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Dichorio-Triamniotic Triplet Pregnancy after Day 3 Single Embryo Transfer

Case Report

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* Equal work

Abstract

A 31 year-old woman had a single embryo transfer on day 3 after assisted hatching (AH) and intracytoplasmic sperm injection (ICSI) treatment. Ultrasound examination performed 6 weeks after oocyte retrieval revealed a triplet pregnancy combining monochorionic diamniotic twins and a singleton. If zygote splitting resulting in monochorionic triamniotic triplets following IVF has already been described, this case is about an incredibly rare phenomenon after single embryo transfer. Naturally, a concurrent spontaneous conception cannot be excluded. To our knowledge, this is the first time a dichorionic triplet pregnancy after single embryo transfer is reported.

Keywords: Triplet Pregnancy; Dichorio-Triamniotic; Single Embryo Transfer; Assisted Hatching; Concurrent Natural Conception.

Introduction

Multiple births are associated with higher risk of obstetrical and perinatal complications, such as pre-eclampsia, preterm delivery and low birth weight. A great concern has been made about multiple pregnancies these last years in ART (assisted reproductive technology). In France, the mean number of transferred embryos has dramatically decreased over the last 10 years. The French biomedicine agency reports a drop from 1,88 to 1,79 between 2008 and 2011. Furthermore, more and more single embryo transfers are performed (+ 6% over the past 4 years) [1].

However, single embryo transfer cannot prevent from monozygotic (MZ) twins. Patients undergoing IVF/ICSI are at higher risk to have MZ twins compared with general population (among 5% versus less than 1%).

In natural conception, the type of twinning depends on the moment it originates. Diamniotic dichorionic MZ twins result from an early splitting on the first days of development, creating two distinct blastocysts with each an inner cell mass (ICM) and a cavity. Diamniotic monochorionic MZ twins, more frequent, originate later and result from two inner cell masses included in a unique blastocoel [2].

In ART, various procedures have been associated with this splitting risk, such as AH or late embryo stage transfer. The type of chorionicity is correlated with the technique used: day 3 AH provides more dichorionic MZ twins, whereas extended culture and advanced embryonic transfer is linked to more monochorionic MZ twins [3].

Moreover, when natural conception is possible, the risk of DZ twins cannot be excluded even after single embryo transfer.

About twenty cases of monochorionic triamniotic triplets after IVF have been reported in the literature and a few cases of DZ twins after single embryo transfer have already been published.

This paper relates the first case report about non monochorionic triplet pregnancy after single embryo transfer.

Case Presentation

A nulliparous young woman presented at our ART center with five years of infertility history. She was 31 years old and her partner 28. Day 3 hormonal biomarkers of ovarian reserve, ovulation, tubal patency evaluation (hysterosalpingography) and husband's sperm analysis showed no abnormalities. They had three unsus-

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cessful intrauterine insemination (IUI) cycles in a previous IVF center.

The couple was then referred to our ART center. The unexplained infertility led to a laparoscopy. An endometriosis stage II according to revised American Fertility Society classification [4] was diagnosed and completely treated by surgery. Six months later, as no spontaneous pregnancy occurred, the couple was planned for IVF.

A standard long Gn-RH agonist protocol was chosen for the first attempt. Unfortunately, the stimulation did not begin because of persistent ovarian cyst and poor endometrial quality. Four months later, a controlled ovarian stimulation (COS) with a Gn-RH antagonist protocol was started. The patient received 150 UI of recombinant FSH (Gonal F®, Merck Serono) during five days followed by 125 UI during four days. On the 6th day, antagonist was introduced (Orgalutran 0.25 mg/0.5 ml, MSD). On day 9 of COS, 5 follicles had reached 17 mm diameter and 3 were 15mm, E2 level was 1124 ng/mL and endometrium thickness was 10 mm; the ovulation was then triggered with recombinant hCG (Ovitrelle®, Merck Serono). Transvaginal ultrasound guided egg retrieval was performed 36 h later. We yielded 11 oocytes and 8 metaphase II oocytes were injected by ICSI and cultured individually (G-1™ PLUS, Vitrolife). ICSI was performed rather than conventional IVF because of a moderate asthenozoospermia at the day of the oocytes retrieval. We obtained 4 embryos. On day 3, a top quality embryo, with 8 regular cells and no fragmentation, was transferred after laser pulse AH for thick zona pellucida. Embryo transfer was ultrasound guided and performed with a soft catheter (Inventath eco®, CCD). Luteal phase support begun on the pick up day and consisted in 15 days of vaginal micronized progesterone (600 mg/day). One blastocyst was cryopreserved on day 6 after prolonged culture. The two remaining embryos were discarded as they didn't reach the blastocyst stage.

Two weeks after oocyte retrieval, the bhCG serum level was 251 UI. A second blood test at 48 hours confirmed the ongoing pregnancy with 626 UI. Ultrasound examination performed 6 weeks later showed a triplet pregnancy combining monochorionic diamniotic twins plus a singleton. Each fetus had a cardiac activity and normal biometry and morphology.

Because of the unexpected triplet pregnancy after single embryo transfer, the couple was asked if they had unprotected intercourse between egg retrieval and embryo transfer, which they confirmed. To improve perinatal issues, the couple was counseled to undergo a selective fetal reduction. Reduction of the twins has been preferred because of the superior risk of a monochorionic diamniotic pregnancy in comparison with a single pregnancy. The reduction was done at 10 weeks of pregnancy by selective intracardiac administration of KCL. The procedure was not complicated and to date, the pregnancy is still ongoing.

Discussion

ART is associated with higher multiple pregnancy risk, despite the reduction of the number of embryo transferred. According to Vitthala's meta-analysis, there is at least a 2-fold rise in the incidence of monozygotic twinning after ART compared with natural conception [5].

Several techniques have been thought to enhance the risk of zy-

gote splitting, such as AH. AH is used to thin zona pellucida and thus favor embryo eclosion and implantation. A very recent retrospective study significantly links AH to twin and triplet pregnancy [6]. These results confirm data previously published in the Cochrane database in 2012 [7]. The patients we discuss here did benefit from AH by laser pulse prior to transfer. We also have to note that we used the ICSI technique for fertilization. However, the effect of ICSI treatment on MZ twinning is very controversial [8].

In the case we present here, a triplet pregnancy occurred after a single embryo transfer to a young woman with unexplained infertility.

One hypothesis could be a two-steps zygote splitting: an early division leading to two distinct gestational sacs, followed by a second division in one of them creating monochorionic diamniotic twins plus a singleton. Nevertheless, in the present case, zygosity has not been assessed.

Guilherme et al. [9] studied zygosity and chorionicity in spontaneous and IVF triplet pregnancies. On 31 sets of triplet obtained after ART, dichorioamniotic triplets were always DZ and trichorioamniotic triplets were almost always trizygotic (TZ).

Based on these data, the hypothesis of a concurrent spontaneous pregnancy seems to be more plausible.

We found four case reports (Table 1) in the literature mentioning DZ twinning after single embryo transfer [10-13]. Four patients had a late stage embryo transfer (morula or blastocyst) and only one an early cleavage-stage embryo transfer as in our case. Each time, natural conception was possible and couples attested having had unprotected intercourse during transfer period in four cases. As mentioned by Takehara et al. [11], there is indeed a possibility of spontaneous ovulation of the remaining oocytes after aspiration of follicles.

An interesting study on twin zygosity following single embryo transfer suggest that as many as 1 in 5 twins born after single embryo transfer (SET) may be the result of a concurrent natural conception [14]. Additionally, this phenomenon may be underestimated because same sex twins are too often wrongly considered as MZ twins. Genetic remains the only valid tool to assess zygosity.

Finally, the assumption of a transfer of two embryos instead of one has been considered. However, this probability was not retained because in our *in vitro* embryo culture system (individual micro drop), each embryo including supernumerary had his own follow up until day 6 (discarded or cryopreserved).

Again, to the best of our knowledge, our present case is the first about a dichorio-triamniotic triplet pregnancy after single embryo transfer.

We must caution that two quite similar phenomenons have been published in 2001 and 2003: two quadruplet pregnancies occurred after the transfer of two embryos and resulted in each case in four living babies with different zygosities [15, 16].

Here, we cannot assess the origin of each fetus, but the most likely hypothesis is that twins originate from the embryo transferred

Table 1. Systematic review of dizygotic twins after single embryo transfer.

	Author	Infertility etiology	Cycle type	Stage of embryo transfer	Fertilization technique	Echography aspects	Zygoty assessment
Case 1	Kyono, 2009	Not documented	Fresh embryo transfer	Morula	ICSI	Dichorionic twins	Karyotypes
Case 2	Sugawara, 2010 (1)	Unexplained infertility	Fresh embryo transfer	Blastocyst	IVF	Dichorionic twins	Different sex twins
Case 3	Sugawara, 2010 (2)	Tubal infertility	Frozen-warmed embryo	Blastocyst	ICSI	Dichorionic twins	Different sex twins
Case 4	van der Hoorn, 2010	Tubal infertility	Frozen-thawed embryo	Day 3	IVF	Dichorionic twins	HLA typing
Case 5	Takehara, 2014	Unexplained fertility	Frozen-warmed embryo	Blastocyst	IVF	Dichorionic twins	Karyotypes
Current case	Gala, 2015	Unexplained fertility	Fresh embryo transfer	Day 3	ICSI	Monochorionic-diamniotic twins plus a singleton	No assessment

and the singleton from a concurrent natural conception.

Even if this is the first time we diagnose a triplet pregnancy after SET, we suggest that efforts to reduce multiple pregnancies in ART should include advices on avoiding intercourse during transfer period when natural conception is possible. Couple counseling might be improved about multiple pregnancy risk, because most of the patients are not aware of mother and fetal complications and expect above all the much-wanted pregnancy.

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