Trizygotic quintuplet pregnancy following simultaneous embryo splitting in an oocyte donation cycle

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Received: 8 May 2005 / Accepted: 3 January 2006 / Published online: 20 May 2006
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Abstract

Purpose To report a trizygotic quintuplet pregnancy following simultaneous embryo splitting in an oocyte donation cycle after transfer of 3 embryos.

Methods A 40-year-old Caucasian female G3P1 with two previous spontaneous abortions and diminished ovarian reserve presented for IVF. The patient underwent an oocyte donation cycle secondary to diminished ovarian reserve. Three embryos were transferred per patient request.

Results The three embryo transfer resulted in a trizygotic quintuplet pregnancy. Selective embryo reduction was performed at 11 weeks leaving a dizygotic twin gestation. The patient underwent SVD, or spontaneous vaginal delivery at 36 weeks gestation with respective weights and apgars of 2673 g (apgars 7(1), 9(5)) and 2722 g (apgars 7(1), 9(5)). The twins are presently doing well without complications.

Conclusions Although rare, the possibility of simultaneous embryo splitting must be factored into determining number of embryos for fresh transfer.

Keywords Multiple gestation · Embryo splitting · Monozygotic · Quintuplet pregnancy

Introduction

The increased incidence of multiple gestations that is seen with assisted reproduction is a major concern. Multiples are linked to an increased rate of preterm delivery, cerebral palsy, and perinatal death. Monozygotic twins, thought to occur

naturally in about 0.42% of all deliveries, carry additional risks over those of dizygotic twins.

Of particular concern to reproductive endocrinologists is the apparent increase in monozygotic twins resulting from IVF treatment. Previous reports have linked the higher rates of monozygotic twins to ovulation induction itself, in vitro culture conditions, blastocyst culture, and micromanipulation including assisted hatching.

We report the case of a trizygotic quintuplet pregnancy resulting from a double monozygotic twinning. This pregnancy was achieved after a donor IVF/ICSI cycle.

Case report

The patient, a 40 year old Caucasian female, gravida 3, para 1, SAB 2, underwent a donor IVF/ICSI cycle.

The selected donor was a 26 year old G3P2SAB2 female with a history of two prior donor cycles, one of which resulted in a singleton pregnancy. She had no family history of twin pregnancies.

Following pituitary desensitization with Lupron the patient was started on a regimen of estrogen replacement using estradiol patches with the addition of progesterone on the day prior to donor oocyte retrieval.

The donor underwent a long Lupron cycle with Follistim and had 4 oocytes retrieved. Three oocytes fertilized following ICSI, and at 48 hr, three 4-cell, grade 1 embryos, were placed in the patient's uterus. The couple elected to transfer three embryos despite our recommendation that only two embryos be transferred. The couple was counseled regarding the potential increased risk for multiple gestations with three embryos transferred.

Two weeks following embryo transfer the patient's initial β -hCG was 655 IU/L. A transvaginal ultrasound

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performed 4 weeks post-transfer showed 4 gestational sacs. A repeat ultrasound one week later demonstrated a trizygotic quintuplet pregnancy. The risks of preterm delivery and its attendant consequences as well as the possibility of multifetal pregnancy reduction were discussed and MFM and psychological counseling consults were arranged. An ultrasound performed at the time of the MFM consult at 8 weeks gestational age demonstrated 4 sacs. One sac was empty, one held a singleton gestation, while each of the other two sacs contained twins. In the twin sacs a single layer dividing membrane through each of the twin sacs suggested these were two sets of monochorionic, diamniotic twins, which was strongly suggestive of simultaneous embryo splitting (Fig. 1a–d). Subsequently, the couple requested and underwent embryo reduction to a twin pregnancy. At 36 weeks gestational age, the patient underwent a spontaneous vaginal delivery of twins with weights and apgars of 2673 g (apgars 7¹, 9⁵) and 2722 g (apgars 7¹, 9⁵)

Discussion

The problems of increased twinning, both monozygotic and dizygotic, with ART pose a challenge to reproductive endocrinologists. In the present case the patient underwent a donor IVF cycle with ICSI. It is unclear exactly what lead to the double twinning, but as mentioned previously, various investigators have implicated IVF treatment itself, culture conditions, blastocyst culture, and zona manipulation procedures. This patient had a fairly routine IVF cycle with donor eggs from a young donor who had no family history of twinning. The only explanatory factor in this case, outside of IVF itself, was the zona manipulation inherent in the ICSI procedure.

Various investigators have postulated an association between zona manipulation and monozygotic twinning. In spontaneous pregnancies one of the few known associations is maternal age. There is a known gradual decrease in the average thickness of the zona pellucida with increasing age. This thinning may allow the blastocyst to protrude at more than one site, which may cause a pinching off of the inner cell mass resulting in twinning. Assisted hatching (AH) may cause a similar situation and Malter and Cohen [1] did observe a blastocyst which twinned spontaneously as it was caught between the thick ridges in a hole artificially made in the zona. Some reports suggest a link between assisted hatching and the rate of monozygotic twinning. However, the largest published series of monozygotic twin sets from a single center failed to show a significant difference between zona manipulated and zona intact embryos [2] and, in fact, there was a non-significant increase in monozygotic twinning with no manipulation compared to when either AH nor ICSI was performed.

In addition to assisted hatching, the other commonly employed procedure that involves manipulation of the zona is ICSI. Our patient did undergo the ICSI procedure. While zona openings with AH are in the range of 25–35 μm in diameter, the defects caused by the ICSI procedure are typically in the 7–8 μm range. Again, some studies support the association of ICSI with monozygotic twinning while others do not. Tarlatzis [3] reported on blastocyst transfers in 125 patients and 181 cycles and found an overall rate of monozygotic twinning or 3.3%. They found that the rate of multiple pregnancies (10.8% vs. 2.6%) and monozygotic twinning (5.9% vs. 0) was increased in the ICSI group compared to the conventional IVF group ($P=0.039$ and $P=0.033$, respectively). Alikani *et al.* [4] reviewed all IVF cycles in their program over the preceding seven years that resulted in a positive fetal heart at 6 weeks gestational age and showed an overall rate of monozygotic twinning of 1.88%. In examining the role of ICSI they reported a rate of monozygotic twinning of 2.35% (31/1537) with ICSI and 1.58% (35/2185) with standard insemination. While the rate was higher with ICSI the difference was not statistically significant. Sills *et al.* [2] reviewed a total of 4493 cycles between January 1995 and March 1998. They reported an overall rate of monozygotic twinning of 1.2% (23/1911). For fresh IVF cycles they reported monozygotic twinning rates of 1.4% (8/589) for AH only, 0.7% (1/151) for ICSI only, 0.9% (7/813) for AH + ICSI, and 2.5% (3/121) for cycles with neither AH or ICSI. Interestingly, the rates of monozygotic twinning were higher in the group with neither AH or ICSI but the differences were not statistically significant ($P=0.4$). Schacter *et al.* [5] reviewed 731 pregnancies achieved after assisted reproductive procedures over the 3 year period from 1997–1999. Including pregnancies from COH, IVF, and ICSI procedures they found an overall rate of monozygotic twinning rate of 0.95% (7/731). For ART cycles this corresponded to a rate of 0.72% (1/139) after conventional IVF, and 0.86% (4/463) after IVF-ICSI/AH suggesting no increased rate after zonal manipulation. Behr *et al.* [6] showed a rate of monozygotic twinning of 5% (10/199) following blastocyst transfer that is higher than the naturally occurring rate. However, they found that the incidence of monozygotic twins appeared to be unrelated to ICSI as they noted a higher number of the monozygotic twins came from conventional IVF rather than ICSI cases.

In ART procedures, multiple embryos are placed in the uterus, leading to an increased probability that monozygotic twinning will occur. A natural rate of twinning of 0.42% multiplied by 3 embryos replaced yields an expected rate of 1.3% that is in keeping with the rates that many of the larger studies report. It would seem that the preponderance of literature would not support the notion that ICSI leads to an increase in monozygotic twinning. However, due to the clinical rarity of monozygotic twinning, the study of the

Fig. 1 Ultrasound of quintuplet pregnancy.

(a) Ultrasound showing 4 of 5 sacs. (b) Ultrasound showing sac with singleton pregnancy (embryo 1). (c) Ultrasound showing sac with monozygotic/diamniotic embryos 2 and 3. (d) Ultrasound showing sac with monozygotic/diamniotic embryos 4 and 5

Fig. 1 Continued

phenomenon is fraught with statistical difficulties. In order to detect meaningful differences with statistical power it is estimated that samples in the range of 10,000 cases would be required [5]. It thus becomes difficult to say whether in the present case the use of the ICSI procedure was causative or merely associative.

The challenge for infertility specialists is to maximize the chances for pregnancy while minimizing the risk of multiple gestations. The possibility of monozygotic twinning means that even as numbers of embryos replaced are being reduced the problems of twinning will not be totally eliminated but will approach the natural rate of twins and triplets as we approach single embryo replacement. Although the risk of monozygotic twinning is a low, simultaneous embryo splitting is even more unlikely. However, patients should be counseled about this rare possibility when considering maximum number of embryos to transfer.

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