Monochorionic triamniotic triplets following conventional *in vitro* fertilization and blastocyst transfer

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ABSTRACT

Multiple pregnancy in *in vitro* fertilization (IVF) is on the decline with a reduction in number of embryos transferred. But the risk of monozygotic splitting persists. The risk of monozygotic twinning in women undergoing IVF is reported to be twice that of natural conception, and monochorionic triplets are even rarer at 100 times more than natural conception. We report a case of monochorionic triamniotic (MCTA) triplets following conventional IVF and blastocyst transfer without zona manipulation. This report highlights the possibility of zygotic splitting in IVF in young couples with no family history, in centers with good experience with blastocyst transfer. MCTA triplets carry a high risk of perinatal mortality and morbidity and need multidisciplinary care. Prevention and prediction of zygotic splitting ought to be realized with better reporting and identification of possible risk factors.

KEY WORDS: Blastocyst transfer, *in vitro* fertilization, monochorionic triamniotic triplet, zygotic splitting

INTRODUCTION

A significant decline in the incidence of higher order multiple pregnancy has been achieved worldwide with the reduction in the number of embryos transferred during assisted reproduction. Despite this, the prevalence of zygotic splitting and monozygotic multiple pregnancies persists. The risk of monozygotic twinning in women undergoing *in vitro* fertilization (IVF) is reported to be twice that of natural conception (0.9% vs. 0.4%, respectively). The incidence of monochorionic triplets is even rarer at 0.048%, which is 100 times more than natural conception.[1]

Various theories have been proposed to explain the increased risk of monozygotic splitting after assisted reproduction. They include advanced maternal age, ovarian stimulation, culture media, prolonged *in vitro* culture and blastocyst transfer, zona manipulation such as intracytoplasmic sperm injection (ICSI) and assisted hatching. Monochorionic triamniotic (MCTA) triplets are rather uncommon and highly challenging to manage as they are associated with much greater chances of obstetric and perinatal morbidity and mortality. Most of the cases of MCTA triplets reported to date are consequent to some form of zona manipulation either ICSI or assisted laser hatching. To the best of our knowledge, there have been 20 reports of MCTA triplets published in the literature. 11 of these reports are following some form of zona manipulation (ICSI or Assisted hatching) and 8 are following conventional IVF (2 frozen embryo transfer [FET]; 3 day 3 transfer and 3 day 5 transfer) [Table 1].

In this publication, we report a case of MCTA triplets following IVF in a young couple following blastocyst transfer. This is the fourth reported case following blastocyst transfer and conventional IVF.

CASE REPORT

A 29-year-old woman presented with secondary infertility of 3-year duration. The

Table 1: Published case reports of MCTA triplets following IVF

Author	Year	Journal	Age of patient	Indication	IVF/ ICSI	Fresh transfer /Frozen embryo transfer	Family history	Protocol	Media	Day of transfer	No transferred	Outcome	Delivery details
Day 3 transfer													
Salat-Baroux	1994	Human reproduction	26	PCOS, astheno	IVF			Long		3			
Tal	2012	Case report online general	29	Unexplained infertility	IVF			Antagonist		3	3	Fetal reduction of triplets and LSCS of twins	
FET													
Belaisch-Allart	1995	Human reproduction	37	PCOS, tubal	IVF	FET		Long		3			
Faraj	2008	Fertility and sterility	27	Donor oocyte		FET						PT LSCS 32 weeks	
Day 5 blastocyst transfer													
Dessolle	2010	RBM online	27	Unexplained infertility	IVF		Yes	Antagonist	G1-2, G2-2	5	1	Fetal reduction at 15 weeks and LSCS at 34 weeks	1970 g, 1320 g girls
Jain	2004	Journal of Assisted Reproduction and Genetics	23	Donor oocyte	IVF			Agonist	Irvine	5	2	LSCS 30 weeks	
Henne	2005	Fertility and Sterility		Donor oocyte	IVF					5		MTP 10 weeks	
Our report			29	Tubal factor	IVF		No	Antagonist	Vitrolife	5	2	PPROM at 17 weeks	

MCTA=Monochorionic triamniotic, IVF=*In vitro* fertilization, ICSI=Intracytoplasmic sperm injection, PCOS=Polycystic ovary syndrome, FET=Frozen embryo transfer, PPROM=Preterm premature rupture of membranes, LSCS=Lower segment caesarean section, PT=Prothrombin time, MTP=Massive transfusion protocols

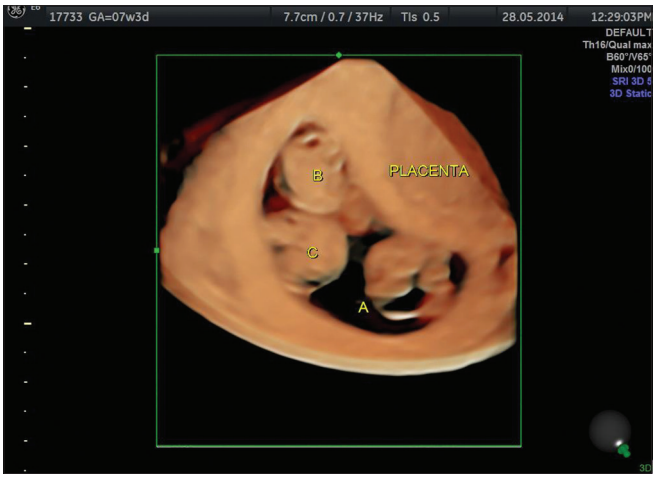

Figure 1: Three-dimensional scan showing three separate gestational sacs and a single placenta

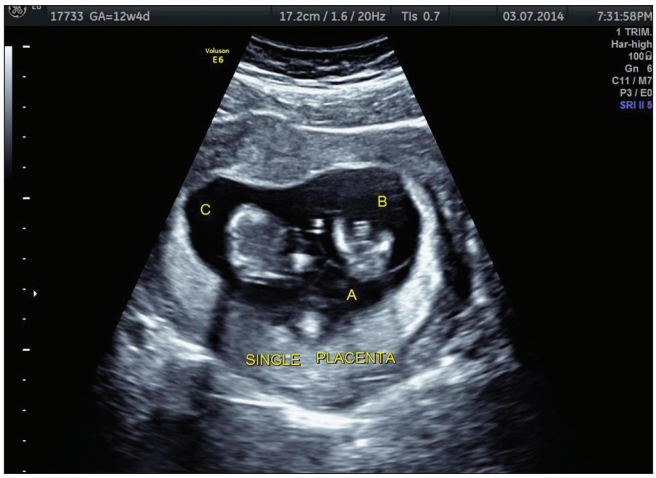

Figure 2: Two-dimensional scan showing three sacs and a single placenta

couple was married for 6 years with regular menstrual cycles and normal husband's semen analysis. Her reproductive history included an ectopic pregnancy for which she had undergone the right salpingectomy and a missed miscarriage at 8 weeks pregnancy in the past. She had 4 failed intrauterine insemination cycles and was then planned for IVF in view of tubal factor.

She was started on the standard antagonist protocol and stimulated with 150 iu of recombinant follicle-stimulating hormone (rFSH; Gonal-F, Merck Serono, Geneva, Switzerland) and 75 iu of HMG-HP (Menopur, Ferring Pharmaceuticals, Sweden) daily. GnRH antagonist was started on day 6 of stimulation and administered daily till the day of human chorionic gonadotropin (hCG). Egg retrieval was performed 35 h after administration of 250 ug of recombinant hCG (rhCG; Ovitrelle, Merck Serono) and 16 oocytes were retrieved. The 15 metaphase II oocytes were subjected to conventional IVF since semen parameters were normal. 14 oocytes fertilized and after 5 days of *in vitro* culture (Vitrolife G1.3, Göteborg, Sweden), 6 blastocysts were obtained. Two top quality blastocysts (4AA, 2AA) were transferred, and 4 were cryopreserved. She received standard luteal support with vaginal progesterone gel (Crinone gel 8%, Merck Serono). A positive beta hCG was obtained 14 days after embryo transfer. Ultrasound performed at 5 weeks of pregnancy showed a single gestational sac. At 7 weeks of gestation, ultrasound revealed MCTA triplets with three yolk sacs and three fetal poles with cardiac activity in each [Figures 1 and 2]. In view of monochorionic gestation, she was offered fetal reduction by selective cord ligation at 16 weeks. Despite counseling about increased chances of antenatal complications with triplets, the couple chose to continue pregnancy without fetal reduction. She had an uneventful pregnancy till 17 weeks gestation after which she developed preterm premature rupture of membranes and cord prolapse. Her pregnancy was terminated using medical management.

DISCUSSION

This is the fourth reported case of MCTA triplet following conventional IVF and blastocyst transfer without zona manipulation.[1-3] There are two reported cases following day 3 transfer[4,5] and two following FET[6,7] [Table 1]. These cases reveal that with the exception of one patient of age 37, most patients were of young age, the average age being 28 years. There was no predilection for any etiology of infertility, drug used, protocol, family history, culture media used. This case report is mainly to highlight that complications such as MCTA triplets can occur in young couples with no family history of twinning and no zona manipulation; in centers with good experience with blastocyst transfer.

There have been various theories proposed to elucidate the reasons for zygotic splitting in such situations. They include anomalies in apoptosis-related remodeling of the inner cell mass during extended culture or excessive growth of the inner cell mass.[1]

Data from a recent meta-analysis have indicated that the risk of monozygotic twinning following assisted reproductive technology (ART) is 0.9%; which is a 2-fold increase compared to natural conception. Blastocyst transfer is associated with a higher rate of monozygotic twinning at 1.7%.[8] There are inadequate data regarding the incidence of monozygotic triplet pregnancies. It has been reported to occur in 0.004% of all natural pregnancies.[9] Though there have been no studies quoting the actual prevalence

following IVF, reports range from 10 to 100 times that of natural conception.[10]

Management of MCTA triplets is highly challenging and needs multidisciplinary care as MCTA triplets are associated with a high chance of miscarriage, preterm birth, low birth weight, twin-twin transfusion syndrome (TTTS), structural abnormalities, and perinatal mortality. TTTS is a major possible complicating factor, the prevalence of which is unknown in triplet.

Selective fetal reduction to twins is an option to improve perinatal outcome. This could be performed by cord occlusion (using ultrasound guided bipolar diathermy or radiofrequency ablation). The potential risks of the procedure include 3–5% chance of pregnancy loss. Couple declined this option understanding the pros and cons.

One of the major goals of IVF, today, is to achieve the birth of a healthy singleton and reduce perinatal morbidity and mortality. Popularizing single embryo transfer has been one of the main interventions to achieve this target. Having said that patients should be counseled that the risk of monozygotic splitting persists. Since zygotic splitting is much more common in ART pregnancies compared to natural conception, efforts must be made to identify the factors which predispose to zygotic splitting. This would assist in the prevention and patient counseling. Patients must be counseled about the higher chances of antenatal and perinatal morbidity and mortality in monozygotic multiple pregnancies.

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