CASE REPORT

Successfully Managing Cornual Heterotopic Pregnancy: A Case Report and Literature Review

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Abstract Cornual heterotopic pregnancy is an extremely rare, life-threatening complication during pregnancy. Here, we report a 33-year-old woman who suffered cornual heterotopic pregnancy after *in vitro* fertilization embryo transfer. To prevent rupture during heterotopic pregnancy, she received laparoscopic surgery to remove the ectopic gestational sac at 7⁺² weeks of gestation. Ultimately, she delivered a healthy boy at 38⁺³ weeks of gestation. Here, we also review the clinical presentations, risk factors, treatment options and outcomes of cornual heterotopic pregnancy.

HETEROTOPIC pregnancy (HP) is a pathological pregnancy in which one or more viable embryos implant outside the uterine cavity.^[1] Up to 98% of ectopic gestations are located in the fallopian tube.^[2] The incidence of HP is approximately between 1/3900 to 1/30 000 in natural pregnancies.^[3, 4] Cornual heterotopic pregnancy (CHP), where the embryo implants in the lateral angle of the uterine cavity close to the internal ostium of the fallopian tube, is a rare event.^[5] With increases in infertility and the wide use of assisted reproduction techniques (ART), the risk of CHP has increased to 1%-3% in some regions.^[4, 6] Women who have a history of salpingectomy or tubal ligation are at increased risk of having an interstitial or cornual pregnancy after ART.^[7]

HP diagnosis is a challenging task because patients usually have no symptoms or only present non-specific symptoms. Meanwhile, for women who have difficulty in getting pregnant naturally and who con-

ceive after *in vitro* fertilization embryo transfer (IVF-ET), treatments designed to terminate extra-uterine pregnancy through minimally invasive procedures, if possible, while preserving intrauterine pregnancy, pose a challenge to doctors. We report a case of ongoing intrauterine pregnancy in which a healthy infant was delivered after laparoscopic mini-cornual excision to terminate a cornual pregnancy. Before publishing our findings, we obtained written consent from the patient.

In addition, we searched all published case reports, case series and cohort studies with at least one case report of CHP on the MEDLINE (PubMed) database using the following phrases "heterotopic pregnancy," "cornual heterotopic pregnancy" and "assisted reproduction technology". We then generated a description of clinical presentations, risk factors, treatment options and outcomes of CHP to provide suggestions on how this kind of case should be managed.

CASE DESCRIPTION

A 33-year-old woman was admitted to our

Figure 3. A. Laparoscopy showing an un-ruptured cornual gestational sac (arrow). B. Histological examination results of the cornual gestational sac. C. Ultrasound images at the 10th day after surgery showed an abnormal mass with a blood flow signal (measuring 5.4 cm × 3.7 cm, arrow).

Figure 4. The abnormal tissue at the edge of the placenta (arrow).

pregnancy,” “cornual heterotopic pregnancy” and “assisted reproduction technology” on the MEDLINE (PubMed) database. We screened these cases by manually searching for references of reports and review articles of relevant case reports. Finally, we found 84 CHP cases^[7-43] and described the clinical presentations, risk factors, treatment options and outcomes of CHP (**Table 1**).

Clinical presentation

The gestational age at diagnosis of CHP ranged from 5 to 17 weeks. And most cornual pregnancies were diagnosed between 5 to 7 weeks of gestation. Three cases of CHP were misdiagnosed on the first ultrasound examination, thus resulting in cornual rupture with severe hemorrhage.^[32, 38] And one of them had an intrauterine abortion owing to cornual rupture at 13 weeks after embryo transfer.^[32] Totally, 25.00% (21/84) of patients presented with cornual rupture. About 50% (43/84) patients were asymptomatic who were diag-

nosed with CHP during routine ultrasonic scans. The remaining patients had varying degrees of abdominal pain and vaginal bleeding.

Risk factors

95.24% (80 cases) CHP occurred after IVF-ET, all of which had been transferred two or more embryos. Only three (3.57%) cases had spontaneous pregnancies, and one (1.19%) case was diagnosed with CHP after induced ovulation. Fifty (50/84, 59.52%) patients had a history of tubal damage. Among them, forty-four (44/84, 52.38%) had undergone salpingectomy, of which 40 (90.91%) received bilateral salpingectomy. Six (7.14%) patients had a history of tubal ligation or tuboplasty. Three cases were caused by the dissection of the uterine septum, polycystic ovary syndrome (PCOS) and endometriosis, respectively. Three (3.57%) patients had no risk factors for tubal infertility. Only one case of CHP may be attributed to tubal factor combined with a masculine factor. The histories of 27 (32.14%) cases were not available.

Treatment methods and outcomes of intrauterine pregnancy

Fifty-eight (69.05%) patients underwent surgery as an initial treatment, of which 74.14% (43/58) cases were treated with laparoscopy and 25.86% (15/58) with laparotomy. For those managed *via* laparoscopy, only four had a spontaneous abortion, and the miscarriage rate was 9.30% (4/43); three had preterm birth, and the live birth rate was 90.70% (39/43). Four cases had preterm birth after laparotomy, in addition, there were three such cases with spontaneous abortion, and the miscarriage rate was 20% (3/15). Among these cases, laparotomy for terminating extrauterine pregnancy accidentally caused rupture of the intrauterine gestational sac in one case because the two gestational sacs

Table 1. Review of the literatures describing cornual heterotopic pregnancy

References	Case no. (fertilization way)	Risk factors	Manifestations and GA at diagnoses (weeks)	Treatment of CHP	Outcome of intrauterine pregnancy
Lower <i>et al.</i> ^[8]	1 (IVF-ET)	Left salpingectomy	Cornual rupture (8)	Laparotomy	Term delivery
Gamberdella <i>et al.</i> ^[9]	1 (IVF-ET)	No data	Cornual rupture (8)	Laparotomy	Term delivery
Chen <i>et al.</i> ^[10]	1 (IVF-ET)	Bilateral salpingectomy	Cornual rupture (10)	Laparotomy	Miscarriage (no fetal heart beats of intrauterine fetuses)
Trma-Tritsch <i>et al.</i> ^[11]	1 (IVF-ET)	No data	Free of symptoms (9)	Cornual injection of KCl	Miscarriage
Fernandez <i>et al.</i> ^[12]	3 (IVF-ET) 1 (Spontaneous)	Bilateral salpingectomy No tubal history	Free of symptoms (6-8)	1 expectant management, 3 cornual injection of KCl	1 term delivery, 2 miscarriage at 8 and 10 weeks separately, 1 term delivery
Pérez <i>et al.</i> ^[13]	1 (IVF-ET)	No data	Free of symptoms (7)	Cornual injection of KCl	Term delivery
Vilos <i>et al.</i> ^[14]	1 (ovulation induction)	Bilateral salpingectomy	Free of symptoms (7 ⁺⁵)	Laparoscopy	Term delivery
Loret de Mola <i>et al.</i> ^[15]	2 (IVF-ET)	Bilateral salpingectomy	Cornual rupture (9)	Laparotomy	1 preterm birth at 28 weeks, 1 term delivery
Gaudier <i>et al.</i> ^[16]	1 (IVF-ET)	Bilateral salpingectomy	Cornual rupture (7)	Laparotomy	Preterm birth at 34 weeks
Benifla <i>et al.</i> ^[17]	2 (IVF-ET)	No data	Free of symptoms (6-7)	Cornual injection of KCl	1 miscarriage, 1 term delivery
Baker <i>et al.</i> ^[18]	1 (IVF-ET)	No data	Free of symptoms (7)	TVS injection of MTX	Term delivery
Kasum <i>et al.</i> ^[19]	1 (IVF-ET)	Bilateral salpingectomy	Cornual rupture (7)	Laparotomy	Preterm birth at 36 weeks
van der Weiden <i>et al.</i> ^[20]	1 (IVF-ET)	Bilateral salpingectomy	Free of symptoms (8)	Cornual injection of KCl	Term delivery
Oyawoye <i>et al.</i> ^[21]	1 (IVF-ET)	PCOS	Free of symptoms (6 ⁺³)	TVS injection of MTX	Term delivery
Chin <i>et al.</i> ^[7]	2 (IVF-ET)	Bilateral salpingectomy	Cornual rupture (12/17)	Laparotomy	2 Term delivery
Bhat <i>et al.</i> ^[22]	1 (IVF-ET)	Bilateral salpingectomy	Cornual rupture (12)	laparotomy	Term delivery
Robin <i>et al.</i> ^[23]	1 (IVF-ET)	Bilateral salpingectomy	Free of symptoms (8)	Cornual injection of KCl	Term delivery
Ozgun <i>et al.</i> ^[24]	1 (IVF-ET)	Tubal ligation or tubo- plasty	Free of symptoms (9)	Cornual injection of KCl	Uterus rupture at 11 weeks
Ben-Ami <i>et al.</i> ^[25]	1 (IVF-ET)	Bilateral salpingectomy	Cornual rupture (7)	Laparoscopy	Term delivery
Blazar <i>et al.</i> ^[26]	1 (IVF-ET)	Bilateral salpingectomy	Cornual rupture (6)	Laparotomy	Term delivery
Divry <i>et al.</i> ^[27]	1 (IVF-ET)	Tubal factor combined with a masculine factor	Cornual rupture (6)	Laparotomy	Preterm birth at 31 weeks
Parquet <i>et al.</i> ^[28]	1 (IVF-ET)	Right salpingectomy	Free of symptoms (6)	Cornual injection of KCl	Term delivery
Poujade <i>et al.</i> ^[29]	1 (spontaneous)	No tubal history	Abdominal pain and bleeding (9)	Laparoscopic injection of MTX	Miscarriage
Sentilhes <i>et al.</i> ^[30]	1 (IVF-ET)	Endometriosis	Free of symptoms (7)	Expectant management	Term delivery

Continued Table 1. Review of the literatures describing cornual heterotopic pregnancy

References	Case no. (fertilization way)	Risk factors	Manifestations and GA at diagnoses (weeks)	Treatment of CHP	Outcome of intrauterine pregnancy
Soriano <i>et al.</i> ^[31]	3 (IVF-ET)	Bilateral salpingectomy	Vaginal bleeding (7-8)	Laparoscopy	3 term delivery
Qiong <i>et al.</i> ^[32]	9 (IVF-ET)	3 (bilateral salpingecto- my), 6 (no data)	6, abdominal pain; 3, free of symptoms (4-6)	1 laparotomy, 3 expectant management, 5 selective embryo reduction	1 miscarriage, 3 term delivery, 2 miscarriage, 3 term delivery
Lukášová <i>et al.</i> ^[33]	1 (IVF-ET)	Bilateral salpingectomy	Vaginal bleeding (6)	Laparoscopy	Term delivery
Mayer <i>et al.</i> ^[34]	1 (IVF-ET)	Dissection of uterine septum	Free of symptoms (7)	Expectant manage- ment	Preterm birth at 31 weeks (uterine rupture)
Prorocic <i>et al.</i> ^[35]	1 (IVF-ET)	Right salpingectomy	Free of symptoms (7)	Cornual injection of hypertonic NaCl	Term delivery
Alvarez <i>et al.</i> ^[36]	1 (IVF-ET)	Left salpingectomy	Cornual rupture (5)	Laparotomy	Term delivery
Oral <i>et al.</i> ^[37]	1 (IVF-ET)	Bilateral salpingectomy	Cornual rupture (7)	Laparoscopy	Term delivery
Tufan <i>et al.</i> ^[38]	1 (sponta- neous)	No tubal history	Cornual rupture (8)	Laparotomy	Miscarriage (intrauterine gestational sac rupture)
Kim <i>et al.</i> ^[39]	13 (IVF-ET)	8 (bilateral salpingectomy) 5 (tubal ligation or tuboplasty)	4, abdominal pain; 2, vaginal bleeding; 7, free of symptoms (5 ⁺⁴ -10)	Laparoscopy	7 term delivery, 3 preterm birth, 3 miscarriage
Peker <i>et al.</i> ^[40]	1 (IVF-ET)	No data	Abdominal pain (11)	Laparoscopy	Term delivery
Xu <i>et al.</i> ^[41]	14 (IVF-ET)	No data	4, cornual rupture; 10, free of symptoms (5-9)	Laparoscopy	All term delivery
Wu <i>et al.</i> ^[42]	5 (IVF-ET)	Bilateral salpingectomy	2, abdominal pain and viginal bleeding; 3, free of symptoms (7-9)	Laparoscopy	Term delivery
Eom <i>et al.</i> ^[43]	3 (IVF-ET)	Bilateral salpingectomy	1, cornual rupture; 2, free of symptoms (7-8)	Laparoscopy	1 miscarriage, 2 term delivery

GA: gestational age; CHP: cornual heterotopic pregnancy; IVF-ET: *in vitro* fertilization-embryo transfer; KCl: potassium chloride; TVS: transvaginal ultrasonography; MTX: methotrexate; NaCl: sodium chloride; PCOS: polycystic ovary syndrome.

were in close proximity to each other.^[38]

Among the six patients choosing expectant management, one case with uterine rupture at the 31st week of gestation underwent emergency hysterectomy,^[34] and another five cases delivered healthy infants at term. Repeated clinical and ultrasonographic examinations performed on this six cases weekly demonstrated a gradual resolution of the ectopic gestational sac and complete resolution was achieved in the end.

In addition to surgical treatment and expectant management, conservative treatment with medication and selective embryo reduction have also been report-

ed. In total, five patients underwent puncturing and aspirating CHP under TVS guidance, of which three delivered healthy babies, and two aborted a child. Alternatively, Prorocic *et al.*^[35] have reported that a cornual pregnancy was successfully aborted *via* the local administration of hypertonic sodium chloride (NaCl), and that an intrauterine pregnancy was successfully maintained with delivery of a healthy newborn baby. In the eleven cases treated by potassium chloride (KCl), six delivered at term, and five of them had spontaneous abortion. The ectopic sac of three cases was aspirated under ultrasound guidance following local injection of 12.5 mg methotrexate (MTX). After surgery,

intrauterine pregnancy of two cases progressed uneventfully, and the other one had uterine rupture.

DISCUSSION

An HP involves coexisting pregnancies at two different implantation sites. The pathogenic mechanisms of HP are unclear. Risk factors associated with HP include periadnexal adhesions, endometriosis, the widely used ART and elevated circulating hormone levels.^[44] Its incidence has risen substantially due to the increasing use of exogenous gonadotropins and ART. Women who have undergone ART procedures have a much higher incidence of HP than those who spontaneously conceive. Through our statistical analysis, we found that 95.24% of CHPs occurred after IVF-ET, whereas only 3.57% occurred after spontaneous pregnancies (**Table 1**). Researchers believe that the possible etiology includes the hydrostatic force used to deliver the embryo into the cornual or tubal area and the increased incidence of pelvic inflammation in infertility patients.^[45, 46] Tubal infertility has been shown to be a risk factor for HP among women treated with IVF.^[47] The data show that more than half of all patients with CHP underwent tubal surgery, especially for salpingectomy. The patient in our study had bilateral fallopian tube blockage, which can cause infertility just as oviduct resection or ligation can. Despite the risk factors for HP, she had CHP. Moreover, women undergoing ART procedures with two or more embryos transferred have a much higher incidence of HP than those with one embryo.^[48, 49] Some studies have shown, however, that the number of embryos transferred is not a risk factor for ectopic pregnancy.^[50, 51] Thus, whether or not decreasing the number of embryos transferred can decrease the incidence of HP is a controversial topic. More researches should be conducted to shed light on this question.

The diagnosis of HP is extremely challenging because both serum beta-hCG concentrations and ultrasonography results can be misleading. Serial beta-hCG levels are confusing in such cases because intrauterine pregnancy causes beta-hCG levels to naturally rise. Clinical manifestations can sometimes assist in these diagnoses, but this is often atypical. Because HP is associated with a higher risk of uterine rupture, early diagnosis is particularly important. According to our statistical analysis, 51.19% of cases with no symptoms were diagnosed during routine ultrasonic scans. Twen-

ty (25%) patients were treated with surgery because of extensive hemoperitoneum and a ruptured uterine cornua, which increased the probability of transfusion and the risk of intrauterine abortion. Thus, TVS is often used to assist in early diagnosis, especially with asymptomatic patients like ours. The most useful sonographic feature in diagnosing a cornual pregnancy tends to be the thin myometrial layer surrounding the cornual gestational sac. Eccentric localization can be difficult to distinguish from an eccentrically located intrauterine pregnancy. Ultrasonography revealed both an intrauterine pregnancy and a cornual pregnancy at day 27 in our patient, during her first scheduled TVS. With the help of an ultrasound, HP can be diagnosed and treated earlier and more accurately, thus improving pregnancy outcomes. Therefore, high resolution TVS is the most important diagnostic method for HP.^[52]

The treatment of HP is challenging due to the desire to preserve the normal pregnancy, especially since this occurs more frequently in infertile patients treated with ART. Management options are determined by patients' characteristics, including gestational age, the viability of the cornual pregnancy, symptoms and whether or not the cornual pregnancy having ruptured. Both surgical treatment and conservative medications can cause miscarriage. Because of the high incidence of rupture, especially for cornual pregnancy, the current standard of treatment is surgical treatment. Surgical treatment includes laparotomy or laparoscopy to remove the cornual pregnancy *via* cornual resection or wedge incision. According to our statistics, surgery was performed in 69.05% of all cases, of which laparoscopy accounted for 74.14%. The live birth rate for intrauterine pregnancy in patients undergoing laparoscopy was 90.70% (39/43). Recently, laparoscopy has been the gold standard for treatment in select cases due to its safety, less invasive nature and shorter recovery times.^[6] Laparoscopic cornuostomy or cornual repair, is an effective treatment for CHP, even in cases of rupture.^[40] The presence of a coexisting intrauterine pregnancy limits the operating techniques that can be employed. Thus, for safety reasons, these operations should be performed in an institution with well-trained gynecological laparoscopists and experienced support teams. It is important that the uterus be disturbed as little as possible during the course of surgery, and instrumental manipulation of the uterus should be avoided. Hemostasis is a major concern because of the abundant vascularization of the cornu. A recent

study reports that an intrauterine gestational sac was accidentally ruptured because of its close proximity to an ectopic pregnancy during laparotomy.^[38] The latest research by CHA Bundang Medical Center shows that if immediate management is performed after diagnosis, a favorable prognosis for HP can be expected, with the gestational age at treatment being the only independent risk factor for miscarriage in patients with HP, regardless of treatment methods.^[53] Also, they report that the mean gestational age at treatment was 5.97 ± 0.50 weeks. In the case we reported in this study, an urgent laparoscopic surgery was performed due to the thin uterine serous layer (with a thickness less than 0.08 cm) at 6⁺ weeks of gestation. Furthermore, the left cornual sac was partly located in the internal ostium of the fallopian tube and was close to the normal sac (with a distance of only 0.1 cm), which increased the difficulty of the surgery as well as the risk of abortion. Fortunately, the final outcome was excellent.

We cannot, however, state whether conservative treatment would have led to a good result, though rupture during ectopic pregnancy would surely have led to intrauterine fetal demise. Our statistics show that, among the six patients choosing expectant management, one underwent uterine rupture and hysterectomy during her 31st week of gestation, whereas another five delivered healthy infants at term. Although expectant management for CHP can be considered a successful option in a symptom-free patient,^[30] this confirms that expectant management for CHP may be a successful option for symptom-free patients in which the ectopic embryo has a limited craniocaudal length and no cardiac activity. Also, a close follow-up is crucial, albeit difficult, since serial HCG follow-up is useless because of the presence of a viable intrauterine pregnancy as well as its reliance on serial ultrasound. Since hemorrhagic shock significantly affects both the patient herself as well as her intrauterine gestation, it is clear that early surgical intervention is critical. Medical management includes the local injection of feticide drugs such as MTX or a hypertonic NaCl or KCl solution in the cornual gestational sac or fetal heart, sometimes followed by the aspiration of this content. Although studies have shown that local injections of low-dose MTX following the aspiration of a cornual pregnancy can effectively halt the growth of ectopic trophoblasts without adversely affecting a coexistent intrauterine pregnancy,^[54] the use of MTX can often be avoided

since it may cause fetal death or teratogenic effects when administered to pregnant women. The local injection of hypertonic NaCl into the cornual sac has also proven useful, as demonstrated by early papers. The indications for all of these conservative treatments are a small, asymptomatic and un-ruptured CHP that is detected early. The failure of such medical treatments, however, as well as continued trophoblastic activity and cornual rupture, is possible, as demonstrated by Bornstein *et al.*^[55] Furthermore, an increased miscarriage rate for intrauterine pregnancy compared to surgery has been described.

According to the research reports of Chinese scholars, early intervention to puncture and aspirate a CHP is useful for patients with stable vital signs. This approach can avoid anesthesia and surgical risk. Also, it is less invasive and less expensive.^[32] In addition, the latest findings by Chinese researchers at Zhejiang University show that, compared with surgery, embryo suction with or without proper local drug injection is advisable for patients with cervical, cornual or interstitial pregnancy, as this can preserve the intrauterine pregnancy.^[42] In our case, the embryo in the lateral angle of the uterine cavity close to the internal ostium of the fallopian tube was a rare form of ectopic pregnancy. Since it was close to the normal embryo, we could not completely remove the pregnancy tissue in the left horn during operation. Therefore, a mass remained after surgery. Although it grew a little, it did not cause any harm, possibly due to surgical damage. Retrospective analysis and consideration of our treatment options are particularly important. It is worth thinking about whether it is possible to destroy or completely remove a cornual pregnancy *via* puncturing and aspiration to achieve favorable pregnancy outcomes. More studies are needed to confirm this hypothesis, but it does offer guidance for the future clinical treatment of CHP.

It is worth noting that no matter what surgical method is adopted, the removal of a uterine horn pregnancy will inevitably lead to uterine scar formation. Uterine rupture in mid-to-late pregnancy is the most serious complication. But of the 27 cases of CHP patients undergoing laparoscopic surgery as reported by Kim and Xu *et al.*, none experienced uterine rupture during subsequent pregnancy.^[39, 41] In addition, previous studies also suggest that the abortion rate for intrauterine pregnancy may be lower than that of fetal reduction.^[56]

In summary, we have presented a CHP case by

ART, which is extremely rare and presents a diagnostic and therapeutic challenge. A diligent ultrasound is of great value in diagnosing HP, especially in asymptomatic patients. A significant number of patients, however, present with cornual rupture. Likewise, CHP episodes, though rare, should be on the mind of physicians in charge of symptomatic patients with bilateral tube blockage in the uterine horn or post salpingectomy in the case of infertility/IVF. Treatment options consist of watchful waiting, medical treatment or surgery, all depending on clinical presentation and medical experience. Laparoscopic surgery after diagnosis may improve the prognosis of HP. The indications for operation must be strictly accessed, and suture skills during operation are also critical. Finally, patients must be given thorough follow-ups throughout the entire course of pregnancy. Cesarean section is the appropriate method of delivery.

Conflicts of Interest Statement

The authors declare no conflicts of interest.

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中文摘要

一例反复发作的心肌梗死和儿茶酚胺心肌病病例报告

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摘要

嗜铬细胞瘤 / 副神经节瘤是罕见的神经内分泌肿瘤。部分临床表现不典型患者的诊断比较困难。我们报道了 1 例以反复心肌梗死和心肌病为临床表现的嗜铬细胞瘤和副神经节瘤患者的诊治经过。因此, 嗜铬细胞瘤 / 副神经节瘤应作为不明原因急性冠脉综合征或心肌病的鉴别诊断之一。

关键词: 嗜铬细胞瘤、副神经节瘤、心肌病、心肌梗死

中文摘要

成功诊治宫内合并宫角妊娠 1 例及文献复习

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摘要

宫内合并宫角妊娠是一种罕见的严重妊娠并发症。本文报告一例 33 岁妇女, 在体外受精 - 胚胎移植后发生宫内合并宫角妊娠。为了防止宫角妊娠破裂, 宫角妊娠物在妊娠 7⁺² 周时经腹腔镜手术被清除。在妊娠 38⁺³ 周时, 此孕妇顺利分娩一名健康男婴。此外, 我们还回顾 MEDLINE (PubMed) 数据库收录的所有关于 CHP 的病例报告、病例系列和队列研究, 分析了 CHP 的临床表现、危险因素、治疗方法及妊娠结局。

关键词: 宫内合并宫角妊娠; 阴道超声; 腹腔镜; 辅助生殖技术