The Current Status of Weinberg's Differential Rule

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Abstract. A reanalysis of the data presented in a recent large twin study suggests that opposite-sexed (OS) pairs may be not as exhaustively tested as same-sexed (SS) pairs on genetic markers. This is contrary to an assumption I made in estimating that there are about 8 SS dizygotic pairs to every 7 OS pairs (thus impugning Weinberg's differential rule). If this assumption is false also in regard to the samples I discussed, then that estimate is unsound and Weinberg's rule is unscathed by empirical data. However, regardless of such considerations, there are strong theoretical reasons for questioning the status of Weinberg's rule. It is based on two assumptions, namely that p (the probability that a dizygotic twin zygote is male) is equal and independent for all dizygotic twin zygotes. Data are adduced here to suggest that both assumptions are false. The upshot is that, at present, without testing, we cannot know, of any given population, whether the rule holds or not. Otherwise, though Weinberg's rule may be useful (like Hellin's law) as a rule-of-thumb, it cannot be assumed as a basis for serious scientific argument.

Key words: Weinberg's rule, Twinning, Sex combination

INTRODUCTION

Suppose p (the probability that a dizygotic (DZ) twin zygote is male) were equal and independent for all DZ twin zygotes. Then within DZ pairs, the sex combinations MM, MF and FF will be distributed as the binomial coefficients

$$p^2 : 2 p (1-p) : (1-p)^2,$$

and if the value of p is close to ½, then the number of same-sexed (SS) pairs will approximately equal the number of opposite-sexed (OS) pairs. This is the basis of Wein-

berg's differential rule. It will be seen that there are two assumptions underlying the rule, viz:

a) the value of *p* is constant across all DZ twin parents, and

b) the two probabilities within a given twin conception are independent.

This note will contain three parts, the first being devoted to the empirical evidence on the rule, and the other two to considerations of these assumptions.

THE EMPIRICAL EVIDENCE

In determining the zygosity of twin pairs, it is usual to employ the following three criteria:

a) Monochorionic pairs are taken as monozygotic (MZ).

b) Opposite-sexed twins are taken as DZ, and

c) Same-sexed pairs with discordant genetic markers are taken as DZ.

The remaining dichorionic pairs (concordant for sex and markers) are a source of trouble. Some of them, in spite of the concordant markers, are DZ, and it is necessary to estimate this number or to make adjustment for it. This can be done in two ways:

1) One can make adjustment by subtracting from the observed OS pairs, those who are concordant on all markers (to compensate for the number of SS DZ pairs who are also concordant on markers and who are accordingly lost, being wrongly diagnosed as MZ).

2) Alternatively, one can estimate the likelihood (eg, by using lod scores) that a given dichorionic same-sexed pair who are concordant on markers are, in fact, MZ. If this likelihood is p_i, then the total number of dichorionic MZ pairs in the sample is estimated by $\Sigma\, p_i$. So if there are *n* dichorionic pairs who are concordant for sex and markers, then the number of DZ pairs among them is estimated by $n - \Sigma\, p_i$.

THE AVAILABLE DATA

Table 1 gives all the data known to me on the numbers of SS and OS pairs known to be DZ on the basis of autosomal markers alone. The expected values of SS and OS pairs are not exactly equal, adjustment being necessary for the fact that the sex ratio (proportion of males) of DZ twins is not exactly 0.5. I have suggested that in contrast with a Caucasian live birth sex ratio of 0.515, the sex ratio of DZ twins is slightly higher, say 0.518 [18]. Using this parameter estimate, and making Weinberg's assumption of binomial sampling, the expected values of SS and OS pairs are respectively 1314.7 and 1311.3. The disparity between these expectations and the pooled observed values in Table 1 is assessed by $\chi^2 = 9.3$, $p \simeq 0.002$.

On the face of it therefore, there is something wrong with the rule. This is also the judgment of Orlebeke [30] on the basis of parental assessment of the zygosity of twins. In his sample, a much greater number of same-sexed pairs were judged DZ (390) than

Table 1 - **The numbers of same-sexed and opposite-sexed pairs known to be dizygotic on the basis of autosomal markers alone**

Source	Same-sexed	Opposite-sexed
James [20]	1316	1159
Nielsen et al [29]	38	31
Machin [26]	39	43
Total	**1393**	**1233**

The data of Machin [26] are based on DNA fingerprinting as reported in his paper [27] and the data of Nielsen et al [29] are based on MHC haplotypes. These techniques may be presumed to eliminate most twins of doubtful zygosity. So the frequencies may be accepted as representative of SS DZ and OS pairs.

the observed number (290) of OS pairs [31]. However, two studies have recently been published in this journal which concluded that the rule is not flawed [10,37]. These will now be reexamined.

The Data of Husby et Al

These authors [10] reported a total of 265 SS and 87 OS pairs. Of the SS pairs, 85 were classified as DZ on the basis of markers, and 36 were not classified. Among these latter, one was a conjoined pair which we may accept as MZ. Among the 229 SS pairs where zygosity was diagnosed on the basis of placental or genetic markers, 85 (as noted above) were DZ. One may provisionally suppose that among the undiagnosed pairs, there were the same proportions of DZ and MZ pairs. Whence one would estimate that the undiagnosed twins contained

$$\frac{35 \times 85}{229} \simeq 13$$

DZ pairs. If this procedure is valid, the overall estimate of SS DZ pairs is 98 in contrast with the 87 observed OS pairs. This disparity, such as it is, favours my formulation (of 8 SS DZ pairs to every 7 OS pairs) [16] rather than Weinberg's (though admittedly when treated in isolation, it casts no serious doubt on Weinberg).

However, there are qualifications. The authors remark that "73% of the unclassified group had single placentae as compared with 60% of the defined group". It may be confirmed (using the data in their Table) that this makes no appreciable difference to the estimated number of DZ pairs among the unclassified pairs, viz 13. Lastly, these authors remark that a major part of the unclassified group was not examined because of birth complications. They urge that since birth complications occur more often among MC twins, therefore the majority of the unclassified cases were MZ.

If the 8:7 ratio were correct, the expected number of SS DZ pairs is $87 \times 8/7 \simeq 99$: if Weinberg is correct, this expected value is 87. Hence if I am correct, the expected number of DZ pairs among the 35 unclassified pairs is 14, and if Weinberg is correct, the

number is 2. At present, the data of Husby et al [10] are consistent with both Weinberg's formulation and mine. As such, these data cannot be said to offer much support to either formulation, though this position might be changed if the unclassified twins (or those among them who remain alive) were reexamined for zygosity.

The Data of Vlietinck et Al

These authors [37] reported on 714 OS pairs and 654 SS pairs with different markers. In addition, there were 463 dichorionic pairs concordant for sex and markers, 11 dichorionic SS pairs without known markers, and 1 dichorionic pair without known sex or markers. The ratio of SS:OS among DZ twins may be estimated using the two methods outlined above:

a) The numbers of SS and OS pairs identified as DZ on the basis of autosomal markers alone were 654 and 604. So, using this method, there is estimated to be a nonsignificant excess of SS DZ pairs, in conformity with my suggestion.

b) The sum of the probabilities of dizygosity of the individual dichorionic pairs concordant for sex and markers (as estimated from the authors' Table 2) is roughly 52. This value of 52 is quite different from the authors' estimate of 26 DZ pairs concordant for sex and markers. The latter I suggest is invalid (being simply the number of such pairs for whom the probability of monozygosity was less than 0.5). The total SS DZ pairs may now be estimated as this 52 plus the 654 SS pairs with discordant markers, plus a few more from the 11 dichorionic SS pairs without known markers. This estimated total of SS DZ pairs is thus very similar to the known number of OS pairs, 714. This method supports Weinberg's, rather than my, formulation. It might be remarked that the standard error of the estimate of 52 above must be large, being based on lod scores which themselves are based on estimates of gene frequencies. However, a protagonist of Weinberg might further urge that this second method of estimating the SS:OS ratio in DZ pairs is preferable because the first method may be invalid. This is so because it seems that the SS pairs were tested more thoroughly than the OS pairs in Vlietinck's study.

Table 2 - Same-sexed and opposite-sexed dizygotic twin pairs by number of discordant genetic markers (Data of Vlietinck et al [37])

No. of discordant genetic markers	Opposite-sexed	Same-sexed
0	110	?
1+	604	654

The "?" denotes the SS DZ pairs who are concordant on markers. Vlietinck et al [37] estimated 26 pairs for these data: I estimated 52. The point to notice is not the disparity between these estimates, but that neither number remotely approaches the 110 OS pairs with concordant markers. In principle, this might be explained if markers were more likely to be concordant in OS than SS DZ pairs. However, in contrast with such a suggestion, Nielsen et al [29] reported a disproportionate number of SS DZ pairs concordant on HLA haplotypes. So, a more plausible explanation is that testing was not so exhaustive on OS pairs because their zygosity was not in doubt anyway.

And therefore the numbers of OS and SS DZ pairs concordant for markers would not be expected to be the same. Whence the adjustment (of subtracting the OS pairs concordant for markers to compensate for the lost concordant SS DZ pairs) is invalid. This important point is illustrated in Table 2. Lastly, one might wonder to what extent the same objection may be levelled at some of the earlier studies cited in my review [15].

So the main empirical ground for questioning the rule is itself in doubt. However, the reader who supposes that this is the end of the matter, would be wrong. There are good theoretical reasons for supposing that *something* is defective with the rule. These will now be discussed.

THEORETICAL CONSIDERATIONS

A. The First Assumption

This assumption is that there is no Lexis variation across DZ twin parents in the probability of producing a male zygote. Three attempts have been made to estimate the extent of this variation across all parents (viz, those of singletons and multiples). The variance estimates (using different estimation procedures) were remarkably similar, viz 0.0025 [5], 0.002 [11] and 0.00265 [33]. It has since become clear that these estimates are themselves dependent on the assumption that Markov variation does not exist within human sibships (viz, that the sex of one pregnancy does not affect the sex of subsequent pregnancies) [4]. However, I know no biological (or other) reason for supposing the existence of such Markov variation: moreover, I have noted that there is good reason for proposing (an admittedly unquantified measure of) Lexis variation [23]. This being so, it seems reasonable to conceptualise p (the probability of a male zygote in Caucasian populations) as having a mean of 0.514 with a standard deviation of about 0.05. In regard to DZ twin parents, one may propose a slightly higher mean, say 0.518 [18]: the associated standard deviation is simply not known, but one might suppose a similar degree of variation across this selected sample of parents too. It has been shown [13] that among DZ twin pairs, the expected proportion of opposite-sexed pairs is

$$(1) \qquad\qquad 2(m - m^2 - v)$$

where m is the mean probability of producing a boy and v its variance across couples. Taking the above parameter estimates, one would calculate the expected proportion of OS pairs in a sample of DZ twins as 0.494. So the ratio of SS DZ to OS pairs would be about 42:41.

The probability of a male birth has been shown to exemplify Lexis variation of a comparable magnitude in other mammalian species, eg, cattle [1,2,28,34] and rabbit [25].

This source of error in Weinberg's rule is not substantial: it would result in an underestimate of only 1 DZ pair in 83. However, if the true MZ rate were invariant across populations, the extent by which it would be overestimated by Weinberg's rule would depend on the true DZ rate, and the extent of this overestimate would be appreciable in those populations where the true DZ rate is high.

B. The Second Assumption

This assumption is that the two zygotes in a pair of DZ twins have independent probabilities of being male. Let us consider a model which contradicts this assumption. Suppose p (the probability that a zygote is male) were partially dependent on the time of insemination within the cycle, and that p moves smoothly with time across the fertile period. Suppose that the two zygotes in a DZ twin pregnancy were not formed simultaneously. Then let p take the values p_1 and p_2 in respect of the two zygotes. Then the probability P that a pair of DZ twins is same-sexed is given by

$$P = p_1 p_2 + (1-p_1)(1-p_2)$$

$$= 2 \left(p_1 - \frac{1}{2} \right) \left(p_2 - \frac{1}{2} \right) + \frac{1}{2}.$$

Hence if p_1 and p_2 lie on the same side of the value ½, P exceeds ½: and if p_1 and p_2 lie on opposite sides of ½, then P is less than ½. It would follow that the smaller the time interval between the fertilizations of the two zygotes, the more likely they are to be of the same sex. In other words, if this model were correct, then in general the numbers of SS and OS DZ pairs would not be equal, and the direction of the inequality would be determined by the distribution of time intervals between the formation of the two zygotes.

If these time intervals were large, p_1 and p_2 would be more likely to differ substantially (and hence to straddle the value ½ and hence OS > SS pairs. If these intervals were small, $p_1 \simeq p_2$, and they would not straddle ½, and SS > OS pairs.

It is interesting to consider the maximum effects attributable to such a phenomenon. The data of Guerrero [7] suggest that p varies from about 0.4 to 0.6 across the menstrual cycle. If DZ twin conceptions were always simultaneous, then the proportion of SS pairs could not exceed 0.52 (= 0.36 + 0.16). And if DZ twin conceptions always occurred so as to maximise the proportion of OS pairs, that proportion could not exceed 0.52 either. In these two extremes, the ratio of SS:OS DZ pairs would be 13:12 and 12:13, respectively. So it appears that even if Weinberg's rule is flawed in this way, there are strong constraints on the extent of the flaw.

I want now to consider the data which suggest that this model is applicable (and which *ipso facto* suggest that Weinberg's rule is flawed).

Sex Ratio and Time of Insemination Within the Cycle

In regard to variation in sex ratio by time of insemination of humans, the data of Guerrero [7] and Harlap [8] remain the most persuasive, and further data on the point have been reviewed [19,20]. Moreover, a recent meta-analysis on six studies [6] suggests that the difference between sex ratios of fertilizations on the most fertile days of the cycle and those on other days is highly significant ($\chi^2 = 10.99$, $p < 0.001$). Sceptical readers are referred to the fact that in some other mammalian species, the evidence is overwhelming that time of insemination within the cycle is associated with sex of offspring,

eg, white-tailed deer [36], Barbary macaque [32], hamster [35] and rat [9]. In all four of these papers, the authors offer evidence that sex-related foetal mortality is not the cause of the differential. So, even if there were not strong direct human evidence, it would be reasonable to suspect such a phenomenon in man.

The Distributions of the Combinations of the Sexes in Mammalian Litters

As noted above, if p (the probability that a zygote is male) varies with time across the cycle, then the distribution of the combinations of the sexes within DZ pairs would not be expected to be binomial (as Weinberg proposed). Analogously, in larger litters of polytocous mammals, the distributions of the combinations of the sexes would not be binomial either. Data on this have been reviewed [12,14]. In the case of some species, eg, the dog, these distributions have variances greater than binomial: this may be explained by the suggestion that bitches vary between one another in the probability of delivering male pups. Sub-binomial variances have been reported in the distributions of the combinations of the sexes in litters of pigs, rabbits and mice [12] and sheep [14]. The most striking illustration of this phenomenon occurs in the pig, and it has been shown that the data on the sex combinations in pig litters are consistent with a U-shaped regression of sex ratio on time across the interval during which the zygotes within a litter are being formed [3]. To conclude: just as Weinberg's rule is of doubtful applicability to human twins, extensions of it to data on litters in other species would certainly be inapplicable.

Hormones and Sex Ratio

I have adduced a very substantial quantity of data to support the hypothesis that the sexes of mammalian (including human) zygotes are influenced by the hormone levels of both parents at the time of conception [20-22,24] testosterone and estrogen favouring the production of males, and gonadotrophin and progesterone of females. If this were correct, then all this variation in mammalian sex ratios with time of insemination might be explained as secondary to the ∩-shaped regression of gonadotrophin on time within the mammalian fertile period. If this hypothesis were true, then Weinberg's rule must be suspect.

THE PRESENT STATUS OF THE RULE

It is, of course, perfectly possible that even if the assumptions underlying Weinberg's rule are false, the rule itself may be valid, or approximately so. If the Lexis variation exists, it will cause SS DZ pairs to outnumber OS pairs (assuming that spontaneous abortion does not bear more heavily on SS than OS DZ pairs). But we cannot specify beforehand what effect follows from the variation of p with time of fertilization across the cycle. It may increase the ratio SS:OS among DZ pairs (as suggested by some evidence that the time interval between DZ conceptions is typically brief [17]), or it may decrease it in contrast with binomial expectation. Thus, even though there are good reasons for supposing that the assumptions underlying the rule are false, we do not know

for certain whether the effect is to inflate the number of SS pairs or the number of OS pairs, though the former suspicion must prevail at present. Moreover, the rule may hold for some populations but not others depending inter alia on:

a) whether the magnitude of Lexis variation differs in different populations, and

b) whether the distributions of time intervals between the formations of zygotes within DZ pairs differ in different populations.

These uncertainties (*a* and *b* above) are at present so remote from solution that at best Weinberg's rule can now be invoked (like Hellin's law) as an approximate rule-of-thumb, useful perhaps in some circumstances, but unsound as a basis for serious scientific argument. For the latter purpose, I suggest that the rule should be tested on each population to determine its applicability to that population: yet, that testing would itself establish the parameters that the rule is designed to estimate.

PROSPECTS FOR A DEFINITIVE EVALUATION OF WEINBERG'S RULE

I offered a power analysis suggesting that if something like 4000 twin pairs were ascertained and tested, we would stand 8 chances in 10 of discrediting Weinberg's rule at the 5% level of significance (assuming that I was correct in proposing that SS DZ pairs outnumber OS pairs in a ratio of about 8:7) [20, p 890]. That suggestion should now be qualified.

There is now no prior reason to offer the 8:7 ratio of SS:OS DZ pairs. However, workers thinking of testing the rule and wishing to use methods of power analysis to forecast necessary sample sizes may feel that *any* estimate is better than none. So, in spite of all the uncertainties outlined above, it may nevertheless be useful to try offering an estimate of the likely extent to which the rule may be flawed. The two sources of difficulty are (a) the Lexis variation of p across couples, and (b) the Poisson variation of p within cycles of individual women. One may envisage a model incorporating both. Suppose that p, the probability of a male birth, varies across the cycle of woman i in a rectangular distribution from $p_i - d$ to $p_i + d$ with mean p_i. For illustrative purposes we may be guided by the data of Guerrero [7] and set d at 0.1. (In Guerrero's data, p varies roughly from 0.4 to 0.6). The variance of this rectangular distribution is 0.0033. Let the p vary across couples with a Lexis variance which, as noted above, may provisionally be taken as 0.0025. If it is assumed that DZ twin zygotes are formed simultaneously, then it would be reasonable to sum these two variances $0.0025 + 0.0033 = 0.0058$ and insert this value in equation 1 above. Whence one would estimate that there are about 21 SS DZ pairs to every 20 OS pairs. This may *overestimate* the proportion of SS pairs because the assumption is made that DZ zygotes are formed simultaneously: but it may *underestimate* the proportion of SS pairs because, given that there *is* such Poisson variation, estimates of it as made by Guerrero [7] would probably be attenuated by inevitable errors of measurement. At this point we seem to have reached the limits of useful speculation.

RESEARCH PROPOSAL

I suggest that it is only by reducing the area of uncertainty in each twin study that Weinberg's rule will be adequately assessed. For instance, in the study of Vlietinck et al [37], the total number of twin pairs was 2589. Among these were 401 dichorionic pairs who, though concordant for sex and markers, were assigned probabilities of monozygosity of less than 0.99: about one half of them had probabilities of less than 0.95. It seems that instead of setting up fresh studies, it would be highly cost-effective to retest those pairs (or those who survive) especially those among them with lower probabilities. In principle, such retested pairs *could* exclude quite small deviations from Weinberg's rule, whereas at present the data are consistent with Weinberg's rule *and* with quite substantial deviations from it. Similarly, a retesting of the doubtful pairs in the data of Husby et al [10] could, in principle, yield a result that is significantly counter to Weinberg. The conclusion of both sets of authors that their data at present are consistent with Weinberg's rule is true: but they are also consistent with the hypothesis that the rule is appreciably flawed. This latter hypothesis cannot be excluded until substantial numbers of the uncertain pairs have been rediagnosed as DZ or reassigned a higher probability of monozygosity. The work involved should be greatly reduced by the new more powerful methods of establishing zygosity.

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