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# INSURANCE OVULATION, EMBRYO MORTALITY AND TWINNING

HELEN L. BALL AND CATHERINE M. HILL

*Department of Anthropology and University College, Stockton, University of Durham, 43 Old Elvet, Durham DH1 3HN*

**Summary.** The 'insurance ova' hypothesis (Anderson, 1990) views dizygotic twinning as a by-product of selection for multiple ovulation which sometimes – in error – results in the birth of twins. From this viewpoint, polyovulation is a mechanism which reduces the risks of fertilization failure or embryo defect/mortality. If DZ twin births are a 'side-effect' of a mechanism which compensates for defective embryos one might predict that embryo defect rates and twinning rates will covary. This prediction is tested using national-level data on twinning rates and rates of trisomy-21 (Down's syndrome), and a strong positive correlation is found, even when controlling for maternal age. One suggestion that follows from this finding is that intra- and interpopulation variation in both twinning rates and Down's syndrome rates may result, in part, from individual variation in pre-implantation rejection of embryos in the very early stages of pregnancy. In this paper it is proposed that the 'insurance ova' explanation for twinning in humans could be expanded to incorporate a model of rejection of anomalous embryos, be they anomalies of number or type. Variation in the efficiency of an embryo rejection mechanism, combined with variation in frequency of polyovulation, would have consequences for individual reproductive success.

## Introduction

The incidence of twin births in human populations varies by more than an order of magnitude, from 3·3/1000 (Millis, 1959) to 55·7/1000 (Little & Thompson, 1988). Interpopulation differences appear, primarily, to be due to differences in the frequency of dizygotic twinning, as the rate of monozygotic twin births is relatively constant across populations (although see Boklage, 1987). Differences within populations, across mothers of different age-groups, also seem to be due to the frequency of dizygotic twinning, which increases with increasing maternal age, while monozygotic twinning rates do not fluctuate across maternal age categories (Bulmer, 1970). In a species which is well adapted for the production of a single infant per gestation (Martin, 1992), the consistent production of twins, and especially the variable rate of dizygotic twinning, requires some explanation (e.g. see Allen & Schachter, 1970; Kamimura, 1976;



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Nylander, 1979; Harlap, Shahar & Baras, 1985; Philippe, 1985; James, 1986; Campbell, 1988; Little & Thompson, 1988; Eriksonn *et al*., 1988; Haukioja, Lemmetyinen & Pikkola, 1989; Anderson, 1990; Chauduri *et al*., 1993; Nonaka, Iniura & Peter, 1993; Gleeson, Clark & Dugatkin, 1994). Because of its prevalence across human populations it is suggested that twinning might be adaptive (e.g. Gabler & Voland, 1994). Haukioja *et al*. (1989) found no evidence of increased reproductive fitness associated with twinning in their 18th and 19th century data from Finland. However, Gabler & Voland (1994), using 18th and 19th century German data, determined that while the birth of a pair of male twins had lower productivity than a single boy, the birth of a female pair of twins led to more live-born grandchildren than the birth of a single girl. They concluded that mothers of twins achieved greater reproductive success than mothers of singletons only, but that this was achieved via the generally higher fecundity and higher fertility of the mothers of twins, rather than the birth of twins itself.

In response to the findings of Haukioja and colleagues, Anderson (1990) proposed that the delivery of twins, while not directly increasing reproductive success, is an evolutionary epiphenomenon of another adaptive pattern. He suggested that humans have evolved a tendency towards polyovulation as a compensating measure for fertilization failure or early embryo loss. This 'insurance ova' hypothesis proposes that DZ twinning is a by-product of selection for multiple ovulation which sometimes, 'in error', results in multiple birth. If polyovulation is a mechanism which compensates for fertilization or implantation failure and confers insurance against embryo mortality, then women who polyovulate would have increased fitness over women who are monovulatory. Anderson also proposes the insurance ova hypothesis as an explanation for the known increase in DZ twinning rates with maternal age, arguing that it confers an advantage on women who polyovulate towards the end of their reproductive lives, as compensation for the production of defective ova which is also age related. The 'insurance ova' hypothesis implies, however, that production, as opposed to the conception, of twins would be expected to reduce, rather than increase, the mother's fitness (Gabler & Voland, 1994). It would seem that it is necessary, therefore, to have an effective embryo-rejection mechanism as a component of an adaptive insurance ova model. If such a process were operating efficiently one would expect to observe low DZ twinning rates (supernumerary embryos being rejected early in pregnancy), but where embryo rejection was less efficient (relaxed), the production of more DZ twins would be expected. This model anticipates that there is individual variation in both frequency of polyovulation, and efficiency of embryo rejection.

It is also possible that efficiency of embryo rejection may vary with age and one could imagine that embryo rejection is a component that can be usefully added to the model to explain increased twinning with increasing maternal age. Anderson, in part, bases the insurance ova hypothesis on the assumption that production of defective eggs (which are presumably being compensated for by polyovulation) is age related, occurring more frequently in older mothers. It is known that certain types of birth defects increase with maternal age, and these have their aetiology in chromosomal abnormalities (Baird, Sadovnick & Yee, 1991). There is some debate, however, over whether production of eggs with genetic defects increases with maternal age, or whether *failure to reject* them increases with maternal age (e.g. Stein & Stein, 1986). While the genetics literature indicates that a high proportion of chromosomal abnormalities are

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caused by non-disjunction of homologous chromosomes in ageing ova (Lamb *et al*., 1996; Petersen *et al*., 1993, although see Phillips *et al*., 1995) they are neither exclusively maternal in origin, nor exclusively age related (e.g. Gaulden, 1992; Griffin, 1996; Wyrobek *et al*., 1996). A modification of the insurance ova hypothesis, therefore, would suggest that polyovulation (which may compensate for fertilization failure or defective embryos) would be advantageous in those women with effective embryo rejection (e.g. young mothers). Furthermore, it seems reasonable to assume that post-conception brood reduction, and post-conception rejection of defective conceptuses, could be components of the same mechanism, and, if the process of pre-implantation selection and embryo rejection relaxes as women approach the end of their reproductive lives, this could contribute to both an increased frequency of DZ twinning and an increased rate of genetic defects among the births of older mothers. Therefore, increased twinning with increased maternal age may result from both an *increase* in polyovulation towards the end of reproductive life, and from a *decrease* in the rejection of multiple conceptuses.

*Variation in twinning rates across maternal age*

It has been proposed (Aymé & Lippman-Hand, 1982; Stein & Stein, 1986) that the observed increase with maternal age of both trisomic pregnancies and trisomic live births results from a decrease in the rate of rejection of trisomic conceptuses. Kloss & Nesse (1992) suggest that this *relaxation of embryo rejection* may be adaptive for the mother with low reproductive value (towards the end of her reproductive life). They conclude: 'As the mother nears the end of her reproductive life, the risk of rejecting a viable zygote may increase relative to the risk of delivering a defective child' (p. 286). By contrast a younger mother would be better served by rejecting a possibly defective conceptus and conserving resources for a normal child later. Likewise it could be argued that the risks associated with a twin maternity at the end of a woman's reproductive life would have a less detrimental effect on her overall reproductive success than would an earlier twin maternity. As Gabler & Voland (1994) did not break down their data to show the increased or decreased fitness of twin maternities at different maternal ages, this assumption remains to be tested.

Indirect evidence exists to support the above suggestion, however. Hansen (1986) notes that there appears to be a greater risk for spontaneous abortion with increasing maternal age, and in the products of spontaneous abortions, chromosome abnormalities (especially trisomies 13, 18 and 21, and sex chromosome aneuploidies) increase exponentially with maternal age (Stein & Stein, 1986; Mikkelsen, 1988). Some of these also contribute to the higher stillbirth rate seen in older mothers. If older women have a reduced conceptus rejection mechanism in the pre-clinical recognition phase of pregnancy, rejection of defective embryos might occur later in the pregnancy (more spontaneous abortions), occur at term (more stillbirths), or appear as liveborn infants (more chromosomal birth defects). Given that many trisomic zygotes are conceived, but generally appear as clinically recognized pregnancies in 'older' mothers, and likewise many DZ twins are conceived, but appear most frequently among 'older' mothers also, it is possible that decreased embryo rejection in the pre-recognition phase of pregnancy might be affecting increased DZ twinning rates as maternal age increases.

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To test this hypothesis it would be necessary to obtain data on whether polyovulations and twin conceptions are constant across women of differing age-groups, or whether there is a rise in polyovulation and twin conception with age. Nylander (1975) commented that the 'increasing incidence of DZ twinning with maternal age is probably due to increasing ovarian activity possibly under hormonal stimulus causing increased double ovulation . . . as the menopause approaches' (p. 101). Martin *et al.* (1991), however, found that when matched for age and parity with the mothers of singletons, women who had at least one set of spontaneous DZ twins had elevated secretion of, or sensitivity to, gonadotropin-releasing hormones. This finding suggests that there is variability across individuals with respect to their rate of polyovulation. If the frequency with which a woman polyovulates, and thus might conceive DZ twins, is relatively constant across her reproductive lifetime, 'relaxed' embryo rejection with increasing maternal age may allow more DZ twin pregnancies to be carried to term among women who normally polyovulate. A wealth of evidence is now available which demonstrates that twin conceptions occur many times more frequently than do twin births (the vanishing twin phenomenon) (Schneider, Bessis & Simonnet, 1979; Landy, Keith & Keith, 1982; Jackson & Benirschke, 1989; Kelly *et al.*, 1991; Blumenfeld *et al.*, 1992), indicating that multiple ovulation occurs more frequently than previously suspected. However, these studies do not indicate maternal age.

The juxtaposition of the predictions of the insurance ova hypothesis with the pre-implantation selection hypothesis (PIS) is shown in Fig. 1. The insurance ova hypothesis (Anderson, 1990) predicts that frequency of polyovulation affects the DZ twinning rate. The PIS hypothesis predicts that rates of pre-implantation selection may influence the genetic defect rate (Hook, 1983; Stein & Stein, 1986; Kloss Nesse, 1992). The proposed combined model suggests that the rates of PIS may also affect DZ twinning rates via the rejection of surplus embryos when multiple ovulation has resulted in multiple conceptions, PIS being potentially more 'efficient' in some cases than in others.

*Variation in twinning rates across populations*

The 'insurance conception/pre-implantation selection model' may be a useful device for understanding interpopulation variation in DZ twinning rates. One could predict, based on this model, that a low genetic defect rate indicates relatively 'strong' PIS within a population, and thus would expect to see low DZ twinning rates within that population (see also Hewitt & Stewart, 1970). Likewise, if genetic defect rates are high one could predict that insurance ovulation and 'weak' PIS will mean DZ twinning rates would also be relatively high. To test this hypothesis data on Down's syndrome rates are used as these are widely available for many countries, and the syndrome's genetic basis is well understood.

## Methods

Published data on twinning rates (TRs) were tabulated for a broad sample of societies, together with information regarding: (a) MZ and DZ twinning rates, (b) time period to which twinning rates applied, (c) nature of study population, e.g. prospective

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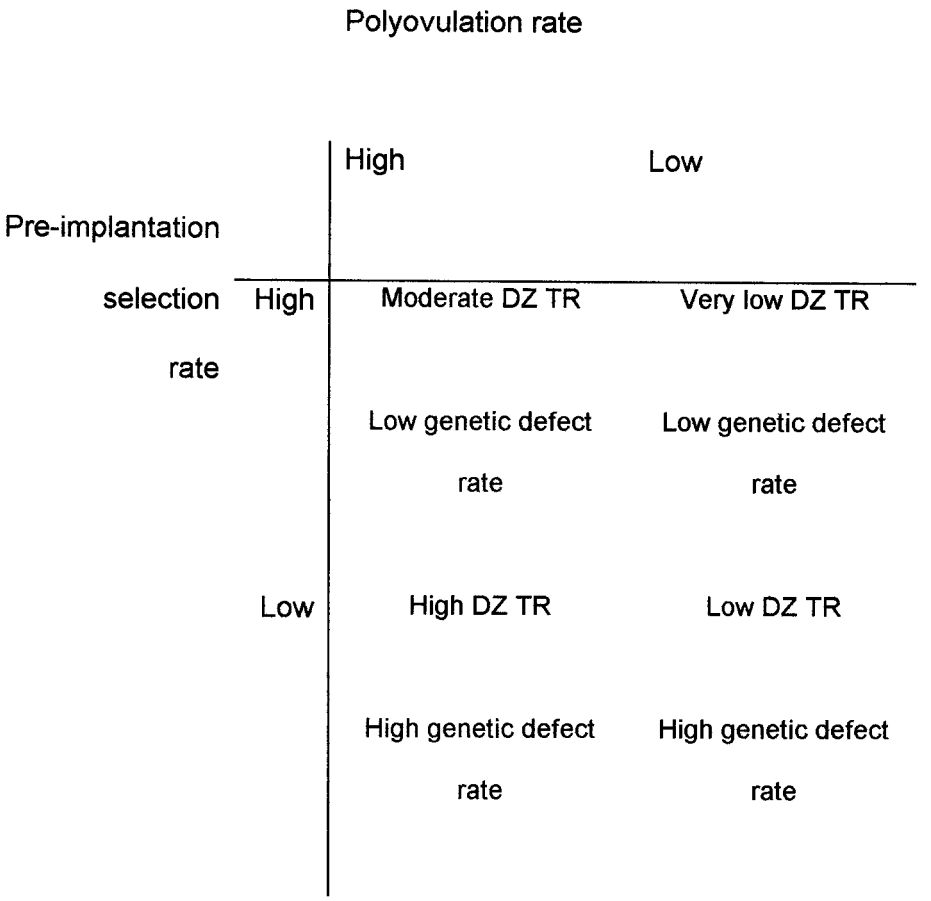



**Fig. 1.** Insurance ova/pre-implantation selection model.

hospital study, national statistics, birth certificate survey etc. and (d) ethnic group. Genetic defect rates (specifically Down's syndrome rates) were obtained for as many of these populations as were available in the published literature. Along with Down's syndrome rates (DSRs), information was also collected (where available) on: (a) breakdown of Down's syndrome conceptions, spontaneous and induced abortions, and term births; (b) time period to which DSRs applied; (c) whether prenatal screening programmes were in operation; (d) source of data, e.g. prospective hospital study, congenital defect screening programme data, retrospective medical records survey etc. Populations for which both TRs and DSRs were available were included in the database, matched as closely as possible by time period of studies. Down's syndrome rates were included for a population where figures were given for live births if no screening programmes were in effect, or the estimated live-birth rate where prenatal screening and elective termination data were available (adjusted for 'predicted fetal wastage'; Gilbert *et al.*, 1996).

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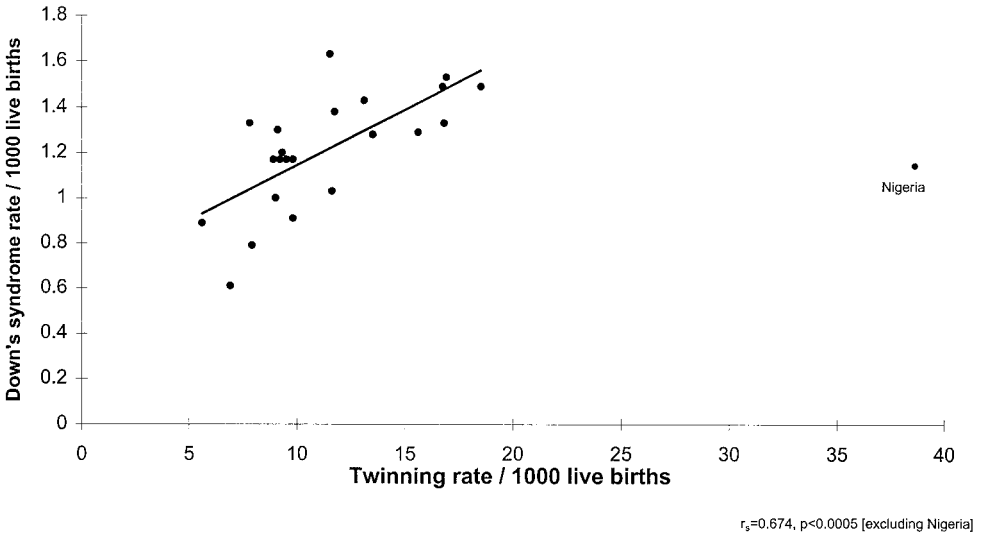



**Fig. 2.** Twinning rates and Down's syndrome rates for 25 populations.

## Results

Data on both TRs and DSRs were available for 25 populations (see Table 1). Due to lack of data on DZ vs MZ twinning rates for most populations it was necessary to use the composite twinning rate. It is generally accepted, however, that variation in overall twinning rate is due to DZ twinning, with MZ rates seemingly remaining constant across populations (Bulmer, 1970). A plot of TR by DSR reveals a strong positive correlation (Spearman's rank correlation coefficient of 0·583, $p < 0{\cdot}003$, $n = 25$; see Fig. 2). To eliminate the possible confounding effect of maternal age (a population of predominantly young mothers would have lower TRs and DSRs than a population of predominantly older mothers) data on mean maternal age (MMA) were obtained for 20 of the 25 societies, matched for the time periods for which the TR and DSR data applied. A Kendall's partial correlation for TR against DSR, controlling for MMA ($T_{xy,z} = 0{\cdot}6482$, $n = 20$, $p = 0{\cdot}003$), indicates the correlation between TR and DSR is not confounded by MMA. There is no obvious phylogenetic link between populations clustering together in the correlation (see Table 1).

## Discussion

If low DSR is an adequate variable to represent a 'stringent' level of pre-implantation selection within a population, then this correlation supports the hypothesis that PIS is relevant in understanding variation in twinning rates. It may be useful, therefore, to incorporate the idea that there is interpopulation variation in PIS, as well as in polyovulation, in models to explain twinning rate variability. Some populations might be more 'stringent' in weeding out anomalous conceptuses prior to clinical recognition of pregnancy, be they aberrations of type (e.g. genetic defects) or number (e.g. multiple conceptuses); other populations may be physiologically 'less efficient' about early

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**Table 1.** Down's syndrome rate (DSR) and twinning rate (TR) per 1000 live births, and mean maternal age (MMA) in years

| Country | DSR | Period | Source | TR | Period | Source | MMA | Source |
|---|---|---|---|---|---|---|---|---|
| Australia | 1·17 | 1981–1988 | Int. Clearinghouse (1991) | 9·5 | 1973–1979 | UN Demog. Yrbk (1981) | 25·70 | UN Demog. Yrbk (1981) |
| Burma | 1·38 | 1971–1972 | Kyu *et al.* (1981) | 11·73 | 1971–1972 | Kyu *et al.* (1981) | 27·00 | UN Demog. Yrbk (1981) |
| Canada | 1·00 | | Hamerton *et al.* (1975) | 9·0 | 1972–1979 | Little & Thompson (1988) | 27·10 | UN Demog. Yrbk (1975) |
| Czech. | 0·79 | 1974–1988 | Int. Clearinghouse (1991) | 7·9 | 1978 | UN Demog. Yrbk (1981) | 24·60 | UN Demog. Yrbk (1981) |
| England | 1·09 | 1977–1979 | Owens *et al.* (1983) | 9·8 | 1971–1975 | Brown & Daw (1980) | 25·70 | UN Demog. Yrbk (1975) |
| France | 1·17 | 1976–1988 | Int. Clearinghouse (1991) | 8·9 | 1974 | UN Demog. Yrbk (1981) | 26·00 | UN Demog. Yrbk (1981) |
| Hungary | 1·30 | 1973–1982 | Czeizel (1988) | 9·1 | 1960–1971 | Little & Thompson (1988) | 25·00 | UN Demog. Yrbk (1975) |
| India | 1·17 | | Isaac *et al.* (1985) | 9·8 | 1969–1973 | Ghosh & Raman (1979) | 25·80 | UN Demog. Yrbk (1975) |
| Ireland | 1·03 | 1981 | Mulcahy & Reynolds (1985) | 11·6 | 1977 | UN Demog. Yrbk (1975) | 28·30 | UN Demog. Yrbk (1975) |
| Israel | 1·07 | | Halevi (1967) | 9·8 | 1972–1980 | Little & Thompson (1988) | 26·50 | UN Demog. Yrbk (1975) |
| Italy | 1·29 | 1978–1988 | Int. Clearinghouse (1991) | 15·6 | 1977–1979 | UN Demog. Yrbk (1981) | 23·40 | UN Demog. Yrbk (1981) |
| Japan (Osaka) | 0·61 | 1948–1990 | Imaizumi *et al.* (1991) | 6·9 | 1948–1990 | Imaizumi *et al.* (1991) | 27·35 | UN Demog. Yrbk (1981) |
| Japan (Tokyo) | 0·89 | 1973–1977 | Higurashi *et al.* (1979) | 5·6 | 1972–1974 | UN Demog. Yrbk (1975) | 27·35 | UN Demog. Yrbk (1975) |
| N. Zealand | 0·91 | 1980–1988 | Int. Clearinghouse (1991) | 9·8 | 1972–1979 | Little & Thompson (1988) | 25·00 | UN Demog. Yrbk (1975) |
| N. Ireland | 1·49 | 1981–1985 | Int. Clearinghouse (1991) | 18·5 | 1968–1969 | Dean & Keane (1972) | 27·00 | UN Demog. Yrbk (1975) |
| Nigeria | 1·16 | 1972–1980 | Adeyokunnu (1982) | 39·7 | 1974–1978 | Rehan & Tafida (1980) | | Unavailable |
| Poland | 1·63 | | Pietrzyk & Maerska (1987) | 11·5 | 1949–1971 | Little & Thompson (1988) | 26·70 | UN Demog. Yrbk (1975) |
| Russia | 1·33 | 1982–1989 | Kovalera *et al.* (1994) | 7·8 | 1973 | Little & Thompson (1988) | 26·50 | UN Demog. Yrbk (1975) |
| S. Africa | 1·33 | 1986–1989 | Delport *et al.* (1995) | 16·8 | 1963 | UN Demog. Yrbk (1975) | | Unavailable |
| S. America | 1·49 | 1974–1988 | Int. Clearinghouse (1991) | 16·73 | 1972–1980 | Little & Thompson (1988) | | Unavailable |
| Scotland | 1·20 | 1980–1990 | Lopez *et al.* (1995) | 9·3 | 1980 | UN Demog. Yrbk (1981) | 25·70 | UN Demog. Yrbk (1981) |
| Singapore | 1·43 | 1986–1989 | Thein *et al.* (1992) | 13·1 | 1972–1980 | UN Demog. Yrbk (1975) | 26·80 | UN Demog. Yrbk (1975) |
| Spain | 1·53 | 1976–1988 | Int. Clearinghouse (1991) | 16·9 | 1976 | UN Demog. Yrbk (1981) | 27·60 | UN Demog. Yrbk (1981) |
| Sweden | 1·28 | 1974–1988 | Int. Clearinghouse (1991) | 13·5 | 1921–1950 | Little & Thompson (1988) | 27·70 | UN Demog. Yrbk (1975) |
| USA | 1·17 | 1970–1989 | Krivchenia *et al.* (1993) | 9·2 | 1972–1975 | Little & Thompson (1988) | | Unavailable |

screening, and not reject embryos until post-clinical recognition of pregnancy (spontaneous abortions and/or stillbirths), or not reject embryos and fetuses at all and experience greater numbers of both multiple births and chromosomal birth defects. This hypothesis would be further supported if rates of other congenital malformations also correlate with DZ twinning rates. It has been reported in one study that neural tube defects (particularly anencephaly, and anencephaly with spina bifida) were positively correlated with twinning rate, standardized for maternal age, across populations (Stevenson *et al*., 1966).

The only 'outlier' in the sample is Nigeria, a country with exceedingly variable localized twinning rates, and extremely high DZ twinning rates in some ethnic groups [e.g. Yoruba (Nylander, 1979), Ibo (Cox, 1963) and Igbo (Azubuike, 1982)]. Nigeria's position on Fig. 1 suggests that excessively high rates of polyovulation, rather than unusually low rates of embryo rejection, are implicated in their high twin frequencies (Hill & Ball, 1996). When the Nigerian data are excluded from the analysis the Spearman's rank correlation becomes 0·674 ($p < 0{\cdot}0005$, $n = 24$).

## Conclusion

The authors propose a model based on insurance conception and pre-implantation rejection of embryos to explain DZ twinning rate variability both within and between populations. The model incorporates both 'bet-hedging' against fertilization failure (insurance ova hypothesis), and 'bet-hedging' against fertilization of defective gametes (pre-implantation selection hypothesis) as a strategy to enhance maternal reproductive success.

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