

Ovarian Heterotopic Pregnancy after Ovulation Induction with Clomiphene Citrate

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Abstract

Background: An ovarian heterotopic pregnancy is a rare entity associated with life-threatening consequences in case of delayed diagnosis.

Case: A 33-year-old nulliparous woman with idiopathic primary infertility underwent a cycle of ovulation induction using Clomiphene Citrate and intrauterine insemination. Although the patient was asymptomatic, the ultrasound demonstrated a missed abortion with a right ovarian heterotopic pregnancy. The patient underwent suction dilatation and curettage of the missed abortion and laparoscopic resection of the ovarian heterotopic pregnancy with preservation of the affected ovary.

Conclusion: Increased awareness of the risk of heterotopic pregnancies following fertility treatments can prevent fatal outcomes and allow for conservative treatments and preservation of fertility.

Keywords: Heterotopic pregnancy; Ovarian pregnancy; Clomiphene citrate; Intrauterine insemination

Introduction

A heterotopic pregnancy (HTP) is a rare entity associated with high morbidity and adverse consequences for future fertility. In 1948, Devoe and Pratt estimated a theoretical incidence of one heterotopic pregnancy per 30,000 natural conceptions [1]. With the advent of ovulation induction and assisted reproductive technologies (ART), the incidence of HTP is now estimated to be 1.5 /1000 ART pregnancies [2].

The ovary is an uncommon site for ectopic implantation and heterotopic pregnancies involving an ovary account for 2.3% of heterotopic pregnancies [3]. Diagnosis of such pregnancies requires vigilance, and suspicion of an ovarian pregnancy should be raised in pregnancies resulting from assisted reproductive techniques. This case report highlights the importance of clinical awareness regarding the possibility of HTP in asymptomatic patients.

Case Report

A 33-year-old nulliparous Caucasian woman presented to the office with primary infertility for 1.5 years. Her past medical, surgical and gynecological history was unremarkable and she had regular 28 day ovulatory cycles. A hysterosalpingogram (HSG) demonstrated a normal uterine cavity and bilateral fallopian tube patency. Assessment of ovarian reserve demonstrated a serum Anti-Mullerian Hormone (AMH) level of 2.4ng/mL and day 3 serum follicle stimulating hormone (FSH) and estradiol levels of 6mIU/mL and 32pg/mL, respectively. The patient's husband was a healthy 36-year-old man with a normal semen analysis by WHO criteria [4].

The patient underwent a cycle of ovulation induction using Clomiphene Citrate (CC). Intrauterine insemination (IUI) was performed 36 hours after administration of human chorionic gonadotropin. A serum β -hCG level assessed 18 days after the IUI was 140mIU/mL; 72 hours later the level rose to 429mIU/mL. Transvaginal ultrasonography performed at 5 weeks 3 days gestation demonstrated a uterine pregnancy with a 6.4mm gestational sac and a yolk sac. A repeat sonogram two weeks later demonstrated an intrauterine missed abortion of 6 weeks size as well as a 1.7 x 1.8cm thick-walled cystic

mass at the periphery of the right ovary – the mass contained a fetal pole with cardiac activity suspicious for an ovarian pregnancy (Figure 1). The patient was asymptomatic and after extensive counseling underwent suction dilatation and curettage and operative laparoscopy. At the time of laparoscopy, the uterus and fallopian tubes were normal in appearance and there was no bleeding from either fimbria. The right ovary contained a bluish cystic mass measuring 2cm in maximum diameter consistent with an ovarian ectopic pregnancy (Figure 2). There were filmy adhesions adjacent to the right ovary. Laparoscopic resection of the ovarian ectopic pregnancy was performed using a harmonic scalpel without complications and preservation of the right ovary was achieved. The postoperative course was unremarkable and the serum β -hCG level dropped from 14,383mIU/mL on the day of surgery to 5,663mIU/mL on postoperative day 1. Serial β -hCG levels declined to zero. Pathological evaluation of the uterine curettage specimen revealed chorionic villi, decidua and hypersecretory endometrium. The ovarian specimen revealed a corpus luteum, a portion of the ovarian wall and chorionic villi (Figure 3).

Discussion

Sonographic visualization of a HTP pregnancy after ovulation induction therapy, especially in a low-risk, asymptomatic patient, may be diagnostically challenging. Reece described four common presenting clinical features of a HTP: abdominal pain, adnexal mass, peritoneal signs and an enlarged uterus [5]. Pain, bleeding and an enlarging uterus are common also to intrauterine pregnancies often causing physicians to not suspect a HTP.

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Figure 1: Right ovarian cystic mass of 1.7 x 1.8cm suggestive of an ovarian ectopic pregnancy.



Figure 2: Intact right fallopian tube with a paratubal cyst. Ovarian bluish cystic mass consistent with an ovarian pregnancy.

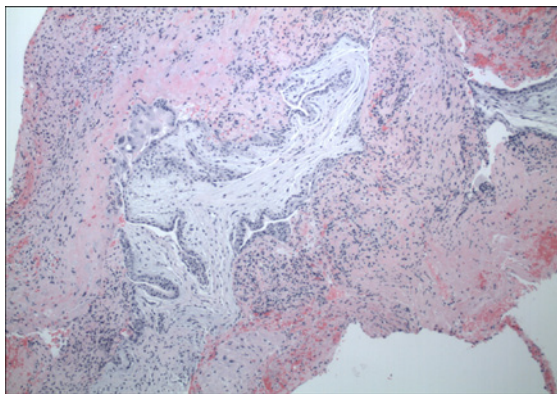


Figure 3: Hematoxylin- Eosin, medium power magnification 20X; showing chorionic villi (arrow) with adjacent ovarian wall.

The etiology of an ovarian pregnancy is currently unknown but postulated causes include a failure of follicular extrusion and/or secondary implantation of a tubal pregnancy [6]. Multiple risk factors for a HTP have been described, including pelvic inflammatory disease, the use of intrauterine devices, endometriosis and assisted reproductive technologies [6-10]. A 300-fold increase in the incidence of HTP has been reported with ART [3]. Ovulation induction with CC can cause multiple follicular development and a heterotopic ovarian pregnancy following CC stimulation has been reported [11].

A corpus luteum cyst may be difficult to distinguish from an ovarian ectopic pregnancy as the sonographic image of a well-vascularized ring within the ovary may be difficult to interpret. A wide ring that appears more echogenic than surrounding ovarian parenchyma is suggestive

of an ovarian ectopic pregnancy. The additional presence of a yolk sac and/or fetal parts aids in confirming the diagnosis [7,12]. In contrast, a corpus luteum cyst is typically characterized by lower wall echogenicity than the endometrium or ovarian stroma [13]. A significant challenge is distinguishing between a tubal and an ovarian ectopic pregnancy. Spiegelberg described four criteria for an ovarian ectopic pregnancy that can only be established intraoperatively and histopathologically. This case meets all four criteria: both fallopian tubes must be intact and separate from the ovary, the gestational sac must occupy the normal position of the ovary, the ovary and gestational sac must be attached to the uterus through the utero-ovarian ligament, and there must be ovarian tissue in the wall of the gestational sac [14].

The traditional method for management of an ovarian ectopic pregnancy is surgical excision of the ectopic pregnancy, either by ipsilateral oophorectomy or by wedge resection via laparotomy or laparoscopy. Early detection of an ovarian ectopic pregnancy allows a more conservative therapeutic approach with ovarian preservation. Successful treatment of an ovarian ectopic pregnancy with systemic Methotrexate has been reported; however, limited data are available and factors predicting the success of Methotrexate are ill-defined [15]. There are case reports of local feticidal injections of Methotrexate, Etoposide, KCL or hyperosmolar glucose into the heterotopic sac under direct ultrasound guidance [16]. These methods offer the theoretical advantage of selectively reducing the ectopic pregnancy and conserving a concurrent intrauterine pregnancy but data are limited. Surgical management remains the gold standard at this time.

Conclusion

An ovarian HTP following CC stimulation is an unusual phenomenon that can be associated with high morbidity and adverse consequences for future fertility. The diagnosis may be challenging but may be determined by combining a pertinent history of risk factors, clinical symptoms, β -hCG titers, and ultrasonographic findings. The diagnosis is confirmed at time of surgery and by histological assessment. In patients undergoing fertility treatment, a high index of suspicion is the mainstay even in the presence of an intrauterine pregnancy and in asymptomatic patients.

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