Management and outcome of heterotopic interstitial pregnancy: Case report and review of literature

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Abstract

Objective: To report a case of heterotopic interstitial pregnancy after in vitro fertilization-embryo transfer (IVF-ET), presenting with a second trimester uterine rupture. To review the clinical presentations, risk factors, treatment options, and outcome of heterotopic interstitial pregnancies.

Methods: We describe the clinical presentation, management, and outcome of a patient with a heterotopic interstitial pregnancy, diagnosed following second trimester rupture of the interstitial pregnancy. We reviewed all published cases of heterotopic interstitial pregnancies.

Results: A 35-year-old pregnant woman with a past history of right adnexectomy and 16 weeks pregnant with dichorionic diamniotic twins following IVF-ET, was admitted to our department with unexplained recurrent abdominal pain and anemia. Further investigation showed a hemoperitoneum and because of hypovolemic shock an emergency laparotomy was performed, with diagnosis of a ruptured heterotopic interstitial pregnancy. The uterine defect was sutured using simple interrupted sutures. The intrauterine pregnancy progressed uneventful afterwards.

We found 86 cases in the published literature, reporting on heterotopic interstitial pregnancies. 80.2% (69/86) occurred after IVF-ET. History of uni- or bilateral salpingectomy is a major risk factor, present in 39.5% (34/86). 37.2% (32/86) presented with cornual rupture. Surgery was performed in 53.5% (46/86) of cases. Medical management was possible in case of unruptured, early diagnosed heterotopic interstitial pregnancy (32.6% (28/86)). Watchful waiting was only possible when the interstitial pregnancy miscarried (5.8% (5/86)). The live birth rate of the intrauterine pregnancy, when viable at presentation, was 70.0% (56/80). The live birth rate of the interstitial pregnancy was only 4.7% (4/86).

Conclusions: The majority of cases are diagnosed by detailed ultrasound in the setting of early follow-up after IVF-ET and are asymptomatic at diagnosis. Yet, a substantial number of patients present with cornual rupture. Risk factors are IVF-ET and a history of salpingectomy. Depending on clinical presentation, treatment options include watchful waiting, medical treatment, or surgery. Unfortunately, the interstitial pregnancy is generally lost, and only has a chance of survival in case of presentation at a viable gestational age. The outcome of the coexisting intrauterine pregnancy is generally good.

Keywords

Heterotopic pregnancy, ectopic pregnancy, interstitial pregnancy, uterine rupture, artificial reproduction technology, in vitro fertilization

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Introduction

Ectopic pregnancies occur in 1–2% of all pregnancies. Interstitial pregnancies are a rare type of ectopic

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pregnancy where the pregnancy is located in the interstitial part of the fallopian tube, and account for 1–4% of all ectopics.^{1,2} A heterotopic pregnancy implies the coexistence of an intrauterine and an ectopic pregnancy. It occurs 1 in 30,000 naturally conceived pregnancies. However, the more frequent use of assisted reproductive technologies (ART), including ovulation-induction, intrauterine insemination (IUI), in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI), leads to a rise in both ectopic pregnancy as well as dizygotic twinning rates, consequently leads to an increase in incidence of heterotopic pregnancy to 1.5% in pregnancies after ART. Subsequently, the overall incidence of heterotopic pregnancy has risen to 1 in 3900 pregnancies.³ The risk is higher when more embryos are transferred or when a tubal infertility factor is present.⁴ Previous data suggest that women with a history of salpingectomy have an increased risk of developing an interstitial pregnancy after IVF.⁵ The incidence of heterotopic interstitial pregnancy after IVF is unknown, yet through calculation of combined incidences it can be estimated to be as high as 1 in 3600 IVF pregnancies.^{5,6}

We report a case of ongoing intrauterine pregnancy and delivery of a healthy infant after second trimester rupture of a heterotopic interstitial pregnancy.

Case report

A 35-year-old patient was referred by her general practitioner because of the incidental finding of anemia, with a hemoglobin level of 6.9 g/dL. She was 16 weeks and 2 days pregnant with a dichorionic diamniotic twin, following ICSI fertilization with frozen embryo transfer of two embryos, with an apparent normal pregnancy evolution until then. It was her second pregnancy (Figure 1), yet the first miscarried at 6 weeks of gestation

Figure 1. Ultrasound of twin pregnancy performed at gestational age of 12 weeks. White arrow: intrauterine pregnancy; black arrow: interstitial pregnancy.

and was treated surgically with evacuation of the uterine cavity. Her medical history showed a right adnexectomy because of a benign ovarian cyst at birth and a laparoscopic ovarioplasty and adhesiolysis one year earlier.

Ten days before admission, the patient consulted at our emergency department because of intermittent colicky pain in the right iliac fossa with nausea and constipation. Abdominal and obstetrical ultrasound were reassuring, as well as the biochemical results, with a hemoglobin level of 10.6 g/dL, leucocyte count of $10.1 \times 10^9/L$ and C-reactive protein (CRP) level of 22 mg/L. She was thought to be suffering from constipation and bowel colics and was discharged from the hospital.

When readmitted because of anemia, abdominal ultrasound showed a moderate amount of peritoneal fluid. Biochemistry confirmed the hemoglobin level of 6.9 g/dL, no leucocytosis, CRP level of 94 mg/L and a normal kidney and liver function. MRI (Figure 2) was performed and revealed a hemoperitoneum with signal characteristics of recent and semi-recent bleeding. A clot was adherent to the right lateral side of the uterus. The twin pregnancy was viable and apparently intrauterine. Other intra-abdominal organs appeared normal.

Initial treatment was conservative and the patient was transfused with three units packed cells. However, 2 days later she developed hypovolemic shock. Urgent diagnostic laparoscopy with conversion to median laparotomy was performed, revealing a ruptured right uterine cornu

Figure 2. MRI performed during hospitalization because of anemia and abdominal pain, revealing hemoperitoneum.

with one fetus being located in the abdominal cavity. The cornual defect was repaired with simple interrupted stitches using a synthetic, absorbable, polyfilament suture. Intra- and postoperative assessment of the fetal well-being of the remaining fetus was reassuring. Patient was discharged from the hospital 5 days afterwards.

Further follow-up consisted of repeated ultrasound scans to evaluate myometrial thickness and fetal well-being. MRI was performed at 26 and 33 weeks of gestation and demonstrated a posterior placenta previa and an intact myometrial lining at level of the right cornu with minimal myometrial thickness of 3.7 mm at 26 and 2.3 mm at 33 weeks of gestation.

After administration of corticosteroids, an elective cesarean section was performed at 33 weeks of gestation. A healthy male infant was born, with birth weight of 2110 g and Apgar 8/9. Because of postpartum hemorrhage with persistent bleeding of the placental bed, a Bakri balloon was inserted. She could be discharged from the hospital 6 days after delivery.

Methods

A Medline computer search was performed using search terms “heterotopic interstitial pregnancy” and “heterotopic cornual pregnancy”, completed by manual searching for references of reports and review articles for relevant case reports.

All case reports of heterotopic interstitial pregnancies were selected, regardless of management or outcome. We registered reported data regarding clinical presentation, risk factors, management and outcome. Some reports did not report all of these data.

Results

We found 86 cases of heterotopic interstitial pregnancy in published literature. Our own case was not included in the analysis.

Risk factors

Sixty-nine cases (80.2%) occurred after IVF-embryo transfer, 12 (14.0%) were spontaneous pregnancies and 3 (3.5%) resulted after ovulation induction, once in combination with intrauterine insemination. Two cases did not mention the method of conception (Table 1).

Fifty (58.1%) patients had some history of tubal damage. 34 (39.5%) had undergone salpingectomy, of which 20 were bilateral. In 13 patients, salpingectomy was performed because of an ectopic pregnancy. 8 (9.3%) patients previously had some sort of tubal surgery, including salpingotomy, tubal ligation, reanastomosis, or tuboplasty. Three had a history of PID and in five other cases the “tubal factor” was not further

Table 1. Method of conception

Method of conception	Number (n=86)	%
IVF-ET	69	80.2
Spontaneous	12	14.0
Ovulation induction	3	3.5
No data	2	2.3

IVF-ET: in vitro fertilization – embryo transfer.

Table 2. Tubal history

Tubal history	Number (n=86)	%
Tubal factor	50	58.1
Salpingectomy	34	39.5
Unilateral	14	16.3
Bilateral	20	23.3
Tubal surgery	8	9.3
PID	3	3.5
Tubal factor NOS	5	5.8
No tubal history	11	12.8
No data	25	29.0

PID: pelvic inflammatory disease; NOS: not otherwise specified.

specified. Eleven (12.8%) patients did not have any tubal history and in 25 (29.0%) cases no information was provided (Table 2).

Presentation

The gestational age at diagnosis ranged from 4 to 30 weeks (mean $\pm$ SD; 9.2 ± 5.2 weeks) (Figure 3). The interstitial pregnancy was diagnosed in the first gestational trimester in 63 cases (73.3%) and in the second trimester in 6 (7.0%). Only 4 (4.7%) were not diagnosed before the third trimester of pregnancy. In 13 cases, no information about gestational age was available.

About 37.2% (32/86) of patients presented with cornual rupture, whilst 53.5% (46/86) were diagnosed during routine scans in asymptomatic patients.

Figure 3. Gestational age at diagnosis of heterotopic pregnancy.

Eight reports did not mention whether the ectopic pregnancy was ruptured or not.

Initial treatment

When the heterotopic interstitial pregnancy was diagnosed, patients were either treated surgically, medically or by expectant management. An overview is depicted in Table 3.

Forty-six patients (53.5%) underwent surgery as initial treatment, which consisted of laparotomy in 60.9% (28/46) and laparoscopy in 37.0% (17/46) of cases. Laparoscopy gained importance over time, from 10.5% (2/19) of cases before 2000, to 35.7% (5/14) from 2000 to 2010 and 76.9% (10/13) after 2010 (Figure 4). Mean gestational age was 10.7 ± 6.0 weeks (mean $\pm$ SD). In three cases, a hysterectomy needed to be performed. In one case no details about the surgical approach were provided.

Twenty-eight patients (32.6%) were initially treated medically. Mean gestational age at diagnosis in this medical group was earlier than that of the surgical group, namely 6.8 ± 1.1 weeks versus 10.7 ± 6.0 weeks (mean $\pm$ SD) respectively. Various treatment regimes were administered. Generally, the interstitial pregnancy was punctured using a 16 to 17 gauge double lumen needle. In 53.6% (15/28) of the patients, 1 mL of 15–20% or 2 mEq potassium chloride (KCl) was administered locally, before or after aspiration of the ectopic pregnancy contents. Alternatively, the local administration of hyperosmolar glucose was described in five cases by Wang et al.,⁷ and simple aspiration of the gestational products was reported in five cases by Qiong et al.⁸ In two cases, methotrexate (MTX) was used. The first mentions the aspiration of the ectopic sac, followed by the local instillation of 12.5 mg MTX.⁹ In the second case, a mixture of 1 mL of 20% potassium chloride with 12.5 mg MTX was injected to stop

Table 3. Initial treatment at the time of diagnosis of heterotopic interstitial pregnancy

Treatment	Number (n=86)	% total [% subgroup]
Surgery	46	53.5
Laparoscopy	17	19.8 (37.0)
Laparotomy	28	32.6 (60.9)
NOS	1	1.2 (2.2)
Medical treatment	28	32.6
KCl	15	17.4 (53.6)
Hyperosmolar glucose	5	5.8 (17.9)
Aspiration only	5	5.8 (17.9)
MTX	1	1.2 (3.6)
MTX + KCl	1	1.2 (3.6)
Hypertonic NaCl	1	1.2 (3.6)
Watchful waiting	5	5.8
No data	7	8.1

NOS: not otherwise specified; KCl: potassium chloride; MTX: methotrexate; NaCl: sodium chloride.

cardiac activity, followed by aspiration of the contents.¹⁰ Another case describes the use of hypertonic sodium chloride.¹¹ In both cases where MTX was used, authors substantiate that they chose to use MTX because the risk of toxicity to the developing fetus was balanced against the potentially significant maternal and fetal risk of continued trophoblast

Figure 4. Evolution of treatment over time.

development. It was to halt this trophoblast proliferation that they chose to use MTX. Yet, Baker et al.¹⁰ stated that, given the extremely low dose of MTX remaining after aspiration of some of the injected solution, and since other authors described the resolution of interstitial pregnancy by using just KCl, they would approach their next case of heterotopic interstitial pregnancy using the latter method to minimize the risk to the intrauterine gestation.

In one case,¹² a patient was initially treated medically with local KCl, but subsequently developed a cornual rupture, making supplementary surgery, by laparotomy, inevitable. Nevertheless, this is the only reported case in which initial medical management failed.

Five cases (5.8%) reported expectant management.^{4,8,13}

All patients presenting with cornual rupture (37.2%, 32/86) were treated surgically in an emergency setting, yet, also in 14 out of 46 patients without cornual rupture, a surgical approach was chosen electively to excise the interstitial pregnancy. In 8 cases (9.3%) authors did not mention whether cornual rupture occurred or not. Medical management was only possible in case of unruptured interstitial pregnancy at an early gestational age, although the interstitial pregnancy often still had a positive heartbeat at the time of diagnosis. Watchful waiting was only possible in case of an unruptured, nonviable interstitial pregnancy.

Outcome

In 6 of 86 cases, the intrauterine pregnancy miscarried before the heterotopic interstitial pregnancy was diagnosed. In all six cases, a surgical approach was chosen to treat the interstitial pregnancy.

In 80 other cases, the intrauterine pregnancy was viable when the heterotopic pregnancy was diagnosed. In these patients, the miscarriage rate for the intrauterine pregnancy was 21.3% (17/80). All but one occurred in the first gestational trimester. The miscarriage rate was also higher in case of medical compared to a surgical treatment, 28.6% (8/28) and 20.0% (8/40), respectively. There were no miscarriages after watchful waiting (0/5). In one case ending in a miscarriage, treatment mode was not specified. In one case of miscarriage after surgical treatment, the miscarried fetus was diagnosed with trisomy 21.¹⁴

In the case reported by Arbab et al.,¹⁵ a total hysterectomy was performed with the second, intrauterine fetus still in situ.

In another case,¹⁶ the intrauterine pregnancy was terminated 2 days after surgical treatment of the interstitial pregnancy and pathology showed a partial molar gestation intrauterine.

In five cases, no information about pregnancy outcome was provided.

For the 80 cases presenting with a viable intrauterine pregnancy, the live birth rate was 70.0% (56/80 pregnancies), with birth of 70 infants. In ten of these cases the intrauterine pregnancy was a multiple pregnancy, more specifically nine twins and one triplet.

The interstitial pregnancy survived in four cases, this is 4.7% of all cases (4/86). All were diagnosed in the third gestational trimester.

In the case reported by Beck et al.¹⁷ in 1990, diagnosis was made at 26 weeks of gestation. Laparotomy and cesarean section were performed and the interstitial fetus was delivered alive with a birth weight of 960 g. The intrauterine pregnancy, however, did not survive and, subsequently, hysterectomy had to be performed.

In 1997, Luckas et al.¹⁸ described the pregnancy with the furthest gestational age at diagnosis, being 30 weeks. The patient, carrying a triplet pregnancy, presented at 30 weeks with right-sided abdominal pain and signs of peritonism. A cesarean section was performed because of fetal distress in the most right placed fetus. They found only two fetuses to be inside the uterine cavity, whilst the third fetus was found in a separate cavity in the right interstitial portion of the uterus with cornual rupture. All three fetuses survived, with birth weights of 1000, 1140, and 1000 g respectively.

In the third case, described by Sharma et al.¹⁹ in 2004, the patient presented with abdominal pain, vomiting and a decrease in hemoglobin levels at 27 weeks of gestation in a twin pregnancy. During laparotomy, hemoperitoneum was found with the head of the right twin partially extruded through a rupture at the right uterine cornu. Both fetuses were

Figure 5. Outcome.

delivered alive, with birth weights of 1260 and 1410 g. Because of adherent placentae, a subtotal hysterectomy was performed afterwards.

The last case, described by Paradise et al.²⁰ in 2015, a women pregnant with twins was hospitalized three times because of unexplained abdominal pain, each time with spontaneous resolution. At 26 weeks, ultrasound revealed the left fetus to be extrauterine in the left upper abdominal quadrant. Laparotomy revealed a ruptured left cornu, the intra-abdominal fetus was delivered and a separate uterine incision had to be made to deliver the intra-uterine fetus, since she was unable to be delivered through the rupture side because of a segment of myometrium physically separating these two regions. Both infants survived, with birth weights of 725 and 635 g.

An outcome summary is provided in Figure 5. Of 56 cases with live birth, the delivery mode was a cesarean section in 66.0% (37/56). This includes the four cases where intrauterine and interstitial pregnancy were delivered at the time of presentation in the third trimester of pregnancy. Eight cases (14.3%) were delivered vaginally. This was after a medical treatment in four cases and expectant management in one, but also after surgical treatment in two cases. In one of these eight cases the treatment mode was not specified. In 11 cases (19.6%) a healthy infant was delivered, but no information about the delivery mode was provided.

In the case reported by Sentilhes et al.,⁴ the interstitial pregnancy was treated by expectant management. At the time of delivery of the intrauterine pregnancy, an emergency cesarean section needed to be performed because of dystocia, when a preruptured state of this uterine cornu containing the interstitial pregnancy was detected.

Discussion

Diagnostic issues

The most important tool in diagnosing an interstitial pregnancy is high-resolution transvaginal ultrasound.

Although ultrasound imaging has made great improvement over the last decades, diagnosing an interstitial pregnancy remains challenging and it is often misdiagnosed. As a result, 20% to 50% of the patients with an interstitial pregnancy present with a cornual rupture.¹ Furthermore, there is a higher morbidity and mortality rate associated with interstitial pregnancy compared to other types of ectopic pregnancy. Possible causes include higher chance to misjudge the entity, the tendency to rupture later in pregnancy and the high vascularization of the cornual region, being vascularized from ovarian and uterine arterial branches, resulting in massive blood loss upon rupturing. In case of a heterotopic interstitial pregnancy, even more diagnostic challenges arise due to a normal rise in β -human chorionic gonadotropin (β -HCG) levels and the presence of the concomitant intrauterine pregnancy, which often falsely reassures the examiner.

The most useful sonographic feature in diagnosing an interstitial pregnancy tends to be the thin myometrial layer surrounding the interstitial gestational sac. The eccentric localization can be difficult to distinguish from an eccentrically located intrauterine pregnancy.² The interstitial line sign can also be helpful.^{2,21} This is the hyperechogenic line connecting the endometrium with the interstitial gestational sac.

Therapy

The presence of a coexisting viable intrauterine pregnancy makes the management of an interstitial heterotopic pregnancy challenging, especially since they occur more frequently in infertile patients treated with ART. Treatment needs to be as minimally invasive as possible to preserve the intrauterine pregnancy.

Management options are determined by patient characteristics, including the gestational age, viability of the interstitial pregnancy, symptoms, and whether or not the interstitial pregnancy has ruptured.

Three treatment modalities have been described in management of interstitial heterotopic pregnancy,

including surgery, medical treatment and expectant management.

Surgical treatment includes laparotomy or laparoscopy in order to remove the interstitial pregnancy by cornual resection, wedge incision, or cornuostomy,¹⁶ although in some cases the need for hysterectomy has been described.⁵

The presence of the coexisting intrauterine pregnancy limits the usable operating techniques. One cannot use an intrauterine manipulator and excessive manipulation of the pregnant uterus should be avoided. Hemostasis is a major concern because of the abundant vascularization of the cornu. The use of local injection of vasopressin or coagulation of the ovarian and uterine arteries are impossible when the viable intrauterine pregnancy is to be preserved.²² Some suggest to minimize the use of coagulation techniques anyway in order to avoid tissue necrosis, which might increase the chance of uterine rupture.^{22,23} Applying a purse string suture at the base of the interstitial pregnancy,²⁴ meticulous suturing of the cornual defect and the use of hemostatic agents such as Surgicell,²⁵ are the most frequently described techniques to achieve adequate hemostasis.²²

Surgery is the only treatment option in case of cornual rupture and in second or third trimester interstitial pregnancies.

Medical management includes the local injection of feticide drugs such as MTX, prostaglandins or KCl in the interstitial gestational sac or fetal heart, sometimes followed by aspiration of the contents. However, because of the presence of a viable intrauterine pregnancy in case of a heterotopic interstitial pregnancy, the use of MTX or prostaglandins should be avoided since they can cause fetal death or teratogenic effects when administered to pregnant women. Nevertheless, the use of local cornual methotrexate injection has been described with allegedly favorable outcome for the intrauterine pregnancy.⁹ About 1 to 2 mL of 2 mEq potassium chloride can be injected, as well as hypertonic sodium chloride or hyperosmolar glucose,¹¹ or the avoidance of feticide drugs by only puncturing and aspirating the fetal heart and pregnancy.⁸ The puncture preferentially occurs via transvaginal or transabdominal²⁶ route in an ultrasound-guided procedure in order to avoid anesthesia and surgical risk, although it can be performed during laparoscopy as well.⁵ Indications are an early detected, small, asymptomatic and unruptured heterotopic interstitial pregnancy. Close follow-up is crucial yet difficult, since serial β -HCG follow-up is useless because of the presence of a viable intrauterine pregnancy, and has serial ultrasound as its main cornerstone. Failure of medical treatment with continued trophoblastic activity and cornual rupture is possible, as demonstrated by Bornstein et al.¹² Furthermore, an increased miscarriage rate for

the intrauterine pregnancy compared to surgery has been described. This could be due to the close proximity of the intrauterine pregnancy to the interstitial gestation, with diffusion of the injected drug to the intrauterine pregnancy,⁴ or myometrial reaction to the injection.²⁷ However, because of the generally younger gestational age of heterotopic pregnancies treated medically, this observation could be due to spontaneous miscarriages unrelated to the procedure as well.^{4,5}

Expectant management could be considered in case of an asymptomatic patient with a rather small interstitial pregnancy without cardiac activity.^{4,8} Its main advantage is the avoidance of potential adverse effects of surgery and medical management with cornual puncture and injection of potassium chloride. Likewise, in these cases a thorough follow-up is obligatory.

Most authors advise an elective cesarean section to deliver the continuing intrauterine pregnancy.^{2,22,28,29} This advice is supported by peroperative findings of a thinned out²² and even preruptured state⁴ of the affected cornu, even after expectant management of a nonviable interstitial heterotopic pregnancy.⁴ Nevertheless, some authors have described a successful vaginal delivery after early treatment for interstitial pregnancy.³⁰

Conclusion

In conclusion, a heterotopic interstitial pregnancy is extremely rare and implicates a diagnostic and therapeutic challenge. The majority of cases are diagnosed by detailed ultrasound in the setting of early follow-up after IVF-ET and are asymptomatic at diagnosis. However, a significant number of patients present with cornual rupture. Risk factors are IVF-ET and a history of salpingectomy. Treatment options consist of watchful waiting, medical treatment or surgery, all depending on clinical presentation and medical experience. During medical treatment, the use of feticide and teratogenic drugs, such as MTX, should be avoided. Unfortunately, the interstitial pregnancy is generally lost, and only has a chance of survival in case of presentation at a viable gestational age. Outcome of the coexisting intrauterine pregnancy is generally good and a cesarean section is advised as delivery mode.

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Contributors

WD researched literature and wrote the first draft of the manuscript. JCS and GM and CVH were treating gynaecologists of the patient. LM and GV were radiologists performing MRI scans. WD and CVH wrote the final version of the manuscript. All authors approved the final version of the manuscript.

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