offspring of men who have undergone selected chemical exposures, selected occupational exposures, or illnesses are illuminating. Table 1 illustrates this point. In a sense it is my whole point (namely that a range of adverse chemical, occupational, and medical exposures to men are associated—presumably causally—with declines in both offspring sex ratios and testosterone/gonadotropin ratios). This table summarizes the reported effects (or associations) of eight different sorts of chemical exposure to men, four different illnesses to men, and four different forms of occupational exposure. The table suggests two relationships: many forms of illness or adverse paternal exposure are associated with subsequently siring significant excesses of daughters and such exposed or ill men have significantly low testosterone/gonadotropin ratios.

I have argued elsewhere that the one is the cause of the other: namely, this endocrine profile causes the men to sire excesses of daughters (James, 1996, 2004). However, it is no essential part of the present note to argue this. I simply wish to emphasize the association; viz. there are a large number of reported adverse circumstances under which men both (a) have low testosterone/gonadotropin ratios and (b) sire significant excesses of daughters. The usefulness of these observations to workers investigating endocrine disruption depends on their generality. I have adduced evidence that parental hormone levels and offspring sex ratios are associated in mammals in general—not simply in humans (James, 1996, 2004). This evidence will not be entirely reproduced here, but the hypothesis should be specified more precisely. It is that high parental periconceptional levels of testosterone and estrogen are ex hypothesi associated with an increased probability of subsequently producing sons and high parental levels of gonadotropins and progesterone with daughters. Ex hypothesi these hormones affect the probability with which an X- or Y-bearing sperm fertilizes the ovum. Thus the hypothesis invokes something other than sex-related fetal mortality to explain variations in live birth sex ratios. Sex-related fetal mortality is admittedly the explanation of some variation in mammalian sex ratios at birth, but I contend that it is not the sole explanation. However, strictly speaking, the explanation is irrelevant here: it is merely the association (between parental hormone levels and offspring sex ratios) that is relevant.

I have offered a mechanism for this association (James, 1997a). The proposed explanation depends on the curious facts that glycerylphosphorylcholine (GPC) exists in the male reproductive tract and that its diesterase exists in the female reproductive tract; why they are there is unknown. Moreover, GPC and its diesterase are reportedly controlled by hormones in a manner consistent with the notion that hormones ultimately control offspring sex ratios. I mention this merely to tease experimentalists who might be motivated to test the hypothesis.

Feminists may feel uneasy with the suggestion that having daughters is a criterion by which to judge that men were ill or were exposed to deleterious environmental agents at the time of conception. This unease may be assuaged by three points. (1) Whatever the other determinants of biological sex, chance would seem to be major. So arguments based on individual sibships are unlikely to be valid. (2) Some classes of pathology apparently cause women to produce excesses of sons. This is reportedly so, for example, of women who conceive when they have multiple sclerosis (James, 1994) or polycystic ovarian syndrome (Kitzinger and Willmott, 2002) or when they are hepatitis B carriers (Chahnazarian et al., 1988) or X-chromosomal recessive retinoschisis carriers (Fellman et al., 2002). (3) Some classes of ill men also produce excesses of sons, e.g., those who are destined to suffer prostatic cancer (James, 1990) and those who are hepatitis B carriers (Chahnazarian et al., 1988).

However, it seems that, in general, most sorts of adverse chemical exposures to men are associated with subsequently siring statistically significant excesses of daughters (though the generalization is far from perfect; see the reports cited below in Table 3). In contrast, there are few data on the sex ratios of offspring of women (mated to unexposed men) following suspect chemical or occupational exposure, though there are strong suggestions that under some adverse circumstances their offspring sex ratios are biased in one direction or the other; e.g., they apparently produce excesses of sons following exposure to heavy metals (Fertmann et al., 1997) and perhaps dioxin (Mocarelli et al., 2000). However, under other circumstances they reportedly produce significant excesses of daughters, e.g., with exposure to polychlorinated biphenyls (PCBs) (Taylor et al., 1989) and nonionizing radiation (Larsen et al., 1991; Irgens et al., 1997).

I realize that a proposal to use an untested, unexplained criterion such as sex ratio is like a red rag to some bullish endocrinologists. However, I am not sure that they can afford to be bullish. Endocrine disruption is a term that was coined some years ago; yet not a lot of hard evidence has been since gleaned about