The sex ratio of offspring of women with congenital adrenal hyperplasia

Sir,

Hagenfeldt et al. (2008) reported that the offspring born to their sample of women with congenital adrenal hyperplasia (CAH) numbered 6 boys and 19 girls. This sex ratio (proportion males) was significantly lower than that of offspring of a control sample. The authors remarked that this result was unexpected. To explore the point further, I examined the sex ratios in the papers cited by these authors. (In parenthesis, it should be noted that these are extremely rare data: attempts to extract further such data using Medline proved fruitless.) Table I here gives these data. The pooled set of fresh data is also significantly different from the expected population live birth sex ratio of contemporary European countries of 0.513. So there can be no reasonable doubt that pregnant CAH women reportedly produce a statistically significant excess of daughters. This phenomenon stands in need of explanation.

Classical CAH is an autosomal recessive condition causing androgen excess in cases. I have hypothesized that (in contrast with the above result) high parental levels of androgens around the time of conception are associated with subsequent births of boys (James, 1996, 2004, 2008). However, an explanation may be offered for the reported statistically significant excess of girls among the offspring of CAH mothers. It is that prior to conception in CAH women, most have been treated to suppress the androgens. This is acknowledged by all authors cited here. For instance, Hagenfeldt et al. (2008) noted such treatment variously consisting in increases in glucocorticosteroid dose, or addition of fludrocortisone, or infertility treatment, or gonadotrophin treatment or corticosteroid doses with metformin. In this context, it should be noted that the reported sex ratio of children following the induction of ovulation with gonadotrophins or clomiphene is low (James, 1985a). That result was highly significant (P < 10^-6, tested against an expected contemporaneous live birth sex ratio of 0.514 in the USA). It was apparently not due to any association between offspring sex ratio and maternal subfertility: this may be inferred from the report that the sex ratio of artificial insemination offspring is also significantly lower if ovulation is hormonally induced than if ovulation occurs naturally (James, 1985b). Accordingly, I suggest that the excess of daughters born to CAH mothers is due to the hormonal treatment of these women prior to conception (which was designed to lower their formerly high androgen concentrations to below-average levels, and which may also have raised their gonadotrophin concentrations). Ex hypothesis either of these changes to the hormone profile would be responsible for the excess of daughters.

Table I The sexes of offspring born to women with CAH

<table>
<thead>
<tr>
<th>Source</th>
<th>Males</th>
<th>Females</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dumic et al. (2005)</td>
<td>0</td>
<td>4</td>
<td>Croatia</td>
</tr>
<tr>
<td>Hagenfeldt et al. (2008)</td>
<td>6</td>
<td>19</td>
<td>Sweden</td>
</tr>
<tr>
<td>Hoepfner et al. (2004)</td>
<td>4</td>
<td>4</td>
<td>Germany</td>
</tr>
<tr>
<td>Jaaskelainen et al. (2000)</td>
<td>4</td>
<td>6</td>
<td>Finland</td>
</tr>
<tr>
<td>Krone et al. (2001)</td>
<td>13</td>
<td>18</td>
<td>Germany</td>
</tr>
<tr>
<td>Lo et al. (1999)</td>
<td>0</td>
<td>4</td>
<td>San Francisco, CA</td>
</tr>
<tr>
<td>Totals</td>
<td>27</td>
<td>55</td>
<td></td>
</tr>
</tbody>
</table>

Notes: (1) Tested against a contemporary European live birth sex ratio of 0.513, the data of Hagenfeldt et al. (2008) yield a chi-squared value of 7.8, P = 0.005. (2) Tested against a European live birth sex ratio of 0.513, the remaining five sets of data (when pooled) yield a chi-squared value of 4.7, P < 0.05. (3) Tested against a European live birth sex ratio of 0.513, the pooled six data sets yield a chi-squared value of 11.1, P < 0.001.

References


James WH. Evidence that mammalian sex ratios at birth are partially controlled by parental hormone levels at the time of conception. J Theor Biol 1996;186:271–286.

James WH. Further evidence that mammalian sex ratios at birth are partially controlled by parental hormone levels around the time of conception. Hum Reprod 2004;19:1250–1256.

James WH. Evidence that mammalian sex ratios at birth are partially controlled by parental hormone levels around the time of conception. J Endocrinol 2008;198:3–15.


**Reply: The sex ratio of offspring of women with congenital adrenal hyperplasia**

Sir,

We have with great interest read the comments made by Dr James concerning our paper ‘Fertility and pregnancy outcome in women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency’ recently published in *Human Reproduction* (Hagenfeldt et al., 2008). We have also enjoyed reading some of his extensive work in the area concerning sex ratio in mammals.

We appreciate that Dr James is confirming the data we presented in our paper on the sex of children born to women with congenital adrenal hyperplasia (CAH). In addition to the data given in Table 1 in Dr James’ comments, another 22 girls and 11 boys were reported by Lo and Grumbach (2001). Hence, including our own data, the number so far reported in the literature (apart from cases that are reported twice) are 68 girls and 34 boys (sex ratio 0.33).

Dr James proposes that the reason for this difference in sex ratio of children born to women with CAH could be depressed androgen levels in the women at conception. This is an interesting hypothesis and seems reasonable since most women with CAH need to have suppressed androgen levels in order to ovulate regularly. Concerning the effect of gonadotrophin stimulation, only one of our patients needed this treatment; she delivered one girl after each of these treatments. As far as we know the sex ratio in women who underwent IVF is normal. In our material, only one woman needed IVF.

We are looking forward to a future discussion concerning the possible explanation to the unequal sex ratio in children born to CAH women.

**References**
