


Bilateral tubal pregnancies after a single-embryo transfer

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Abstract

Case: To present an extremely rare case of bilateral tubal pregnancies following a single-embryo transfer in a woman with a 4 year history of infertility prior to seeking assisted reproductive technology.

Outcome: A pregnancy resulted from the transfer of an embryo that had been thawed from a frozen blastocyst during a hormone replacement cycle. An ultrasound that was performed at 5 weeks and 5 days of gestation revealed a gestational sac, embryo, and heartbeat in the right fallopian tube and similar signs of a gestational sac in the left fallopian tube. A laparoscopy revealed clear signs of an ectopic pregnancy in the ampulla of the right fallopian tube. Signs of swelling also were seen in the ampulla of the left fallopian tube. As the possibility of bilateral tubal pregnancies could not be ruled out, both fallopian tubes were removed. Pathological tests revealed chorionic villi and trophoblasts in both the left and right fallopian tubes.

Conclusion: All previously reported cases of bilateral tubal pregnancies have been a result of multiple ovulations or multiple-embryo transfer and no case of bilateral tubal pregnancies after a single-embryo transfer has ever been reported. No genetic testing was performed; thus, it cannot be definitively stated that the divided chorionic villi and trophoblasts came from only one embryo.

KEYWORDS

ectopic pregnancy, in vitro fertilization, laparoscopic surgery, single-embryo transfer, tubal pregnancy

1 | INTRODUCTION

In 2008, the Japan Society of Obstetrics and Gynecology (JSOG) indicated that only the transfer of single embryos would be sanctioned. Since then, the single-embryo transfer has become the standard protocol in Japan and the number of ectopic pregnancies is believed to have declined. According to a recent report, the incidence of ectopic pregnancy as a result of assisted reproductive technology (ART) was ~0.8% in 2014.¹ The reported rate of bilateral tubal pregnancies after ART was 1 in every 750-1850 ectopic

pregnancies. Bilateral tubal pregnancies are extremely rare in natural pregnancies, with an incidence of only 1 in 200 000.² All previously reported cases of bilateral tubal pregnancies, both in Japan and overseas, have been a result of multiple ovulations³⁻⁵ or multiple-embryo transfer.⁶⁻¹³ As far as can be ascertained from a database search, no case of bilateral tubal pregnancies after a single-embryo transfer has been reported. Reported herein is an extremely rare case of bilateral tubal pregnancies following a single-embryo transfer as a blastocyst in ART. This appears to be the first such case to be reported worldwide.

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2 | CASE REPORT

A woman was first examined in May 2004, complaining of infertility for 4 years. Bilateral hydrosalpinx was diagnosed on the basis of a hysterosalpingography. The patient was positive for *Chlamydia* immunoglobulins G and A and antibiotics therefore were prescribed. The basal level of serum prolactin was 52.3 ng/mL, so terguride was prescribed.

In August 2004, the bilateral hydrosalpinx were treated with a laparoscopic uterine adnexal adhesiolysis and salpingostomy. A natural pregnancy subsequently was not achieved after six cycles of the timing method and the patient proceeded to in vitro fertilization (IVF) and embryo transfer. Between 2006 and 2011, the woman conceived and delivered three children via IVF.

The patient presented again in 2014 with the intention of conceiving a fourth child. Short-protocol controlled ovarian stimulation was carried out. As there was a risk of ovarian hyperstimulation syndrome, all the embryos were frozen using vitrification. The medium that was used was Continuous Single Culture™ (Irvine Scientific, Santa Ana, CA, USA).

A pregnancy resulted from the transfer of a single embryo (Gardner classification: 5AA) that had been thawed from a frozen blastocyst (Gardner classification: 3AA) (Figure 1) during a hormone replacement cycle using an estradiol (E2) patch and progesterone (P4) vaginal suppository. Three days after the transfer of the embryo, the serum E2 level was 74.6 pg/mL and the serum P4 level was 10.31 ng/mL. An ultrasound that was performed at 5 weeks and 5 days of gestation revealed a gestational sac (GS), embryo, and heartbeat in the right fallopian tube. Signs resembling those of a GS also were seen in the left fallopian tube (Figure 2). The serum concentration of β -human chorionic gonadotropin was 15 665.0 mIU/mL and an ectopic pregnancy therefore was diagnosed.

Laparoscopic surgery was performed and revealed clear signs of an ectopic pregnancy in the ampulla of the right fallopian tube. Signs of swelling also were seen in the ampulla of the left fallopian tube (Figure 3). As the possibility of bilateral tubal pregnancies could not be ruled out, both fallopian tubes were removed (Figure 4). Pathological tests revealed chorionic villi and trophoblasts in both the left and right fallopian tubes (Figures 5 and 6). Thus, bilateral tubal pregnancies

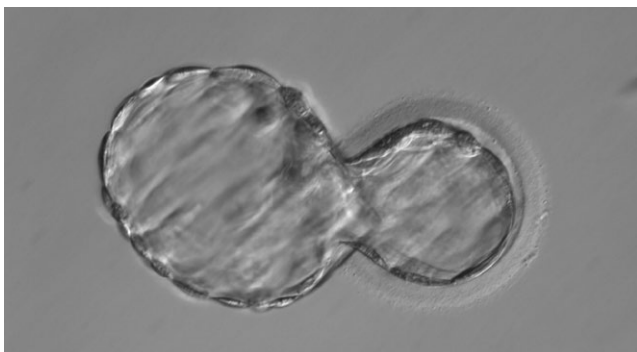


FIGURE 1 Transferred blastocyst (Gardner classification 5AA) $\times 300$. Assisted hatching(+)

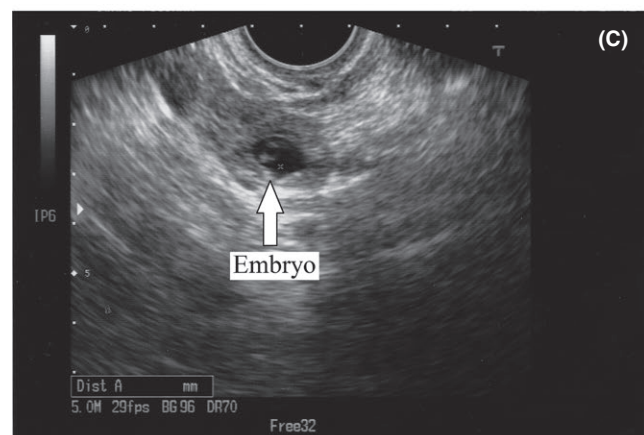
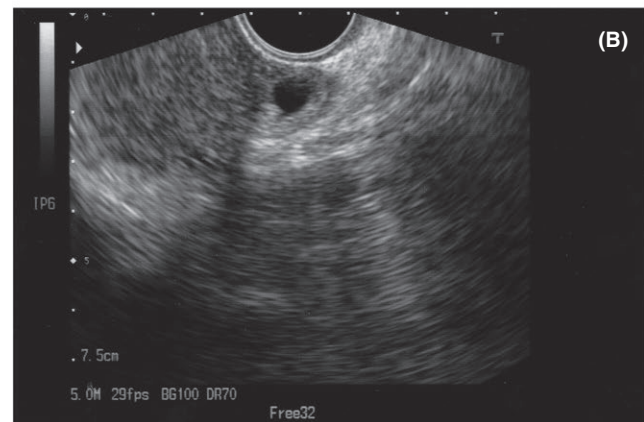
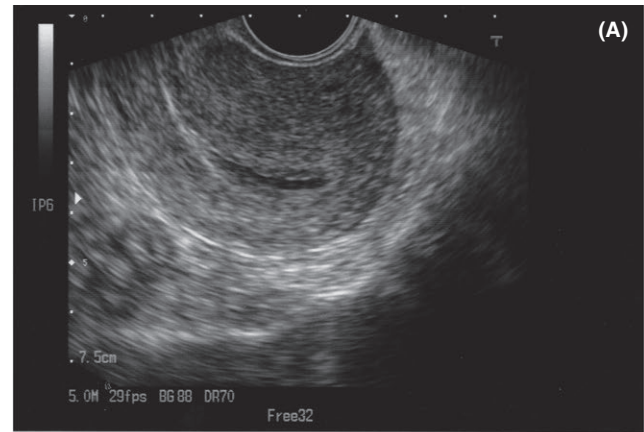


FIGURE 2 Ultrasound findings. A, Gestational sac (GS)(-) in the uterus; B, GS(+) in the left fallopian tube; and C, GS(+) in the right fallopian tube and heartbeat(+)

resulting from the embryo transfer of a single blastocyst, an extremely rare occurrence, therefore was diagnosed.

3 | DISCUSSION

This report describes an extremely rare case in which a single embryo that was fertilized by ART and transferred into the uterus subsequently resulted in bilateral tubal pregnancies. This procedure was performed by using a frozen-thawed embryo in a blastocyst

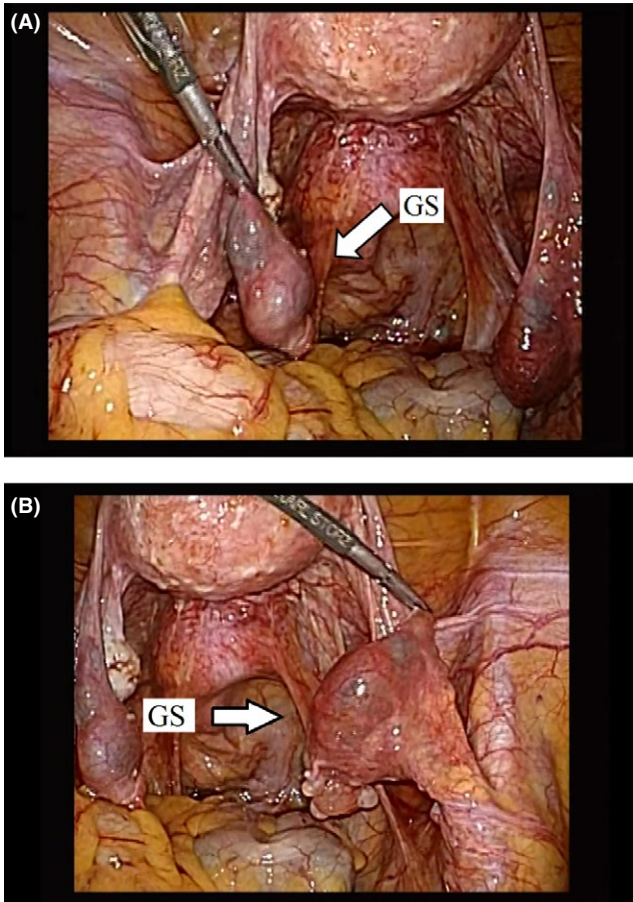


FIGURE 3 Laparoscopic findings. A, Gestational sac (GS) in the left fallopian tube; and B, GS in the right fallopian tube

transfer during a hormone replacement cycle using an E2 patch and a P4 vaginal suppository and then monitored by ultrasound and hormonal testing. No growing follicle was detected at the time of the embryo transfer; therefore, it was thought that natural ovulation did not occur. Although previous case reports have described bilateral tubal pregnancies due to multiple ovulations³⁻⁵ or multiple-embryo

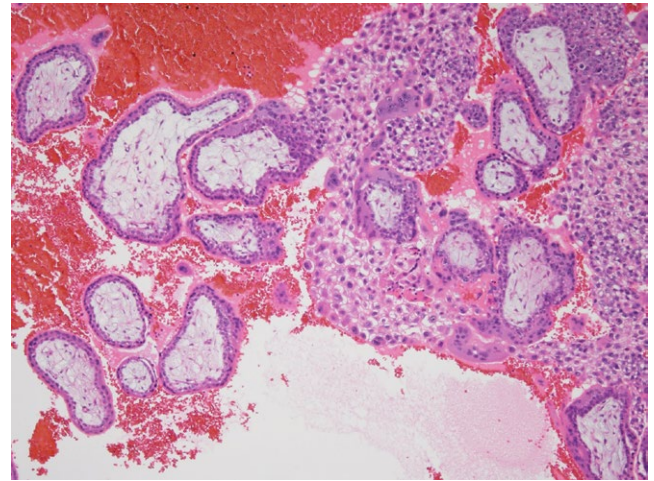


FIGURE 5 Pathological findings (right fallopian tube) $\times 400$. Chorionic villi(+)

transfer,⁶⁻¹³ as far as can be ascertained from a database search, this represents the first case of bilateral tubal pregnancies after a single-embryo transfer to be reported worldwide. In the present case, the embryo was conjectured to have divided in the uterus after the transfer, forming monozygotic twins (MZT). These then traveled separately, with the inner cell mass and a portion of the trophoblast entering the right fallopian tube and the remaining part of the trophoblast entering the left fallopian tube before implantation. The authors believe that the divided chorionic villi and trophoblasts came from only a single embryo in this case, although there is no real proof due to a lack of genetic testing. The occurrence of MZT as a result of IVF was first reported in 1984¹⁴ and some cases of MZT born after ART have been reported since.¹⁵ Monozygotic twins can be generated when a blastocyst splits into two, on emerging from the zona pellucid.¹⁶ This theory is based on the increased frequency of MZT with intracytoplasmic sperm injection (ICSI) and assisted hatching (AH) and the frequency of MZT has been reported to be higher with ICSI, when compared with conventional IVF.¹⁷ The frequency is particularly high when AH



FIGURE 4 Removed fallopian tubes

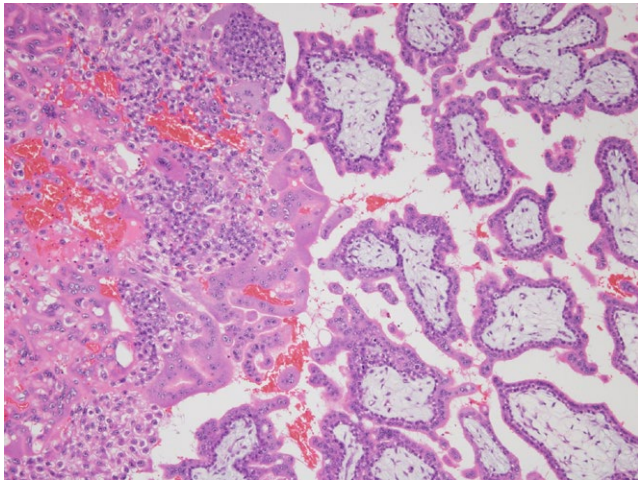


FIGURE 6 Pathological findings (left fallopian tube) $\times 400$. Chorionic villi(+)

is used.^{18,19} Other studies, however, have failed to establish any association between ICSI or AH and MZT.²⁰ The frequency of MZT also reportedly differs, depending on the method of ovarian stimulation, although the detailed mechanisms remain unclear.²¹

Previous studies have shown that the incidence of MZT is higher after blastocyst transfer, compared with that of early embryo transfer.²²⁻²⁴ A blastocyst transfer also was performed in the present case. In 2006, the American Society for Reproductive Medicine reported that, based on a discussion of the literature, the incidence of MZT in ART was 2.7%-13.2% and that this rate had risen with the increase in blastocyst transfers.²⁵ According to another retrospective study, the incidence of MZT was 1.57%, significantly higher than the 0% rate with early embryo transfer.²⁶ However, one study used a multivariate analysis of variance to show that, although MZT increased significantly with blastocyst transfer, compared with early embryo transfer, the rate has not risen since 2002.²⁷ Furthermore, the multivariate analysis of variance included only two papers, one of which included only a small number of patients; thus, the possibility cannot be ruled out that this improvement was related to as-yet-unexplained patient-specific variables, rather than to ART techniques. Conversely, another study reported that the rate of MZT was 2.6% for early embryo transfer, but 1.8% for blastocyst transfer.²⁸ Therefore, the authors have concluded that firm evidence remains insufficient for the notion that blastocyst transfer actually increases the incidence of MZT. Some authors also consider that long-term culture could be another cause.²⁰ According to this view, the reason is that hardening of the zona pellucida during long-term culture causes changes in its structure. Still others hold that the cause might be related to glucose concentrations in the culture solution, rather than the effect of long-term culture.¹⁶ According to the Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology,²⁵ keeping blastocysts in a low-glucose environment for long periods weakens cell binding in the inner cell mass, which is associated with MZT. However, one study stated

that the incidence of MZT had fallen during the last 8 years.²⁷ It was conjectured that this might be related to improvements in the blastocyst culture solution. Improved skills on the part of embryologists might be another reason for this decline.

In any case, the woman in this case report experienced bilateral tubal pregnancies after a single embryo was transferred into the uterus and presumably formed MZT that separated and traveled into the right and left fallopian tubes, where they implanted. Bilateral tubal pregnancies reportedly account for between 1 in 750 and 1 in 1850 ectopic pregnancies following ART and bilateral tubal pregnancies are extremely rare in natural pregnancies, with an incidence of only 1 in 200 000. Despite this rarity, a small number of case reports have described bilateral tubal pregnancies in natural pregnancy.²⁹⁻³² The possibility of this condition therefore must be considered when managing even natural pregnancies. Bilateral tubal pregnancies are far more likely to occur after ovulation induction or ART, compared with natural pregnancy, and thus more careful clinical observation is required.

DISCLOSURES

Conflict of interest: The authors declare no conflict of interest. *Human and Animal Rights:* Informed consent was obtained. This article does not contain any study with human or animal participants that has been performed by any of the authors.

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