Triple heterotopic pregnancy comprising ectopic tubal and double monochorial intrauterine pregnancy: a case report and review of the literature

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Abstract
Introduction
We present the case of a 47-year-old woman with triple heterotopic pregnancy following in vitro fertilisation therapy, characterised by double monochorial, biamniotic intrauterine pregnancy coexisting with ectopic tubal pregnancy.

Case report
A 47-year-old nulliparous woman in her second pregnancy presented with a history of one previous miscarriage. The diagnosis was established very early by vaginal ultrasound, thereby allowing for surgical treatment before the development of complications. The monochorial pregnancy progressed unfavourably, with late feto-foetal transfusion syndrome, preeclampsia and premature delivery in 30 weeks of pregnancy.

Conclusion
A diagnosis of heterotopic pregnancy must be considered in all patients with risk factors such as endometriosis, uterine or adnexal surgery or the use of assisted reproduction techniques.

Introduction
Heterotopic pregnancy is defined as ectopic pregnancy associated with intrauterine pregnancy. Its frequency ranges between 1/8,000 and 30,000 live newborn infants, though the rate reaches up to 1/100 in patients subjected to assisted reproduction and ovulation induction techniques.1,3–6

Case report
A 47-year-old nulliparous woman in her second pregnancy (week 6+3 of amenorrhea, according to the date of embryo transfer) presented with a history of one previous miscarriage. She reported to the emergency room of our hospital referred from a private centre, with a diagnosis of heterotopic pregnancy.

The patient presented no clinical history of interest other than hysteroscopic surgery due to the presence of an endometrial polyp, and antecedents of primary infertility for which assisted reproduction treatment had been provided. An in vitro fertilisation–intracytoplasmic sperm injection cycle was performed, with double-embryo transfer on day 5 of development. The patient presented without pain, bleeding or other symptoms. The gynaecological examination proved normal, without pain in response to cervical mobilisation or bimanual palpation. No bleeding, masses or clinical signs of acute abdomen were noted. The blood beta-human chorionic gonadotropin (BHCG) level was 423 mU/ml over the previous 14 days.

Vaginal ultrasound revealed a 15-mm twin monochorial biamniotic intrauterine pregnancy (Figure 1) with

Figure 1: Initial monochorial biamniotic intrauterine pregnancy (6 weeks).

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Two embryonic images: a 4-mm first vitelline vesicle with a 6.2-mm embryo showing positive cardiac activity and a 3.3-mm second vitelline vesicle with a 5.8-mm embryo likewise showing positive cardiac activity. In addition, an 8-mm extraterine gestational sac was observed in the left tube (Figure 2), characterised by a 2.6-mm vitelline vesicle with a 4-mm embryo showing positive cardiac activity (Figure 3). The right fallopian tube proved normal. No free fluid was observed in the pouch of Douglas.

The patient was admitted for treatment. A laparoscopic partial left salpingectomy was performed the next day to remove the ectopic implantation. The procedure was uneventful, and the pathology report confirmed the presence of the fallopian tube with luminal pregnancy, placenta accreta, hematosalphinx and paratubal cysts. The postoperative course was good, allowing patient discharge 72 h after the operation. Ultrasound prior to discharge confirmed vitality of the two intrauterine embryos.

Late feto-foetal transfusion syndrome was diagnosed in week 26. Considering the gestational age, patient control and monitorisation was decided. Ultrasound showed a first foetus with an estimated weight of 936 g (p45), a visible bladder, a maximum amniotic fluid column of 2 cm and normal umbilical artery and middle cerebral artery Doppler ultrasound findings. The second foetus in turn had an estimated weight of 1358 g (p99), a visible bladder, a maximum amniotic fluid column of 12 cm and normal umbilical artery and middle cerebral artery Doppler ultrasound findings. In week 26+2, the patient was admitted due to premature membrane rupture, and prophylactic antibiotic treatment was started.

One week after admission, the patient presented blood pressure elevation, with increased transaminase levels. Oral labetalol was therefore started. In week 30+2, emergency caesarean section was required because of a pathological cardiotocographic recording, with the delivery of two females (1620 g – Apgar 8/9 and 1580 g – Apgar 7/8, respectively). After birth, both infants were admitted to the neonatal intensive care unit, where respiratory support was required due to the development of a neonatal respiratory distress, followed by a favourable course. There were no other complications secondary to prematurity, and the infants were discharged 35 days after admission, with subsequent control in the paediatric unit.

Discussion

As has been commented, heterotopic pregnancy is an uncommon condition in which a high degree of suspicion is needed in order to establish the diagnosis, though up to 71% of all patients with heterotopic pregnancies present risk factors that are similar to those associated with simple ectopic pregnancies, such as pelvic inflammatory disease, tubal surgery, tubal damage or malformations, previous ectopic pregnancy and fertility treatment techniques (ovulation induction and in vitro fertilisation as in our case)²,³,⁷,⁹. Such clinical antecedents and risk factors, the clinical manifestations of the patient, the BHCG levels and the existence of suggestive ultrasound findings can help us establish a definitive diagnosis in 41–66% of the cases²,⁵. However, in a substantial percentage of patients (up to 18%), the diagnosis is established by surgery².

In assisted reproduction techniques, the risk is increased by the use of abundant fluid in transfer, a larger number of transferred embryos and embryo positioning in the depths of the uterus instead of in the mid-portion of the uterine cavity⁶. The Trendelenburg position possibly might also represent a contributing factor²,⁶. The most common location of the ectopic component is in the fallopian tube (up to 62–72% of all cases)²,³,⁵, though other locations are...
The diagnosis is thus difficult to establish, and assessment should not be limited to verification of an intrauterine pregnancy. In effect, we always should use ultrasound to evaluate the adnexa and rule out other conditions, particularly in women with risk factors and subjected to treatment with assisted reproduction techniques.11

Ninety per cent of all cases are diagnosed in the first 3 months of pregnancy7–9,12, though reports have also been published of cases diagnosed in the second trimester9. The presence of cardiac activity as established by ultrasound in an adnexal mass confirms the diagnosis13. In the absence of cardiac activity, certain ultrasound findings can cause us to suspect a heterotopic tubal pregnancy, provided the cavity is not empty, e.g. an adnexal mass or hyper-echogenic ring around the presumed extrauterine gestational sac.1 One of the most common differentiating ultrasound findings is a haemorrhagic corpus luteum.7,10. In the case of heterotopic pregnancies after ovarian stimulation in the context of in vitro fertilisation, the presence of ascites can be confused with the haemoperitoneum accompanying damage-producing ectopic pregnancies.14

The blood BHCG levels may contribute to the diagnosis, though this parameter could be misleading, since intrauterine pregnancy can mask BHCG production by the placenta itself4,5,11. Nevertheless, subsequent patient follow-up may detect a decrease in BHCG with persistence of the intrauterine pregnancy.

Culdocentesis may be useful for diagnosing haemoperitoneum, though this procedure practically has been displaced by the new ultrasound techniques5,11.

Case report

One of the key aspects in relation to patients of this kind is the type of treatment required. Both clinical and surgical methods are available, and we can decide to use one option or the other depending on the state of the intrauterine pregnancy and the haemodynamic condition of the patient. In some cases, conservative medical follow-up may be decided, though hormonal or ultrasound monitoring has not been demonstrated to be of help4. Regarding medical treatment, different systemic or local modalities have been proposed, involving the injection of methotrexate, potassium chloride and hyperosmolar glucose1,2,5,8–10—though such procedures involve an increased risk for the intrauterine pregnancy (particularly when systemic methods are used). Methotrexate must be discarded due to its teratogenic effects in the case of evolving intrauterine pregnancy. On the other hand, these techniques pose a risk of infection and ectopic pregnancy rupture6 and are associated with a subsequent need for surgery in up to 55% of the cases.7 Local injection of a mixture of potassium chloride and methotrexate has been described in ectopic pregnancy, producing collapse of the gestational sac, which is then extracted. This approach lessens the duration and magnitude of exposure of the intrauterine component.8

Surgery usually constitutes definitive treatment. The route (laparotomy versus laparoscopy) is decided depending on the haemodynamic status of the patient and the surgical urgency at the time of the operation. The laparoscopic route should be used in cases of small ectopic pregnancies in the absence of damage, while laparotomy is indicated in damage-producing ectopic pregnancies and life-threatening circumstances11. The main complications of laparoscopy are hypercapnia and foetal acid–base changes secondary to the absorption of carbon dioxide, as well as exposure to the smoke.

Figure 3: Tubal ectopic pregnancy and embryonic heart beat.
and toxic gases of electrocoagulation (the most harmful gas being carbon monoxide) and uterine perforation with the Veress needles. Successful laparoscopic techniques without gas have been described with a view to avoiding these complications. The briefer the duration of uterine manipulation, the lesser the risk of harmful effects for the intrauterine pregnancy, minimising irritability and postoperative contractions. As potential negative effects, we have miscarriage, bleeding or possible chorioamnionitis.

Clayton et al. conducted a review of intrauterine pregnancies in the presence of heterotopic pregnancies and found the probability of miscarriage to be two times greater than in simple pregnancies. In turn, the risk of induced termination of pregnancy was seen to be up to 10 times higher in heterotopic pregnancies. Furthermore, the probability of delivering a healthy child was 30% lower in pregnancies of this kind than in single pregnancies.

Conclusion
The possibility of heterotopic pregnancy in patients with risk factors (endometriosis, uterine or adnexal surgery and assisted reproduction techniques) must be kept in mind, given the lack of specificity of the clinical manifestations and diagnostic test findings. An early diagnosis with rapid treatment can be important (as in our patient) for both maternal health and for the viability of the intrauterine component, since the probability of pregnancy to term is high when early treatment is provided. This is confirmed by our own case, in which the patient gave birth to two girls with a good Apgar score at birth and a favourable posterior course.

Consent
Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal.

Abbreviations list
BHC, beta-human chorionic gonadotropin.

References