



Ruptured ectopic pregnancy following a cycle of freeze-all in vitro fertilization: A case report

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ABSTRACT

Patients undergoing assisted reproduction are advised to abstain from intercourse to prevent the possibility of multiple pregnancy. If patients do not follow this advice, multiple dizygotic pregnancy or even a heterotopic pregnancy can result. We report the case of a 28-year-old nulliparous female with unexplained infertility who underwent freeze-all vaginal oocyte retrieval. Twenty-one days later she presented with vaginal bleeding (similar to menstruation) and right lower-quadrant pain. The results of ultrasound scanning and a laboratory work-up were consistent with an ectopic pregnancy. She underwent laparoscopic right salpingectomy for a tubal ectopic pregnancy. We recommend sexual abstinence during assisted reproduction to lower the risk of multiple pregnancy and especially of heterotopic pregnancy.

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1. Introduction

Over the last half century, assisted reproductive technology (ART) has enhanced the opportunity for pregnancy. However, ART has been associated with an increased risk of multiple pregnancy. In fact, the rate of multiple pregnancy after ART is 2.25 times higher than in the general population [1]. Current guidelines recommend single embryo transfer in patients with a good prognosis to reduce the risk of multiple pregnancy, which is associated with a marked increased risk of maternal and fetal morbidity. For the same reason, patients are generally advised to abstain from unprotected sex during cycles of in vitro fertilization (IVF).

When a twin pregnancy results from a single embryo transfer, the embryos are generally presumed to be monozygotic. However, there are reports of dizygotic twin pregnancies after single embryo transfer with, for example, twins of both sexes. This is due to spontaneous pregnancy near the time of embryo transfer. Ovarian stimulation immediately prior to transfer increases this risk. If an embryo is transferred soon after a spontaneous conception, there is the potential for multiple pregnancy or even heterotopic pregnancy.

2. Case Report

A 28-year-old nulliparous woman presented with a 3-year history of unexplained infertility. She had a normal hysterosalpingogram (HSG), decreased ovarian reserve with antimüllerian hormone (AMH) of 1.2,

an antral follicle count (AFC) of 17, and otherwise normal hormonal testing. Her spouse had a normal sperm count. After failing to conceive after 3 letrozole cycles, she requested IVF. She underwent an antagonist protocol with peak estradiol of 2541 pg/mL. She was triggered with 5000 IU hCG. She underwent vaginal oocyte retrieval, which yielded 12 oocytes. Due to the risk of ovarian hyperstimulation syndrome, all embryos were frozen for interval transfer. Six viable blastocysts were frozen.

Twenty-two days after oocyte retrieval she presented for follow-up and reported intermittent vaginal bleeding and acute onset of lower abdominal pain. A transvaginal ultrasound scan demonstrated a complex fluid collection measuring 3.8 × 3.5 cm consistent with blood clot in the cul-de-sac and no evidence of intrauterine pregnancy. There was clinical concern that she might have an ectopic pregnancy. A quantitative beta HCG test was elevated at 756. The patient said she had sexual intercourse several days prior to oocyte retrieval but that she had not had intercourse since that time.

A presumed diagnosis of ectopic pregnancy was made and the patient was transferred to a tertiary care center for further evaluation. She underwent laparoscopic right salpingectomy for a ruptured tubal ectopic pregnancy. Pathology evaluation was consistent with a tubal ectopic pregnancy.

The patient had an uncomplicated post-operative course and a complete recovery. She subsequently pursued frozen embryo transfer (FET).

3. Discussion

Our patient experienced a spontaneous pregnancy due to sexual activity during ovarian stimulation for assisted reproduction. She was

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diagnosed with an ectopic pregnancy prior to FET. Had she undergone embryo transfer prior to treatment of the ectopic pregnancy, she might have had a heterotopic pregnancy.

Superfecundation is the fertilization of two or more ova from the same cycle by sperm from separate acts of sexual intercourse. Heteropaternal superfecundation is the fertilization of two separate ova by separate partners and is more common in animals than humans. Monopaternal superfecundation is the fertilization of separate ova from the same partner, leading to dizygotic pregnancies [2]. Cases of monopaternal superfecundation have been reported by Peigne et al. and Amselem et al. [3, 4].

Multiple gestations can also result from a subtly different phenomenon called superfetation, which is the fertilization and implantation of a second embryo during an ongoing pregnancy. It is unlikely that superfetation can occur spontaneously, reported cases are suspected to be the result of undiagnosed growth discordance, interval delivery leading to the appearance of different gestational age, or initial misdiagnosis of a singleton pregnancy due to sonographic error. Nonetheless, superfetation may occur as a consequence of the cycle manipulation associated with assisted reproduction.

Potentially, if our patient had an (early and undetected) intrauterine pregnancy rather than an ectopic pregnancy, FET could have led to a multiple gestation. That is, our patient would have experienced two fertilization events during the same cycle, or superfecundation. However, depending on the timing of implantation, this could also have been superfetation if there was an ongoing pregnancy at the time of the embryo transfer.

Historically, twins from pregnancies resulting from assisted reproduction were most commonly dizygotic due to the high frequency of multiple embryo transfers. Recently, practice standards have shifted to favor predominantly single embryo transfer (SET), and therefore more twin pregnancies are now monozygotic [2]. In the setting of SET, it is typically assumed that multiple pregnancies are monozygotic. However, this assumption has been challenged. Takehara et al. [5] published a report of five cases of twins of different sex after SET. More recently, Vega et al. [6] published an analysis of 32,600 SET cycles and concluded that the incidence of twin pregnancies after SET is approximately 2% and that up to 18% of those twins are dizygotic. They also found that the main risk factor for dizygotic twins was a diagnosis of unexplained infertility or obesity.

Both Takehara [5] and Vega [6] used infant sex as the primary method to determine zygosity. However, dizygotic twins of the same sex are also possible and therefore it is likely that the number of dizygotic twins is underreported. Other ways of determining zygosity include assessing chorionicity and amnionicity, placental characteristics, infant blood type, HLA typing, and DNA fingerprinting. These methods, however, are both invasive and expensive. It is possible that the rate of superfecundation during assisted reproduction is higher than previously thought, since it is usually not suspected unless the fetuses are of different sex.

Patients should not engage in sexual activity during ovarian stimulation and one could argue that they should not do so during an entire ART cycle. However, counter to this, one study has demonstrated a benefit of sexual activity during ART, presumably due to exposure to semen [7]. Tremellen et al. [7] designed a multicenter prospective randomized

controlled trial in which participants either had thawed embryo transfer or fresh embryo transfers. No significant differences were observed in the pregnancy rates between the intercourse and abstinence groups (23.6% vs 21.2%). However, the proportion of transferred embryos that remained viable at 6–8 weeks of gestation was significantly higher in the intercourse group than in the abstinence group (11.01 vs 7.69 viable embryos per 100 transferred embryos, $p = 0.036$).

Cases of superfecundation during ART are presumed to be due to spontaneous pregnancy around the time of the ovarian stimulation. Patients should be carefully informed of the reasoning behind and timing of abstinence during ART cycles. While it is likely that most twin pregnancies after SET are monozygotic, chorionicity, amnionicity, and infant gender should always be assessed by ultrasonography even after SET.

Contributors

All authors contributed equally to the preparation of this case report and saw and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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Patient Consent

Obtained.

Provenance and Peer Review

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