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Dizygotic twinning as a measure of human fertility

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There is widespread concern about a possible decline in human fertility in recent decades. The spontaneous dizygotic twinning rate provides a way of measuring a combination of male plus female fertility as it reflects the frequency of double ovulation, the probability of fertilization, and the survival of the zygote. There was a decline in dizygotic twinning rates in developed countries which began around 1960 and continued until the late 1970s. The exact cause of the fall remains unknown. We suggest that it could have been due to a depression in the twin ovulation rate in women who stopped taking the oral contraceptive pill. The rise in the dizygotic twinning rates which occurred from the 1980s onwards in developed countries is almost certainly due to increasing use of ovulation-inducing agents, but this rise may have masked a continuing decline in dizygotic twinning. Monozygotic twinning rates have remained remarkably constant or increased only very slightly in recent decades. This makes it possible to use the dizygotic:monozygotic twinning ratio to monitor dizygotic twinning in populations where true incidence rates cannot be calculated, e.g. in hospitals where there may be selective referral of twins.

Key words: dizygotic twins/fertility/monozygotic twins/twinning

Introduction

There has been growing concern about a possible decline in male fertility over the past few decades with reports of an increasing incidence of cryptorchidism (Chilvers *et al*., 1984), testicular cancer (Hoff Wanderås *et al*., 1995) hypospadias (Campbell *et al*., 1973), falling sperm counts (Carlsen *et al*., 1992; Auger *et al*., 1995) and a decrease in testicular size (Pajarinen *et al*., 1997). Sharpe and Skakkebaek (1993) postulated that environmental oestrogens may be the culprit for these disorders, but this remains to be proved, and as yet, nobody has shown that male fertility has actually declined.

Dizygotic twinning rates can be used as a useful index of fertility (Lazar *et al*., 1977; James, 1982, 1997). Here we outline the reasons why dizygotic twinning is a good index of fertility, provide an overview of secular trends in twinning rates over recent decades and describe how the dizygotic:monozygotic twinning ratio (Tong *et al*., 1997) could be used as a cheap, simple and effective international monitor of human fertility in the future.

How dizygotic twinning rates measure human fertility

The chance of a twin-prone woman conceiving dizygotic twins and carrying them to term is dependent on four independent probabilities. These are: that double ovulation occurs, that coitus occurs within the fertile period, that both ova are fertilized and that neither conceptus suffers embryonic or fetal death (Lazar *et al*., 1977; James, 1982, 1997). Dizygotic twinning could therefore be used to monitor human male and female fertility over time if its incidence is recorded. A decline in sperm counts, for instance, might reduce the incidence of twins by lowering the probability of fertilization of both ova (James, 1982) whereas the use of ovulation-inducing agents, or an increased maternal age, would increase the rate of double ovulation. Tubal pathology arising from sexually transmitted diseases would lower the incidence of dizygotic twinning. However, it might not always be obvious which of the four parameters described above were the cause of any observed changes in dizygotic rates (James, 1997).

Factors that influence the dizygotic twinning rates

Dizygotic twinning has a high heritability, with the risk of having twins roughly doubled in a woman whose mother or sister has had dizygotic twins (Parazzini *et al*., 1994). The gene(s) for dizygotic twinning is yet to be mapped in humans, and it is still uncertain whether it is an autosomal dominant or recessive (Meulemans and Lambalk, 1996).

Race also has a substantial effect on dizygotic twinning rates. Drawing on data collected before the advent of ovulation-inducing agents, Bulmer gave a useful rule of thumb: Caucasians have an incidence of eight pairs of dizygotic twins per 1000 maternities, Orientals 4/1000 and Negroids ~16/1000 (Bulmer, 1970).

Maternal age also has an extremely important influence on dizygotic twinning rates which increase >4-fold from age 15 to 37 years, followed by an abrupt decline (Bulmer, 1970; Allen, 1977). Parity also has some effect independent of maternal age, with an increase in the twinning rate of ~50% from parities of 0 to 10 (Allen, 1977). Nutrition is also important; studies of dizygotic rates in occupied European countries during the Second World War have shown that malnutrition caused an acute fall (Bulmer, 1970).

Ovulation-inducing agents are obviously an important iatrogenic influence on the dizygotic twinning rate. Treatment with clomiphene citrate increases the risk of twin pregnancy by 6–10% (Schenker, 1981; Derom *et al*., 1995) and the risk is substantially higher following gonadotrophin treatment. The proportion of twins resulting from ovulation-inducing agents in East Flanders, Belgium was 2% in 1976, but rose rapidly from the mid-1980s onwards so that by 1992, this accounted for approximately a third of all twin conceptions (Derom *et al*., 1993).

Factors that influence the monozygotic twinning rate

Monozygotic twinning is generally believed to be a random embryological event which is not subject to environmental influences and is not genetically determined. Hence the incidence of monozygotic twinning is largely independent of race, maternal age, parity and malnutrition. However, it has been shown that the artificial induction of ovulation more than doubles the incidence of monozygotic twins (Derom *et al*., 1987). Recently, it has also been shown that a mother who is a monozygotic twin has a significantly increased risk of herself having monozygotic twins (Lichtenstein *et al*., 1996), so there must be some genetic predisposition to monozygotic twinning.

Secular changes in dizygotic twinning rates

A global decline in dizygotic twinning rates in developed countries began around 1960 and continued until the mid-1970s. This occurred in all European countries. In Italy, for example, dizygotic rates fell from around 9/1000 to 5.5/1000 maternities (Parazzini *et al*., 1991); in The Netherlands they fell from 10.3/1000 to 5.8/1000 maternities (Orlebeke *et al*., 1991); and in England and Wales there was a decline from 8/1000 to 5.5/1000 maternities (Murphy and Hey, 1997). The fall also occurred in Canada, parts of Central and South America, New Zealand (James, 1982), Australia (Doherty and Lancaster, 1986), Japan (Imaizumi, 1992) and Hong Kong (Tong *et al*., 1997).

James has previously suggested that environmental pollutants (James, 1982) or decreasing sperm counts (James, 1986) were responsible for this worldwide decline, but the exact cause still remains unknown. There was much concern at the time about this decline, as summarized in a 1976 *British Medical Journal* editorial which stated that 'it is disquieting that something should have affected the human reproductive system for 15 years without anyone having any evidence of what it is.' (Editorial, 1976).

To shed further light on the cause of this fall, it would be useful to see whether it also occurred in developing countries. However, there is little information on dizygotic trends from such countries. Most studies from Africa are hospital-based and have not corrected for the selective referral of twins. Twinning rates have remained stable in Bangladesh between 1968 and 1983 (Razzaque *et al*., 1990).

Is it possible that the fall could be the consequence of post oral contraceptive pill infertility? The pill has been shown to depress female fertility for up to 4 years after discontinuation (Vessey *et al*., 1978). The oral contraceptive pill was first licensed for use in 1960, about the time at which global dizygotic rates first began to fall. It is intriguing that whilst a slight (but non-significant) decline in dizygotic twinning rates was observed among the Caucasian and Oriental populations of South Africa, there was a highly significant increase among the black population (James, 1982). Presumably, the black South Africans at that time had little access to oral contraception. Though a decline in dizygotic twinning was also observed in Japan where oral contraceptives are still not licensed for general use, the fall was very small, amounting to only 0.6/1000 maternities (Imaizumi *et al*., 1992), which is far less than the decline experienced by most developed countries. Studies of the direct effect of prior oral contraceptive use on twinning rates have been conflicting. A prospective study by Vessey *et al*. (1979) found a reduced incidence of twins in women who had ever used the pill in comparison with those who had never done so, although the difference was not statistically significant. Harlap (1979) found a similar non-significant decline, whereas others have failed to find one (Parrazini *et al*., 1994). Of three studies which reported that discontinuation of the pill caused an increase in twinning incidence, one failed to achieve statistical significance (Rothman, 1977), another did not correct for the increase in dizygotic rates arising from ovulation-inducing agents (Murphy *et al*., 1989) and the third did not account for maternal age (Bracken, 1979).

From around the 1980s, an increase in dizygotic twinning rates occurred in many European countries such as Denmark (Westergaard *et al*., 1997), The Netherlands (Orlebeke *et al*., 1991), Italy (Parazzini *et al*., 1991), Belgium (Derom *et al*., 1993), England and Wales (James, 1995), Scotland (Murphy *et al*., 1989), Luxembourg (Derom *et al*., 1995), West Germany (Derom *et al*., 1995) and in other countries such as the USA (Taffel, 1995), Israel (Picard *et al*., 1989), Hong Kong (Tong *et al*., 1997), Japan (Imaizumi, 1992), and Taiwan (Chen *et al*., 1987). It now seems certain that ovulation-inducing agents are largely if not wholly responsible for this rise (Derom *et al*., 1993; James, 1995; Westergaard *et al*., 1997). However, this iatrogenically induced increase may have masked a serious and continuing decline in the true rate of dizygotic twinning. We are therefore completely in the dark about what has been happening to spontaneous dizygotic twinning rates over the last 20 years.

Conflicting reports from the USA show that either dizygotic rates fell until 1970 then rose (Taffel, 1995), or that they declined from the 1930s to 1964 and then remained roughly stable until the late 1970s when they increased (Allen, 1987). Thus the USA showed no persistent decline throughout the 1970s, in contrast to most other countries, most notably its neighbour Canada, where rates declined from 1957–1977 (James, 1997). This may be because clomiphene citrate began to be used in the USA considerably earlier than in other countries, causing an earlier upturn in twinning rates.

Secular changes in the monozygotic twinning rate

It is generally assumed that the incidence of monozygotic twinning has remained remarkably stable at 3.5–4/1000 maternities (Bulmer, 1970; James, 1982). Reports of the monozygotic twinning rate in recent decades have shown that it has remained stable in Italy (Parazzini *et al*., 1991), Denmark (Westergaard *et al*., 1997) and Israel (Picard *et al*., 1989), or increased very slightly in a number of countries such as England and Wales (Murphy and Hey, 1997), Germany (Derom *et al*., 1995), The Netherlands (Orlebeke *et al*., 1991) and Japan (Imaizumi, 1992). The gradual increase, possibly the result of improved obstetrical care of mothers carrying twins, and the use of ovulation-inducing agents, is negligable when compared to the great changes in dizygotic twinning.

Using the dizygotic:monozygotic ratio to measure fertility

To measure spontaneous twinning rates, it is obvious that twinning arising from ovulation-inducing agents must be excluded. This can only be done in hospital-based studies where patient records are edited so that all mothers of twins are specifically excluded if they have taken such agents. As a small excess or deficit of twins can cause very significant skewing of twinning rates, estimates of twinning rates would always be subject to considerable random error (Tong *et al*., 1997).

The zygosity of twins can be determined by Weinberg's differential method (Bulmer, 1970). Doubling the number of opposite-sexed twins gives an estimate of the total number of dizygotic twins, the remainder being monozygotic. This calculation assumes that the sex ratio of dizygotic twins is 50:50.

Twinning rates have usually been calculated from national statistics and expressed as the number of pairs of twins per thousand maternities. However, in hospital-based data we would expect twins to be over-represented due to selective referral. This could be overcome by expressing the data as a dizygotic:monozygotic ratio since the monozygotic twinning rate is relatively constant. By applying the dizygotic:monozygotic ratio to data taken from a single hospital, we were able to show that the recent upturn in dizygotic twinning had also occurred in Hong Kong (Tong *et al*., 1997).

In all studies of twinning rates, maternal age must always be taken into account by direct or indirect standardization (Fellman and Eriksson, 1990). Parity is usually not corrected for, since its effect is relatively minor and there is a possibility that the relationship is only a chance association because twin-prone women may simply be more fertile (Allen, 1977). If this is the case, it would be inappropriate to perform an adjustment.

Even in the largest tertiary hospitals with $\geqslant$7000 deliveries a year there would only be about 80 pairs of twins born, and, since the presence or absence of a few pairs of twins can cause large fluctuations in twinning rates (Fellman and Eriksson, 1990), the dizygotic:monozygotic ratio method is best suited to a multi-centre study.

After recording the dizygotic:monozygotic ratio from collaborating hospitals, it would also be useful to collect data on national monozygotic twinning rates so that there is confirmation that monozygotic twinning has remained relatively constant. If monozygotic and dizygotic twinning rates were both to fall (even though the ratio were to remain unchanged) this would be very serious, since it would point to something that was increasing the incidence of embryonic or fetal death.

It would be particularly interesting to collect data on the dizygotic:monozygotic ratio from developing countries where the use of ovulation-inducing agents and the oral contraceptive pill would be much reduced. We would therefore expect the initial fall followed by the rise in dizygotic:monozygotic ratios to be much reduced in amplitude. A falling dizygotic:monozygotic ratio may also be indicative of the spread of sexually transmitted diseases.

Conclusion

The dizygotic twinning rate has been described by Lazar *et al*. (1977) as a precious tool—probably one of the best—for studying the aetiology of reproductive failures, but in recent years its usefulness has largely been forgotten. With the continuing debate about whether there has been a decline in human fertility, and its possible environmental causes, we believe that it is vitally important that there is global monitoring of the dizygotic:monozygotic ratio. Used correctly, it would be the simplest, cheapest and most precise way of answering the vital question: is human fertility on the decline?

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