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# Case report

# Heterotopic abdominal pregnancy following ovulation induction with clomiphene citrate

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## Abstract

**Background:** Heterotopic abdominal pregnancy is a rare entity which poses unique management challenges.

**Case:** A 24-year-old Gravida 1 woman with history of two years infertility and treatment with clomiphene citrate presented with acute right lower quadrant abdominal pain. Heterotopic abdominal pregnancy was recognized at 16 weeks gestation by transvaginal ultrasound scan. We aimed to remove ectopic pregnancy with prevention of maternal complications and preservation of intrauterine pregnancy (IUP). Surgical removal of the ectopic fetus and placenta was done. Abdominal pregnancy removed successfully without intra- or post-procedural complications, but the IUP was aborted spontaneously on the second postoperative day.

**Conclusion:** Gynecologists should consider the possibility of heterotopic pregnancy following ovulation induction with clomiphene citrate which is increasing in recent years. A high index of suspicion to heterotopic pregnancy may be followed by a nonsurgical approach safely and affectively, if they are clinically stable and the abdominal pregnancy is recognized early in gestation.

***Key words:*** *Abdominal pregnancy, Clomiphene citrate, Heterotopic pregnancy symptom, Ovulation induction.*

## Introduction

Heterotopic pregnancy (HP) is the coexistence of a pregnancy (single or multiple) of intrauterine development and at least one ectopic pregnancy (EP) of any topography. In spontaneous pregnancies, HP is a rare entity and the estimated incidence is between 1:30,000 and 1:8,000 pregnancies.

Clomiphene citrate has been the most widely used treatment for fertility enhancement in recent years.

It is used to induce ovulation in selected populations with oligo-ovulation or anovulation as a strategy to increase follicular number and enhance fertility (1).

Clomiphene citrate increases the rate of twining and could be associated with HP in up to1:900 of the cases. Because HP is a life threatening condition, its early diagnosis is of great importance. Pre-operative diagnosis is difficult and requires a high index of suspicion.

Clinical features can vary widely from asymptomatic to severe abdominal pain and vaginal bleeding. Serial hCG levels often are not helpful because the intrauterine pregnancy (IUP) causes the hCG level to rise appropriately. Despite the increasing use of ultrasound equipments, HP is definitely diagnosed by laparoscopy or laparotomy in 60%-73% and by ultrasound scan in 26%-41% of the cases (2).

Along with diagnosis, treatment of HP is another major challenge. While, salpingectomy is usually approached for tubal EP, management of the placenta in an abdominal pregnancy is a matter of debate. Abdominal pregnancies comprise

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approximately 1.4% of EPs and 2.7% of HPs, but they have a maternal mortality almost eight times greater than that of tubal pregnancy (3).

In this report, we present a rare case of heterotopic abdominal pregnancy following ovulation induction with clomiphene citrate.

## Case report

A 24-year-old woman (Gravida 1) was admitted to our university tertiary care hospital with a history of two days lower abdominal pain. She had a history of two years infertility (because of oligo-ovulation) and treatment with clomiphene citrate (100 mg daily from day 5 to 9 of the menstrual cycle).

There was no history of pelvic inflammatory diseases. She had also a positive βhCG with previous (nine weeks before admission) ultrasound scan of a single viable IUP of seven weeks of gestation. On examination, her pulse rate was 100 beats/min and regular and her blood pressure was 90/60 mmHg.

Abdominal examination revealed diffused lower abdominal tenderness but no marked guarding or rebound tenderness. Transvaginal ultrasound scan revealed simultaneous live intrauterine and abdominal pregnancies with 16 weeks of gestation. The abdominal pregnancy filled the Pouch of Douglas, behind the uterus, equivalent to 16 weeks gestation with positive cardiac activity. There was minimal free fluid in the pelvis (Figure 1). Laparotomy was performed which confirmed the diagnosis of HP; there was an abdominal pregnancy with intact amniotic sac in Pouch of Douglas posterior to the uterus.

Placenta has been attached to the right side of posterior leaf of the broad ligament and posterior vagina. After opening the amniotic cavity, a female infant was delivered. The main blood supply to the placenta was identified as rising from the left hypogastric artery, so hypogastric ligation was performed.

The fallopian tubes and ovaries were normal. The placenta was totally removed from the abdomen. To control hemorrhage, we used successive clamps and interrupted chromic catgut no. zero sutures.

After operation, magnesium sulfate (4gr stat and 2gr/h infusion) was prescribed for prevention of uterine contractions. Unfortunately, she aborted spontaneously on the second postoperative day. She was discharged uneventfully on postoperative day 5.

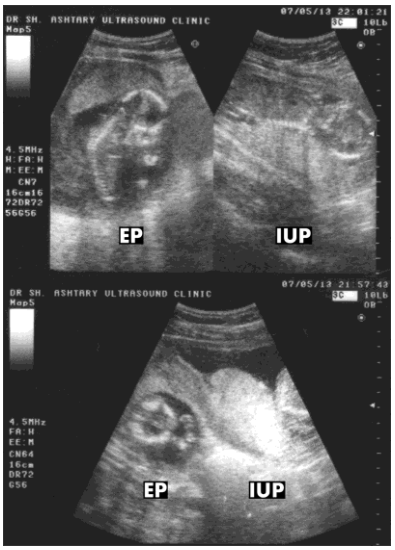


**Figure 1.**Transvaginal ultrasound showing IUP and EP at 16 weeks of gestation.

## Discussion

We described a rare case of heterotopic abdominal pregnancy following ovulation induction with clomiphene citrate. HP has been reported following treatment with clomiphene citrate (4) but to the best of our knowledge, abdominal pregnancy with this drug has not been reported previously (2). The only risk factor we found in this case was ovulation induction by clomiphene citrate and we did not detect endometriosis or tubal anomalies (according to post operative salpingography). The increased risk is due to ovulation induction leading to multifollicular development and high estrogen concentration. It is, however, interesting that in our case as well as the case that is reported by Naki *et al* (5). The drug had been given from days 5 to 9 of the cycle, a time when the resultant FSH surge is more likely to enhance development of the dominant follicle only. In some previous reports, the drug had been given from days 2 to 6 of the cycle, when it is more likely to result in maturation of multiple follicles (6, 7).

HP is a rare entity with a difficult pre-operative diagnosis. The presence of IUP, either viable or not, may actually mask the ectopic component of HP and result in a delay in diagnosis (8). Although less than half of patients are diagnosed by ultrasound scan, transvaginal ultrasound has an important role in early diagnosis of HP. Careful sonographic assessment of the whole pelvis in such cases is critical. According to reviews, in 77%-85% of patients in whom diagnosis was via ultrasound scan, diagnosis was made between 5-8 weeks of gestation. In our case, however, HP was not diagnosed early. Delay in diagnosis and failure to

urgent treatment require anesthesia and surgery that can jeopardize both maternal well-being and survival of the intrauterine fetus. With early diagnosis and treatment, the outcome would be good (about 70% delivered in term) (2). Unfortunately, delayed diagnosis in our case led to spontaneously abortion of the IUP. The present case emphasizes that the presence of a viable IUP on ultrasound scan with lower abdominal pain, must not prevent us to continue investigating for extrauterine pathology as a HP, particularly if ovulation induction or ARTs have done.

In addition to diagnostic pitfalls, management of HP still remains controversial. The least invasive HP treatment should be used to preserve the developing IUP. However, even with a high index of suspicions, HP is usually diagnosed after rupture of the fallopian tube, in cases with tubal EP. Surgical therapy has been the traditional mainstay, but invasive surgical and anesthetic with a risk of both to the mother and the IUP have been reported up to 40% loss of viable IUP (2). The known risks of surgical treatment with an abdominal pregnancy further complicate this particular patient's course situation. Recently, the non-surgical management of HP has gained popularity. However, systemic medical therapy (e.g. methotrexate) is contraindicated in the presence of a viable intrauterine gestation (9) and in other cases it is not always successful (10). If the pregnancy is in early stage and has not been ruptured, the local injection into the sac, in expert hands and under sonographic guidance, is an effective treatment. Substances for injection should have high therapeutic effectiveness with low toxicity to the concurrent IUP. Two options are potassium chloride (KCL) and hyperosmolar glucose (2, 11). However, since the risks of continued growth and rapture still exist with such non-surgical management, repeated weekly ultrasound examination and follow-up and close monitoring of clinical symptoms are essential. A literature review of cases of HP treated with KCL injection noted that 55% failed this therapy and required surgical intervention (12).

If diagnosis of heterotopic abdominal pregnancy is late, and pregnancy is less than 24 weeks, immediate operative intervention is indicated because of unpredictability of placenta separation and the resultant massive hemorrhage with poor prognosis for the baby if the pregnancy continues (3).

Debate has arisen, however, concerning the appropriateness of a conservative approach in situations where the patient presents after 24 weeks of gestation. In such cases, the pregnancy can be closely observed and surgery be delayed to allow time for the fetus to mature. Also, intracardiac KCL injection into the ectopic pregnancy is reported successful (13). These approaches, however, requires close surveillance when the beneficial to the fetus are weighted against the placental risks to the mother such as the sudden onset of life threatening hemorrhage. The patient needs to be admitted to the hospital where surgical expertise, anesthesia, and 24 hours blood bank service are all available (8).

The other significant problem of the operation is whether or not to remove the placenta interference. It may lead to uncontrollable hemorrhage and if it is left insitu, though it is usually the procedure of choice, the morbidity from abscess formation would be high. Removal of the placenta should be undertaken if it is safe depending upon the accessibility of ligation of the maternal vessels supplying the placenta (8). This reduces the duration of hospital stay and maternal morbidity, as was the case in our patient who was discharged uneventfully on the fifth post-operative day. Removal of the placenta should not be undertaken if it is not safe due to inaccessibility of ligation of the supplying maternal vessels. In this case, cord should be ligated in close proximity of the placenta (8). It has been estimated that the placenta can remain functional for approximately 50 days from the operation and total regression of placenta function is usually completed within four months. Complications may include ileus, peritonitis, abscess formation, prolonged hospital stay, and fever (14).

In conclusion, it should be emphasized that although HP is a rare event, it may occur in up to 1% of patients with ovulation induction and ARTs. It is essential to remain vigilant in order to diagnose this event in early stages if associated symptoms appeared (e.g. vaginal bleeding, abdominal pain). It is also important to respect the necessity of a systemic exploration and comprehensive evaluation of the pelvis upon the first ultrasound scan of the pregnancy performed at 5-8 weeks of gestation even if there are no apparent risk factors or symptoms. When diagnosis is reached in a timely manner, the rate of term pregnancy would be encouraging.

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