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Obstetric and Perinatal Outcomes in Multiple Pregnancies Conceived with Assisted Reproduction Techniques

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Summary

The results of studies comparing obstetric and perinatal evolution of ART twins versus spontaneously-conceived twins are controversial.

We performed a retrospective case-control study of 148 multiple pregnancies monitored at the University Hospital of the Canary Islands during 1996-2002. Of these, 72 were conceived after ovarian stimulation and ART treatment, considered as the study group, while 76 were spontaneously conceived, considered as the control group.

Mean maternal age (33.3 ± 4.35 vs 30.0 ± 4.56 , $p < 0.001$) and the number of women >35 years were significantly higher in the ART group than in the spontaneous group (74.2% vs 25.8%, $p < 0.001$).

The percentage of women with pregnancy complications was higher in the ART group (34.7% vs 21.1%, $p < 0.04$), as was the percentage of complications such as increased risk of preterm delivery (12.5% vs 11.8%), preeclampsia (6.9% vs 3.9%), uterine bleeding (2.8% vs 1.3%), and diabetes (12.5% vs 3.9%).

Mean gestational age was significantly lower in the study group than in the control group and the percentage of women who delivered before 34 weeks' gestation was significantly higher (34.87 vs 35.97, $p < 0.05$).

Cesarean section rate was higher in the ART group than in the spontaneous group (88.8% vs 69.7%, $p < 0.01$).

Mean birth-weight was not significantly different between the groups (2213.36 vs 2216.26 gr.), nor was the 5-minute Apgar score of <7 (6.0% vs 8.6%).

In conclusion, the women with multiple pregnancies conceived by assisted reproductive techniques were older, had more complications during pregnancy, had more preterm deliveries and were more likely to undergo elective caesarean delivery, although neonatal outcomes were comparable with those of spontaneously conceived newborns.

Introduction

The number of multiple pregnancies (MPs) is higher in assisted reproduction therapy (ART) cycles owing to the need for ovarian overstimulation and excessive embryo transfer in an attempt to achieve reasonable pregnancy rates (1.-Kerin 1983)

The latest European data are from the year 2000, with the following percentages of MPs conceived in 142,174 ART cycles: 24.4% twins, 2.0% triplets and 0.04% quadruplets. The incidence of MPs following IVF or ICSI is 26.9%, as in previous years, although the number of triplets has decreased (2.- Andersen N. 2004).

For USA, the rate of MPs has increased from 11.2% to 13.6%, with ART-conceived pregnancies accounting for 42.5% of all MPs and 17.7% of quadruplets (3.- Reynolds, 2003).

Multiparity entails greater maternal-fetal morbidity and mortality (4.- Makhseed M. 1998, 5.- Sebire 2001), with obstetric complications such as uterine bleeding, late miscarriage, premature birth, low newborn birthweight and intrauterine fetal death. It also increases the burden of neonatal care for pathologies like cerebral palsy or necrotizing enterocolitis (6.- Schenker, 1994), and the corresponding costs, bearing in mind that average hospital costs associated with multiparity are higher than average costs of IVF or ICSI (7.- Callahan 1994).

The results of studies comparing obstetric and perinatal evolution of ART twins versus spontaneously-conceived twins are controversial.

In a previous study, we found greater obstetric and perinatal risk in ART pregnancies in general, which we attributed to increased multiparity (8.- Rodríguez 2001). In the present study this variable was introduced to allow comparison of outcomes between ART-conceived and spontaneously-conceived multiple pregnancies and resulting newborns.

Patients and Methods

We performed a retrospective case-control study of 148 multiple pregnancies monitored at the University Hospital of the Canary Islands during 1996-2002. Of these, 72 were conceived after ovarian stimulation and ART treatment, considered as the study group, while 76 were spontaneously conceived, considered as the control group.

ART techniques applied were: only ovarian stimulation 5.6%, this with artificial insemination 25% (13.9% male partner and 11.1% do-

nor), with IVF in 40.3% and ICSI in 29.1%.

The following maternal data were analyzed: age, parity, pathology during pregnancy and duration of pregnancy. Complications included uterine bleeding, pregnancy-induced diabetes or hypertension and threatened preterm delivery or premature birth.

We analyzed the evolution of 52 twins and 20 triplets of ART patients (the study group), and 76 twins conceived spontaneously (controls). The following newborn data were recorded: gestational age, 5-minute Apgar, birthweight, neonatal ICU admission, complications, congenital malformation and neonatal death.

Gestational age was determined using the date of embryo transfer and/or ultrasound studies. Newborn birthweight was classified as low if it was < 2500 grams and very low if it was < 1500 grams. Birth was classified as eutócico or by forceps, caesarean or internal version and breech extraction.

We compared the gestational data obtained from the study group with those of the controls, as well as the data relating to the resulting newborns in both groups.

Statistical analysis was performed using Windows SPSS 10.2. We used Pearson's χ^2 for the contrast of proportions and Student's t test for the comparison of averages. Significance was defined as <0.05.

Results

We performed a retrospective case-control study of 148 multiple pregnancies monitored at the University Hospital of the Canary Islands during 1996-2002. Of these, 72 were conceived after ovarian stimulation and ART treatment, considered as the study group, while 76 were spontaneously conceived, considered as the control group.

Mean maternal age (33.3 ± 4.35 vs 30.0 ± 4.56 , $p < 0.001$) and the number of women >35 years were significantly higher in the ART group than in the spontaneous group (74.2% vs 25.8%, $p < 0.001$).

The percentage of women with pregnancy complications was higher in the ART group (34.7% vs 21.1%, $p < 0.04$), as was the percentage of complications such as increased risk of preterm delivery (12.5% vs 11.8%), preeclampsia (6.9% vs 3.9%), uterine bleeding (2.8% vs 1.3%), and diabetes (12.5% vs 3.9%).

Mean gestational age was significantly lower in the study group than in the control group and the percentage of women who delivered before 34 weeks' gestation was significantly higher (34.87 vs 35.97, $p < 0.05$).

Cesarean section rate was higher in the ART group than in the spontaneous group (88.8% vs 69.7%, $p < 0.01$).

Mean birth-weight was not significantly different between the groups (2213.36 vs 2216.26 gr.), nor was the 5-minute Apgar score of <7 (6.0% vs 8.6%).

Fewer neonates from the study group were admitted to the neonatal ICU (40.0% vs 44.3%), and the mean stay in this unit was similar (9.54 vs 8.73 days). The incidence of respiratory disorders (14.8% vs 15.3%, NS), and neurologic disorders (0.9% vs 5.3%) were not significantly different.

Globally, no complications were recorded in 50% of all first neonates ($p < 0.001$), 1.2% of the second, and 6.7% of the third neonate.

There were no differences in kind of neonatal complication between the groups (NS). Malformation rate did not differ, with 6.6% neonates affected, of whom 28.6% had cardiovascular, 4.8% neurologic, 4.7% intestinal, 9.5% urological, 19% osteoarticular, 4.8% hypoplasia palate, and the same proportion of umbilical hernia and epididymary cyst.

We found no difference in intrauterine death rate between the groups: 6.5% in ART group and 5.9% in the spontaneous group. The death rate of the first twin was 4.1%, the second was 6.9%, and in triplets the third was 17.6% (NS).

Neonatal death rate was 1.2% (0.0% vs 2.3%, NS): 0.8% for the first twin, 1.7% for the second twin, and in triplets the third neonate was 0%.

Discussion

An important advantage of this study is that only one hospital, and one obstetric and gynaecology department was involved, and the reproductive and pregnancy management was similar in all patients.

Several reports have suggested that assisted conception poses an added risk in pregnancy with higher rates of intrauterine growth retardation, pre-term delivery and perinatal loss, even among singleton pregnancies (9.- Daniel 2000, 10.- McFaul 1993).

Multiple pregnancy has an increased number of adverse effects like earlier delivery, more complicated pregnancy and delivery, and more intrauterine growth retardation (11.- ESHRE Capri, 2000).

In this study we found increased risk for adverse outcomes in assisted reproduction vs spontaneously conceived multiple pregnancies, with more pregnancy complications, higher incidence of preterm deliveries and caesarean section. Other studies have demonstrated that ART pregnancies carry an increased risk of complication and preterm deliveries, low birth weight and perinatal mortality (12.-IVFNAT 1995). The main reason may be that women undergoing ART procedures are older and primiparous who have more pregnancy complications, caesarean sections and neonates with lower birth weight (9.- Daniel 2000). Indeed, in our study, women from the ART group were three years older than the spontaneous group, as in other publications (13.- Dhont 1999, 14.- Luke 2004), and also the incidence of multiple pregnancy that increases the obstetric risk (15.- Kozinsky 2003).

We found higher incidences of pregnancy-induced hypertension and

diabetes, as in previous studies (16.- Tan), although others do not confirm these results (14.- Luke 2004, 15.- Kozinsky 2003).

In other studies (16.- Tan), like ours, the mean gestational age at delivery was significantly lower in the ART group. However, Kozinsky (15.- 2003) found lower rates after ART, but without any statistical difference. Other authors did not find the same results (13.- Dhont 1999, 17.- Reubinoff 1997). Some investigators suggest that infertility per se may increase the risk of low birth rate, small for gestational age and preterm birth (18.- Ghazi 1991), but others consider that ART may affect adverse outcome (19.-Petersen 1995).

Caesarean delivery rate in our ART patients was higher than in the control group. Some of these caesarean deliveries were not performed following medical indications but rather because of overconcern of the patient and the obstetrician, with increased elective caesarean delivery due to the older age of primiparous women. Other factors which may have contributed to the higher rate of caesarean delivery have been previously described, such as when ART is necessary there is a great anxiety in both parents and obstetricians until pregnancy ends successfully (15.- Kozinsky 2003, 17.- Reubinoff 1997, 20- Bernasko1997), and also because of the known higher incidence of multiple pregnancies.

Birth-weight was not different between groups. Lynch (21.- 2003) found no difference in low newborn birthweight, retarded growth or preterm birth, but other investigators report that the use of ART accounts for a disproportionate number of low birth-weight and very low birth-weight babies, partly due to multiple gestation and partly due to the ART technique used. (22.- Schieve 2002).

Dhont (13.- 1999) found that the perinatal outcome of ART twin pregnancies is similar to that of normally conceived twins, considering differences in perinatal mortality, neonatal ICU admission and incidence of congenital malformations (3.1% and 2.4%). We obtained the same results, but the proportion of neonates with malformation was higher without differences in ART or spontaneous neonates, as other authors have noted (16.- Tan, 23.- Rufat 1994).

In our study the first twin had fewer complications than the second or third newborn, with poorer outcome than that of the first twin (24.- Fowler 1991), for both groups.

We found no differences in death rate between the groups, as did other authors (13.- Dhont 1999, 16.- Tan, 17.- Reubinoff 1997). Daniel (9.- 2000) find increased death of the second twin.

In conclusion, the women with multiple pregnancies conceived by assisted reproductive techniques were older, had more complications during pregnancy, had more preterm deliveries and were more likely to undergo elective caesarean delivery, although neonatal outcomes were comparable with those of spontaneously conceived newborns.

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