Successful quintuplet pregnancy of monochorionic male quadruplets and single female after double embryo transfer: case report and review of the literature

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Objective: To report a rare case of quintuplets with monochorionic male quadruplets and a single female after two-blastocyst transfer.

Design: Case report.

Setting: University teaching hospital.

Patient(s): A 37-year-old gravida 1, para 1, presenting after two-embryo IVF with monochorionic male quadruplets and a single female.

Intervention(s): Ultrasound examinations and cesarean delivery.

Main Outcome Measure(s): Successful delivery of five live-born infants at 28 weeks and 6 days of gestation for preterm labor.

Result(s): The patient was diagnosed with quintuplets consisting of monochorionic male quadruplets and a single female after the placement of two embryos in blastocyst stage. She was followed closely with ultrasound examinations and hospitalized at 23 weeks’ gestation. Cesarean delivery was performed at 28 weeks and 6 days of gestation, with eventual discharge of all infants in healthy condition.

Conclusion(s): This case represents successful assisted reproductive technology quintuplets with monochorionic quadruplets and a co-sibling. Higher-order monozygotic pregnancies with monochorionic quadruplets are exceedingly rare and a potential complication of IVF. (Fertil Steril® 2018;109:284–8. ©2017 by American Society for Reproductive Medicine.)

Key Words: ART, higher-order birth, monochorionic quadruplets, monozygotic twinning, quintuplets

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Assisted reproductive technology (ART) has transformed the way in which infertility is approached while at the same time generating concern over the increase in multiple-birth pregnancies. In 2013, according to the Centers for Disease Control and Prevention National ART Surveillance System, multiple-birth deliveries were greatly increased among infants conceived with ART, accounting for approximately 18.7% of all higher-order births in the United States (1). In contrast, ART-conceived infants made up a more diminutive 1.6% of all infants in the total birth population in 2013. Approximately 39% of ART-conceived infants were twins, and 2% were higher-order multiples (three or more). Recent attention has also targeted the incidence of monozygotic twinning (MZT) in ART as additional complications, and poor outcomes are prevalent in associated pregnancies.

In spontaneous pregnancies MZT occurs at approximately 0.4%–0.45%; however, it has been shown to be increased in the ART population (2). With ART the incidence of MZT is postulated to be approximately 2–12 times higher (3–5). Although the exact mechanism of this increase is controversial, disruption of the zona pellucida, transfer of embryo in the blastocyst stage, advanced maternal age, and temperature effect of cryopreservation are among proposed theories.
The occurrence of higher-order monozygotic gestations is rare in both the general and ART populations. Concerning monochorionic quadruplets from ART, there have been no cases reported in which live infants were born successfully, owing to either reduction or miscarriage. Saravelos et al. (2) reported the first case of ART monochorionic quadramniotic quadruplets in 2015, which was reduced to two fetuses that delivered successfully. Two cases of spontaneous monochorionic quadruplets have been reported previously, with successful outcomes (6, 7). Monozygotic identical quadruplets are exceedingly rare in spontaneous conceptions, being reported with an incidence of 1 in 10–15 million pregnancies. Here we present a case of live-born ART quintuplets consisting of monochorionic quadramniotic male quadruplets and a single female from transfer of two embryos, with a specific review on MZT.

MATERIALS AND METHODS

The case report is from Kapiolani Medical Center for Women and Children in Honolulu, Hawaii. Institutional review board approval was not required by the institution, but express written consent was obtained from the patient. A healthy 34-year-old nulligravid woman presented for fertility treatment in 2012. Her 59-year-old husband had undergone vasectomy in 1991, and they desired IVF with surgical sperm extraction. She had monthly menstrual cycles, normal results on pelvic ultrasound, and her body mass index was 38.04 kg/m². In the early follicular phase her antimüllerian hormone level was 0.72 ng/mL, FSH 7.5 mLU/mL, E₂ 45 pg/mL, and her antral follicle count was 9. Saline-infused sonohysterogram revealed multiple intracavitary lesions, so an uncomplicated hysteroscopic polypectomy was performed.

Two months after surgery, serial ultrasound scans were performed during an unstimulated cycle. Once the dominant follicle measured 22 × 18 mm, 5,000 units of chorionic gonadotropin (Novare; Ferring Pharmaceuticals) were administered IM to induce ovulation. Late luteal phase suppression began 10 days later with an E₂ 0.1 mg/d patch (Climara; Bayer); the patch was changed every 2 days until gonadotropin stimulation began, and the last E₂ patch remained in place for 7 days. A daily GnRH antagonist (Ganirelix; Merck) was administered for 3 days starting 12 days after chorionic gonadotropin. Controlled ovarian hyperstimulation commenced the next day with 450 IU recombinant FSH (Follistim; Merck) and 75 IU menotropins (Menopur; Ferring) daily.

The cycle was canceled after 6 days of stimulation owing to inadequate response with the emergence of only three follicles from the starting pool of 13 antral follicles. Chorionic gonadotropin (5,000 U) was administered, and the late luteal phase suppression with E₂ patches and GnRH antagonist was restarted. There were nine antral follicles at the beginning of ovarian stimulation with twice-daily FSH (300 IU Follistim) and menotropins (75 IU Menopur). The GnRH antagonist (Ganirelix) was reintroduced on the seventh day of stimulation to suppress ovulation. The total dose of gonadotropins was 8,175 IU. On the day of hCG (10,000 IU Novare) administration, her E₂ was 2,135 pg/mL, P was 1.7 ng/mL, and 16 follicles were visible, of which 8 were ≥16 mm.

Transvaginal ultrasound-guided aspiration performed 35 hours later yielded 16 oocytes. The 11 mature oocytes were injected with sperm that had been percutaneously aspirated from the patient’s husband’s epididymis. Nine oocytes fertilized, and all progressed to the blastocyst stage. After being counseled about success rates and the risk of multiple gestation, the patient and her husband chose to transfer two embryos to maximize the likelihood of pregnancy. Two good-quality blastocysts were easily transferred 5 days after the oocyte retrieval. Assisted hatching was not performed, nor were the embryos biopsied for preimplantation genetic testing. The remaining seven blastocysts were vitrified.

The patient’s β-hCG value was 68 mIU/mL 7 days after the ET. An ultrasound performed at 7 weeks’ gestation revealed a single gestational sac containing a viable embryo. The patient’s prenatal course was uncomplicated, and she delivered a term male infant.

The patient and her husband returned in 2015 to use their frozen embryos. With menses, she began oral contraceptive pills containing desogestrel 0.15 mg and ethinyl E₂ 0.03 mg daily. When pituitary down-regulation was achieved with leuprolide acetate, the oral contraceptive pills were discontinued. Endometrial development was stimulated with E₂ patches (0.1 mg/d, titrated up to three patches). On the 13th day of E₂ treatment the patient’s endometrium was 8.4 mm with trilaminar architecture. The patient and her husband had been counseled again about success rates and the risk for multiple gestation. They had transferred two blastocysts in the fresh cycle, which resulted in a singleton gestation, and desired to again transfer two blastocysts.

Progesterone-in-oil (50 mg/mL) was administered IM for 7 days (1 mL daily for 2 days, then 2 mL daily for 5 days), followed by the easy transfer of two fair-good-quality blastocysts. The patient’s β-hCG value was 43 mIU/mL 6 days after the ET. At 6 weeks 2 days’ gestation, the patient began bleeding and presented to the emergency department. Ultrasound performed by the emergency medicine physician showed two gestational sacs. One sac contained an embryo with apparent cardiac activity.

The patient had an ultrasound scan performed in the fertility clinic 3 days later (6 weeks 5 days’ gestation), at which time three gestational sacs were seen, each containing one yolk sac and one embryo with cardiac activity. The crown–rump lengths corresponded to embryos of 6 weeks 2 days, 6 weeks 6 days, and 6 weeks 2 days, respectively. The following week (7 weeks 5 days’ gestation), four gestational sacs were seen, each containing an embryo with cardiac motion. The embryos sizes were as follows: 7 weeks 3 days, 7 weeks 2 days, 6 weeks 5 days, and 7 weeks 0 days. Serial ultrasound scans in the fertility clinic showed four gestational sacs, each with a live embryo. One embryo continued to lag in size by 5 to 6 days but had progressive growth.

At 12 weeks 1 day’s gestation, the patient was seen by a maternal–fetal medicine specialist. Each of the four gestational sacs contained a live fetus, but fetus B was again 6 days smaller than expected. Fetus A and fetus B were each thought to have had a separate placenta, but fetus C and D were appreciated to share a placenta. The patient declined multi-fetal pregnancy reduction.
RESULTS
At 14 weeks 3 days’ gestation the patient was seen again by the maternal–fetal medicine specialist. At this time a fifth gestational sac was seen. The newly discovered fetus E was male, as were fetuses B, C, and D. Fetus A was female. At this there was concern for two monochorionic male pairs or what appeared to be monochorionic quadramniotic males because the placentas were all fused. The patient was again advised of poor pregnancy outcomes with quintuplets, specifically with attention to mortality and prematurity, but did not wish to undergo fetal reduction. At 17 weeks there was concern for twin-to-twin transfusion in fetus C and D; a one-time fluid reduction was performed in fetus D. Analysis of this fluid revealed normal 46,XY karyotype. The patient had ultrasound examinations every 2 weeks to look for further signs of twin-to-twin transfusion and observe fetal growth. Fetal echocardiograms were also performed. She was admitted with threatened preterm labor at 23 weeks of gestation and remained in the hospital. She subsequently carried the infants until 28 weeks and 6 days, when she had a cesarean section for preterm labor at 6 cm of dilation. The fetal weights, Apgar scores, and length of stay are recorded in Table 1. All of the infants were eventually discharged in stable and healthy condition. The placenta was taken to pathology, where monochorionic a quadramniotic and monochorionic monoamniotic finding was confirmed (Fig. 1). Four separate amnions and one chorionic membrane were observed in the quadruplets. No histologic pathology was observed in the placentas, with the exception of a single umbilical artery in twin B.

DISCUSSION
In reviewing the literature there are no existing cases of successful quintuplets live born consisting of monochorionic quadramniotic quadruplets and a single female sibling. In this case the quadruplets were monozygotic because they were males, and there was a single female; one embryo placed was XY, and the other was XX.

The natural history of spontaneous monozygotic twinning is not necessarily well understood in the scientific community, but ART is associated with increase of zygotic splitting [8]. Infertility research has postulated numerous theories for increase of MZT in ART; however, a paucity of animal models has demonstrated production of MZT consistently. Although MZT is relatively rare in most mammals, including humans, Blickstein et al. (9) examined the natural occurrence of twinning in the armadillo. The armadillo is thought to be the only animal model to demonstrate monozygotic quadruplets due to delayed blastocyst implantation and double binary fission. The authors proposed that some oocytes are genetically predisposed to splitting and that ovulation induction protocols may up-regulate this genetic subset preferentially in a “dose-dependent” manner. In ART, MZT has been shown by multiple studies to be increased, and recent efforts to focus on causation may have implications for maternal and fetal outcomes (2-5). In 2016 Parazzi et al. (10) performed a population-based study of more than 460,000 pregnancies, finding an increase of 60% of MZT in ART gestations. Monozygotic twinning has been linked with day of blastocyst transfer, micro-manipulation of the zona pellucida, cryopreservation, maternal age, and other components of ART, such as culture media and ovulatory induction.

Several studies have suggested that the day of blastocyst transfer may be linked to MZT. Our patient underwent frozen embryo transfer cycle with day-5 blastocysts. In a recent survey performed by Kanter et al. (11) in extrapolating data from the National ART Surveillance System between 2003 and 2012, trends in monozygotic twinning after single embryo transfer were examined. The overall incidence of MZT was 2.24%, and when taking into account day of transfer the occurrence of MZT in day-2–3 transfers in comparison with day-5–6 transfers was 1.71% and 2.59%, respectively. Another study, by Knopman et al. (12), displayed similar results from a survey of ART cycles at a single university center. They found that the overall incidence of MZT was 2.1%, and that day-5 transfers had a 50% increase risk for MZT over day-3 transfers. The group also performed univariate outcomes analysis relating MZT with low (<2,500 g) and very low (≤1,500 g) birth weight, preterm delivery, and triplet gestations. A recent European systematic review also found an overall 0.9% rate of MZT with blastocyst transfer on any day associated with a 4.25-fold increase in risk for MZT (4).

Assisted reproductive technology protocols routinely include blastocyst culture, to cultivate a blastocyst with the best quality to be transferred. Extension of culture media

TABLE 1

<table>
<thead>
<tr>
<th>Twin</th>
<th>Birth weight (g)</th>
<th>Apgar 1</th>
<th>Apgar 5</th>
<th>LOS (d)</th>
<th>Major morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twin A (single)</td>
<td>964</td>
<td>7</td>
<td>9</td>
<td>64</td>
<td>No</td>
</tr>
<tr>
<td>Twin B</td>
<td>1,219</td>
<td>8</td>
<td>9</td>
<td>73</td>
<td>No</td>
</tr>
<tr>
<td>Twin C</td>
<td>1,106</td>
<td>7</td>
<td>8</td>
<td>64</td>
<td>No</td>
</tr>
<tr>
<td>Twin D</td>
<td>737</td>
<td>5</td>
<td>9</td>
<td>73</td>
<td>No</td>
</tr>
<tr>
<td>Twin E</td>
<td>1,191</td>
<td>6</td>
<td>7</td>
<td>65</td>
<td>No</td>
</tr>
</tbody>
</table>

Note: LOS = length of stay.

time, culture media composition, and the experience level of a reproductive laboratory composition have been implicated in later-stage blastocyst MZT. Multiple efforts have provided evidence that extension of blastocyst culture media time is related to increase in MZT. Kawachiya et al. [13] performed a retrospective review of single embryo transfers at stratified time points resulting in MZT over a 6-year period at a single site. The group found that transfer in the cleavage stage was less associated with MZT when compared with fresh blastocyst transfer without affecting live birth rate. In a recently performed mouse model study to delineate the effects of blastocyst culture media, Yan et al. [14] compared in vivo and in vitro culture environments. There was an increased frequency of inner cell mass splitting among in vitro mouse blastocysts, suggesting a foundation for MZT in ART procedures with IVF. The inherent nature of current IVF includes both culture of the blastocyst and micromanipulation of the zona pellucida.

Assisted hatching in ART is thought to increase the rate of successful conception by creating a micro-breach in the zona pellucida that causes mechanical splitting of the blastocyst. It is proposed that disruption of the zona pellucida may have a pivotal role in the incidence of MZT, with some studies finding an increase odds ratio of up to 3.2 [3]. Others have found that assisted hatching in 2–3-day transfers was associated with a twofold increase in MZT, whereas day-5–6 transfers did not have an increase in risk [11]. The authors proposed that the difference in assisted hatching and day-5 transfer may have been difficult to delineate because day-5 blastocyst transfer already denotes a higher chance of MZT. Disturbance of the zona by intracytoplasmic sperm injection has also received attention for a role in MZT. Several studies have evaluated intracytoplasmic sperm injection but failed to show a definitive effect on the incidence of MZT [15, 16].

Few have addressed the role of cryopreservation in MZT; however, past research has shown that cryopreservation does increase the cumulative pregnancy rate [17]. Regarding MZT, historical proposals postulated that temperature fluctuations could have an adverse effect on embryo splitting, resulting in monochorionic pregnancies [18]. In a retrospective study frozen blastocyst transfer was associated with an almost twofold increase in risk for MZT in comparison with cleavage-stage transfer; however, the live birth rate in the frozen transfer group was considerably increased [13]. Cryopreservation alone may not contribute to the increased rate of MZT, but rather thickening of the zona during storage and ART manipulation of the blastocyst are more likely responsible. There are no studies that address the length of freezing in conjunction with rate of twinning and pregnancy outcome.

Another theory for increase in MZT is relation to advanced maternal age, thought to be secondary to functional changes that take place within the zona pellucida. Our patient had embryos that were frozen at a maternal age of 35 years, which may have conferred an increased risk of MZT. Parazzini et al. [10] showed an increase in maternal age associated with a risk for MZT in a population-based study. Interestingly, some studies have failed to show a relationship between advanced maternal age and MZT, demonstrating a lower rate of MZT in older mothers [16]. Salihu et al. [19] studied the effects of advanced maternal age on early mortality among quadruplets and quintuplets, finding that increasing maternal age was associated with a more favorable outcome. At the time of delivery our patient was 37 years of age, which may have been a factor in outcome.

We would also like to address that single embryo transfer is recommended in patients with a favorable prognosis for live-birth pregnancy outcome. In this case the patient was strongly counseled about standard single embryo transfer and the risks that are associated with higher-order multiple pregnancies. The patient was educated and given detailed information about success rates and twinning in double and single embryo transfers. After careful consideration our patient felt that the right choice for her husband and herself was double embryo transfer to maximize the potential of live-born success. The double blastocyst transfer invariably increased her risk for MZT because we understand that blastocyst-stage transfer alone is associated with higher rates of MZT.

In conclusion, protocols and procedures in ART are postulated to increase the rate of MZT. Although patients and infertility specialists are focused on a successful live birth, the risk of a higher-order multiple gestation or miscarriage in pregnancy is a clinical concern. To our knowledge this is the first case of ART quintuplets with monochorionic monozygotic quadruplets and a monochorionic sibling after two-embryo transfer that were live born. Patients should be counseled about the increased risk of MZT in assisted reproductive pregnancies and the association with high-risk outcomes. This case adds to the small number of higher-order ART monozygotic pregnancies that currently exist in the literature.

REFERENCES


