Spontaneous conception in subfertile couples

Dear Sir,

The paper by Snick et al. (1997) was an important contribution to the prediction of the ability of subfertile couples to conceive spontaneously. Collecting such accurate data on a well-defined population is an achievement that is rarely accomplished. The authors present a prediction model based on a secondary care setting and compare it with a previously published model based on tertiary centres in Canada (Collins et al., 1995).

The prediction model should be corrected, however, because it becomes misleading for couples with a favourable prognosis. The formula for the life birth rate prediction after 3–36 months is stated to be the average baseline prognosis of life birth (ABPLB)×the multiplication factors (MF). If this formula were applied, for example, to an unexplained primary infertility of a couple with a female age <28 years of age, it predicts a life birth probability of 88.0% (41.9×1.5×1.4) at 24 months, and of 97.0% (46.2×1.5×1.4) at 36 months, when the alternate model is applied. Such figures are counter-intuitively high! The results become even absurd when we take the same couple, but this time with secondary infertility, because the predicted probabilities lead to 132 and 145.5% life birth probability after 2 or 3 years respectively.

The explanation of this phenomenon lies in the fact that the simplified formula, which the authors apply, is only after 2 or 3 years respectively

\[ 1 - (1 - \text{ABPLB}/100)^{\text{MF(s)}} \]

where \( ^{\wedge} = \) exponentiation; \( a ^{\wedge} b = a \) to the power \( b \). The probabilities for the primary infertile couple become 1 –(1–0.419) \( ^{\wedge} (1.5\times1.4) = 0.680 \) being 68% at 24 months and 72.8% at 36 months and for the secondary infertile couple, 81.9 and 85.8% respectively. These figures are more realistic.

We alert the reader to the fact that, in the paper based on the Canadian data (Collins et al., 1995), the same approximative formula for small probabilities is used. For that study it is also possible to use the formula corresponding to the Cox proportional hazard model as described above. We think the quality of these two important studies will further improve if the correct formula is applied.

References


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Dear Sir,

We appreciate the interest of Drs Eijkemans, Habbema and Te Velde in our work. We submit, however, that their suggestions reflect a statistical view of the world. For clinicians, our paper provided a ‘rough and ready’ summary of the baseline prognosis and the multiplication factors. Of course, the ‘correct formula’ was the source of the tables in our paper and these insightful experts were able to compute that ‘correct formula’ from the exponentials given. However, we think that the average clinician will not be inclined to sit down and calculate:

\[ 1 - (1 - \text{ABPLB}/100)^{\text{MF(s)}} \]

every time he sees a patient. Also, nomograms are numbing, if not totally anaesthetizing, and so we have aimed at providing clinicians with an easily remembered formula – multiply the average live birth rate by the exponential for the BMI and multiply it by 1.5, 0.5 and/or 0.1 works and offers a good enough estimate for counselling patients.

Clearly this formula is of more benefit in the mainstream patient and might not be entirely correct in the outskirts of subfertility practice. On this point, we were actually reassured that the ‘correct’ estimates provided by Drs Eijkemans, Habbema and Te Velde were not even further off from the ‘rough and ready’ estimates; but in reality how often do we see a patient who is aged <28 years with unexplained secondary subfertility?

Readers may be interested to know that the Rotterdam, Utrecht, Walcheren, Maastricht and Canadian authors are co-operating to construct an even better prediction score from their combined data. This plot over the bows from the Rotterdam-Utrecht axis highlights one of the many issues we will have to resolve together in order to present
the most accurate, but still user friendly, prediction score for subfertility. Stay tuned to this station for future developments.

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Variation of sex ratio within very large sibships

Juntunen et al. (1997) report some remarkable data on the variation of sex ratio (proportion male) at birth within sibships of 10+ children (largely produced by devout Lutherans in northern Finland). They found that the sex ratio declined significantly with birth order, maternal age and paternal age. However, stepwise logistic regression suggested that, of these variables, maternal age was the only significant independent one, and these authors concluded that their high maternal age ‘explains why grand grand multiparous women deliver more girls than boys’. I suggest that, in general, such women do not deliver more girls than boys, and that these authors were wrong to generalize from their data – which in turn need explaining.

It is interesting to juxtapose these data with those from very large populations. Juntunen’s data show an excess of males in the first nine birth orders (pooled) but an excess of females in the later birth orders (again pooled). In contrast, large data sets, as derived from national vital statistics, show excesses of males at all birth orders (although admittedly the excess is slightly larger in the first few birth orders). For instance, the sex ratios of US White live births by birth order for the year 1992 declined from 0.5139 at birth order 1 to 0.5010 at birth order 4 and remained roughly stable at higher birth orders. Similar data have been offered in respect of the US 1927–1929 (Russell, 1936); US White births 1942–1950 (Myers, 1954); Italy 1930–1952 (Colombo, 1955) and Finland 1939–1948 (Jalavisto, 1952). In the latter data, the legitimate live birth sex ratio declined from 0.5161 at birth order 1 to 0.5024 at birth orders 11+. Thus, there can be no doubt that in large samples of births, including those in Finland, there is a slight excess of boys in birth orders 10+.

In general, little of interest seems to attach to these data: the magnitude of such variation suggests that it is too ‘far’ from the cause(s) to be helpful in identifying those causes. In contrast, the data of Juntunen et al. (1997) suggest variation of a far greater magnitude, thus offering some prospect of elucidating those causes. So, two important related problems may be posed in relation to these data: firstly, why do these data contain an excess of daughters in birth orders 10+ (which is significant when tested against an expected sex ratio of 0.51 for contemporary Finland)?; and secondly, why is the decline in sex ratio with birth order (or maternal age or paternal age) in these data so much greater than in the larger data sets?

In relation to this second problem, it is not impossible that a couple’s probability of having a male child varies quite substantially within that couple’s reproductive lifetime. Such a suggestion has been made on very large data sets by two exceptionally able mathematicians (Schützenberger, 1949; Gini, 1952). If that were correct, then the comparative absence of such variation in national vital statistics may simply be due to heterogeneity across couples of a form that is resistant to identification by purely statistical means.

Accordingly, I would like to suggest two lines of research: (i) sex ratio data must exist on comparable samples elsewhere, e.g. on the Amish and Hutterites. It would be very interesting to know whether they too produce more daughters than sons at their higher birth orders; (ii) I have suggested that human sex ratios at birth are subject to hormonally-mediated stabilizing processes (James, 1995). If these work in response to the sex ratio perceived in one’s environment, they would be expected to work much more rapidly in small societies than large societies (because in a small society, everyone’s perception is based on the same facts). If the parents in Juntunen’s sample inhabit restricted social groups centred on their churches, and if those groups have been (and still are) relatively unassimilated, it may be possible retrospectively to assess whether Juntunen’s sex ratio data seem to be secondary to secular variations in group sex ratios (caused by, e.g. adult female emigration or death). It would be interesting to see the result of such a study. Those with access to Amish or Hutterite data might contemplate similar studies on their material.

References


Juntunen, K.S.T., Kvist, A.-P. and Kauppila, A.J.I. (1997) A shift from a male excess of newborns in families with 10 or more children (Juntunen et al., 1997) and his comments and proposals. We agree that our

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Dear Sir,

We thank Dr James for his interest in our study on the sex of newborns in families with 10 or more children (Juntunen et al., 1997) and his comments and proposals. We agree that our
interpretation of the significance of the increasing age of the mother as a determinant factor for a shift from a male to a female majority of the newborns of grand grand multiparas was perhaps too conclusive to be generalized as such. In our study, each of the three variables, maternal age and paternal age and birth order, was significant in a single factor analysis with an approximately similar power. Since these three variables are interdependent, we performed stepwise multifactorial regression analysis which indicated that maternal age was the most significant factor. Owing to the relatively small number of mothers ($n = 143$) and their newborns ($n = 1795$), there is a slight risk of random results and consequent misinterpretations. We want to emphasize that the couples in our study are not ethnically different from the other people in our country (so they can be seen as representative of the main population in Finland), and that the Laestadian movement within the Lutheran church is not older than ~150 years, and its members are not isolated from society.

Compared with the data published between 1936 and 1955, which was referred to in James’ letter, the dominance of females in the birth order category 10 or more deliveries was really drastic in our study (see Table I).

### Table I. The rate of male and female newborns in different birth order groups

<table>
<thead>
<tr>
<th>Birth order</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>$%$</td>
<td>$n$</td>
</tr>
<tr>
<td>1</td>
<td>78</td>
<td>52.7</td>
<td>70</td>
</tr>
<tr>
<td>2–5</td>
<td>306</td>
<td>53.4</td>
<td>248</td>
</tr>
<tr>
<td>6–9</td>
<td>295</td>
<td>50.9</td>
<td>285</td>
</tr>
<tr>
<td>10–12</td>
<td>176</td>
<td>47.1</td>
<td>198</td>
</tr>
<tr>
<td>13–20</td>
<td>51</td>
<td>42.9</td>
<td>68</td>
</tr>
</tbody>
</table>

As presented in James’ letter, the rate of the boys has also been shown to decrease with increasing number of the births in several other studies but the excess of boys has prevailed up to 10+ deliveries (Jalavisto, 1952). In our study the shift to a female dominance took place around the 10th delivery. It is important to recognize that there is a time span of nearly 50 years between our study and the older studies. Maternal age, the most important determinant for the gender of the newborns in our study, may have been lower in the higher birth categories in the old cohorts than in the present one. In addition, the old studies employed a cross-sectional evaluation of heterogeneous populations, whereas our homogeneous population (comprising only grand grand multiparous women) underwent longitudinal evaluation. It is also significant that several milieu factors (standard of life, family planning and the environment) were totally different for the present couples and those living before, during and/or just after the second World War. Hence, the older and the present data are not directly comparable. Of course, we also were astonished about the findings in our study.

We are happy to inform Dr James that we had already started further investigations in the way he proposes. With nationwide data of grand grand multiparas and their children collected from the Finnish national censure register, we want to investigate again the effects of birth order and maternal age on the sex of newborns. The time period covered will also be long enough for an evaluation of calendar effects.

We appreciate the valuable comments by Dr James.

### References


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