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Session I

Incidence and Factors of Twinning



The Etiology of Human Dizygotic Twinning With Special Reference to Spontaneous Abortions

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The comparison of 622 twin and 622 singleton births allowed us to confirm the association of dizygotic twinning with maternal age, parity, and maternal weight and height, as well as the occurrence of unlike-sex twins in the mother's family. It was also shown that none of these associations, except for maternal height, can be explained by the others. Dizygotic twinning was also found to be negatively correlated with previous use of oral contraceptives and with irregularity of menstrual cycle. Finally, the relationship between spontaneous abortion in previous pregnancies and maternal exposure to medical irradiation was investigated.

Key words: Abortion, Oral contraceptives, Dizygotic twinning, Pelvic irradiation, Maternal age, Parity, Maternal height and weight

INTRODUCTION

Human twinning is a complex process involving phenomena which are either specific, like polyovulation, or nonspecific, like intrauterine mortality. The understanding of human twinning is thus of considerable interest.

First, considering human twinning for itself, it is of interest to understand one of the aspects of human reproduction. Then, from an obstetrical point of view, the knowledge of factors associated with twinning can help to screen those pregnancies which are more likely to be multiple before using more sophisticated and expensive methods of diagnosis, like ultrasonography. Last, on a more theoretical point, the understanding of human twinning, which appears to have been counterselected during evolution [7], can throw some light on the evolution of human reproduction.

Human twinning also involves phenomena which exert their influence on all pregnancies such as intrauterine mortality [11, 19]. It is indeed well established now that a large proportion of conceptions are lost during pregnancy even though most spontaneous abortions

are not observed at the clinical level [5, 10, 16]. Intrauterine mortality also affects multiple conceptions [11, 12, 17, 21]. As chromosomal aberrations are now considered to be the major source of early intrauterine mortality, the study of dizygotic (DZ) twinning is particularly relevant to improve our knowledge of the etiology of reproduction failures.

A considerable amount of work has been devoted to the understanding of the etiology of human twinning, and present knowledge in the field is well summarized in the books of Bulmer [7] and MacGillivray et al [13]. However, many issues remain open.

First, it seems that the interrelations of the different factors investigated separately have not been considered systematically, except for maternal age and parity. It also seems that not enough attention has been given to evaluating the relative influence of polyovulation and intrauterine mortality in the genesis of twinning.

For these reasons, a retrospective case (twin birth) control (singleton birth) survey was set up. It was aimed at finding factors associated with DZ twinning and assessing the effect of each separate factor after allowing adjustments for the effect of the others. Moreover, particular attention was given to the relationship between spontaneous abortions and DZ twinning.

MATERIAL AND METHODS

The 622 twin deliveries which took place in 23 French maternity hospitals between April 1976 and October 1978 were studied using the previous singleton births in the same hospitals as controls. The same interviewer administered a questionnaire to the mother of twins and the control mother the same day.

Details of all pregnancies, physiopathologic information on both parents, their exposure to environmental risk factors (smoking and irradiation), and the occurrence of twin births in their families were recorded.

Zygoty was not determined biologically for economic reasons. Pairs of unlike-sex ($n = 199$) were taken as "pure" DZ, the like-sex ones ($n = 423$) being divided into 199 DZ (17%) and 224 monozygotic (MZ) (53%) according to Hardy-Weinberg's rule [8]. For any variable discriminating DZ twins specifically, the like-sex twins should be intermediate between the controls and the unlike-sex twins, and the differences statistically significant.

Several studies summarized by Wyshak [24] have shown that use of fertility drugs increases the incidence of polyovulations. In this series the percentage of pregnancies induced by a fertility drug is seven-fold in the unlike-sex twins as compared to the controls (Table 1). In order to obtain information concerning "noninduced" twinning, all case-control pairs were excluded where either the twin or singleton pregnancy, or both, were obtained with the aid of a fertility drug. The results presented concern a restricted sample of 546 singleton deliveries, 384 like-sex twin deliveries (42% DZ) and 161 unlike-sex twin deliveries.

RESULTS

Maternal age, birth rank, maternal weight and height, as well as familial occurrence of unlike-sex twins in the mother's families are positively associated with DZ twinning (Table 2). The association is statistically significant for each factor independently, except for maternal weight and height. The association between DZ twinning and maternal height disappears when adjusted for maternal weight and the association with maternal weight remains unaltered when controlled for height.

Previous use of oral contraceptives and reported irregularity of menstrual cycles are negatively associated with DZ twinning (Table 2). Although both characteristics are negatively correlated with maternal age, control for age leaves both associations still statistically significant.

TABLE 1. Pregnancies Obtained After Using a Fertility Drug (% Values)

Controls	Like-sex twins	Unlike-sex twins	Comparison of the three groups
2.2 ± 0.6	9.0 ± 1.4	16.6 ± 2.6	P < 0.001

TABLE 2. Factors Associated With Dizygotic Twinning

	Controls	Like-sex twins	Unlike-sex twins	Comparison of the three groups (P)
Maternal age (years)	26.5 ± 0.2	27.2 ± 0.3	28.3 ± 0.4	< 0.001
Birth rank	1.75 ± 0.05	1.94 ± 0.07	2.19 ± 0.11	< 0.001
Maternal height (cm)	161.9 ± 0.3	162.3 ± 0.3	163.2 ± 0.5	< 0.05
Maternal weight (kg)	55.6 ± 0.4	55.5 ± 0.5	58.3 ± 0.8	< 0.01
Mothers with unlike sex twins in their families (%)	7.8 ± 1.2	13.0 ± 1.8	17.5 ± 3.1	< 0.001
Mothers having used oral contraceptives previously (%)	52.1 ± 2.1	48.3 ± 2.6	37.6 ± 3.9	< 0.01
Mothers with irregular menstrual cycles (%)	23.5 ± 1.8	18.1 ± 2.0	11.6 ± 2.6	< 0.01

TABLE 3. Early Spontaneous Abortion Rate Among Previous Pregnancies (% Values)

Familial occurrence of unlike-sex twins in the mothers' families	Singletons	Like-sex twins	Unlike-sex twins
No	12.4 ± 1.7	14.0 ± 2.1	15.6 ± 3.2
Yes	22.2 ± 6.8	10.4 ± 3.6	22.2 ± 8.7
Total	14.2 ± 1.7	14.1 ± 1.9	16.1 ± 3.0

Computation of the average rate of previous spontaneous abortion among multigravidae showed no significant association with DZ twinning (Table 3, bottom line). The distinction between twin proneness (the occurrence of unlike sex twins in the mother's family) and effective twinning (the status of the index by birth) was investigated tentatively (Table 3). The higher spontaneous abortion rate in previous pregnancies of singleton mothers compared to that in twin-prone mothers was not statistically significant (P = 0.09).

As maternal exposure to medical irradiation is thought to increase the incidence of chromosomal aberrations among the conceptuses [Alberman et al: 1, 2], its association with DZ twinning was investigated (Table 4). No significant association was observed, although maternal age and delay between medical irradiation and the index birth were considered according to Alberman's analysis.

DISCUSSION

This study confirms the well-known associations between DZ twinning and maternal age, parity, maternal weight and height, and the familial occurrence of DZ twins in the mother's family. Except in the case of maternal height, these associations are independent of each other. The relationship between DZ twinning and previous use of oral contracep-

TABLE 4. Mothers or Fathers Previously Exposed to Radiography of the Pelvic Region (% Values)

	Controls	Like-sex twins	Unlike-sex twins	Comparison of the three groups (P)
Mothers	24.8 ± 1.9	23.4 ± 2.5	23.3 ± 3.9	> 0.05
Fathers	12.0 ± 1.4	7.9 ± 1.5	12.7 ± 2.7	> 0.05

TABLE 5. Early Spontaneous Abortions Rate Among Previous Pregnancies According to Exposure to Medical Irradiations of the Pelvic Region (% Values)

	Unexposed	Exposed	Comparison of exposed and unexposed (P)
Mothers	13.9 ± 1.5	20.1 ± 3.2	0.05
Fathers	14.1 ± 1.7	14.6 ± 1.6	> 0.05

tives, as well as the reported irregularity of the menstrual cycles, are negative. Finally, the relationship between DZ twinning and spontaneous abortions is discussed.

A negative association between the previous use of oral contraceptives and DZ twinning was first noticed by Vessey [22]. In his large-scale prospective survey the number of twin births observed was too small for the association described by Vessey to reach statistical significance. This negative association should be distinguished from the positive association observed in other studies [9, 18] between DZ twinning and conception occurring within two months of discontinuation of oral contraceptives. Indeed, these studies involved ex-oral contraceptive users only, whereas Vessey's study and ours compared users and non-users. It is not clear that the association described by Rothmann [18] is specific to the previous use of oral contraceptives, since it is well known that twin-prone women have a higher fecundability [3, 6, 15]. Oral contraceptive-like substances have been used in animal farm experiments to induce synchronized estrus [14] and, following their use, a decrease in fertility was observed. For these reasons, it may be thought that the negative association between previous use of oral contraceptives and DZ twinning is a direct physiological one.

Treolar et al [20], followed by Vollman [23] and Bean et al [4], established that there are large discrepancies between objectively recorded and subjectively reported characteristics of the menstrual cycle. To our knowledge the correlation between both kinds of information has not been attempted. In this study bias in the reporting of menstrual "irregularity" associated with the particular condition of a twin birth seems unlikely. Any such bias should give the same value for MZ and DZ twins but, as Table 2 shows, like-sex twins are intermediate between unlike-sex twins and singletons.

From epidemiological evidence Lazar [11] predicted a negative effect of spontaneous abortion on DZ twinning. This effect is now well documented using ultrasonography [12, 17, 21]. The present study does not show a negative association between DZ twinning and individual proneness to spontaneous abortion, which suggests that individual DZ twin proneness may be associated with higher propensity to spontaneous abortion, even though exogenous factors encouraging spontaneous abortion tend to decrease the ability to give birth to twins. The association between the occurrence of twin births in the mother's families and early spontaneous abortion rate among previous pregnancies, although just below statistical significance, supports this hypothesis. It is clear this association needs further investigation.

Much work has been devoted to the relationship between maternal exposure to medical irradiation and the presence of chromosomal aberrations in subsequent conceptions. Alberman et al [1, 2] carefully allowed for any bias in reporting to affect cases and controls equally. Our observations (Table 5) agree with those of Alberman. A positive association is found between maternal past exposure to medical irradiation and spontaneous abortion incidence whereas no such relationship is found for paternal exposure. However, DZ twinning is not negatively correlated with maternal exposure to medical irradiation. In view of this new evidence, it can be wondered whether the association described by Alberman cannot be explained by some particular condition of women who needed radiography in the past.

CONCLUSION

More detailed studies are clearly necessary to identify which steps of the twinning process are involved in the different associations discussed: polyovulation, successful fecundation of both ova, viability of both zygotes, or sufficient uterine capacity of the mother. The issue is of general interest since it opens the possibility of using the DZ twinning rate to elucidate some of the causes of human reproductive failures. Because the registration of human twinning is reliable and available on large populations, this opens promising perspectives for epidemiological investigations.

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