Comparison of outcome of pregnancy after intra-uterine insemination (IUI) and IVF

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INTRODUCTION: Pregnancy outcome after IVF has been shown to be worse than after spontaneous conception. There is discussion as to whether this results from the technique itself or the patient characteristics. This study compares pregnancy outcome after IVF and intra-uterine insemination (IUI) in a matched patient group.

METHODS: Data were obtained from our IVF and IUI databases (1997–2001). Matching was performed for maternal age, parity and plurality, and 126 IUI pregnancies were compared with 126 IVF pregnancies. Outcome variables were pregnancy duration, birth weight, Caesarean section rates, preterm contraction rates, neonatal intensive care unit admission, Apgar score, blood loss rates and maternal hypertension.

RESULTS: None of the analysed parameters was statistically different between the groups. CONCLUSION: This matched case–control study does not show different pregnancy outcomes after IVF and IUI. Since there is no reason to believe that the IUI technique in itself leads to an increased obstetric or neonatal risk, this study suggests that the worse pregnancy outcome after IVF as compared with spontaneous conceptions is due to the specific patient characteristics, rather than to the use of IVF itself.

Key words: intra-uterine insemination/IVF/perinatal outcome/pregnancy

Introduction

Since the widespread introduction of assisted reproductive technology (ART) in infertility treatment, several studies have shown a poorer perinatal outcome after ART than after spontaneous conceptions (Rufat et al., 1994; Gissler et al., 1995; Bergh et al., 1999; Schieve et al., 2002, 2004). IVF has been shown to lead to an increase in premature birth rates and to low birth weight (Tanbo et al., 1995; Verlaenen et al., 1995; Schieve et al., 2002). In some studies, the incidence of miscarriage, ectopic pregnancy and bleeding also seems to be increased after IVF (Craft and Al-Shawaf, 1991; Dhont et al., 1999; Pezeshki et al., 2000). Moreover, concern has arisen about the possibly increased risk of chromosomal and other congenital anomalies in the children born after ART (Bonduelle et al., 1995, 1998; for a review see Kurinczuk et al., 2004). Also, not much is known about the long-term effects such as neuromotor or psychological outcome of the children born after IVF and related techniques, although a recent Swedish registry study has shown that IVF singletons have a higher risk of cerebral palsy than spontaneously conceived singletons (Stromberg et al., 2002). Overall, there is redundant evidence from the literature that perinatal and neonatal outcome is worse after ART than after spontaneous conception (for a review see Helmerhorst et al., 2004). Also ART pregnancies are managed in a more careful way than spontaneously occurring pregnancies, and the Caesarean section rates are higher, whether or not there is a medical indication (Rufat et al., 1994; Gissler et al., 1995; Tanbo et al., 1995; Verlaenen et al., 1995; Bergh et al., 1999; Dhont et al., 1999; Ozturk et al., 2002).

One of the main reasons for the increased risk of ART pregnancies is the high rate of multiple pregnancies after ART (Craft and Al-Shawaf, 1991; Tanbo et al., 1995; Bernasko et al., 1997; Bergh et al., 1999; Draper et al., 1999; ESHRE Capri Workshop Group, 2000; Ozturk et al., 2001; Adamson and Baker, 2004) but, even after correction for this confounder, the outcome remains of poorer quality (Wang et al., 1994, Wang et al., 2002; Tanbo et al., 1995; Bergh et al., 1999; Dhont et al., 1999; Tarlatzis and Grimbizis, 1999; Schieve et al., 2002; Jackson et al., 2004). An important question is whether this is to be attributed to the characteristics of the patients (maternal age, parity, duration of infertility, etc.) or to the ART procedures themselves. Indeed, Wang et al. (2002) have reported a 50% higher prematurity rate after intra-uterine insemination (IUI) as well as after other forms of ART. Also in a recent retrospective study comparing IUI pregnancies with spontaneous conceptions (Gaudoin et al., 2003), patients treated with IUI were at increased risk for preterm birth and low birth weight infants. On the other hand, Nuojua-Huttunen et al. (1999)
have shown that IUI in itself does not lead to any increase in perinatal risk, except when hormonal stimulation is used, resulting in multiple pregnancies. Specific characteristics of an infertility population, such as higher maternal age and lower parity, are well known obstetric risk factors, so that it could a priori be expected that pregnancy outcome is poor in this group, whatever the method of treatment used to obtain a pregnancy (Craft and Al Shawaf, 1991; Gissler et al., 1995; Verlaenen et al., 1995; Dhont et al., 1999; Westergaard et al., 1999; Olivennes et al., 2002; Wang et al., 2002). Some studies suggest that the infertility in itself could increase the risks for low birth weight and preterm birth (Craft and Al Shawaf, 1991; Draper et al., 1999; Olivennes et al., 2002; Wang et al., 2002), although not all authors agree on this (Tanbo et al., 1995). In a recent literature review (Lambert, 2003), it is also strongly suggested that indeed the infertility itself is to be held responsible for the worse perinatal outcome, both after IVF and after IUI.

The present study is a matched case–control study which aims to compare two ART methods, namely IVF and IUI, as treatment methods in an infertile population. The purpose of this study is to analyse whether IVF has an intrinsically higher perinatal risk than IUI in this matched patient population, so that confounding factors, such as life-style and infertility-related issues, are eliminated, and possible differences are not to be attributed to patient characteristics, but to the technique itself.

Materials and methods

**IUI**

Patients undergoing IUI were treated with donor sperm in cases of male infertility (especially patients refusing IVF), or with the husband’s sperm in other indications (mild male infertility, mild endometriosis and unexplained infertility). Only spontaneous cycles or cycles in which clomiphene citrate was used (100 mg from cycle day 5 onwards after discontinuation of the oral contraceptive pill) were included for analysis. In all patients, the same procedure was followed. Cycle monitoring allowed detection of the presence of one or more pre-ovulatory follicles, and 5000 IU of HCG (Pregnyl, Organon, The Netherlands) was administered when the leading follicle had attained a mean diameter of at least 18 mm. Insemination was carried out 38 h later. In cases where a premature LH surge had been detected on the day of HCG administration, insemination took place 14 and 38 h after HCG. Sperm was prepared in the laboratory by centrifugation and swim-up, and transferred into the uterine cavity by means of a flexible catheter. No luteal supplementation was given.

**IVF**

Only patients who were treated with IVF for mild male or unexplained infertility or endometriosis were analysed. No severe male infertility cases undergoing ICSI were included in the present study. All patients underwent controlled ovarian stimulation after cycle synchronization with a standard contraceptive pill for 2–6 weeks. In >90% of our patients, a short GnRH agonist protocol was used, consisting of 0.1 mg of triptorelin (Decapeptyl, Ipsen, France), injected s.c. from day 5 onwards after discontinuation of the oral contraceptive. This was followed by HMG (either Humegon, Organon, The Netherlands or Menopur, Ferring, Germany) or recombinant FSH (either Gonal-F, Serono, Switzerland or Puregon, Organon, The Netherlands) from day 5 onwards. The starting dose in a first cycle was always 225 IU, but this dose was adjusted after 7 days, according to the individual response of the patient. The follicular phase was monitored by means of transvaginal ultrasound scanning of the ovaries and serum estradiol measurements (the latter especially in poor responders and in patients at risk for the ovarian hyperstimulation syndrome).

In ~10% of our patients, a long GnRH agonist protocol was used. Triptorelin (Decapeptyl, Ipsen, France) 3.75 mg i.m. was administered when the patient had been taking her contraceptive pill for at least 2 weeks. Another 2 weeks after triptorelin administration she could stop the pill and start 1 week later with the gonadotrophin injections. Monitoring was similar to the monitoring in patients treated with the short protocol.

HCG (Pregnyl, Organon, The Netherlands) 5000 or 10000 IU was administered when half of all mature follicles had reached a mean diameter of at least 20 mm, measured in two planes. At 34 h after HCG injection, oocytes were retrieved by transvaginal ultrasound-guided follicular puncture under general anaesthesia using propofol. IVF was performed as described elsewhere (Laverge et al., 2001). No major changes in techniques or culture conditions were introduced during the study period.

In 1997 we started transferring one embryo in good prognosis cases, especially in patients of <37 years old, in first or second treatment cycles and when at least one excellent or good quality embryo was present (De Sutter et al., 2003). In other cases, two embryos were transferred.

The luteal phase was supported by either progesterone i.m. injections 50 mg daily or intravaginally 3 x 200 mg (Utrogestan, Piette Laboratories, Belgium), or three injections of 1500 IU of HCG (Pregnyl, Organon, The Netherlands).

**Pregnancy detection**

Pregnancy was diagnosed by the detection of a positive serum HCG at least 14 days after insemination or embryo transfer, followed by a rise in HCG levels. All patients received a transvaginal ultrasound scan between 6 and 7 weeks to differentiate between biochemical and clinical (presence of an intra-uterine fetal sac) pregnancies and to diagnose ectopic implantations. All pregnancies were monitored further by transvaginal ultrasound until 12 weeks amenorrhoea. Both singleton and twin pregnancies were included. Pregnancy duration was calculated exactly from the date of insemination or of oocyte retrieval.

**Pregnancy outcome parameters**

Primary pregnancy outcome parameters recorded were duration of pregnancy, birth weight, perinatal mortality, presentation of the child and Caesarean section rates. Secondary outcome measures were incidence of preterm contractions, stay in a neonatological intensive care unit, Apgar score, incidence of blood loss in the first, second and third trimester, and maternal hypertension. A preterm delivery was defined as a delivery at a pregnancy duration of <37 completed weeks, and low birth weight as <2500 g. Perinatal mortality rates included stillbirths with a birth weight of ≥500 g and neonatal deaths during the first postnatal week.

**Patient selection and matching**

Since our IVF database is larger and more complete than the IUI database, we started by selecting all patients having become pregnant after IUI and treated between January 1997 and December 2001. In total, 413 patients were retrieved from the IUI database and, in order to gather the necessary detailed data for the present
study, 385 questionnaires were sent to couples for whom the address was available. We received 182 replies and could include 166 patients in the study. Sixteen questionnaires were incomplete and therefore rejected. For these 166 patients, a match was searched for in the IVF database on the basis of the following criteria: maternal age identical ± 2 years, parity and plurality identical, and date of delivery identical ± 31 days for singletons and ± 365 days for twins. Matching was not done for fetal sex, because it was not possible to find an appropriate control for each case. Fetal sex rates did, however, not differ between both groups. Each match was unique and for 40 cases no control could be found so that the final study was performed on 126 pairs of patients, 112 singletons and 14 twins each after IVF and after IUI.

Statistics
Because none of the analysed parameters were normally distributed, non-parametric tests were used, namely the Wilcoxon paired test for continuous parameters and the McNemar paired test for categorical variables. Apgar scores were compared using Fisher’s exact test, using a cut-off level of 7. Because of the matched case–control design, sample size was sufficient to reach enough power to compare the primary outcome parameters, anticipating the same percentage of premature births after IUI as in the general population and estimating a 3-fold increase after IVF. The level of statistical significance was set at \( P = 0.05 \). For the analysis, S-PLUS® 6.1 for Windows was used.

Results
To get a general idea about the populations from which the paired samples were taken, we first performed an analysis on the complete IVF and IUI databases. The mean age of the IVF mothers was 31.7 ± 1.8 and of the IUI mothers 30.3 ± 3.6 years (\( P < 0.0001 \)). The percentage of mothers above 35 years of age was 10.8% in the IVF group and 18.4% in the IVF group (\( P < 0.001 \)). Mean pregnancy duration was 268.4 ± 4.3 days for IVF and 271.7 ± 5.5 days for IUI (\( P < 0.001 \)). In the IVF group, 74% of pregnant women were primiparous, whereas this was 62% in the IUI group (\( P < 0.001 \)). In both groups, exactly 27% of women delivered by Caesarean section. After IVF, 25% of all pregnancies were twins whereas after IUI this was only 9% (\( P < 0.0001 \)).

In the case–control analysis, maternal age, parity and plurality were similar in both groups because of the matching procedure [30.3 ± 3.6 years in the IUI group versus 29.3 ± 4.3 in the IVF group (NS); 91 primiparous and 31 secundiparous women in each group; 112 singletons and 14 twins in each group]. Fetal sex was not matched for, and in the IUI group 55.6% of all children were boys, compared with 43.7% in the IVF group (\( P = 0.115 \)). Congenital anomalies and perinatal deaths were rare events so that no statistical comparison was made (there was one perinatal death in the IUI and two in the IVF group, and four congenital anomalies in the IUI and two in the IVF group, both NS).

Comparisons for primary and secondary outcome measures are shown in Table I. None of the studied parameters was significantly different between groups. Twenty out of 126 babies born after IUI had a low birth weight (15.9%), with two children <1500 g. Of the singletons, only 9.8% weighted <2500 g. In the IVF group, 17 babies had a low birth weight (13.5%; 9.3% of singletons) and one child weighed <1500 g. These differences are not statistically significant.

Discussion
In most published studies assessing ART outcome, a high incidence of prematurity and low birth weight is found. In the present study, these rates are also higher than in the general population. According to the data of the Flemish Study centre for perinatal epidemiology (Studiecentrum voor perinatale epidemiologie, SPE), which is a register of perinatal data of all deliveries in Flanders, 7.3% of all children born weighed <2500 g in 2002 (SPE, 2002). In our study sample, this incidence was exactly double and even for the singletons alone it still was higher than the population mean. Also the incidence of preterm birth was more than double in our study population than in the general population, which is 7.3% (SPE, 2002). For the singletons alone, 10.9% of all deliveries were preterm in the IUI group, but interestingly enough only 7.1% of IVF singletons were born before 37 weeks, which is comparable with the rate of the general population. In our study group, 27% of all deliveries were by means of Caesarean section, while this is only 17.1% in the global Flemish population (SPE, 2002). Although we did not analyse the indication for the Caesarean section, multiplicity, maternal age and more ‘careful’ obstetric follow-up probably account for this increased rate, which interestingly is also higher in the IUI group, and not only in the IVF patients.

It is clear that the global poorer obstetric and perinatal outcome in our study is mostly due to the included twin pregnancies. According to the SPE (2002), only 1.98% of all deliveries in the overall population in our country were twin deliveries, whereas in our data set this rate was 25% for IVF and 9% for IUI. In our matched analysis, it was 9.5%, which is our exact twinning rate after IUI. If the real twinning rate
after IVF had been used for the analysis, the outcome after IVF would obviously have been even worse. The matching procedure did not allow comparison of the real multiple pregnancy rates after both methods of treatment. Anyway, the high rate of multiple pregnancies obviously explains much of the worse outcome after ART as compared with spontaneous conceptions. Fortunately, since 2003, the number of embryos to be transferred in IVF in Belgium has been restricted by law (Royal Decree, 2003), and the multiple pregnancy rate after IVF is expected to decrease in the coming years. Iatrogenic multiple pregnancies will, however, continue to occur as long as no efforts are made to set the correct indications for the use of controlled ovarian stimulation in non-IVF treatment (Kaplan et al., 2002).

The present study did not analyse miscarriage and ectopic pregnancy rates after IUI and IVF, because the groups were matched on date of delivery, and therefore only ongoing pregnancies were included. Blood loss in the first trimester, however, was analysed and, similarly to Pezehski et al. (2000), we also found a higher incidences than in the general population, even after IUI. After IVF, it has been suggested that an abnormal implantation process or subclinical vanishing twins could explain the increased incidence of bleeding during the first trimester, but it is not clear why this would be the case after IUI.

Our data contradict the conclusions of Wang et al. (2002), who detected differences in incidence of preterm birth after different methods of infertility treatment. However, that study was not a matched case–control study, and other confounding factors influencing prematurity may not have been accounted for. The comparison of two methods of treatment in the same patient population is the only way to detect possible intrinsic risks of the procedures themselves. One can expect that matching of the groups eliminates not only possible bias due to age, parity and plurality, but also that due to numerous other possible confounders which are hard to study. Our database does not include registration of life-style factors, such as smoking or alcohol consumption, dietary habits, education and professional activities, and other factors which are known to influence obstetric and neonatal outcome. Since in our programme couples with mild male or unexplained infertility and mild endometriosis are always treated first with IUI before IVF is started, there is a more than reasonable chance that these immeasurable confounders are not different between our IUI and IVF groups.

The present study is the second to compare obstetric and perinatal outcome in a matched case–control setting between IUI and IVF. As in the study of Nuojua-Huttunen et al. (1999), our data indicate that there are no differences between both groups. If anything, the IVF group even performs better than the IUI group. This finding strongly supports the notion that if pregnancy outcome after ART is worse than after spontaneous conception, this is due to the specific characteristics of the population, and not to the methods of treatment themselves. Of course, it could be that both IUI and IVF hold specific risks in themselves. There are many hypotheses which have tried to explain the worse outcome after IVF and, theoretically, even IUI may offer increased risks because of the in vitro sperm preparation and the insemination act, but this is not very probable. From our study, it seems that not only IVF but also IUI pregnancies thus perform less well than spontaneous pregnancies and this should be a reason for national registries of IUI, careful follow-up of the pregnancies and larger studies to analyse the obstetric and neonatal outcome after IUI.

References


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