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Frequency of Triplets and Triplet Zygosity Types among U.S. Births, 1964

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Abstract. The frequency of triplets in the U.S. white population may have reached an all-time low around 1964, at 78 sets per million deliveries. One-fourth of those were monozygotic as estimated by the difference method, or 18% by Bulmer's theoretical model. By 1983 the frequency of triplets had nearly doubled, the increase presumably occurring in dizygotic and trizygotic types. In Belgium most triplet pregnancies now result from artificial induction of ovulation, which is expected to occur mainly in older mothers. In the U.S., however, triplets have increased as much in young mothers as in older mothers, proportionally. This age distribution of the increase may be partly explained by a decrease in parity in older mothers since 1964.

Key words: Triplet frequency, Triplet zygosity types, Difference method

INTRODUCTION

Multiple births, like the secondary sex ratio, seem to be indicators of some fundamental reproductive phenomena. The frequency of twins is known to vary systematically and has been the subject of several theories [1]. The different theories or "models" of the twinning process differ in their predictions of higher order births, and can therefore be tested against triplet frequencies. The value of triplet data in testing models of multiple births is enhanced if the frequency can be broken down into zygosity types, as twins are analyzed in the Weinberg's difference method. My purpose here is to examine recent changes in the frequency of triplets and to try to interpret these changes in terms of the zygosity types and theories of twinning.

Validation of the Formulas Against Tested Triplets

Triplets occur in three zygosity types, identifiable in small series by genetic tests: MZ (monozygotic), DZ (dizygotic) and TZ (trizygotic), derived from one, two and three eggs or zygotes, respectively. In sufficiently large populations the proportion of sex-concordant sets suggests that the zygosity type proportions can be estimated by the triplet difference method [2,8], described below. This method predicts the *absolute* numbers of DZ triplets from expected coincidence of MZ and DZ twinning events, and predicts the *relative* numbers or proportions of the other two types by subtraction.

To predict *absolute* frequencies of all three triplet types requires a model of embryo formation. Theoretical models of varying sophistication are found in the literature [5,7,9,14], but only that of Bulmer [7] fits observed triplet zygosity frequencies reasonably well without employing empirical constants [10,11]. Even Bulmer's theory failed when he extended it to quadruplets, and he admitted that it was based on some unrealistic assumptions [7]. Bulmer's original, 1958, model is expressed by:

$$t = m^2 + 2md + 0.5d^2 \tag{1}$$

where t is the frequency of triplet births, m and d are the frequencies of MZ and DZ twin births (generally estimated by Weinberg's method), and the three terms give frequencies of MZ, DZ and TZ triplets, respectively.

Allen and Firschein, like Das, assumed from the outset that their model would require empirical constants [5,9]. Jenkins and Bulmer later inserted constants in their models [8,15]. Bulmer's coefficient for the third term included the value 0.5 of his 1958 model, giving a formula that is simply the binomial expansion of $(m + d)$ with the empirical constants, k_1 and k_3:

$$t = k_1m^2 + 2md + k_3d^2 \tag{2}$$

Bulmer fitted the formula to type frequencies estimated by the difference method from combined data of U.S., England, Wales, and Italy, and obtained the values, $k_1 = 1.36$ and $k_3 = 0.47$. With these constants the formula accurately predicted the total frequency of triplets by maternal age groups in France. Applied to individually determined triplets (Table 1), the modified formula fits less well than the 1958 model, but well enough to satisfy the chi-square goodness-of-fit test: one of three cells has an expected value a little less than 5, but chi-square is so small that although P may not be greater than 0.50 as calculated, it is certainly greater than 0.05. When the difference method is applied directly to the same data, it yields a negative value for one of the types, as Weinberg's difference method sometimes does with small twin samples, a result of large sampling variance in the difference methods [6].

These data do however provide *indirect* support for the difference method. First, the authors' twin data conform to Weinberg's difference estimates [Vlietinck, personal communication], which rest largely on the same assumptions as the triplet difference method. Second, since Bulmer's modified formula was derived from multinational data by the difference method, the satisfactory fit in Table 1 implies a satisfactory fit of the difference method when numbers are adequate.

Table 1 - Zygosity types in triplets

Zygosity types	Observed	Predicted from [7] $(m^2 + 2md + 0.5d^2) \cdot N$		Predicted from [8] $(1.36m^2 + 2md + 0.47d^2) \cdot N$	
		Estimate	χ^2	Estimate	χ^2
Monozygotic	5	5.4	0.0	7.4	0.8
Dizygotic	11	14.2	0.7	14.2	0.7
Trizygotic	5	4.7	0.0	4.4	0.1
Total	21	24.3	0.7	26.0	1.6

[a] Observed distribution of zygosity types in spontaneous triplets compared by chi-square with distributions predicted by two formulas. [Sources: 10, and C Derom, personal communication]. Calculations employ values of m, d, and N given in [10] as follows: 0.00409, 0.00535, 324,795.

Therefore both Bulmer's 1958 model and the difference method remain viable for estimating triplet zygosity types in any large, adequately documented body of birth data.

MATERIALS AND METHODS

Multiple births reported in the U.S. for 1964 [12] permit difference estimates of triplet zygosity types in that year to be compared with earlier years and with Bulmer's findings [8].

Among deliveries of white mothers ending in one or more live births in 1964, 30,444 resulted in live twin pairs. These are tabulated in Table 2 by maternal age and sex of twins. There were also 262 deliveries resulting in liveborn sets of triplets. For black mothers there were 7,798 liveborn sets of twins and 87 liveborn sets of triplets. When deliveries resulting in one or more stillbirths are included, the proportion of multiple births is somewhat higher. This population is not as large as some previously analyzed [2,8], but it is useful as a new independent sample antedating the widespread use of ovulation stimulants.

From untabulated data in [12] I have derived race- and age-specific numbers of SS (same-sex) and OS (opposite-sex) twins in liveborn sets only and in total sets, including fetal deaths. Matching population denominators (numbers of deliveries, N) were obtained by combining data in [16]: for liveborn twinning rates I subtracted from the total number of live births the extra numbers contributed by multiple births. For total rates I added to livebirth deliveries all fetal death less the number of fetal deaths beyond the first in multiple births. For 1964, total fetal deaths of black race have to be estimated from data for the broader "nonwhite" category.

Table 2 - Numbers of total deliveries, twin deliveries and triplet deliveries by race and by life birth outcome. U.S. 1964. [12,16]

Birth categories	Total deliveries	Twins: Same sex	Twins: Opposite sex	Triplets: Same sex	Triplets: Mixed sex
White					
Deliveries ending in live births	3,338,177	21,151	9,293	148	114
All deliveries	3,384,828	22,542	9,603	164	126
Black					
Deliveries ending in live births	599,588	4,989	2,809	45	42
All deliveries [a]	616,399	5,460	2,978	50	45

[a] Fetal death data are not available for single births to mothers of black race. Total deliveries for black race were therefore estimated by pro-rating nonwhite fetal deaths by number of births in each meternal age group for black vs other nonwhite.

Age-specific twinning rates by zygosity type, m and d, were estimated by applying Weinberg's difference method to the numbers of SS and OS twins reported in each maternal age group and dividing by total deliveries for the respective ages. This was done successively for live births and total births and for each race.

Table 3 - Numbers of each triplet type predicted by Bulmer's 1958 model within race and live birth outcome, tested by implied sex concordance. U.S. 1964[a]

Birth categories	Zygosity types: MZ	DZ	TZ	Sex-concordance types: Total Obs	Total Exp	Same Obs	Same Exp	Mixed Obs	Mixed Exp	χ^2
White										
Live born sets	42	135	59	262	236	148	124	114	112	4.7 $P > 0.05$
All sets	50	149	62	290	261	164	140	126	121	4.3 $P > 0.10$
Black										
Live born sets	8	43	31	87	82	45	37	42	45	1.9 $P > 0.25$
All sets	10	50	33	95	93	50	43	45	50	1.6 $P > 0.25$

[a] Observed values are given in parentheses; Chi square has two degrees of freedom.

Age-total triplet rates by zygosity type are estimated, first, by Bulmer's 1958 model. The three terms of formula (1) are evaluated within each maternal age group

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and summed over all ages. Second, to obtain estimates by the triplet difference method, age-specific values of m, d, and N are multiplied and summed, ΣmdN, to estimate age-total DZ triplets. Half of these, assumed to be of mixed sex, are subtracted from the reported number of mixed-sex triplets, the remaining mixed-sex sets being presumably all TZ. Because 1/4 of TZ triplets should be of same sex, the remainder is multiplied by 4/3 to estimate total TZ. Subtracting the numbers of DZ and TZ triplets from total sets leaves a final remainder that is assumed to comprise all MZ sets.

Bulmer's constant, k_1, is given by dividing the difference estimate of MZ sets by the estimate from Bulmer's 1958 model. k_3 is the ratio of the difference estimate of TZ to the model estimate of TZ, further divided by 2.

RESULTS

Table 3 shows the distribution of triplet types predicted by Bulmer's 1958 model. Based entirely on twins and total deliveries, these estimates are not anchored to total triplets and do not match those totals very closely. Tested against sex-concordance on the assumption, the validity of which is discussed below, that just half of DZ triplets and one-fourth of TZ triplets are of same sex, the estimates fit observations satisfactorily.

Table 4 - Numbers of each triplet type estimated by the diffrence method within race and live birth outcome[a]

Birth categories	Total	Zygosity types			Constants	
		MZ	DZ	TZ	k_1	k_3
White						
Live born sets	262	65	135	62	1.53	0.52
All sets	290	72	149	69	1.45	0.55
Black						
Live born sets	87	17	43	27	2.06	0.45
All sets	95	18	50	27	1.80	0.40

[a] Derived values of Bulmer's constants are based on estimated numbers of MZ and TZ triplets before rounding with formulas,

$$k_1 = \frac{\text{MZ (difference method)}}{\text{MZ (model)}} \qquad k_3 = \frac{\text{TZ (difference method)}}{2 \cdot \text{TZ (model)}}$$

Table 4 shows the distribution of triplet types as predicted by the difference method. These estimates employ the total of triplets and the observed sex-concordance frequencies, so they cannot be tested for goodness of fit. The constants, k_1 and k_3, express the deviation of the binomial expansion from the observed total and from the proportions estimated by the difference method. For

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1964 white liveborn, rates per million are MZ:DZ:TZ=19:40:19. Bulmer's earlier rates for US were 21:58:31, supporting the expectation that the MZ rate is nearly constant in triplets as in twins.

DISCUSSION

Bulmer's simpler model has proved sufficiently accurate to *predict* the total number of triplets not only for the large populations on which he first tested it, but in two subsequent sets of data [10,11]. But when Bulmer tested the model further [8] he found that it underestimated the totals. After applying the difference method he concluded that the excess in the total is due to an excess in monozygotic triplets. He found the average excess to be 36% in white populations. The 1964 data for the U.S. support Bulmer's conclusion but assign even higher values to k_1 (the ratio of estimated MZ sets to the binomial proportion): 1.53 in liveborn whites and 2.06 in liveborn blacks. Thus the zygosity *proportions* differ widely among populations while the *rate* of MZ triplets is almost constant.

Both of Bulmer's models are constructed on the frequencies of MZ and DZ twins, and in really large bodies of birth data these frequencies have always been estimated by Weinberg's difference method. The difference method has been challenged, principally by James [13], who proposed that sex may be correlated in DZ twins so that the true frequency of DZ twins may be higher than under the Weinberg estimates by as much as 9%, and the frequency of MZ twins, lower. Such a change in the parameters of twinning would further impair the fit of the 1958 model, decreasing both the total of triplets and the proportion of MZ sets. Tests of Bulmer's model against sex concordance are subject to the same challenge as tests against Weinberg's difference method. The 1958 model therefore remains somewhat unsatisfactory and the underlying statistical theory, suspect. This does not necessarily mean that estimates by the difference method are better; they cannot be fully tested on available data.

Both Jenkins and Bulmer emphasize the importance of using age-specific twinning rates in estimating triplet types. This applies to estimates that employ the binomial expansion; for 1964, age-total calculations yield an estimate of trizygotic triplets that is smaller than age-specific calculations by 13%. Age-specific calculations are not important, however, when the difference method is used, because it does not square the DZ twinning rate: taking again the same 1964 data for the U.S., use of age-total rates instead of age-specific rates changes values in the first row of Table 4 from 65:135:62 to 66:132:64; the greatest change, in TZ triplets, is only 3%.

Greater accuracy of the estimates, at least from the 1958 model, would be expected if age-*and-parity*-specific twinning were used to obtain the twinning parameters. Further, triplet zygosity type estimates by the difference method employ the age-and-parity-specific distributions of reported triplets; these distributions are likely to be atypical not only by reason of sampling from small numbers, but because both maternal age and parity are expected to be higher than in other deliveries [3]. Such detailed information is rarely available, and in any event these factors may be only a small part of the selection in triplet pregnancies for proneness to multiple ovulation [8]. Nevertheless, if triplet type frequencies have to be predicted in one population from twinning parameters in another population, age and parity may not be similarly related in the two sources, and fully specific rates are clearly advantageous.

In comparison with earlier and later periods, triplet birth rates in the 1964 U.S. white population were relatively low (Table 5). This is true for all maternal ages together, and the contrast is as great for young women as for older women. For older women only, the rate is lower in 1981-83 than in 1923-36, probably owing to low parity in the recent years. In fact, the increase in triplets at all ages would probably be much more marked if adjusted for the decline in mean parity, nearly 50% in women 30-34 [4]. These changes are presumably concentrated in the DZ and TZ triplets, since these types, like DZ twins, are known to vary more in frequency than MZ sets; however, type frequencies cannot be estimated for the recent data for lack of sex-concordance figures.

Table 5 - Long-term changes in liveborn triplet rates for all births within principal maternal age groups, United States[a]

Maternal age group	Triplet sets per million deliveries 1923-1936 [15]	1964 [12]	1981-1983 [16]
All ages	114	78	139
20-24	67	44	93
25-29	104	89	169
30-34	170	111	214
35-39	243	183	214

[a] Rates for 1981-83 are calculated from livebirths in triplet deliveries, divided by 3. Data sources are given in brackets.

The rate increases are greater for triplets than for twins [4]. This is to be expected in mothers given ovulation stimulants, but fertility drugs can not satisfactorily explain the large increase in young mothers, who would rarely receive costly treatments for infertility.

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