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## Case Report

## A rare case of heterotopic quintuplets pregnancy

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## ABSTRACT

**Objective:** We report a rare case of heterotopic pregnancy and high-order pregnancy occurring simultaneously following the use of the assisted reproductive technique (ART).

**Case report:** A 29-year-old woman, Gravida 2 Para 1, became pregnant after receiving intrauterine insemination (IUI). She came to our emergency room due to diffuse low abdominal pain at seven weeks of gestational age. Transabdominal sonography (TAS) revealed a quadruplet intrauterine pregnancy with an enlarged left adnexa and intrapelvic fluid accumulation. Simultaneous occurrence of high-order pregnancy and left tubal pregnancy with internal hemorrhage was suspected. The patient received an emergent laparoscopic resection of the affected Fallopian tube and recovered well for the remaining hospitalization course. Afterwards, she received fetal reduction procedure and eventually gave birth to twin babies.

**Conclusion:** Gynecologist should increase the awareness of heterotopic pregnancy in patients receiving ART. On the other hand, reproductive endocrinologist should reduce the risk of high-order pregnancy without compromising pregnancy rate.

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## Introduction

Both heterotopic pregnancy and high-order multiple gestation are relatively rare in natural conceptions, with incidences of 1/30000 [1] and 3/10000 [2], respectively. However, the incidence increases dramatically through the use of assisted reproductive techniques (ART). For this reason, they are considered as two main complications caused by ART that may greatly increase the obstetric risk. Yet, it is still rare to see these two events occurring concomitantly even in the women receiving ART. We report the first case of a heterotopic pregnancy consisting of a left tubal pregnancy and a quadruplet intrauterine pregnancy following ovulation induction and intrauterine insemination (IUI). Both prevention and management of these two complications are crucial to the obstetric outcome of patients receiving ART.

## Case report

A 29-year-old pregnant woman came to our emergency room due to diffuse low abdominal pain for one day. She had received

combined IUI and ovarian stimulation by gonadotrophin 1 month ago at a local fertility centre. She was at the gestational age of seven weeks when presenting at our hospital. The patient had a history of cesarean delivery due to fetal-pelvic disproportion two years ago, in which her baby died at the age of two years due to unilateral lung agenesis. Her other history included polycystic ovarian syndrome (PCOS) with irregular menstrual cycles for many years. Her anti-müllerian hormone level was 10.32 ng/mL at the time of ovarian stimulation and IUI. Prior to this fertility therapy, she had received several cycles of clomiphene citrate induction, but all failed to result in pregnancy.

At the emergency room, her vital signs were relatively stable except for mild tachycardia (Pulse rate: 104/minute). Transabdominal sonography (TAS) revealed a quadruplet intrauterine pregnancy (Fig. 1) with an enlarged left adnexa (Fig. 2) and intrapelvic fluid accumulation. Heterotopic pregnancy with tubal rupture and internal hemorrhage was suspected. Accordingly, admission for hospitalization and emergent laparoscopic surgery were arranged.

During the operation, left tubal pregnancy with rupture was confirmed. About 500 ml of internal hemorrhage was noted and aspirated. Left salpingectomy was performed subsequently (Fig. 3). There was neither other abnormality noted nor any specific complication occurred during the whole procedure. The patient

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Fig. 1. Quadruplet intrauterine pregnancy.

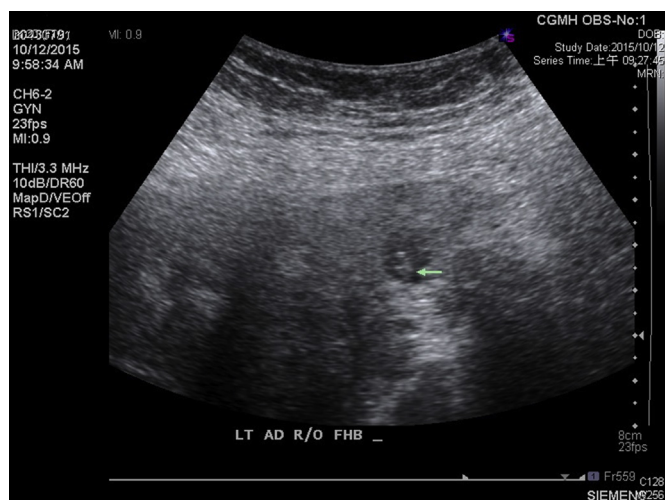


Fig. 2. Left tubal ectopic pregnancy.

recovered well after the surgery and she was discharged two days later under stable condition.

Four weeks later, follow-up TVS showed only triplet intrauterine pregnancy remained (Fig. 4). After a thorough discussion about the risk of high-order pregnancy, the patient agreed for fetal reduction procedure. Potassium chloride was then injected into the heart of one fetus under ultrasound guidance, which resulted in remaining twin pregnancy.

Finally, the patient received a scheduled cesarean section at 36 weeks of gestational age, during which two live babies were delivered successfully.

## Discussion

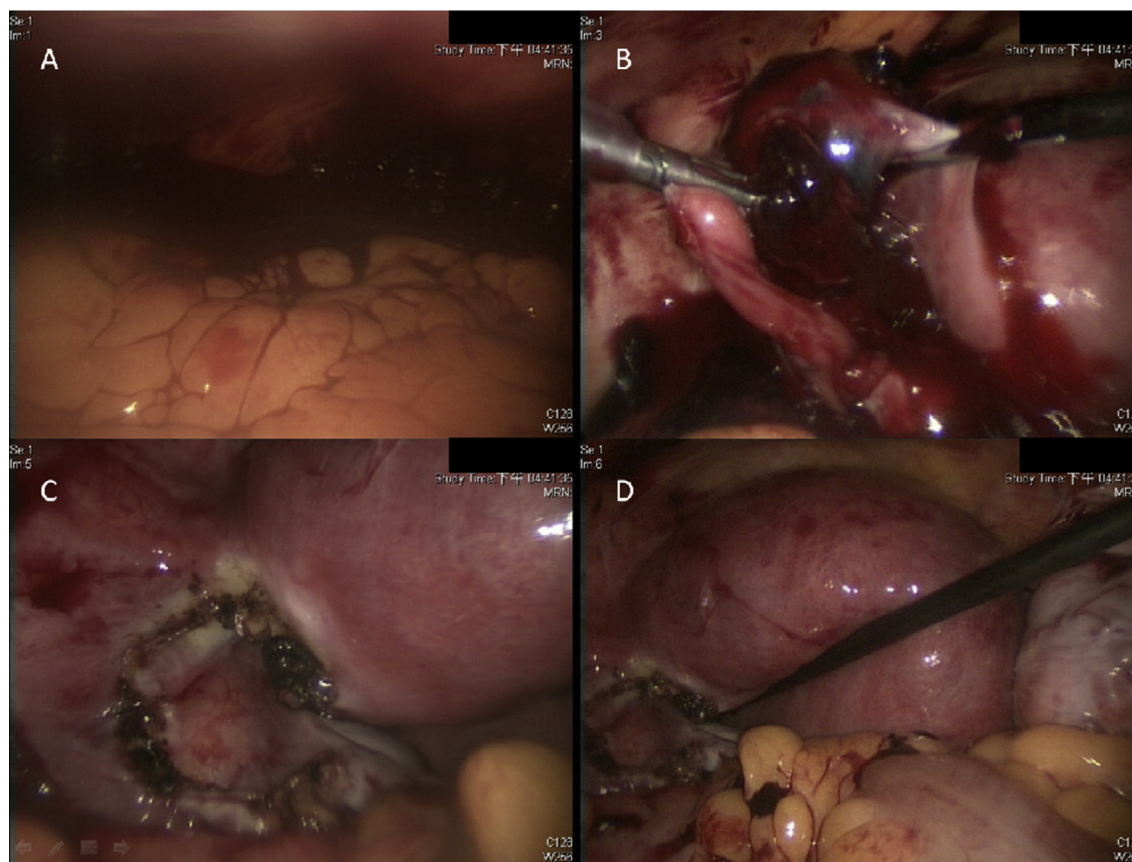
Heterotopic pregnancy is defined as the coexistence of an intrauterine pregnancy and ectopic pregnancy. In natural conceptions, heterotopic pregnancy is a rare event, which has an estimated incidence of 1 in 30000 pregnancies [1]. However, in cases of assisted reproduction techniques (ART), its incidence increases by 300 fold (about 1 in 100 pregnancies) [1]. It is often difficult to make an early diagnosis of heterotopic pregnancy, because a

gynecologist may neglect the small possibility of a concurrent ectopic pregnancy in the presence of an intrauterine pregnancy (IUP) [3]. On the other hand, patients often display no obvious symptoms prior to tubal rupture. Furthermore, imaging study via ultrasound may not always detect an ectopic pregnancy accurately (Previous case report has demonstrated an initial ultrasound mistakenly regarded the ectopic pregnancy as corpus luteum cyst, which resulted in a delay in diagnosis) [4]. Such an event can occur when the serum hCG level is much higher than expected. Therefore, careful evaluation of bilateral adnexa, cervical canal, and uterine horns should be routinely performed during early pregnancy ultrasound examinations even after an IUP has been confirmed, especially for patients receiving ART. Early diagnosis of heterotopic pregnancy is crucial in order to provide prompt management, preventing any morbidity or mortality.

Following the confirmation of heterotopic pregnancy, the next challenge is to remove it successfully without harming the IUP. Since most heterotopic pregnancies are discovered after tubal rupture, similar to our case, the standard management is surgical removal of the affected fallopian tube either by laparoscopy or laparotomy, according to the patient's hemodynamic status. For the lesser group of patients who are diagnosed with a heterotopic pregnancy prior to tubal rupture, alternative management may be considered. These include ultrasound-guided injection of Potassium Chloride [5,6], direct injection of Methotrexate (MTX) via ultrasound guidance into the ectopic sac [7], or ultrasound-guided aspiration of the ectopic sac followed by local MTX injection [8]. These less invasive procedures can successfully prevent serious life-threatening conditions such as tubal rupture without affecting the surviving intrauterine pregnancies [5–8].

Currently, there is no single method that can completely prevent the occurrence of heterotopic pregnancy in patients receiving ART. Previous literature had demonstrated that the increased incidence may be related to high levels of estradiol and progesterone and high numbers of transferred embryos or ovulated oocytes [9,10]. This is corresponding with our case, a PCOS patient receiving hyperstimulation of ovary therapy with an uncontrolled number of fertilized oocytes via the use of IUI. In patients receiving in vitro fertilization (IVF), volume and viscosity of transfer medium, as well as the experience of the doctor performing embryo transfer, may also be the contributing factors [9]. Therefore, choosing IVF instead of super-ovulation combining IUI in patients with PCOS, limiting numbers of embryos to be transferred, using appropriate medium, and emphasizing on the training of embryo transfer technique are reasonable approaches to minimize the incidence of heterotopic pregnancy.

A high-order multiple gestation is also a rare event in natural conception. Similar to heterotopic pregnancy, its incidence increases amongst patients receiving ART. The growing trend of ART practice has led to a significant increase in high-order multiple gestation [11]. The most notable risk of high-order multiple gestation is premature birth. The severity of its associated complications is greatly related to the degree of multiple gestation, because of the higher the order of multiple gestation, the shorter the average length of pregnancy [12]. The previous study had shown that increasing total numbers of follicles and increasing peak serum estradiol concentrations during ovarian stimulation cycles correlated significantly with an increasing risk of high-order multiple pregnancies [13]. The risk can be reduced by using a lesser degree of ovarian stimulation, which results in lower peak serum estradiol concentrations. However, this approach would increase the number of cycle cancellations and therefore sacrifice rates of pregnancy and raise accumulative costs. This often presents a great challenge for a fertility doctor to reduce the risk of high-order multiple gestation without compromising the pregnancy rate.



**Fig. 3.** Emergent laparoscopy showing internal hemorrhage (A), resection of left tubal pregnancy (B), remaining left adnexa (C), and last look prior to completion of surgery (D).



**Fig. 4.** Remaining triplet pregnancy prior to fetal reduction.

In our case, the patient who was diagnosed with PCOS had received a combination of IUI and ovarian stimulation by gonadotrophin injections. Although such ART procedure performed on PCOS patients can improve pregnancy rate to a substantial degree, the risk of high-order multiple gestation is also markedly increased [14]. A recommended approach to reduce such risk without reducing the pregnancy rate is via the use of IVF, especially in

patients with PCOS or high antral follicle count. Through the use of IVF, the number of embryos being transferred can be limited to two or less, in order to prevent high-order multiple gestation [15]. Although IVF may seem to increase the treatment costs when compared with the combination of IUI and ovarian stimulation [16]. Besides, very premature births resulting from high-order multiple gestation is very costly not mentioning its high perinatal complication rate. In this case, fetal reduction provides a better pregnancy outcome with premature birth before 32 weeks reduced to 10.1% from 20.3% and miscarriage before 24 weeks reduced to 5.1% from 11.5% [17]. Nevertheless, the fetal reduction has its own risks, which includes the inexperience of the operator and the possibility that one or more of the remaining fetuses will not survive. Therefore, our focus should be emphasized on preventing the occurrence of high-order multiple gestation rather than management of complication.

In conclusion, both heterotopic pregnancy and high-order multiple gestation are two serious complications associated with ART. Although it is impossible to prevent their occurrences completely, we can reduce the incidence by choosing the appropriate treatment, achieving the goal of individualized therapy for each infertile or subfertile couple. On the other hand, early diagnosis and proper management of these two complications are crucial for both maternal and fetal well-being.

#### Conflict of interest

All the authors have no conflict of interest.



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