Ultrasound diagnosis of ovarian ectopic pregnancy after *in vitro* fertilization with salpingectomy and literature review

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Among ectopic pregnancies, ovarian ones are extremely rare and much less frequent with previous history of salpingectomy. Ultrasonographic diagnosis is feasible although differential diagnosis from the corpus luteum is difficult. The diagnosis includes medical history, physical examination, transvaginal ultrasonography with color and/or power Doppler and serum quantitative β-hCG levels. Monitoring of β-hCG levels and the accuracy of ultrasound diagnosis allowed conservative therapeutic strategy and proper postoperative course. This paper reports one case of right OEP with ipsilateral salpingectomy, and reviews the current concepts and the options for managing these rare types of ectopic pregnancies so to preserve the woman's potential fertility.

Key Words: *Ovarian pregnancy; Salpingectomy; Transvaginal ultrasonography; In vitro fertilization; Intra-cytoplasmatic sperm injection*

Ovarian ectopic pregnancy (OEP) is an uncommon type of ectopic gestation that is difficult to diagnose, may even present as a complex adnexal mass mimicking an ovarian tumor (1,2) and is often discovered during surgery. OEP occurs naturally, but its incidence following *in vitro* fertilization and embryo transfer (IVF-ET) increases. Marcus and Brinsden (3) reported an incidence of 6% of OEP conceived after IVF-ET.

Primary OEP with previous ipsi or bilateral salpingectomy is extremely rare (4-9) and its pathophysiology is not sufficiently known. On the other hand, OEP after ICSI-ET is even rarer and just a few cases have been reported in literature (10-13).

The diagnosis of OEP includes medical history, physical examination, transvaginal ultrasonography (TUS) with color and/or power Doppler and serum quantitative β-hCG levels.

The following sonographic diagnostic criteria for the presence of an OEP have been suggested: a wide echogenic ring with an internal hypoechoic central area on the ovarian surface; the presence of ovarian cortex, including corpus luteum or follicles around the mass; and the echogenicity of the ring usually greater than that of the ovary itself (14).

This paper reports one case of right OEP after IVF and ICSI-ET with ipsilateral salpingectomy, and reviews the current concepts of their pathogenesis as well as the options for managing these rare types of ectopic pregnancy in order to preserve the woman's potential fertility.

CASE

A 31 year old woman, with previous right salpingectomy 1 year before, for right tubal pregnancy, was referred to our Reproduction Unit due to 3 years of primary infertility. The first IVF treatment was performed 12 months after salpingectomy. The patient underwent treatment for ovarian stimulation with antagonist of GnRH protocol, and 8 oocytes being obtained by transvaginal ultrasound; 4 of them were inseminated by conventional method and 4 by ICSI technique. Two embryos, one from ICSI and the other one from the conventional procedure were transferred back to the uterine cavity under guidance of transabdominal ultrasound following a technique previously published by us (15).

On the 24th day after ET, the patient went to the emergency room, relating pain and blood loss after 9 days of ET; TUS did not reveal an intrauterine or extrauterine gestational sac and the β-hCG level was 1,029 IU/L and the patient was referred to her gynecologist.

On the 26th day after ET, she presented pain in right iliac fosae. TUS examination was performed using a GE Voluson E8 machine (GE Medical Systems, Zipf, Austria); a thin endometrial lining with no intrauterine gestational sac was observed. No free fluid was observed in the uterine cavity, neither type A nor B (16) (Figure 1). The left ovary appeared normal with no suspicious mass in the ipsilateral tube. The right ovary was enlarged owing to a 29 mm unilocular anechoic cyst and a 15 mm thick echogenic wall surrounding a central hypoechoic structure clearly seen within the ovary (Figure 2). Serum β-hCG level was 1,163 IU/L.

Two days later (28th day after ET) β-hCG level was 1,928 IU/L and TUS imaging of the ovary grew, measuring 19 mm and power Doppler study showed peripheral vascularity as a ring of fire (Figure 3), suspecting possible OEP. No free fluid was displayed in the pouch of Douglas. The patient previously gave informed consent for a laparoscopy, which was performed on the same day with the suspicion of ectopic pregnancy intimately attached to the right ovary or part thereof. Intraoperative laparoscopic evaluation revealed absence of right fallopian tube and the normal left fallopian tube; the uterus and left ovary were also normal. The enlarged right ovary contained the hemorrhagic corpus luteum and OEP. The OEP was identified and removed preserving the ovary. The postoperative period was uneventful and β-hCG returned to normal levels in a few days. The patient left the hospital the next day.

The histopathologic report showed hemorrhage and fibrin deposits including scant necrotic chorionic villi (Figure 4) and low amounts of extravillous trophoblast. No embryonic tissues were detected. The fibrinohematic material was attached to cortical ovarian fragments in which some primary follicles were seen (Figure 5).

DISCUSSION

Ectopic pregnancy is one of the most frequent complications in patients undergoing assisted reproduction treatment, reaching an incidence of 4.5% (3).

We searched literature for articles reporting OEP published from 1990 through July, 2012. We investigated if it was a common pathology, if there was surgical history of salpingectomy, and whether assisted reproductive techniques were used. We also looked for diagnostic methodology and the types of treatments.

Joseph and Irvine (17), reviewing English language literature, found 250 reported cases, most of them case reports (1 to 3). But we have also identified longer series that set the rates as a percentage of OEP among total ectopic pregnancies, and the surgical procedure by which the treatment has been established (3,18-20). Table 1 shows the series reported, including the number of cases and its rate as a percentage of OEP and their management.

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Figure 1) *Transvaginal ultrasound, showing a longitudinal section of the uterus whose cavity shows no free fluid (yellow arrow)*

Figure 2) *Transvaginal ultrasound, which shows an enlarged right ovary, owing to a 29 mm unilocular anechoic cyst (white arrow) and a 15 mm thick echogenic wall surrounding a central hypoechoic structure clearly seen within the ovary (yellow arrow). This image suggests an ectopic pregnancy in the ovary*

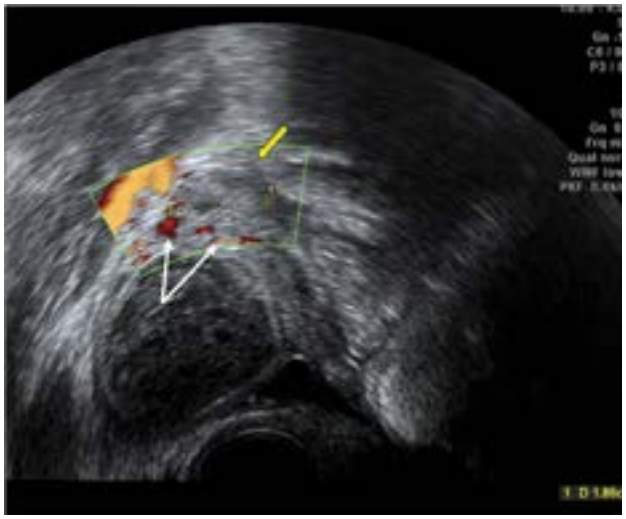

Figure 3) *Transvaginal ultrasound with power Doppler that shows the same ovary two days later. We can see the image of ectopic pregnancy has grown (19 mm) (yellow arrow) and the mapping of color power shows peripheral vascularization (white arrows)*

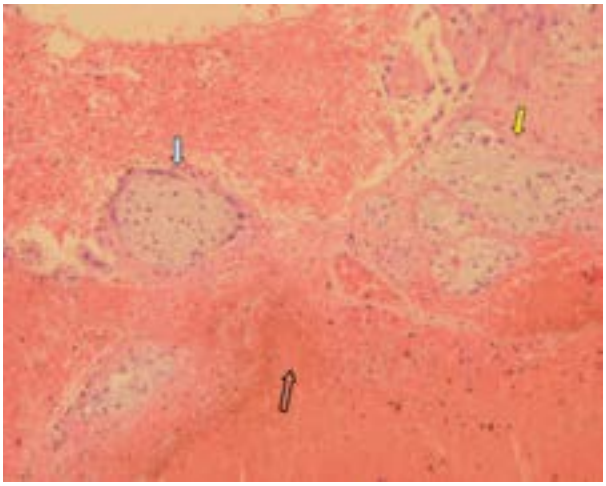

Figure 4) *Chorionic villi (white arrow), some of them with necrosis (yellow arrow), with abundant hemorrhage (H&E ×400) (empty arrow)*

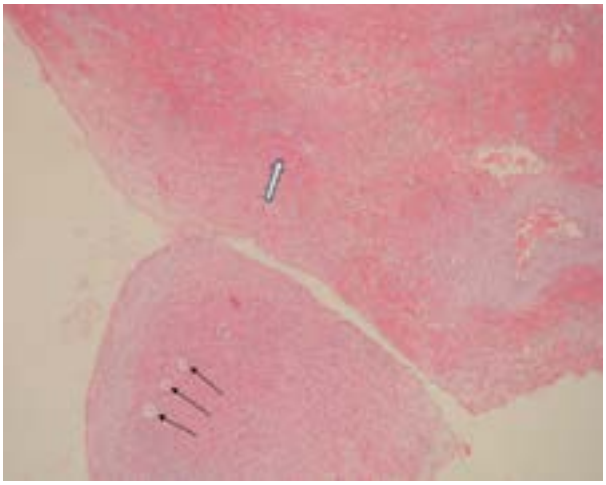

Figure 5) *Ovarian cortex with hemorrhage (white arrow) and three primary follicles (H&E ×40) (black arrows)*

TABLE 1

A review of the series, listing management and the ovarian ectopic pregnancy rates

Authors	Cases	Management	OEP rate (%)
Marcus and Brinsden (3)	7	Laparoscopy	6.0
Seinera (21)	8	Laparoscopy	2.6
Bouyer (18)	54	Conservative 10 laparoscopy	3.2
Raziel (20)	19	8 laparotomy 1 MTX	2.7
Odejinmi (19)	12	Laparoscopy	2.9

Among the published papers, five cases of OEP were found in patients with a history of bilateral salpingectomy (4-6,8,9,21) and ipsilateral salpingectomy for the ovary affected by the OEP in one case (7). In a patient with bilateral salpingectomy, ectopic pregnancy is an unexpected finding. In our case the patient had left tube patency; it may be considered that the transferred embryo migrated through the left tube to the right ovary. Another possibility would be that the placement of embryos into the uterine cavity through the catheter caused an iatrogenic perforation and consequent migration of the embryo; this possibility, in our case, is unlikely because the transfer was done under the ultrasound guidance technique according to that previously described by us (15), which allows us to precisely control the placement of the embryo and the path of the catheter. Also, migration of the embryo from the uterine cavity to the ovary through the fistulous tract in the intramyometrial portion of the tube has been suggested (7,8,22).

The mechanism of OEP after ICSI-ET is not sufficiently known, but there might be an association with prolonged *in vitro* culture in women who had undergone ICSI10. To our knowledge, only five previous cases of OEP have also been reported after the ICSI-ET (10-13). These authors suggest that increased volume of culture medium and the injection pressure at the time of transfer would result in reverse migration. In our case transvaginal ultrasound-guided aspiration yielded 8 oocytes, of which 4 were injected. The resulting embryos were cultured until day 3 and two of them, one from ICSI technique and the other from the conventional technique were transferred on day 3. The two remaining embryos were cryopreserved.

The diagnosis of OEP requires medical history, physical examination, TUS with color and/or power Doppler and serum quantitative β-hCG levels. Symptoms often present with abdominal pain and vaginal bleeding (3,4,19), but can also be asymptomatic (3) or present symptomatology when there is advanced gestation (1,2).

In 1878, Spiegelberg (23) suggested four criteria to distinguish a primary ovarian pregnancy, and these criteria are still used today:

1) The Fallopian tube with its fimbria should be intact and separate from the ovary.

2) The gestational sac should occupy the normal position of the ovary.

3) The gestational sac should be connected to the uterus by the ovary ligament.

4) Ovarian tissue must be present in the specimen attached to the gestational sac.

However, these criteria probably misdiagnosed many OEPs, more often from patients with assisted reproduction treatments (24); on the other hand, unfortunately, these are surgical criteria; none of these criteria can be established by ultrasonography.

The progress made in recent years with the availability of a highly specific radioimmunoassay for HCG, the improvement of TUS and widespread use of laparoscopy, have allowed early diagnosis of OEP. The sensitivity of diagnosing ectopic pregnancy using quantitative β-hCG in combination with TUS detection of an adnexal mass can be as high as 96% and the specificity 100% (25).

Ultrasound diagnosis of OEP shows the empty uterine cavity, the thickened endometrium and free fluid. It is difficult to make the differential diagnosis with a corpus luteum as both structures are located in the ovary. Some studies have showed that in stimulated ovaries, despite large size and vascularization, it is also possible to diagnose OEP with TUS and with serum quantitative β-hCG (26,27). Comstock et al. (4) described the ultrasonic appearances suggestive of OEP as a wide echogenic ring surrounding a central hypoechoic structure; these findings have been documented in other case report (28,29). In evaluation of the walls of the corpus luteum and the ectopics, Stein et al. (14) found that tubal ectopic rings were more echogenic than the corpus luteum. With respect to color Doppler, the results are controversial because there is an overlap distinguishing a corpus luteum from OEP. If a yolk sac or embryo can be seen, the diagnosis is established, but this is infrequent. The following sonographic diagnostic criteria for the presence of an OEP have been suggested: a wide echogenic ring with an internal hypoechoic central area on the ovarian surface; the presence of ovarian cortex, including corpus luteum or follicles around the mass; and the echogenicity of the ring usually greater than that of the ovary itself (14). In our case imaging of the ovary showed a thick echogenic wall surrounding a central hypoechoic structure, clearly seen within the ovary, measuring 19 mm and power Doppler study showed peripheral vascularity as a ring of fire, suspecting possible OEP.

The therapy of early ovarian pregnancy is surgical in the first line, and in the event that the patient desires a future pregnancy, ovarian wedge resection is preferred; the conservation of ovarian tissue is the clinical goal of the treatment. Medical management is rarely used; only a few case reports describe the successful medical management of OEP with methotrexate, either intramuscular (30,31) or by local injection into the sac (32). On the other hand, laparoscopic treatment with systemic methotrexate was reported as a good result (33,34). Considering the great improvements in laparoscopic techniques, medical treatment with methotrexate would be relegated to a secondary option for incomplete resection or trophoblast persistence (26,33). In our case continuous monitoring of the patient with serum values of β-hCG levels, and the detailed and thorough description of ultrasound findings of the right ovary allowed for a conservative therapeutic strategy and proper postoperative course.

CONCLUSION

In conclusion, early diagnosis of OEP is essential and is currently possible with the development of TUS with color and/or power Doppler associated with serum β-hCG levels, in order to perform conservative treatment with laparoscopy, with the objective of preserving fertility.

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