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Letter to the Editor

Reply to W. H. James

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James [12] correctly emphasizes that a significant difference in waiting time to conception, if found, between first-born twins and first-born singletons in twin sibships would not disprove high fertility in these mothers. If the argument I made [2] was misleading, I apologize, but I beg James to tell how one can prove that there is no difference in waiting time, just because one finds none, between mothers of twins and mothers of singletons.

In an earlier draft of the paper cited I discussed my finding of no difference, but because it had no statistical significance I could prove nothing by it. I now present the negative findings in Table 1 for what they are worth. Means include first-born twins adjusted for assumed average prematurity of 19 days. These mothers were not matched on age or family size, nor was there any adjustment for these variables as there was in my comparisons within twin sibships. The data are no longer conveniently accessible to me for further analysis. They were originally provided through the courtesy of Dr. N. C. Myrianthopoulos and the National Institute of Neurological and Communicative Disorders and Stroke.

The difference in waiting time to first conceptions for twins and singletons within twin sibships seemed much more useful than the negative finding shown in Table 1 because it offered an alternative explanation for the high twinning rate in early postmarital conceptions. The probability was low enough to be encouraging ($P = 0.11$, two-tailed). When I needed to simplify the paper for presentation, I omitted the relatively uninteresting comparison between mothers of twins and of singletons.

James says that coital rates seem to offer a better explanation of the data. A close examination of the potential effect of coital frequency on twinning is long overdue.

First, it is undeniable that the spacing of coitus would be important if double ovulation often consisted of two discrete events separated by an interval about as long as the survival of spermatozoa in the female genital tract, but any such interval is virtually out of the question. Ovulation is generally understood to be "a meteoric event climaxing a rapidly changing preovulatory hormonal environment," in the words of Griff T. Ross [personal communication]. Edwards and Steptoe [6] have narrowed the time of ovulation to between 37 and 38 hours after the administration of ovulation inducers and, by inference, after the natural hormonal event known as the "LH surge." These authors reported one instance

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*TABLE 1. Mean Interval From Marriage to First Birth in Mothers of Twins and Singletons. Premarital Conceptions Are Included.**

Ultimate twinning history	Mean interval (days)	Standard deviation	Standard error	Number of women
No twins	345	215	1.7	15,313
MZ	319	198	24.4	66
MZ or DZ	355	228	17.1	177
DZ	334	208	15.3	185

*Source: Unpublished data from the Collaborative Perinatal Project [18].

of triplet embryos of clearly different developmental ages in a woman who had been treated with HCG. Regarding this as extraordinary, they suggested an explanation in terms of the unnaturally long biological half-life of that hormone. Kratochwil et al [14] have observed instances of one Graafian follicle forming while another is rupturing, but only in women treated to induce ovulation. Thus the burden of evidence, admittedly indirect, seems to favor the view that, as a rule, multiple ovulation in untreated women is essentially a single event.

Second, it is undeniable that if the probability is low (eg, less than 0.9) of fertilizing a given ovum on any one optimally timed insemination, then the probability of fertilizing two ova, being the square of that probability, is still lower (eg, less than 0.81). Sperm counts below 20 million per ml, found in recent studies to be frequent, might reduce the probability of fertilization by this much even though they do not impair fertility in planned families [22]. James [10] may therefore be right in attributing the secular decline of twinning to the decline in sperm counts.

However, the decline in sperm counts is a recent phenomenon. In the 1950s, when Bulmer's [4] data on early marital conceptions were collected, and certainly at the time of the post–World War I twinning peak in Italy [19], sperm counts are believed to have been at normal levels and fertilization should have been an efficient process, fertilizing all ova either present at the time of insemination or ovulated soon after. Fertilization of one ovum alone would be likely only after a large proportion of the sperms were no longer capable of effecting fertilization, and the likelihood of ovulation occurring at that time depends not only on the interval between inseminations, but on the variance in survival of spermatozoa in the female tract.

Because spermatozoa survive a long time in the male tract and only a short time in the female tract, it appears that sperm aging starts, essentially, at the time of ejaculation. If so, variance in longevity should be small relative to mean survival. Actual viability of sperm in the female genital tract is unknown [5], but is thought to be between 24 and 48 hours. If we take 36 hours as the mean, and six hours as the standard deviation, then two standard deviations on either side of the mean would span the suspected range. This would imply that about 5% of sperms would survive twice as long as the shortest-lived 5%. However, to be quite conservative, I shall assume that the standard deviation is one-half instead of one-sixth of the mean survival.

The following assumptions seem to give a reasonable and conservative model on which to base calculations: (1) Probability of fertilization depends only on the number (density) of spermatozoa in the female tract at the time of ovulation or insemination. (2) The probability of any viable ovum being fertilized is still as high as 0.95 when half of the spermatozoa of a normal ejaculate remain capable of fertilization. (3) Sperm longevity

is normally distributed about the median or, at least, conforms to the normal curve on the right of the median. (4) Probability of fertilization falls off according to the formula, $P = \exp(-C/D)$, where C is a proportionality constant derived from assumption 2 and D is density of viable sperms.

I cannot provide an analytical solution to our problem, but a good approximation seems to be possible by dividing the right side of the normal curve of sperm survival, as far out as 3 standard deviations, into ten equal intervals and summing the results found at the 11 boundary points. The values and the subsequent calculations are presented in Table 2. Among all fertilizations occurring after median survival of sperm, the twinning rate will be 84% of that couple's maximum. If the standard deviation of sperm survival is one-half the median, then for a couple who always spaced coitus at an interval greater than the maximum survival of sperms, 53% of conceptions would occur in that period of reduced fertility, and their overall twinning rate would be 91% of its maximum value, achieved by very frequent coitus.

In other words, if all couples in the population were this disinterested in sex, and if all of them increased their coital frequency to the level that maintained at least 50% of maximum sperm density in the woman's genital tract, the twinning rate of the population would increase by 10%. This is far from the 26% difference in favor of young married women over young unmarried women reported by James [11], and leaves at least a 16% difference to be explained by superior fertility and/or psychoendocrine effects.

Third, in his last paper, James [11] offered the few recorded cases of superfecundation as evidence that repeated insemination raises the probability of fertilizing both of two ova. He admits that this is not a necessary inference, but to present the phenomenon as in any way indicating an effect of coital frequency is misleading. If a woman has intercourse with two men within 24 hours before double ovulation, spermatozoa of both men

*TABLE 2. Relative Probability of Fertilizing One or Two Ova at Decreasing Sperm Concentrations (explanation in text)**

Time after median survival in standard deviations	Relative density, D, of sperm population	$\frac{C}{D}$	Probability of fertilizing one ovum	Probability of fertilizing two ova
0.0	1.0	0.051	0.95	0.9025
0.3	0.956	0.054	0.9478	0.8982
0.6	0.835	0.061	0.9404	0.8844
0.9	0.667	0.077	0.9260	0.8574
1.2	0.487	0.105	0.9000	0.8100
1.5	0.325	0.158	0.8539	0.7291
1.8	0.198	0.259	0.7717	0.5955
2.1	0.110	0.465	0.6280	0.3944
2.4	0.056	0.914	0.4011	0.1608
2.7	0.026	1.964	0.1403	0.0197
3.0	0.011	4.617	0.0099	0.0001
		Total	7.4691	6.2521

*If the interval from ejaculation to median survival is twice its standard deviation, probability of fertilization is virtually unity for a time span equal to 2 SD. Prior to the point of 50% survival, therefore, we accumulate a value of 1.0 for every 3/10 SD or $2 \times 1.0 \div 3/10 = 6.6667$. Among singleton conceptions, 7.4691/(7.4691 + 6.6667), or 52.8%, would occur after the mean survival time. During that period the relative probabilities for complete fertilization after double and single ovulation, respectively, are 6.25 and 7.47, in the ratio of 0.8371. If insemination occurs at random intervals after death of all sperms of the previous event, the twinning rate will be $0.53 \times 0.84 + (1 - 0.53) \times 1.0 = 0.91$.

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will be present to fertilize the ova immediately upon release. This will be true, and the operational criteria of superfecundation will be met, even if there are sufficient spermatozoa from each man alone to insure fertilization of both ova.

Next, leading into my own explanation of certain elevated twinning rates, James cited as another argument for the relevance of coital frequency his finding [11] that twinning is consistently less frequent in births to unmarried women under 20 than in births to married women of the same ages. This can also be used to support the argument for the promotion of double ovulation through the neuroendocrine effects of sexual thoughts. While I suppose that psychological sexual arousal is generally more intense in connection with extramarital coitus than in marital relations, the frequency of sexual arousal is probably correlated somewhat with the frequency of coitus. Since ovulation does not ordinarily coincide with coitus in humans, psychological state during coitus would not be so important as the average state around the time of ovulation.

James shows very low regard for the potential efficacy of psychological factors in inducing double ovulation. He may not know, as I did not know when writing the paper in question, that sexual arousal (without coitus or orgasm) produces measurable elevation of gonadotrophic hormones in male mice [8], as well as in male humans and in female humans [15,16]. A causal connection between gonadotrophin levels and double ovulation is supported by at least three lines of evidence: (1) The age increase in twinning is paralleled by an increase in gonadotrophin levels [7]. (2) The increase with parity is paralleled by a "ratchet" effect of each successive pregnancy on the size and number of cells in the pituitary [21]. (3) A large body of experimental work in animals and now innumerable observations in humans [7] attest to the efficacy of gonadotrophin administration in inducing multiple ovulation.

Summarizing to this point, while James asserts that coital rates seem to offer a better explanation of elevated twinning rates in premarital conceptions and in early postmarital conceptions than do psychological phenomena, I find the above arguments to be weighted in quite the opposite direction.

Two less central questions may also deserve attention, one of them raised by James.

If the recent decline of twinning in Italy is an effect of industrialization [19,20], why, James asks, has there been no similar recent decline in the United States. I suggest that the relevant events of industrialization, whatever they may be, occurred earlier in the United States. In support of this suggestion, Jeanneret and McMahon [13] observed that in 1937 the twinning rate in the northeastern part of the country was much lower than in most of the rest of the country. In the next dozen years the twinning rate in most of the rest of the country dropped to the level of the eastern states, while their twinning rate remained nearly constant. The convulsion of life-styles and the extension of industrial development during World War II may offer clues to the essential changes. The fact that twinning in the eastern states did not drop further at that time shows that whatever it is that depresses the twinning rate need not affect a whole population simultaneously, even within a single country.

The last point I would make argues somewhat against the fecundability or "demographic selection" theory [9], but not clearly for any other. The postwar, 1946, peak of twinning in the USA occurred at the start of a sharp rise in total births, as required by the fecundability theory. The same is true of the twinning peak in Italy after World War I [19]. A hitherto unreported postwar peak also occurred in the United States in 1919 [3], but this was associated with little or no rise in general births. At least the rise in total

births was proportionately smaller than the twinning peak, contrary to the relation observed in 1946–1947.

I would not insist that a single mechanism can explain all the temporal changes in twinning rates. The long-term decline, in particular, may include a component related to sperm counts or to the frequency of early chromosomal lethals [17,23]. In the interest of parsimony, however, if one mechanism were needed to explain everything, psychoendocrine phenomena show the most promise at this juncture.

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