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Case Report

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Monochorionic quadramniotic quadruplet pregnancy after single-embryo transfer

Ahmet Karataş[1], Yaprak Engin Üstün[1], Cavidan Gülerman[1], Yeşim Bardakçı[2], Nafiye Yılmaz[1]

[1]*Reproductive Endocrinology Clinic, Zekai Tahir Burak Maternal Health Training and Research Hospital, Ankara, Turkey*
[2]*Embryology Laboratory, Zekai Tahir Burak Maternal Health Training and Research Hospital, Ankara, Turkey*

Abstract

Objective: Multiple pregnancies have increased in recent years as assisted reproductive technologies (ART) are used widely compared to physiological cycles. To the best of our knowledge, although triplet pregnancies were presented in few case reports in the literature, this is the third case reported as monozygotic quadruplet pregnancy by single-embryo transfer after ART.

Case: Thirty-year-old nulliparous women admitted to our clinic for second fresh in vitro fertilization cycle. Eight oocytes were collected during follicular aspiration; intracytoplasmic sperm was injected to seven of them and a blastocyst embryo was transferred on fifth day. On 12th and 15th days after the transfer, β-hCG levels were mIU/mL and 1204 mIU/mL, respectively. When she came for examination three weeks later, reproduction specialist observed in transvaginal ultrasonography performed on 40th day after transfer that there were four fetuses in a single gestational sac which had no fetal cardiac activity and 18.5 mm of crown-rump lengths. Curettage procedure was performed afterwards.

Conclusion: It would be beneficial to increase the frequency of routine checks due to the possibility of premature loss in monochorionic quadruplets.

Keywords: Assisted reproductive techniques, blastocyst transfer, monozygotic quadruplet pregnancy.

Özet: Tek embriyo transferi sonrası monokoryonik kuadramniyotik dördüz gebelik

Amaç: Çoğul gebelikler, fizyolojik sikluslar ile karşılaştırıldığında yardımcı üreme tekniklerinin (YÜT) yaygın olarak kullanılması nedeniyle son yıllarda artmıştır. Bildiğimiz kadarıyla literatürde birkaç olgu sunumunda üçüz gebelikler sunulmuş olsa da, bu olgu YÜT sonrası tek embriyo transferi ile bildirilen üçüncü monozigotik dördüz gebeliktir.

Olgu: Otuz yaşında nullipar olgu, ikinci taze in-vitro fertilizasyon siklusu için kliniğe başvurdu. Foliküler aspirasyon esnasında sekiz oosit toplandı, bunlardan yedisine intrasitoplazmik sperm enjeksiyonu yapıldı ve beşinci gün bir blastosist embriyosu transfer edildi. Transfer sonrası 12. ve 15. günlerde β-hCG düzeyleri sırasıyla, 383 mIU/mL ve 1204 mIU/mL saptandı. Yaklaşık üç hafta sonra kontrole geldiğinde, üreme tıbbı uzmanı tarafından transfer sonrası 40. günde yapılan transvajinal ultrasonografide tek gebelik kesesi içerisinde baş-popo mesafeleri 18.5 mm olan, fetal kardiyak aktiviteleri saptanamayan dört adet fetüs gözlendi. Daha sonra küretaj işlemi uygulandı.

Sonuç: Monokoryonik dördüzlerde erken kayıp olasılığı nedeniyle rutin kontrollerin sıklaştırılması faydalı olacaktır.

Anahtar sözcükler: Yardımcı üreme teknikleri, blastosist transferi, monozigotik dördüz gebelik.

Introduction

It is intended to obtain a large number of embryos to increase the pregnancy possibility of pregnancy in assisted reproductive techniques (ART), and therefore low, standard and high doses of gonadotropin treatments are applied during ovulation induction considering the age, ovarian reserve, body mass index (BMI) and response to previous treatment cycles of case. Monozygotic (MZ) twin pregnancy after ART was first reported by Yovich et al.[1] in 1984. It was later reported in many studies that the incidence of multiple pregnancies increased due to the increasing use of ART treatments. MZ twin pregnancies

Correspondence: Ahmet Karataş, MD. Zekai Tahir Burak Maternal Health Training and Research Hospital, Ankara, Turkey. e-mail: akaratas1973@hotmail.com

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account for approximately 30% of naturally occurring twin pregnancies. In fertilizations by ART, especially after blastocyst embryo transfer, MZ twin frequency is higher than spontaneous pregnancies.[2,3] Quadruplet pregnancy is not common. MZ quadruplet pregnancy is rarer, it is seen one in 10–15 million cases and only 28 cases documented in detail were reported in the entire USA.[4] MZ quadruplet cases were also reported among spontaneous pregnancies;[5] however, MZ quadruplet pregnancy obtained by ART was reported only in two cases. The first case was reported by Liu et al.[6] in 2010, and second case was reported by Saravelos et al.[7] in 2016. In this report, we aimed to present third monochorionic quadramniotic quadruplet pregnancy case observed in single-embryo transfer after ART.

Case Report

Thirty-year-old nullipara case admitted to our clinic with the complaint of four-year primary infertility. The infertile couple was applied two cycles ovulation inductions with gonadotropin and intrauterine insemination followed by a cycle of fresh in vitro fertilization (IVF), but no pregnancy was achieved. In second fresh IVF cycle, stimulation was applied with GnRH antagonist (0.25 mg Cetrotide; Merck Serono, Istanbul, Turkey) in short protocol and with daily 175 IU recombinant FSH (Puregon; Organon, Istanbul, Turkey), as BMI was 31 kg/m^2. Ten days after starting stimulation, 10,000 IU human chorionic gonadotropin (hCG) (Pregnyl; Organon, Istanbul, Turkey) was applied for last oocyte maturation. Serum E2 level was 3.014 pg/mL on hCG day. Thirty-six hours after hCG injection, eight oocytes, of which seven were metaphase II, were collected under the guidance of ultrasonography. Intracytoplasmic sperm injection (ICSI) was applied to seven oocytes, and a blast embryo was transferred on fifth day (**Fig. 1**). β-hCG levels after the transfer were 383 mIU/mL on 12th day and 1204 mIU/mL on 15th day. Routine two-dimensional (2D) transvaginal ultrasonography was applied by obstetrician/gynecologist on 21st day after transfer. Approximately three weeks later, on the 40th day of the transfer, the pregnant woman was re-examined by reproduction specialist via ultrasonography and it was observed that there were four fetuses in a single gestational sac which had no fetal cardiac activity and 18.5 mm of crown-rump lengths (CRL) (**Fig. 2**). Uterine curettage was applied to the case.

Fig. 1. Blast embryo transferred on fifth day.

Discussion

Although a limited number of embryo transfers are done after ART treatment to avoid multiple pregnancy, MZ twin and triplet pregnancies are reported. Despite the limited information on the reasons of MZ multiple pregnancies, it is known that maternal age, ovarian stimulation, ICSI, in vitro embryo culture and zona pellucida such as assisted hatching may contribute to the condition.[6–11] To the best of our knowledge, there are only two MZ quadruplet pregnancy cases reported after ART treatment. In the first case report, none of the embryos had cardiac activities at 9th week[6] (**Table 1**). In the second case report, the authors reported that they reduced the condition to twin pregnancy by applying selective fetal reduction via radiofrequency ablation method in two sessions (163/7 weeks and 174/7 weeks), and delivered the remaining fetuses by cesarean section at 356/7 weeks.[7] In their literature review consisting of 20 MZ multiple pregnancy cases (≥3 fetuses) Saravelos et al.[7] reported that they occurred after blastocyte transfer in 55% (11/20) of them and after cleavage phase transfer in 45 (9/20) of them. Behr et al.[10] claimed that a possible explanation for MZ multiple pregnancies related with blastocyte transfer could be the injury of zona pellucida after long-term exposure to culture medium. Steinman et al.[11] stated that low calcium concentrations in extended culture mediums weakened intercellular connection within internal cell mass and caused division in embryo. Similar to this statement, the case in this report occurred after blast embryo transfer.

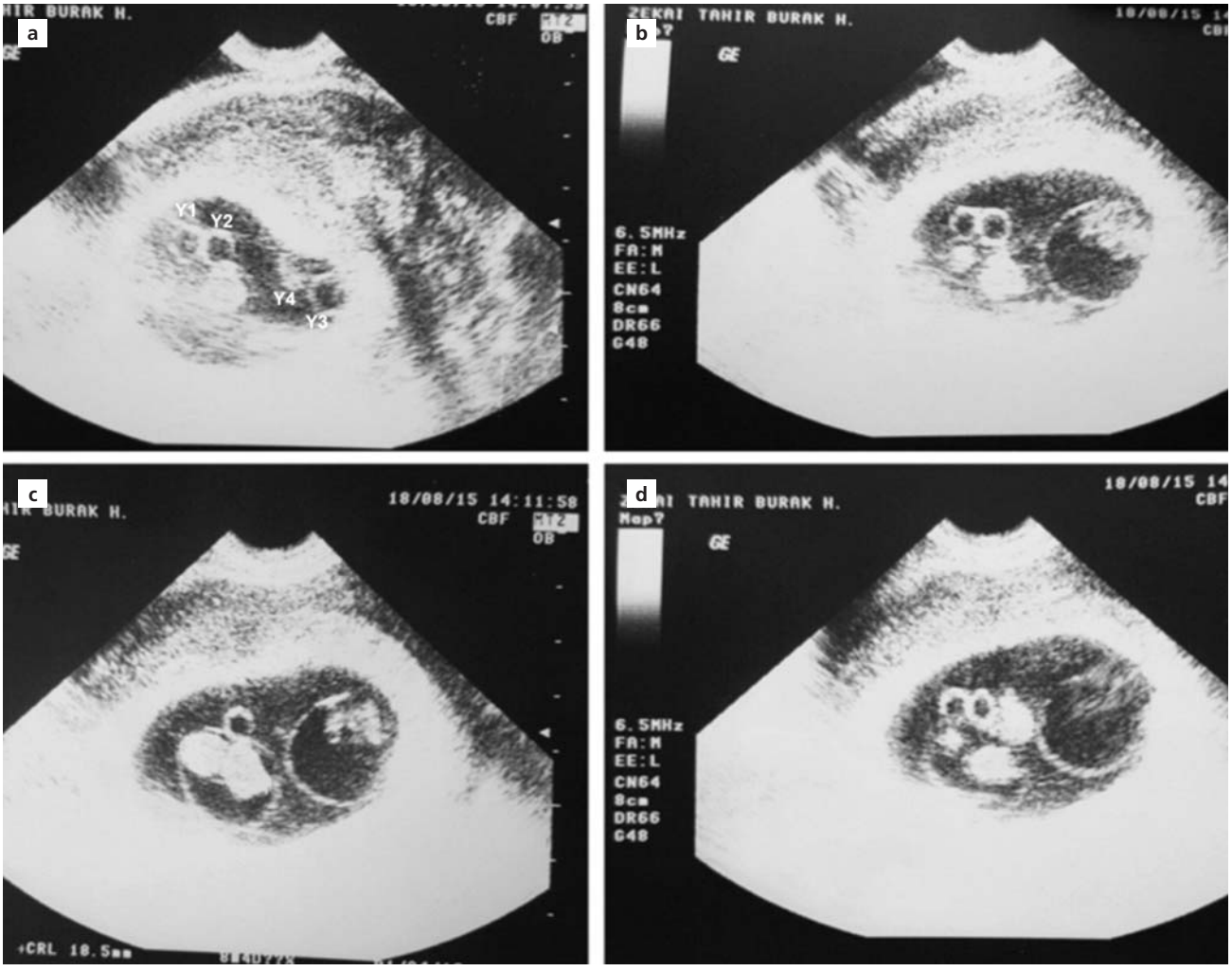

Fig. 2. (**a-d**) Transvaginal ultrasonography of pregnancy at 84/7 weeks: Four fetuses in gestational sac (monochorionic quadramniotic quadruplets; four of them cannot be seen in the same image).

In fact, establishing the diagnosis of MZ multiple pregnancies at early stages can be beneficial for ART. In this case, we performed first imaging at 55/7 weeks. We observed four fetuses in a single gestational sac and the case revisited us for examination three weeks later. Retrospective studies report that the number of aneu-

Table 1. Monochorionic quadramniotic pregnancies after ART reported in the literature up to the present.

Publication	Zona pellucida injury			Embryonic stage	Number of embryos transferred	Pregnancy	Approach	Outcome
	ICSI	Assisted hatching	Embriyo biopsy					
Liu et al., 2010	No	No	No	Cleavage	2	MCQA	-	Low
Saravelos et al., 2015	Yes	No	Yes	4th day	1	MCQA	Reduction	MCDA C/S at $35^{6/7}$ week
Karataş et al., 2016	Yes	No	No	Blastocyte	1	MCQA	Termination	

ICSI: intracytoplasmic sperm injection, **MCDA:** monochorionic diamniotic, **MCQA:** monochorionic quadramniotic

ploid embryo increases as gonadotropin dose increases. Rubio et al.[12] reported in the prospective study comparing standard and low doses of gonadotropin regimes that fertilization rate and normal blastocyte number chromosomally increased significantly despite the decrease in oocyte number with low dose, and pregnancy and live birth rates were similar. Since a few cases of MZ triplet pregnancy and only 3 cases of quadruplet pregnancy occurring after ART were reported in the literature, it is hard to identify specific ART methods causing such cases. Yet, the couples should be informed about the possibility of MZ multiple pregnancy during ART cycle. Also, it may be more appropriate to examine cases more frequently under unclear conditions in particular.

Conclusion

Early diagnosis by ultrasonography and prenatal consultation are very important to determine prognostic indicators affecting perinatal outcomes in ART pregnancies. Although such cases can be prepared for elective reduction procedure in the earliest period with strict follow-up, embryonal-fetal loss possibility can be high due to monozygosis. To the best of our knowledge, this is the third case in the world reported as MZ quadruplet pregnancy by single-embryo transfer after ART.

Conflicts of Interest: No conflicts declared.

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