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Increasing Trend in the Monozygotic Twinning Rate

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Abstract. Recent changes in the estimated incidence of monozygotic twinning in 15 European populations are described. The overall trend was an increase in the monozygotic twinning rate (MZTR) since the 1960s, particularly in those countries in which the use of oral contraceptives (OC) was widespread. A slower increase or even a decrease in the MZTR was observed in countries with low use of OC. Some countries, eg, Sweden, demonstrated an unexpectedly sharp increase since the 1960s. In Poland and the Federal Republic of Germany the MZTR was already strongly increasing as early as in the 1950s, clearly before the introduction of the pill. The influence of several other factors on the MZTR is discussed, such as toxic and teratogenic agents, pelvic infection diseases caused by the use of intrauterine devices, the increased use of ovulation inducers and neuroleptics as well as changes in the registration of perinatal deaths.

Key words: Monozygotic twinning rate, Longitudinal trend, Oral contraceptives

INTRODUCTION

During the past 15 years many investigators have speculated about the relation between twinning and the use of oral contraceptives (OC). Many investigators report the dizygotic twinning rate (DZTR) among former OC users to be slightly lower in comparison with women who had never used OC [23,25,46,52]. However, this could not be confirmed in a small study in Britain [55].

Benirschke and Kim [5] have suggested that cessation of OC use may result in an

increased pituitary gonadotropin release, which in turn may lead to an increase in DZTR. Indeed, an increase in DZTR has been reported for certain subgroups of ex-OC users, for example:

a) women conceiving within one month [45] or 3 months [8] of cessation of OC use;
b) women conceiving after discontinuation of preparations containing high doses of estrogen [23];
c) women conceiving after pill failure [24].

In a retrospective study, based on a large Australian sample, Macourt [32] found a significantly higher MZTR among pregnancies which occurred within 6 months after cessation of OC.

Emery [17] tried to relate the increase in the British MZTR to the use of OC. He based his hypothesis on several studies revealing the effects of contraceptive steroids in man. Coutinho [12] showed that in half the patients treated by continuous low-dose Progestin (megestrol acetate), tubal motility was depressed during the treatment cycle. He suggested that long-term treatment may result in a greater inhibition of tubal motility causing impairment of ovum transport itself and thus a greater chance of MZ twinning. Fredricsson and Björkman [22] reported morphologic alterations in the human oviductal epithelium induced by contraceptive steroids, and Maruffo et al [33] observed ultrastructural modifications in the endometrial mucosa which could have an anti-implantation effect. Delay of implantation is believed to increase polyembryony in armadillos [50] and rats [54].

Factors other than impairment of ovum transport and delayed implantation may also cause MZ twinning. There are indications that the first cycle after withdrawal of combined contraceptive pills is characterized by delayed ovulation [39], which may also increase the MZTR [7,27].

Because the alterations in the oviductal epithelium and in ovulation pattern are not lasting, their suggested influence on the implantation of the fertilized ovum is restricted to those pregnancies which occur soon after cessation of OC and those in which OC are used in an early stage of gestation. It has been estimated that in Europe 2-5% of the women use OC in early pregnancy and a quarter to one-third use OC 3-4 months before conception [49]. Emery [17] has postulated that if the mechanism of delayed implantation and subsequent polyembryony plays a role in human twinning, its effect must be seen in the longitudinal MZTR. As a matter of fact he has shown that the MZTR in Britain has increased since the introduction of oral contraceptives. A rise in MZTR has also been reported from Poland [44] and Australia [15]. In this study we analyzed the MZTR in several European countries to see if there was, in accordance with Emery's hypothesis, a temporal coincidence between use of OC and changes in the MZTR.

MATERIAL AND METHODS

We have estimated the MZTR in 15 European countries with different levels of OC use. Yearly numbers of like-sexed and unlike-sexed pairs of twins as well as total numbers of maternities with live- and still-born children have been obtained from the national statistical offices in these countries. Using Weinberg's differential rule [9,56] we estimated the MZTR and the DZTR. The average increase in MZTR since 1960, when the pill

gradually came into use, was estimated by weighted linear regression. The hypothesis that the regression parameter b is different from zero, was tested as usual [3]. Of course, given the size of the populations under study, even minor changes in the MZTR would result in very small tail probabilities. These small P values do not imply that the increase (or decrease) was "appreciable", only that it cannot be explained by chance alone. Also, we do not claim that the trend (if any) should necessarily be linear.

Nevertheless, the regression parameter b is an appropriate estimate of the average increase or decrease over the period observed.

Although relatively few women were using OC in the period 1960-1966, the dose of hormones in those years was so high that, if there is an effect of OC on the MZTR, one may expect that it will be apparent already in those first years.

Whenever the same kind of information was also available before 1960, we did the same analysis on this period by way of control period, to see if the MZTR had been constant until the 1960s.

RESULTS AND DISCUSSION

The regression coefficients (b) and their levels of significance (P) are shown in the Table. Information about the use of OC among women aged 15 and 44, in the various countries is summarized in Fig. 1 [41].

In the Netherlands about 40% of the women (aged 15-44) were using OC in 1975. The observed increase, $b = 0.31$, is the same as in England and Wales where only 20% were using OC (Fig. 2). In both countries there was only a very slight increase in the MZTR before 1960.

For Belgium and France we found an increase of the same size as we found in the Netherlands, which is in accordance with the use of OC there. Austria and Switzerland show a relatively strong increase in the MZTR since 1960, but in contrast to the other countries Switzerland shows a strong decrease in the 1950s. In the Federal Republic of Germany the use of OC is at the same level as in the countries mentioned above, and the increase in MZTR is also comparable (Fig. 3). Here, however, the MZTR in the period 1950-1959 shows an increase of 0.59 per mil in 10 years. Unfortunately, there is a lack of information about twinning in the 1940s [42], so that we do not know when this rise started. In the period 1901-1937 there was only a slow increase, $b = 0.10$.

In the Scandinavian countries a very slow decrease in the MZTR is found in the period before 1960. In Denmark today 20% of the women are using the pill [6] but we have no clear information about Norway. For both countries, however, the increase of about 0.3 per mil per decade seems to be in accordance with the findings in other European countries. Sweden, however, shows a rather strong increase of 0.71 per mil in 10 years (Fig. 4) while one third of the women were using the pill in 1972 [36]. Finland shows a rather strong increase, $b = 0.22$, already in the period 1942-1959. However, the increase, $b = 0.34$, in the last two decades is about the same as was found in Denmark and Norway.

In Spain, a country with a relatively low use of OC, the observed increase, $b = 0.44$, is a bit higher than is to be expected. Italy's MZTR was relatively constant until 1960 [37]. According to the official statistics there was a sudden and highly significant increase in the years following World War I. However, this increase has been shown to be related

Table - Regression coefficients of MZTR

Country	Period	Average increase (b) in promille per 10 years	Level of significance (P)
Netherlands	1904-1959	0.06	10^{-6}
	1960-1984	0.31	10^{-6}
England & Wales	1939-1959	0.06	N.S.
	1960-1977	0.32	10^{-6}
Belgium	1961-1983	0.31	10^{-6}
France	1960-1984	0.27	10^{-6}
Austria	1950-1960	0.004	N.S.
	1965-1984	0.36	10^{-6}
Switzerland	1951-1959	- 1.47	10^{-6}
	1960-1984	0.37	10^{-6}
Fed. Rep. of Germany	1901-1937	0.10	10^{-6}
	1950-1959	0.59	10^{-6}
	1960-1984	0.24	10^{-6}
Denmark	1911-1959	- 0.016	N.S.
	1960-1984	0.38	10^{-6}
Norway	1931-1959	- 0.19	0.005
	1960-1984	0.27	0.0005
Sweden	1901-1959	- 0.094	10^{-6}
	1961-1984	0.71	10^{-6}
Finland	1942-1959	0.22	0.05
	1960-1983	0.34	10^{-6}
Spain	1942-1959	0.11	0.001
	1960-1979	0.44	10^{-6}
Italy	1931-1959	- 0.076	10^{-5}
	1961-1979	0.13	10^{-6}
Poland	1950-1959	0.38	10^{-6}
	1960-1985	- 0.24	10^{-6}
Czechoslovakia	1950-1959	- 0.17	N.S.
	1960-1984	- 0.19	10^{-6}

to changes in the registration of twin maternities in Italy [38]. Since 1960 thesere is a slow increase of 13 per mil in 10 years which is in accordance with the still relatively low use of OC in Italy.

In Poland there was a significant increase in the MZTR, b = 0.38, between 1950 and 1960. However, after 1960 there is a downward trend of the MZTR. This decrease is caused mainly by the sudden fall in the first part of the 1970s [44]. According to an inquiry among Polish married women under 45 years of age, only approximately 7.7% (SE 0.3%) were using OC [Kania, personal communications, 1986].

Czechoslovakia also has a low level of OC use [6] and again we found a slow decrease in MZTR since 1960.

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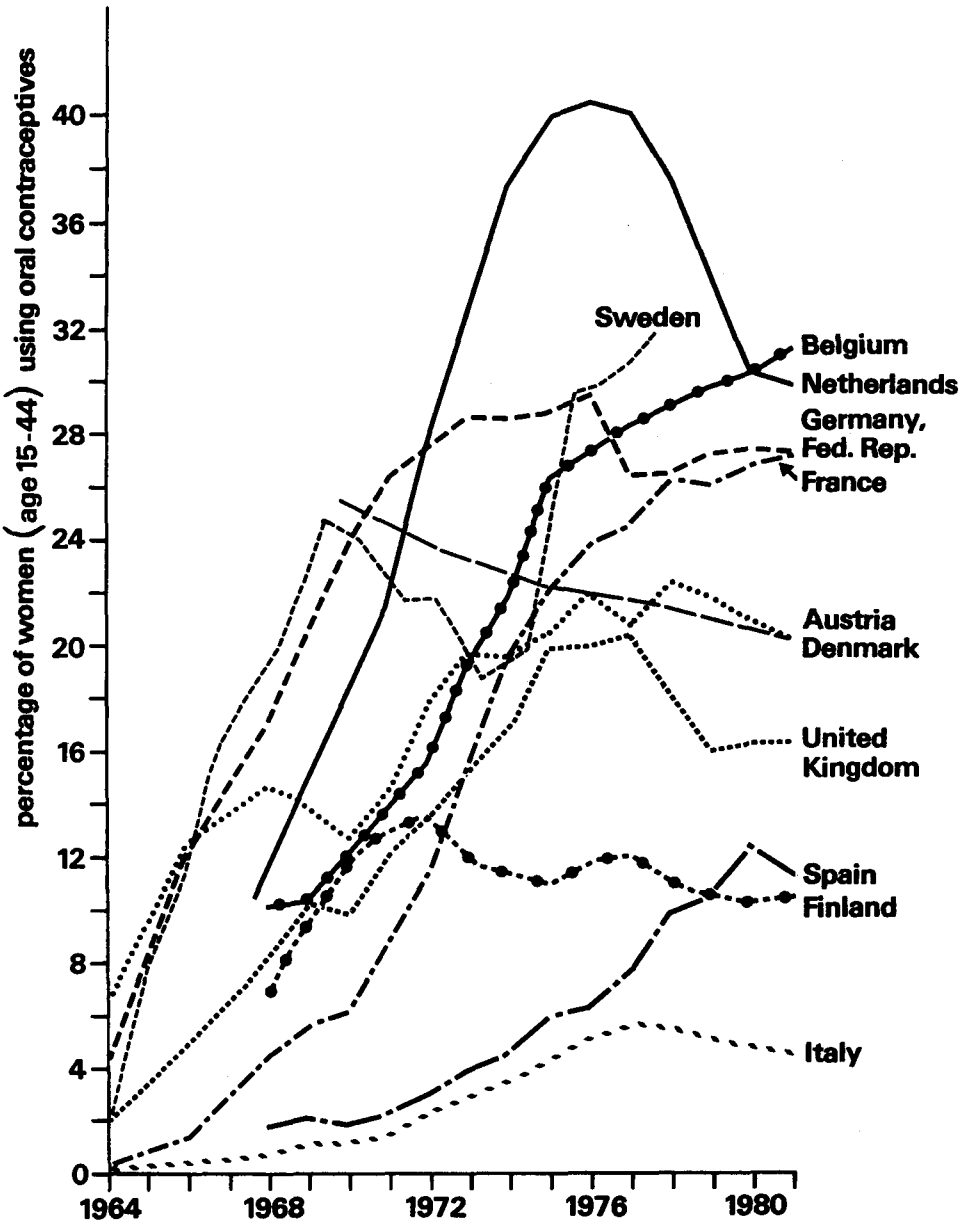

Fig. 1 - Percentage of women (aged 15-44) supplied with oral contraceptives through commercial channels in 11 developed countries, 1964-1981.

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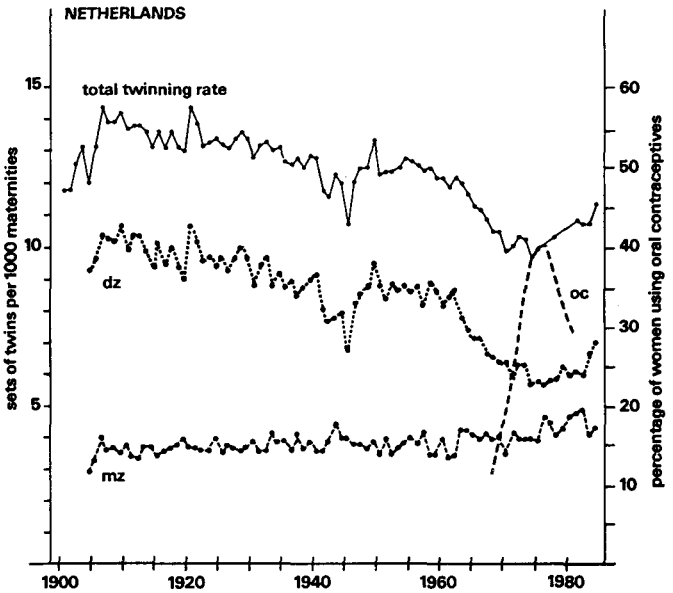

Fig. 2 - Total, dizygotic (DZ), monozygotic (MZ) twinning rates and percentage of women using OC in the Netherlands.

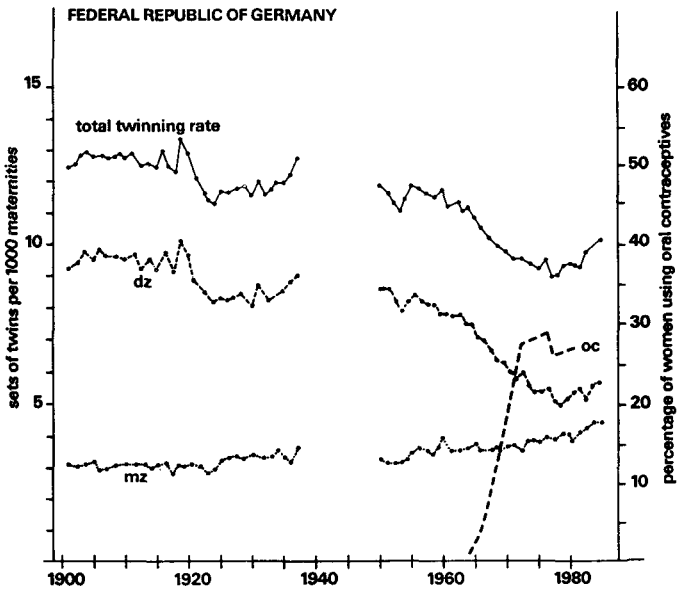

Fig. 3 - Total, dizygotic (DZ), monozygotic (MZ) twinning rates and percentage of women using OC in the Federal Republic of Germany.

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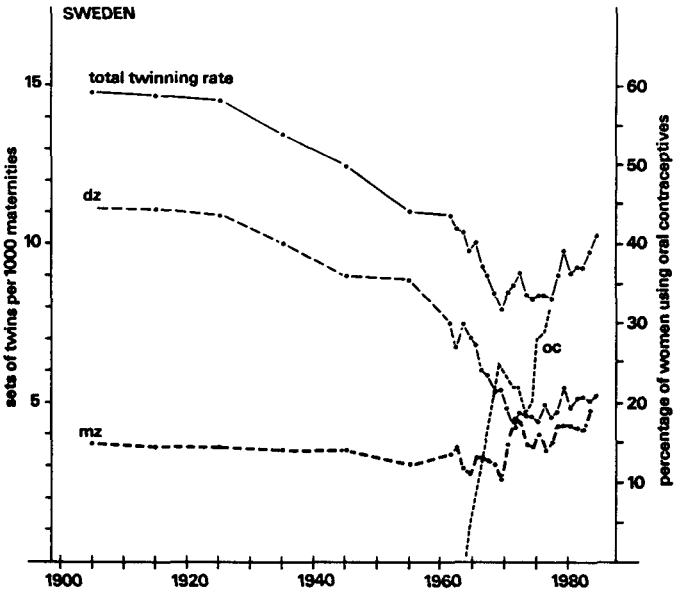

Fig. 4 - Total, dizygotic (DZ), monozygotic (MZ) twinning rates and percentage of women using OC in Sweden.

For Japan, where only less than 1% of the married women use OC, Imaizumi and Inouye reported a decline in the MZTR since 1966 [26].

Thus in three countries with relatively low use of OC (Czechoslovakia, Poland and Japan), the MZTR is not slowly increasing but decreasing. One possible explanation for this could be the decline in mean maternal age. Although there is no general agreement about this, there are indications that the MZTR increases very slowly with maternal age up to about 37 [9,40]. If this can be confirmed, the decline in MZTR due to decrease of mean maternal age may have been overshadowed be the increase due to use of OC or possible other factors in the other countries we have analyzed.

Factors in Malformation Production and MZ Twinning

There is an excess of congenital malformations in twins, entirely due to their increased frequency in MZ twins [9,30,34,35,48,58,59]. Could there be a common factor in the causation of both MZ twins and malformations as has been suggested by some investigators [27,34,48]? Several teratogenic agents, such as vitamin A, dimenthyl sulfoxyde, urethan and vincristine sulphate [20,28], as well as various physical conditions such as temperature and oxygen supply [50], have been observed to affect the MZTR as well as various types of developmental abnormalities in experimental animals [59]. In fact, MZ twinning has been regarded as a congenital anomaly caused by developmental arrest occurring early in embryonic life, before tissue differentiation has begun [50]. In some species of armadillos, implantation of the ovum is delayed and polyembryony is the rule, e g, the nine-banded armadillo regularly produces MZ quadruplets. However, in other mammals in which implantation of blastocysts is delayed, such as the European badger

and the roe deer, this dormant stage for many weeks and months is not accompained by MZ twinning or any recognized harm to the subsequently developing embryo. No direct evidence has been found so far that developmental retardation at a very early stage caused by factors such as lack of oxygen, is correlated with MZ twinning in higher mammals, including man [9].

Studies in chickens [29] and mice [21] indicate that genetic factors may be important even for induction of malformation by exogenous agents. However, in humans there is so far no proof that genetic variability exists for induction of malformations by environmental agents, even if such a conclusion appears plausible. Genetic differences in susceptibility to the teratogenic effects (phocomelia, etc.) of thalidomide are suspected but unproved. If any mutagenic agent inadvertently introduced into our environment was to cause less dramatic and less striking patterns of malformation, and MZ twinning, it might easily be overlooked. However, convincing reports of an increasing trend in malformation rates have not been published so far, in spite of the increased use of pesticides and similar substances during the last decennia.

Maternal Health

The MZTR may also be influenced by other factors, such as improvement in nutrition and the effective development of sociomedical care. As the frequency of twin conceptions, and especially MZ twin gestations lost during the first trimester is high [1,31,51], better maternal care may have a relatively strong effect on this type of pregnancies. So, part of the increase in the MZTR may have its origin in better maternal care. However, increased urbanisation and industrialisation with more sedentary occupations for mothers have in their turn caused a deterioration in physical condition with increased risk to the uterine blood circulation, and the possibility of twin pregnancies ending in singleton births or total abortion [18].

Other Probable Determinant Factors for MZ Twinning

It has also been postulated that pelvic infections may cause inadequate or delayed oxygen supply and thus an increased MZTR in man [2]. To what degree inflammatory changes in the uterus or Fallopian tubes, caused by the increased use of intrauterine contraceptive devices during the last decades, may have increased the MZTR, merits close monitoring. Increased use of ovulation inducers and embryonic manipulations in connection with in vitro fertilization (IVF) seem to cause a higher MZTR than expected [10,14,16,53, Derom and Edwards, personal communications, 1986].

Quite like the MZTR, the incidence of ectopic pregnancies has also been steadily growing during the last decennia [11,47]. The rate of ectopic pregnancies has doubled in Lund in southern Sweden during the last two decades [57]. Ectopic implantations, of which the great majority are situated in the Fallopian tube, have been related to similar causes as for MZ twinning: Progestagen-only contraception, failed postcoital interception (morning after pill), hormonal induction of ovulation, intrauterine contraceptive devices and pelvic inflammatory diseases. However, the only indication for a higher MZTR in tubal pregnancies comes from a study from Arey [2] and as Bulmer pointed out [9] there is a serious bias in this study which explains at least a part of the higher MZTR.

Also DZ twin gestations manifested as simultaneous extra- and intrauterine preg-

nancies [4] or as bilateral tubal pregnancies [13] are relatively rare.

Recently it has been reported [60] that certain psychotropic drugs, eg, haloperidol, delay ovum implantation and effect ovum cleavage in the mouse. Similar studies on women are not known. To what degree the increased use of major tranquilizers during the last decennia influences the MZTR remains an open question.

Changes in Registration of Perinatal Deaths

Our information about twinning came from vital statistics. During the last few decades the definition and registration of still-births has been changed in a number of countries, leading to a somewhat higher number of twin maternities reported. This may explain sudden rises in MZTR. An indication for this comes from secular studies on twinning on the Åland Islands. The slow but highly significant increase in the MZTR there, in the period 1653-1949, may at least partly be explained by incompleteness of registration [19]. Failure to register perinatal deaths diminishes the proportion of especially MZ twins recorded, since the frequency of still-births and neonatal deaths is higher among MZ than among DZ twins.

Estimation of MZTR

It has been suggested that Weinberg's difference rule results in an overestimation of MZ frequencies because of the excess of like-sexed twins in DZ twin maternities [43]. It may easily by seen that the degree of overestimation is proportional to the DZTR, which, in general, has decreased in the period 1960-1984. Therefore, if indeed like-sexed DZ twins are more frequent than unlike-sexed DZ twins, our estimates of the increase in MZTR can only be conservative.

CONCLUSION

The results in the present study are in agreement with Emery's hypothesis. In general there is a temporal association between increasing MZTR and increasing use of OC. However, this should not be interpreted as a proof for a causal relationship between MZ twinning and use of OC. Other factors affecting the MZTR should be further analyzed. Only then may we gain further insight into the fluctuations in the MZTR eg, the very strong increase in Sweden since 1960 and the increase in the Federal Republic of Germany and Poland already in the 1950s.

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