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Gestational age in twins

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SUMMARY Dubowitz *et al.*[1] have offered a scoring system for estimating the gestational age of newborn babies. If the system is applied to twin pairs, the heavier twin is generally estimated to have a greater gestational age than the lighter one. Previously this has been interpreted as a flaw in the scoring system. However, if may well be that in some twin pairs the gestational ages are slightly different and that therefore, the heavier twin would be expected to have a greater gestational age. Such cases would arise through superfecundation (the formation of two zygotes from different coitions). Superfecundation can be proved only in rare cases (those with two fathers). It can be argued that the rarity of such cases is accounted for by the rarity with which women expose themselves to the risk of bearing such twins (and by the improbability of detection), rather than by the rarity of superfecundation. It is inferred that superfecundation by the same man is relatively common and that therefore dizygotic twins quite often have different gestational ages. The scoring system of Dubowitz can be tested for bias by submitting monozygotic pairs to it: the association between weight and estimated gestational age should be absent in such pairs. If the system proves free of such bias, then a finding first reported here will assume some interest: it is that in opposite-sexed twin pairs, the male is significantly more often assessed as having the greater gestational age. It is suggested that this finding should be provisionally accepted as evidence for the hypothesis that male zygotes are formed earlier than females.

It has been independently hypothesised on the basis of direct[2] and indirect data[3] that the sex of a zygote is associated with the time of its formation within the menstrual cycle. Further data supporting the notion have been presented by Guerrero,[4] James,[5–7] and Rostron and James:[8] it also seems to be supported by data on the sex ratio in twins[9] and, among them, in monchorionic twins[10] and acardiac monsters.[11] The hypothesis has been clarified[12] and the evidence for it reviewed.[13]

If the hypothesis were true, then presumably the sexes of the two zygotes in a pair of dizygotic (DZ) twins would not be independent. And if this were so, then Weinberg's differential rule would not be exactly true. Evidence (at the 0·01 level of significance) impugning the rule has been presented.[14]

Even if it were accepted that the rule is flawed, it would not necessarily imply that the hypothesis (outlined above) is true. However, if it could be shown that in opposite-sexed twin pairs, the gestation of the female is generally less than that of the male, the hypothesis would be substantially strengthened.

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Materials and methods

As far as I know, only one set of raw data has been published on estimates of gestational age of twins, and that is the set by Keet *et al.*[15] which used a scoring system devised by Dubowitz *et al.*[1] Of the 15 opposite-sexed pairs with differing estimates of gestation in these data, the male was assessed as having had the longer gestation in 11 pairs and the female in only 4. Tested against the null hypothesis of equal expectations, $\chi^2 = 3 \cdot 27$, and since the hypothesis is directional, one may use a one-tailed test, $P \approx 0 \cdot 035$.

Discussion

Before interpreting this result as evidence in favour of the hypothesis, one must consider whether it is simply a consequence of a scoring system which estimates gestation indirectly from weight, without due regard to the fact that male infants generally weigh more than females ones.

Keet *et al.*[15] touched on this point, noting that the mean estimate of gestational age of the heavier twin was about 0·4 weeks longer than that of the lighter

twin in each pair. They wrote that this was not significant. However in their data there were 26 twin pairs in which 2 members were assigned different gestational ages. And of these, 19 heavier twins were assessed as having had longer gestations, and only 7 lighter twins, $\chi^2 = 5{\cdot}54$, $P<0{\cdot}02$, two-tailed. So there is a suspicion that gestational age is estimated to be rather greater for the heavier twin in a given pair. This suspicion is supported by the data of Woods and Malan[16] who found that, using the same scoring system, the heavier twins in their sample were also assessed as having had longer gestations. Falkner,[17] and Dubowitz and Dubowitz[18] commented on this finding.

What relevance have these findings to the hypothesis outlined? First, it is worth considering the accuracy of the score. Dubowitz *et al.*[1] stated that the 95% confidence limits on a prediction of gestational age were $\pm$ 2 weeks, and that this was reduced to 1·4 weeks if the average of two independent scores was used. So the test seems to be remarkably accurate, bearing in mind that the error variance of the score includes the variance of the preovulatory phase of the cycle (of women selected by Dubowitz *et al.*[1] as having cycles of 28 $\pm$ 2 days). This latter variance is not negligible. It is usually agreed that ovulation is closely associated in time with the luteal hormone surge.[19] So the variance of the postovulatory phase of the cycle may be assessed from data given by Kolodny and Bauman.[20] And this variance is smaller than the variance of the preovulatory phase.[21] One would infer that if it were possible to date fertilisation accurately (instead of using last menstrual period), the performance of the Dubowitz scoring system against this criterion would be very good indeed. Accordingly, one might wonder if the system is not biased, and if there is a true association within DZ twin pairs between weight and gestation. This would imply that in an appreciable proportion of DZ twin pairs, the times of formation of the two zygotes were different: or, in other words, that such twins were the result of superfecundation. Evidence for such a suggestion is as follows: (1) It seems that coital rate is positively associated with DZ twinning rate when maternal age is controlled.[22] It is hard to see how this could occur except as a consequence of superfecundation (the fertilisation of two ova at different coitions). (2) Stieve,[23] reviewing a series of necropsies, concluded that in cases of double ovulation, the times of release of the 2 individual ova within the cycle are unrelated. Of course, one must bear in mind the possibility that if a considerable interval of time separates the release of a second ovum after a first has been fertilised, the fertilisation or implantation of the second may be inhibited. (3) There is direct evidence of superfecundation based on (a) blood group data and (b) twin infants who, at visual inspection, suggest more than one paternal racial origin.

It is impossible to prove superfecundation by the same father. However the existence of these admittedly rare cases by different fathers would lead one to suppose that superfecundation (and hence different gestations) by the same man is quite common. The point may be illustrated by considering the rarity of the circumstances which must precede a case of proved or accepted superfecundation:

(1) About one pregnancy in 150 is of DZ twins in white populations.
(2) The woman has to have unprotected coitus with two different men in the fertile interval(s) surrounding these ovulations. The rarity of such a set of events may roughly be assessed from the fact that nonpaternity (the probability of a child not having been fathered by the mother's husband) has been estimated at $1\frac{1}{2}$–3% in California.[24]
(3) Even if the woman has two sexual partners and even if superfecundation occurs, then the probability of double paternity is still less than one half. This is because it is more likely that the two fertilisations will be by the same man (assuming that the two coitions are in random order, and that the men have unequal probabilities of achieving fertilisations). And this point is strengthened if, as would be realistic, the coital rates of the woman with the two men are also supposed to be unequal.
(4) Either the two fathers must each be of a different race (see Radasch[25] for a review of such cases), or they must both be available for blood testing in circumstances which at least one of them is likely to regard as uncongenial.[26–27]

It would, in principle, be possible to estimate the incidence of superfecundation in DZ twin pairs if one had estimates of the incidence among DZ twin pairs of those fathered by two men, and the frequency with which a woman exposes herself to the risk of producing such twins.

Data given by Terasaki[27–28] enable one to make estimates of these parameters and thus to derive an estimate for the probability of superfecundation. The confidence limits for the estimate are extremely wide but still enable one to infer that the comparative rarity of accepted or proved double paternity is more a consequence of the rarity with which a woman exposes herself to the risk of it (and to the improbability of its being detected) rather than to the rarity of superfecundation (see Appendix). It seems then that superfecundation by the same man may be a

relatively common event and that therefore the association between weight and estimated gestation within twin pairs may not entirely be a flaw of Dubowitz's scoring system but a genuine phenomenon.

The point could be tested by examining the weights and estimated gestations of monozygotic (MZ) twin pairs. These infants (unlike DZ twin pairs) are known to have the same gestational age. If there is anything in the suggestion, then the relationship between weight and estimated gestational age in MZ pairs should be absent or at any rate smaller than that in DZ twin pairs.

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Appendix

An estimate of the incidence of superfecundation.

Superfecundation is the fertilisation of two different ova in the same cycle by sperm from different coitions. Here the incidence of superfecundation by one man is estimated from the (admittedly small) number of cases in which it is known to have happened with two. In 1000 cases of disputed paternity, 25% of the putative fathers were not the true fathers, and 64% were the fathers (with a probability of 90% or greater); 10% could not be resolved.[28] Among these cases was one pair of DZ twins with double paternity.[27]

It is required to estimate the percentage of these women who had unprotected coitus with two men during the fertile period. ('Fertile period' here denotes that time interval during the cycle when the probability of conception is nonzero). It seems clear that of such women, some (by chance) will conceive by the husband, and some by the lover. It also seems

likely that some women conceiving by a lover would not also have had coitus with the husband during the fertile period. So one would estimate that in Terasaki's sample fewer than half (= 2 × 25%) of the women had unprotected coitus with two (or more) men during the fertile period.

Among those who have had coitus with two men and who subsequently have DZ twins, let P be the proportion who conceive them through superfecundation. It is clear that, by chance, less than P/2 of them will in fact achieve double paternity (because though superfecundation occurs, both fertilisations will be by the same man).

We may assume (for illustrative purposes) that paternity is not more frequently disputed after the arrival of twins. DZ twins occur about once in 150 maternities in Caucasian samples, so the data of Terasaki[28] may be expected to contain about 7 pairs of DZ twins. Of these (it is suggested above) fewer than half, say 3, were estimated to have been preceded by coitus with two men. And among these 3, there was one case of double paternity.

$$\text{So } P/2 > \tfrac{1}{3}$$

Whence P, the proportion of DZ twins initiated by superfecundation is estimated at more than $\frac{2}{3}$. Now the lower confidence limit (5%) for a Poisson expectation of 1 (known set of twins with double paternity) is 0·05. So the estimate of P may be high by a factor of 20. But this seems unlikely, bearing in mind the decision during the course of the calculation to use parameter estimates that would lead to a conservative estimate of P.

In summary, this one case of double paternity suggests that superfecundation is not at all rare: it suggests that the proportion of pairs of DZ twins initiated by superfecundation is more than 1 in 30 and perhaps over 1 in 2. At any rate it is sufficiency high to require consideration in validation studies on Dubowitz test scores on twin pairs.