

Modes of conception and multiple pregnancy: a national survey of babies born during one week in 2003 in the United Kingdom

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Objective: To collect data on every baby born in one week in the United Kingdom with respect to mode of conception, multiplicity of pregnancy, and outcome.

Design: A questionnaire completed by the midwife birth attendant.

Setting: All maternity units in the United Kingdom.

Patient(s): All mothers delivering during the week of April 6–12, 2003.

Intervention(s): Questionnaire survey.

Main Outcome Measure(s): Mode of conception (both spontaneous and assisted), type of fertility treatment, multiplicity of pregnancy, mode of delivery, gestational age, and fetal outcome.

Result(s): Data were received from 178 maternity units (72.7%) on 6,913 deliveries: 6,812 (98.54%) were singleton, 100 (1.45%) twin, and 1 (0.01%) triplet. In total, 7,015 babies were born. Of all pregnancies, 6,638 (96%) (including the only triplet) were conceived spontaneously and 133 (1.9%) with assistance. The multiple pregnancy rate was significantly greater in assisted (13.5%) than in spontaneous (1.2%) conceptions. Of the multiple pregnancies after fertility treatment, 16.7% resulted from clomifene citrate therapy, 72.2% from IVF or frozen embryo replacements (FET), and 5.6% from superovulation with intrauterine insemination (IUI). The multiple pregnancy rate after IVF/FET (26%) was significantly higher than the one after clomifene citrate therapy (7.3%). In total, 41 babies were born after clomifene citrate therapy, 50 after IVF/FET, and eight after superovulation IUI. The live birth rate was higher for singleton (98.2%) than multiple pregnancies (93.6%).

Conclusion(s): Multiple pregnancy from IVF and related treatments remains a significant problem and contributes a greater burden than ovulation induction therapies. (Fertil Steril® 2005;84:1727–32. ©2005 by American Society for Reproductive Medicine.)

Key Words: Infertility, multiple pregnancy, in vitro fertilization, ovulation induction, gonadotropin therapy, clomifene citrate

The rate of multiple pregnancy has an increased correlation with the introduction of assisted conception technologies, although now, with greater awareness, the trend should be reversing. Multiple pregnancies carry significantly increased risks to the fetus and mother. Premature delivery is three times as common with twins as with singleton pregnancies, and the risk of all other obstetric complications is increased (e.g., pre-eclampsia, abnormal bleeding, etc.). Triplet and quadruplet pregnancies further magnify the risks, with a mean gestation at delivery of 33.5 and 31.5 weeks, respectively, and neonatal morbidity increased at least 20-fold (1). Cerebral palsy rates have been reported to be 2.3 per 1,000 singletons, 12.6 per 1,000 surviving twins, and 44.8 per 1,000 triplets (2). In addition to the increase in long-term morbidity in survivors of multiple gestation, there are significant effects on family dynamics and the ability of parents to cope, let alone the potential detriment to any existing children (1, 3).

Assisted conception treatments have led to a dramatic increase in the rates of multiple pregnancy as a result of the

transfer of multiple embryos in what is now realized as the mistaken belief that the chance of pregnancy is increased. In the United Kingdom (UK), the incidence of twins has risen from 9.0 per 1,000 births in 1985 to 14.2 per 1,000 births in 2000, and the incidence of triplets has quadrupled in the same time period (4). In 2001, 145 in every 10,000 maternities resulted in the birth of twins, while 4 in every 10,000 maternities led to triplets or more. The rates are higher for older women—among women aged over 40, twins accounted for 194 in every 10,000 maternities, and triplets for 11 in every 10,000 maternities. In comparison, for women under 20, twins accounted for 61 in every 10,000 maternities and triplets for less than 1 in every 10,000 maternities (5).

Guidelines in the UK now recommend the routine transfer of no more than two embryos when eggs are collected from women less than 40 years of age during IVF treatments (6–8), although the maximum that may legally be transferred is still three (9). There have been additional moves toward the transfer of single embryos, which is a further attempt at eliminating the risk of multiple pregnancy without significantly reducing the overall chance of a pregnancy (10). Patients can be selected for elective single ET if they are young (≤ 36 years), are in their first or second cycle of

Received February 2, 2005; revised and accepted May 23, 2005.

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treatment, and have at least one good-quality embryo; in addition, there is the potential for the cryopreservation of surplus good-quality embryos (11).

Assisted reproduction technologies (ART) are carefully regulated and monitored in many countries. In the UK, the Human Fertilisation and Embryology Authority (HFEA) collects and publishes annual data from all clinics and renews the annual license of a clinic to practice based on appropriate standards of care. Careful scrutiny is made of the number of embryos transferred and the multiple pregnancy rate of each clinic. Only treatments involving the handling of gametes and embryos in the laboratory, however, are licensed. Unlicensed treatments therefore include ovulation induction both for anovulatory infertility and empirical treatment of “unexplained infertility,” with either clomifene citrate or gonadotropin therapy. Not only are these treatments performed without audit, they are also often carried out without appropriate ultrasound monitoring of the number of follicles that are destined to ovulate. It is these treatments that many now believe are contributing significantly to the overall increase in multiple pregnancies (12).

The last published report from the HFEA report (13) showed that 26.76% of IVF pregnancies were multiple, with a rate of 25.03% twins and 1.73% triplets. There is a paucity of data on the rate of multiple pregnancy after ovulation induction therapies. We therefore set out to survey the rate of multiple pregnancy in all babies born during one week in England, Scotland, Wales, and Northern Ireland. The aim of this study was to ascertain the mode of conception of both singleton and multiple pregnancies and to determine potential differences between those conceived with and without medical assistance.

MATERIALS AND METHODS

A letter of invitation was sent to each of the 245 maternity units in the UK (England, Wales, Scotland, and Northern Ireland). The aim was to collect data on every baby born during the week of April 6–12, 2003. The initial invitation to participate was sent in January, and a letter of reminder was sent 4 weeks before the study week, which included an information pack with a poster for display in each delivery suite and sufficient survey forms for the anticipated number of deliveries for each maternity unit. Nonidentifying data were requested for each baby born to include details of maternal age, parity, mode of conception, delivery details, and fetal outcome. Specifically, information was requested on infertility treatment, when applicable, to ascertain methods used for assisted conception and whether treatment involved the transfer of embryos or ovulation induction therapy. Advice was sought, and because this was a national survey of anonymous data, Institutional Review Board approval was not required.

Analysis of data was performed using the SigmaStat 2.03 computer package (SPSS product, Chicago, IL). The Kolmog-

orov-Smirnov Normality Test was performed for all groups of data. Parametric tests (*t*-test, one-way analysis of variance [ANOVA], etc.) were used for the parametric data and nonparametric (Mann-Whitney rank sum and Kruskal-Wallis one-way ANOVA on ranks) for the nonparametric data and for the parametric data when the conditions for using the parametric test were not met. Multiple comparisons procedures (Tukey test, Dunn’s method) were used when appropriate. The *z*-test or alternatively the χ^2 analysis of contingency tables and Fisher’s exact test were used for comparisons of rates and proportions. The Yates correction applied to calculations. When data were compared for the statistically significant difference, the probability, difference of proportions, and 95% confidence interval were expressed as a decimal fraction.

RESULTS

Replies were received from 205 units—a response rate of 83.7%. Twenty-seven units felt unable to participate in the study, mostly because of the required workload, and information was collected by 178 maternity units, that is, 72.7% of the total. We have scrutinized the units that participated, and they represent a cross section of maternity units around the UK, with an even spread of deliveries from ART and non-ART cycles. Data were received on 6,913 deliveries of which 6,812 (98.54%) were singleton, 100 (1.45%) twin, and one (0.01%) triplet. Thus, a total of 7,015 babies were born.

In 2001 there were 661,616 maternities in England, Wales, Scotland, and Northern Ireland, which if divided by 52 and assuming no seasonal fluctuations indicates that approximately 12,723 deliveries occur each week (Department of Health [5], Scottish Health Statistics [14], Northern Ireland Statistics and Research Agency [15]). Assuming no change in birth rate since 2001, we are likely to have gathered data on approximately 54.5% of deliveries. Of the deliveries in 2001, 651,836 (98.52%) were singleton, 8,484 (1.44%) were twin, and 216 (0.04%) were triplets, which are almost exactly the proportions that we observed, other than a slightly higher annual rate of triplets than in the week that we studied.

Of the 6,913 pregnancies that resulted in deliveries during the second week of April 2003, 6,638 (96%) were conceived spontaneously, 133 (1.9%) were conceived with assistance, and information was not provided for 142 (2.1%). The mode of conception in relation to multiplicity is recorded in Table 1. The only triplet pregnancy was conceived spontaneously. The rate of multiple pregnancy was significantly greater in assisted (18/133, 13.5%) compared with spontaneous (82/6,638, 1.2%) conceptions (difference, 0.123; 95% confidence interval [CI], 0.102–0.144; $P < .001$). The type of fertility therapies that were employed is outlined in Table 2; these are subdivided into the main therapeutic groups for ease of analysis.

Of all the multiple pregnancies that resulted from fertility treatment, 16.7% were as a result of clomifene citrate ther-

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