Iatrogenic multiple pregnancies in East Flanders, Belgium

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Objective: To evaluate the specific contribution of artificial induction of ovulation to the increasing number of multiple gestations in East Flanders and the effects of this treatment on the frequencies of monozygotic and dizygotic twinning.

Design: Since 1976 the East Flanders Prospective Twin Study has collected data on artificial induction of ovulation for all the multiple births listed in its registry.

Setting: East Flanders Prospective Twin Survey.

Patients: Between 1976 and 1992, 458 twin and 78 triplet pregnancies resulting from artificial induction of ovulation were analyzed.

Main Outcome Measures: Zygosity and frequency of iatrogenic multiple births.

Results: Since 1985 there is an explosive increase in twin and triplet births in East Flanders. This increase has been caused mainly by the sole use of fertility-enhancing drugs and in the last few years by resorting to other technologies of assisted reproduction, such as IVF-ET, GIFT, or zygote intrafallopian transfer.

Conclusion: In view of the elevated risk inherent to multiple pregnancies in terms of perinatal mortality and morbidity, the overenthusiastic or improper use of fertility drugs should be curtailed.

Key Words: Twins, multiple births, zygosity, placentation, prospective twin survey, ovulation induction, in vitro fertilization

It is generally accepted that the rate of monozygotic twinning of 4 per 1,000 pregnancies is relatively constant throughout the world. In contrast, the rate of dizygotic twinning varies widely. In the last decade, drugs that artificially induce ovulation have been used more frequently to treat female, as well as male, infertility. These drugs variably enhance the probability of multiple pregnancies, most of which are polyzygotic (1).

Since 1976 the East Flanders Prospective Twin Survey has collected data on artificial induction of ovulation for each of the multiple births listed in its registry. The availability of this information prompted us to study the specific contribution of artificial induction of ovulation to the increasing numbers of multiple gestations in East Flanders and the effects of this treatment on the frequencies of monozygotic and dizygotic twinning.

MATERIALS AND METHODS

The East Flanders Prospective Twin Survey was begun on July 1, 1964 and is a registry of multiple births within the province of Belgium designated as East Flanders. East Flanders covers 10% of the surface of Belgium and is inhabited by approximately 13% of the Belgian population. As of December 31, 1992, a total of 3,807 twin and 114 triplet...
pregnancies were entered in the registry. These numbers represent the near totality of twins and triplets born in East Flanders during this time period. An earlier investigation documented that this sample is representative of the twin population in East Flanders with respect to maternal age, sex ratio, proportion of pairs of unlike sex, neonatal mortality, and frequency distribution of blood groups (2).

Since the inception of the registry, fetal membranes and placental morphometry were examined for each delivery. ABO, Rh, MNSs, Duffy and Kell blood groups were determined in umbilical cord blood by routine methods and placental alkaline phosphatases were assayed by electrophoresis. DNA restriction fragment length polymorphisms were investigated on fresh or frozen specimens of placenta (3-5). Zygosity was determined by sequential analysis (2). Same-sexed dichorionic twins with at least one different genetic marker and unlike-sexed twins were classified as dizygotic. Monochorionic twins were classified as monozygotic. The probability of monozygosity, based on the number of identical genetic markers, was calculated for all same-sexed dichorionic twins and dichorionic or trichorionic triplets.

From January 1, 1976 to December 31, 1992, a total of 2,480 twin and 98 triplet pregnancies were recorded. Of these, 458 twin births and 78 triplet births were associated with artificial induction of ovulation. Only the deliveries in which one of the children weighed ≥ 500 g and, if birthweight was unknown, the gestational age was ≥ 22 weeks were considered for the present analysis. The zygosities of these pregnancies were compared with the zygosities of spontaneously occurring multiple pregnancies in terms of the respective frequency of the monozygotic and dizygotic condition. All dichorionic monozygotic twins and trichorionic dizygotic triplets born after artificial induction of ovulation had a probability of monozygosity and dizygosity, respectively, of ≥ 0.95.

RESULTS

Figure 1 shows the yearly numbers of spontaneous and induced twin pregnancies registered by the East Flanders Prospective Twin Survey between 1976 and 1992. In 1976, the total number of registered twin pregnancies was approximately 140 per year, whereas by 1991 and 1992 the total was 200. This graph shows that this increase is entirely due to the use of fertility-enhancing agents, as the number of spontaneous twin pregnancies did not raise appreciably during these years. Figure 1 also shows that between 1976 and 1985 the number of induced twin pregnancies increased slowly but substantially. After 1985, this increase was more dramatic so that pregnancies after artificial induction of ovulation accounted for more than one third of all twin births in 1991 and 1992. The decrease in the number of spontaneous twin pregnancies during the years 1983, 1984, and 1985 was due to the decline of the total number of births in East Flanders during these 3 years.

What is true for twin pregnancies is even truer for triplet pregnancies. Before the use of fertility-enhancing agents, the East Flanders Prospective Twin Survey recorded 1 triplet delivery a year whereas, in 1992, 15 triplet pregnancies, of which only 1 was spontaneous, were registered, which signifies that 90% of the triplet pregnancies were the result of artificial induction of ovulation.

Pooled over the years, the data show that most of the induced multiple pregnancies do not result from the advanced technologies of assisted reproduction, such as IVF-ET, GIFT, and zygote intrafallopian transfer (ZIFT), but from the sole use of fertility-enhancing drugs. In 77% (351/458) of the iatrogenic twin pregnancies and 72% (56/78) of the iatrogenic triplet pregnancies, artificial induction of
The explosive increase in twin and triplet births results mainly from the use of fertility-enhancing agents, rather than from more elaborate technologies of assisted reproduction. This is even more true for the higher order multiple births in the East Flanders Prospective Twin Survey (13 quadruplets, 1 quintuplet, 1 sextuplet, and 1 octuplet), which, in all but one, were caused by artificial induction of ovulation only. In the last few years, however, the contribution of the advanced technologies of assisted reproduction to the increase in multiple births in East Flanders gains in importance. Belgium, it should be noted, has at this time no regulation on the limits of oocytes or embryos to transfer.

The increase in the rate of multiple pregnancies represents an important public health problem because, if this trend continues, the rates of very preterm births and very-low-birthweight infants in the population will undoubtedly continue to rise. The skew to infants with birthweights < 1500 g compared with singletons is dramatic. These very-low-birthweight infants have a high perinatal mortality and morbidity, including permanent handicaps. They represent a high cost to the community in terms of an increased patient load to the neonatal intensive care units and an increased number of lifelong physical and mental handicaps (8–10).

The fact that a number of monozygotic twins are born after artificial induction of ovulation and that the frequency of zygotic division after artificial induction of ovulation is higher than after naturally occurring ovulation is of fundamental biological importance: it is clear that hormonal induction of ovulation acts not only on the ovary but also on the zygote, in as much as it stimulates its division.

In contrast to common expectation, all these twin and triplet pregnancies were not dizygotic or trizygotic. As shown in Table 1 and confirming earlier reports (4, 6), the frequency of zygotic splitting after artificial induction of ovulation (1.0%) is higher than observed after spontaneous ovulation (0.45%). There is no significant difference in the rate of zygotic division between the pregnancies that resulted from artificial induction of ovulation only and those that occurred after IVF-ET, GIFT, or ZIFT, nor between the pregnancies induced by clomiphene citrate and those induced by gonadotropins.

Comparing the birthweight distribution between singletons and twins, this study shows that the percentages of twins with birthweights between 1500 and 2500 g and birthweights < 1500 g are >10 times those for singletons. This relationship is even more dramatic for triplets: 27% have birthweights < 1500 g and fewer than 10% have birthweights > 2500 g. The birthweight data for singletons born in 1987 through 1989 were obtained from the Study Centre for Perinatal Epidemiology, which, during this time, covered approximately one half of Flemish births (7).

**DISCUSSION**

The fact that a number of monozygotic twins are born after artificial induction of ovulation and that the frequency of zygotic division after artificial induction of ovulation is higher than after naturally occurring ovulation is of fundamental biological importance: it is clear that hormonal induction of ovulation acts not only on the ovary but also on the zygote, in as much as it stimulates its division. Until now, no conditions were known under which the monozygotic twinning rate could be influenced. Clomiphene citrate and/or gonadotropins are the first drugs to show such action.

**Table 1 Zygosity of Twins and Triplets Born After Artificial Induction of Ovulation***

<table>
<thead>
<tr>
<th></th>
<th>Twins</th>
<th>Triplets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monozygotic</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Dizygotic</td>
<td>347</td>
<td>7†</td>
</tr>
<tr>
<td>Trizygotic</td>
<td></td>
<td>57</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>373</td>
<td>64</td>
</tr>
</tbody>
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† Frequency of zygotic splitting in iatrogenic DZ twinning:

$$\frac{\text{number of dizygotic triplets}}{2 \times \text{number of (dizygotic twins + dizygotic triplets)}} = \frac{7}{2 \times (347 + 7)} = 0.01$$
who have contributed their cases to the East Flanders Prospective Twin Survey.

REFERENCES