

Mini Review

Advances in the Diagnosis and Management of Ovarian Ectopic Pregnancy: A Short Review

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ABSTRACT

The ovarian ectopic pregnancy OPE is one of the most serious and rarest types of extra-uterine pregnancy, where the implantation of the gestational sac occurs in the ovum. Given the rarity of this condition, in addition to the accompanied morbidity, the risk of their complications, and even death, early diagnosis and treatment are crucial. Its diagnosis is not easy and relies on criteria based on preoperative findings, with poor clinical symptomatology and a difficult ultrasound diagnosis. Its management of choice remains surgical therapy despite the progress in medical treatments with fertility preservation. Patients' symptomatology, radiological and lab findings, addition to her obstetric history and desire for future procreation must also be taken into consideration.

Keywords: Ectopic pregnancy; ovarian pregnancy; Treatment; Diagnosis.

Abbreviations

B-hCG: Beta-Human Chorionic Gonadotropin; EP: Ectopic Pregnancy; HP: Heterotopic Pregnancy; IUCD: Intra-uterine Contraceptive Devices; IUDs: Intra-Uterine Devices; MRI: Magnetic Resonance Imaging; MTX: Methotrexate; OPE: Ovarian Ectopic Pregnancy; PID: Pelvic Inflammatory Disease; TV-US: Transvaginal Ultrasonography.

INTRODUCTION

Incorrect implantation or ectopic pregnancy (EP) is a potentially life-threatening condition and it is estimated to be 0.5% - 2.0% of all reported pregnancies.¹ EP refers to the implantation of an ovum outside of the normal uterine cavity.² It is mostly located in the fallopian tube, most commonly in the ampullary region of the fallopian tube. Regarding the implantation outside the fallopian tube, it only occurs in less than 10% of ectopic pregnancies. It includes numerous sites such as myometrium, cervix, abdominal cavity, and ovary, caesarean scar interstitial portion of the fallopian tube, or coincidentally with an intrauterine pregnancy. Heterotopic pregnancy (HP) refers to the coexistence of an EP with an intrauterine pregnancy.³

Ovarian ectopic pregnancy OPE, occurs when a gestational sac implants in the ovum. In other words, the ovum is not released or captured after ovulation however; it is fertilized and implanted in the ovary.⁴ OEP can be classified as either primary OEP or secondary OEP. The etiology of primary OEP remains blurred, and it is suggested to be secondary to the reflux of fertilized oocytes to the ovary.⁵ The first OPE case was described in 1682 by Saint Maurice of France, since then, their overall incidence has been increasing.⁶ The true incidence may be higher given that multiple cases treated medically for pregnancies of an unknown site may present an OEP. Ovarian ectopic pregnancy is a serious and rare type of EP, accounting for almost 0.15 - 3% where its incidence varies between 1:3000 and 1:7000 pregnancies.⁴ Besides the

increase in the incidence rate of OEPs per live births increased, a previous study also reported a rise in the incidence rates of OEPs per EPs and EPs per live births.⁶ The duration of such pregnancy may be up to 4 weeks, with an average period of 45 days, which may cause fatal intra-abdominal bleeding.⁴ Generally, OEP shares similar risk factors with tubal pregnancy including a history of a prior EP, pelvic infections, and use of in-vitro fertilization. The use of intrauterine devices (IUDs) may be associated with higher risk that the pregnancy will be extra-uterine.⁷

Given the rarity of this condition, in addition to the accompanied morbidity, the danger of their complications, and even death, early diagnosis and treatment are crucial.⁴ Due to advances in laboratory testing, transvaginal ultrasound, chemotherapy and laparoscopy, the evaluation, diagnosis and management of OEP have rapidly evolved. Depending on the current published research studies by searching the PubMed and EMBASE online databases, we have tried to systematically summarize the current diagnosis and treatment of patients with OEP. This review adds meaningful information for future research related to this topic given its rarity.

PATHOPHYSIOLOGY

The optimized environment suitable for oocyte transport, fertilization and even embryo migration for implantation to the uterus, is provided by the fallopian tube.⁸ Given the classification of OEP primary OEP is usually due to ovulatory dysfunction, where the ovum is fertilized while being in the follicle, before the expulsion of the follicle from the ovary. On the second hand, secondary OEP, fertilization is located in the fallopian tube and the concept us is regurgitated and implanted in the ovarian stroma.⁹ Attempts have been made to differentiate between intrafollicular (failure of follicular expulsion) and extra follicular. Intrafollicular OEP is rare; the ovum is fertilized in the ovary within the follicle. However, in the case of extra follicular OEP, the ovum is fertilized then migrates to the ovary and implanted.¹⁰

The etiology of OEP remains unknown, yet many speculations have been made an author suggested the alteration of tubal motility due to specific conditions causing fallopian tube epithelial damage, while another proposed that a hindrance in the release of the ovum from the ruptured follicle may also cause OEP.^{11,12} When reviewing the literature, risk factors including history of previous ectopic pregnancy, sexually transmitted disease, pelvic surgery or pelvic inflammatory disease (PID), and endometriosis have been suggested as contributory factors, in addition to other non-modifiable factors such as senior maternal age and infertility (Table 1).^{5,12}

Table 1. Risk factors for OEP

Risk Factors
Advanced Maternal Age
History of previous ectopic pregnancy
History of sexually transmitted disease
Pelvic inflammatory disease
Use of assisted reproductive technologies
Previous pelvic surgery
Endometriosis
Infertility

Furthermore, the association between the use of the intrauterine contraceptive device (IUCD) and the increase in the incidence of

OEP was reported as early as 1976.¹³ As a matter of fact, these provide protection against uterine and tubal implantation but do not an effect ovarian location.^{14,15} It is suggested that they play a role in altering tubal motility, therefore facilitating the implantation in the ovary.¹⁶

DIAGNOSIS

When a woman at a reproductive age complains about pelvic or/and lower abdominal pain, OEP should be suspected. Other symptoms may include vaginal bleeding and menstrual abnormalities.⁹ When an adnexal mass is detected during clinical examination, an ultrasound evaluation must be performed to visualize the position of the mass, as an intraovarian mass moves with the ovary when applying pressure which is known as a positive sliding sign. If there is a presence of coexistent pathology including endometriosis or past PID then sliding signs will be negative. It is difficult to diagnose OEP sonographically, and most patients are diagnosed intraoperatively.¹⁷

A high index of suspicion might be presented when combining ultrasound findings, as well as pre-diagnosis such as increased b-hCG levels. Early-onset rupture and haemoperitoneum can result in hypovolemia which can be a life-threatening gynecological emergency. The majority of OEPs end in rupture during the first trimester, where only 5.3% and 3.7% reach the second and third trimester respectively.¹¹ Nevertheless, a patient presenting with ruptured ovarian ectopic pregnancy with low levels of b-hCG was also documented.¹⁸ Ultrasound and magnetic resonance imaging (MRI) are used as problem-solving tools to further confirm the diagnosis. MRI can provide accurate assessment of abnormal implantation site, and distinguish rupture from non-rupture cases before management.¹⁹ Due to the dramatic quality improvement of ultrasound, improved training and access, transvaginal USG findings are currently considered an integral part of diagnosing ectopic pregnancies while presenting specific criteria (Table 2).⁵ Io et al. reported the usage of MRI for implantation site positioning case it was unclear on TV-US.²⁰

Table 2. Sonographic criteria for the presence of OEP

OPE Sonographic criteria
An empty uterine cavity
A gestational sac adhered to adjacent ovarian parenchyma
A yolk sac and fetal pole, with/without cardiac motion
A wide echogenic outer ring, where its echogenicity larger than the ovary itself
Presence of an ovarian cortex, with corpus luteum or follicles adjacent to the mass

However, definitive diagnosis requires histological confirmation performed by surgery (laparoscopy or laparotomy) to elucidate the management and exclude any differential diagnosis. Laparoscopic procedures are more preferred due to their shorter operation duration and hospital stay, less necessity of analgesia after the operation, and decreased blood loss.¹⁶

Diagnosis is usually made by pathological assessment. The Spiegelberg criteria created in 1878 by Dr. Otto Spiegelberg is very commonly used²¹ consisting of:

- a. The gestational sac occupying the site of the ovary,
- b. The ectopic pregnancy connected to the uterus by the ovarian

ligament,

- c. Ovarian tissue in the sac wall histologically proven,
- d. The intact tube separated from the involved side.

Yet, these criteria can be visualized laparoscopically and can't be confirmed on ultrasound.²² Therefore, Sergent and his colleagues re-evaluated diagnostic criteria for ovarian pregnancies by combining both laboratory and TV-US results:²³

- a. Serum b-hCG levels more than 1,000 IU/L,
- b. Absence of gestational sac on TV-US,
- c. Ovarian involvement must be confirmed on examination, and with bleeding, visualization of chorionic villi, or presence of atypical cysts on the ovary,
- d. Intact fallopian tubes,
- e. No serum b-hCG level following management.

MANAGEMENT

Medical Management

Contrasting results on the administration of intramuscular methotrexate or etoposide (mifepristone, parenteral prostaglandin F2a) have been reported.²² It is recommended to inject a single dose of methotrexate MTX treatment; where a recent study reported an overall success rate of 75.45% after a single MTX dose, and 3.61% required a repeat dose of the drug.²⁴ Few case reports have described successful methotrexate MTX therapy.²⁵ Pagidas et al. administrated MTX treatment for ovarian ectopic patients' diagnosed using transvaginal USG and were healed. The authors suggested that early diagnosis by transvaginal USG can benefit from MTX treatment.²⁶ Similarly, a case report of a 37 years old patient with a history of 2 past cesarean sections and IUD usage was diagnosed at 6 weeks of ectopic ovarian pregnancy using transvaginal USG; she was treated with multi-dose MTX treatment, which achieved healing. The authors highlighted that with adequate clinical evaluation and transvaginal examination, early-staged OPE can be treated medically while preserving the normal anatomy relevant for fertility.²⁷ Laparoscopy-guided methotrexate injection was reported to successfully treat an ovarian ectopic.²⁸ MTX therapy for EP of all routes has a success rate of between 72.4% and 88% suggesting β -hCG levels as a predictive factor of success or failure of treatment of EP with single-dose MTX.²⁹ In one case, methotrexate was required to treat persistent post-surgical trophoblast. However, when compared to surgical treatment, MTX use was associated with higher failure rates and risk of ovarian bleeding. 10 Furthermore, The American Society for Reproductive Medicine did not recommend MTX as a primary OEP treatment.³⁰ Therefore, some criteria were set to consider the administration of MTX including:

- a. Serum b-hCG level lower than 3,500 IU/L
- b. Absence of blood within the pelvis,
- c. Pregnancy size must be more than 3.5 cm with the absence of fetal heart activity,
- d. Absence of hemodynamic compromise.³¹

Surgical Management

Previous evidence suggested that surgery is the gold-standard method

of OEP management, while medical management is less frequent.⁶ The desire for future procreation must be taken into account when determining the optimal management of OEP. Therefore, for fertility preservation, ovarian tissue loss prevention and pelvic adhesions, conservative treatment is applied. It includes enucleation, wedge resection, cystectomy, trophoblast curettage with coagulation or hemostatic suture.³² The most performed procedure is resection of sac and hemostasis most likely with laparoscopy or laparotomy where most of the cases arrive in a collapsed state with uncertain diagnosis and laparoscopy may not be feasible. 10 years' experience, sac excision and hemostasis were performed in 11 patients due to the rupture of sacs by the products of conception extruding in these patients. In 2 previous cases, oophorectomy had to be resorted due to the uncontrolled hemorrhage and hemostasis was not possible.³³ Recently, there was an apparent shift toward laparoscopic surgery for OEP management where Ko et al. reported that 40% of patients performed laparoscopic surgery between 1989 - 1998 to increase to 92% patients between 1999 - 2009.⁶ Generally, surgical procedures are commonly performed in late onset of clinical signs meaning late diagnosis, whereas MTX is used in early-onset patients with stable conditions. Yet, even cases with early phase surgical interventions have a diagnostic and a therapeutic role.³² In most cases, surgical management does not cause postoperatively any complications after close outpatient follow-up during various days. Consequently, serum b-hCG levels should be evaluated and must show a steady decrease and then its absence. Patients with a history of OEP had preserved fertility with no OEP recurrence documented.³⁴

Table 3. Published studies on OEP management

Author	Title	Reference
Sotelo 2019	Ovarian Ectopic Pregnancy: A Clinical Analysis	22
Szadok 2019	Ovarian ectopic pregnancy	4
Andrade 2015	Ovarian ectopic pregnancy in adolescence	35
Birge 2015	Medical management of an ovarian ectopic pregnancy: a case report	32
Elwell 2015	Unruptured second-trimester ovarian pregnancy	36
Goyal 2014	Ovarian ectopic pregnancy: A 10 years' experience and review of literature	33
Tehrani 2014	Ovarian ectopic pregnancy: A rare case	6
Hassan 2012	Primary ovarian pregnancy: case report and review of literature	31
Joseph & Irvine 2012	Ovarian ectopic pregnancy: Aetiology, diagnosis, and challenges in surgical management	15
Ko 2012	Twenty-one years of experience with ovarian ectopic pregnancy at one institution in Taiwan	6
Scutiero 2012	Primary Ovarian Pregnancy and Its Management	37

CONCLUSION

Diagnosis and management of ovarian ectopic remains challenging owing to its rarity. A high index of clinical suspicion should be thought of in presence of risk factors for an ectopic pregnancy. The first line of investigation is the ultrasound pelvis considering recent advances in

ultrasound and the expertise in performing it. A systematic approach in eliciting the history, performing a clinical examination and ultrasound scan can expedite diagnosis. MRI may be helpful in certain situations depending on individual early pregnancy unit practice.

Choosing the convenient treatment method including either medications or surgery, preferably sparing, must be considered individually in each case. Surgery is the gold-standard method of management, while there are still conflicting results in MTX administration.

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