DELAYED OVULATION AND MONOZYGOTIC TWINNING

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Aiming to show that delayed ovulation may induce MZ twinning, follicular maturation was induced in the rabbit by a small quantity of Pregnant Mare Serum Gonadotropin (16 UI four times): coitus, which induces ovulation in the rabbit, was delayed 60 hours after the last injection. From the 387 blastocysts obtained after this treatment, 6 (1.5%) were pairs of MZ twins, twinning being otherwise exceptional in the rabbit. Other anomalies were shown by the embryos, apparently related to a deficient quality of the eggs: high embryonic mortality (62% vs. 27% in controls) and chromosomal anomalies (20%) such as trisomies, triploidies, and chimaeras. The relation between MZ twinning, chromosomal anomalies, and embryonic mortality induced by delayed ovulation, could be connected and related to the poor perinatal conditions frequently observed in human MZ twins.

DZ twinning is well known to be caused by an increased secretion of follicle stimulating hormone (FSH) resulting in polyovulation, whereas MZ twinning is not yet explained. The early embryo cleaves into two different entities, but we do not know when this takes place: it may be at any time between fertilization and two weeks after gestation. Studies of the placenta may give indications of the precise moment of origin; only twins with a monochorial placenta are surely MZ, but they do not represent the totality of monozygosity.

Some general features seem to be connected with the MZ twin condition: (1) a very high perinatal mortality (20% vs. 9% in DZs); (2) a low birth weight, lower than in DZ twins even if all other factors are equal; (3) an abnormally high representation in psychiatric hospitals; and (4) multiple congenital anomalies and chromosome anomalies, the most interesting being represented by MZ heterocaryotic twins.

The simultaneous occurrence of these factors suggests a possible common factor, represented by the quality of the egg, often depending on a physiologic accident, the ageing of gametes. Eggs after ovulation age very rapidly, in few hours, and the same applies to sperms, once in the female genital tract. Both induce chromosome anomalies and prenatal mortality (for review, see Bomsel-Helmreich 1975). The egg may also age before ovulation: overripeness of oocytes, still inside the follicle, seems to have the same consequences as ageing after ovulation.

We studied the quality of the egg, and especially overripeness and delayed ovulation in the rabbit, a particulary convenient experimental animal where coitus is the inducer of ovulation.

Follicular maturation in the doe was induced by a small quantity of Pregnant Mare Serum Gonadotropin (PMSG) with an activity similar to FSH. Coitus was delayed for 60 h after the last injection. Ovulation did not take place before 11 h post coitum (p. c.). A total of 387 blastocysts obtained in this way were studied 158 h p. c., immediately before implantation, measured and caryotyped.

Two types of anomalies appear which show a lack of quality of the eggs: a high embryonic mortality (62% vs. 27% in the controls) and chromosomal anomalies such as trisomies, triploidies or mixoploidies (20%). However, the most remarkable morphological anomaly observed was the presence of MZ twins. We found 6 sets of twins (1.5%). Two of them were small, but 4 had the size of normal blastocysts. The large ones were clearly two blastocysts with cavities and embryonic discs inside the same zona pellucida.

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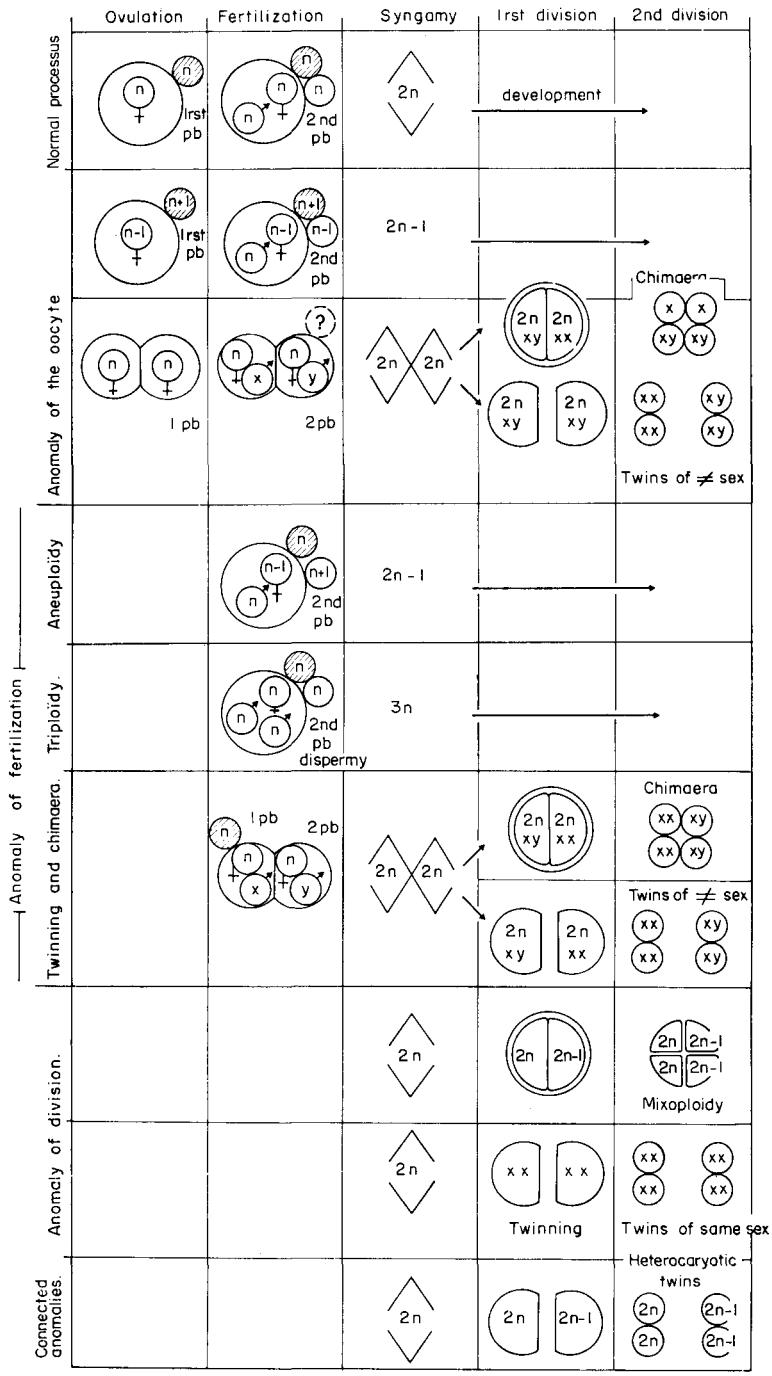

Fig. 1.
Anomalies of ovulation, fertilization, first division, or connected anomalies. Nondisjunction occurs at first or second polar body expulsion or at first division. Triploidy occurs at fertilization. Twinning may occur after equal division of first or second polar body (twins of different sexes). Twins of same sex occur at first division, at the same time as mixoploids.

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MZ twinning is not known to occur spontaneously in the rabbit. Therefore we may assume that these observations establish a direct link between an anomaly of oocyte maturation and MZ twinning. Similar results were described in delayed ovulating rats by Butcher et al. (1969), such as a blastocyst with two celomic cavities and, in later gestation, implantation sites containing two conceptuses of the same sex with separate amnion and chorion, and pairs of fetuses of the same sex with fused placenta. After overripeness in amphibian eggs, similar observations have been recorded and especially conjoined twins (Witschi 1952).

The possible anomalies of ovulation, fertilization and division, which explain the simultaneous occurrence of aneuploid, triploid or mixoploid embryos and twins, are shown in Fig. 1.

The origin of MZ twinning may be explained either by an equal separation of the egg at the expulsion of the first or second polar body, or by a separation of the first two blastomeres. Twinning after overripeness seems to be more likely, all pairs examined being of the same sex. Besides, in the rabbit, the rapid formation of a mucin coat around the zona pellucida in the first hours after fertilization and before cleavage, makes the possibility of fusion of two different eggs absolutely unlikely. This hypothesis is further confirmed by the frequency of mixoploids among the blastocysts with chromo-, some anomalies, which shows that anomalies of first division are especially related to overripeness as mixoploidy necessarily originates as late as the first division. The existence of MZ heterocaryotic twins and the abnormal coincidence between Turner syndrome and twinning (Nance and Uchida 1964, Riekhof et al. 1972) also indicate a relation between chromosomal anomalies and twinning and suggest an origin at first segmentation; they further suggest a common cause to the simultaneous occurrence of two linked anomalies in the same individual (connected anomaly in Fig. 1).

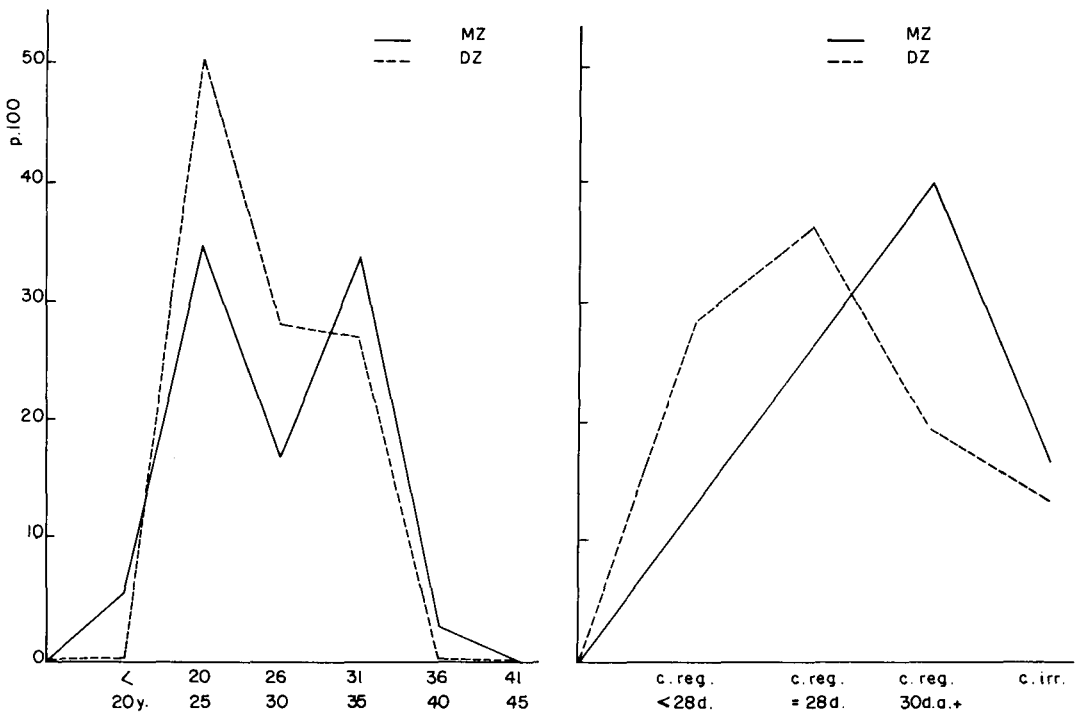

Fig. 2. MZ and DZ twins in relation with maternal age (left) and with regular or irregular cycles of different length (right).

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We would now like to connect these experimental data with our observations made on human MZ twins.

We observed 116 pairs of twins and defined them according to very strict criteria: MZ twins had a monochorial placenta and were of the same sex (35%); DZ twins had a bichorial placenta and were of different sex (35%). When zygosity could not be ascertained, twins were discarded from the observation.

The age of the mothers of DZ twins had a similar distribution to that of the general population. The age of the mothers of MZ twins shows two peaks: a smaller one for the very young mothers and another for mothers of 31-35 years of age. Curiously, these peaks are quite similar to those observed in mothers of children with Down's syndrome (Fig. 2).

Mothers of DZ twins show the same distribution in the length of menstrual cycles as the general population, whereas mothers of MZ twins show an increase in abnormal cycles: either longer or irregular (Fig. 2). Mothers of DZ twins show a higher percentage of heredity of twinning than mothers of MZ twins. But nevertheless, some hereditary factors also seem to exist in the latter. The increased age or longer menstrual cycles which seem to characterize mothers of MZ twins also appear to affect the appearance of chromosomal anomalies in the offspring. This suggests a common origin, i.e., the ageing of the egg, by either delayed ovulation or delayed fertilization, which would interfere with quality of the egg and consequently affect the embryos.

In humans, sexual intercourse is possible at any time of the cycle, whereas in other mammals coitus is only possible during a short period, precisely near ovulation, which synchronises and controls the quality of gametes. Thus, in humans, accidental ageing of the gametes has a much higher probability. The higher frequency of MZ twins in humans than in any other mammals could thus find an explanation.

The relation between MZ twinning, chromosomal anomalies, and embryonic mortality induced in the rabbit by delayed ovulation, could finally be related to the poor perinatal conditions frequently observed in human MZ twins.

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