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Review of Ectopic Pregnancy treatment for IVF patients

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Introduction

Ectopic pregnancy (EP) is the leading cause of maternal morbidity and mortality[1,2]. It occurs in 1.5% to 2% in the general population while it is more common in patients with tubal disease [2,3,4,5].

There are two common ways an EP is treated, either medically with the use of methotrexate (MTX) or surgically with salpingectomy or salpingostomy[6]. Given that the new diagnostic methods such as transvaginal ultrasound scans provide an earlier diagnosis of EP, the need for surgery has decreased[7].

Previous studies have shown a trend favoring salpingostomy over salpingectomy, as preservation of both tubes is assumed to favor fertility[8,9]. However, focusing on EPs occurring in patients who are undergoing IVF, the use of MTX or unilateral salpingectomy are most commonly used, while salpingostomy is thought to be less beneficial as another IVF cycle is often required to achieve pregnancy[6].

It is unclear whether different treatment approaches for an EP affect its recurrence rate and the outcome of future IVF treatment. Previous studies examining patients with history of EP that conceived naturally show that the recurrence rate of EP is comparable between patients who received MTX and those who underwent salpingectomy[10,11]. Similar results were reported by Irani et al.[6] examining the recurrence rate of EP in IVF patients with previous EP by comparing the different treatment approaches. However, others reported a higher recurrence rate of EP post-salpingostomy compared to post-salpingectomy[8].

This review will focus on tubal EP, comparing how different therapies of EP can affect the recurrence of EP and fertility in patients undergoing IVF.

Pathomechanism and Causes of EP in IVF patients

EP is an abnormal pregnancy described by the implantation of a fertilized ovum in a location outside the uterine cavity. It represents 1-2% of pregnancies in the general population and 2-5% in patients undergoing IVF[2,3,4,5].

The most common location of an EP is the fallopian tube[6]. Several theories suggest that abnormal fallopian tube pathology interferes with embryo transport, such as ciliary dysfunction, myosalpinx spasm secondary to prostaglandin release or incomplete relaxation, leading to EP[5,6]. Another common explanation is the chronic inflammation or infection after pelvic inflammatory disease affecting tubal patency[5,12].

Abnormal tubal pathology is thought to be the most common cause of EP both in naturally conceived pregnancies and in pregnancies resulted from IVF-embryo transfer (ET)[13]. Several studies have shown that additional mechanisms are involved in EPs occurring in IVF patients, as no transport of the fertilized ovum occurs along the fallopian tube[6,14]. Such mechanisms include the overexpression of the adhesion molecule E-cadherin in the tubal implantation sites of EPs resulting from IVF treatment compared to natural conceptions[15]. Revel et al.[15] demonstrated that embryos exposed to in vitro cultures lead to overexpression of E-cadherin, a molecule which plays a role in determining the implantation site. In addition, controlled ovarian hyperstimulation (COH) leads to hormonal changes that affect the expression of signaling molecules (cytokines, chemokines etc.) disrupting the interaction among embryo, fallopian tube and endometrium[16]. It is proposed that immunologic changes have also been associated with an increased risk of EP[17].

Risk Factors of EP in IVF patients

Several additional risk factors are associated with the incidence of EP specifically IVF treatment. These include the use of large volume of culture medium during embryo transfer leading to changes in hydrostatic pressure moving the embryo through the tubal ostia[14,18]. In addition, it has been suggested that performing an embryo transfer close to the uterine fundus may result in higher incidence of EP[19]. According to Lesny et al.[20] this could be due to strong random fundal contraction waves generated when the catheter during ET comes in contact with the uterine fundus. Based on a RCT comparing the rate of intrauterine pregnancies and EP in midfundal and deep fundal transfers, findings show the superiority of midfundal transfer, as it resulted in lower EP rate[21].

Focusing on maternal risk factors, it is known that a history of previous EP in IVF patients is strongly associated with subsequent EPs[4,22]. In addition, studies report that each successive occurrence of EP further increases the risk of a future EP[4,6,22]. Findings of Irani et al.[6] are consistent with these results showing that the incidence of EP is positively correlated with the number of previous EPs regardless of the treatment option of EP.

In patients undergoing IVF, another major risk factor is previous pelvic or tubal surgery[14]. The risk depends on the extent of surgery and the degree of damage and anatomic alterations[22]. (OR for recurrence of EP is: 8.52 (95% CI: 5.91-12.27) after adnexal surgery, 11.02 (95% CI: 5.49, 22.15) after surgery for tubal infertility, 5.16 (95% CI: 1.25- 21.21) after surgery for endometriosis and 17.70 (95% CI: 8.11-38.66) after previous abdominal/pelvic surgery[23,24]).

Diagnosis

Today, the available diagnostic methods allow an earlier diagnosis of EP usually before the onset of the symptoms[6,25]. The accepted diagnostic methods used are serial quantitative measurements of serum β-hCG together with transvaginal ultrasound[25,26]. Follow-up of patients by monitoring the serum β-hCG levels is required to confirm resolution of EP[26].

Management of EP

The management of EP involves two different treatment methods, medical and surgical. Although, surgery is the gold-standard therapy of EP, the diagnosis of EP at an earlier stage is now possible favoring a more conservative management based on the clinical status and the future fertility requirements of the patient[6,14].

Medical

The medical management of EP includes the use of intramuscular or intravenous MTX, a folic acid antagonist, which is established as the primary treatment option for stable patients without contraindications[25,27]. According to ACOG and NICE guidelines, MTX is indicated in hemodynamically stable patients with initial serum β-hCG levels < 5000 IU/L and an EP< 3,5 cm in size, who can comply with the follow-up plan[27,28]. MTX treatment has several advantages such as preservation of tubal patency and function, avoidance of surgery, anesthesia and their complications and possibly cost-effectiveness[27]. However, its potential side effects should always be considered when treating an EP. Those include significant risk of tubal rupture in failed MTX cases, abdominal pain due to tubal abortion, need of second MTX dose due to unsuccessful decrease of β-hCG levels and side effects of MTX such as stomatitis and diarrhea[27].

The overall success rate of MTX use for the management of EP ranges from 70% to 90% depending on the use of single or multiple-dose MTX treatment[29]. It is suggested that the success of medical therapy is negatively correlated with the initial serum β-hCG levels, as such its early diagnosis is necessary[27]. It is important to recognize that even with falling β-hCG levels the risk of tubal rupture cannot be excluded[29]. Therefore, surgical therapy is required if evidence of medical treatment failure or indication of tubal rupture exists, namely: hemodynamic instability, rapidly increasing β-hCG, increased abdominal pain regardless of β-hCG levels[11].

Surgical

Surgery is required for patients who are not suitable for MTX treatment and patients who fail MTX therapy[6,25]. Two surgical options are available: salpingostomy or salpingectomy[7]. The most common approach is laparoscopy

as it is associated with less morbidity, faster recovery and shorter hospital stay, while laparotomy is limited to hemodynamically unstable patients[6].

Salpingostomy is indicated for hemodynamically stable patients with unruptured EP <5 cm in dimeter[30]. It offers fertility preservation in patients with an absent or damaged contralateral salpinx[10]. Therefore, it is preferred for patients who might attempt natural conception or intrauterine insemination[7]. However, there is a risk of persistent ectopic tissue after salpingostomy, accounting for 4% to 15% of the cases[31]. Some have considered the use of a prophylactic dose of MTX after salpingostomy, decreasing this risk to 0% to 2%[31].

Salpingectomy is indicated in patients with uncontrolled bleeding, recurrent EP in the same fallopian tube or extensive tubal damage[14]. It is also the preferred treatment option in IVF patients as there is no benefit conserving the fallopian tube[6].

Looking at the success rate of the two surgical approaches, the ESEP study showed a significant difference of persistent trophoblastic tissue post-salpingostomy compared to post-salpingectomy treatment *(14 [7%] vs 1 [<1%]; RR 15·0, 2·0–113·4)*[32]. For this reason, NICE guidelines recommend salpingectomy over salpingostomy to women who must undergo surgical treatment for the resolution of EP[28].

Recurrence rate of EP

Several studies have evaluated the recurrence rate of EPs. Studies have shown comparable recurrence rates of EP after natural conception between patients with previous EPs treated medically (MTX) and those who underwent salpingectomy[10,11].

Other studies, comparing salpingostomy with MTX therapy, show that the recurrence rate of EP after MTX is relatively low (12%), with no significant difference from the observed rate post-salpingostomy (9%)[11,33]. Xu et al.[34] report that medical treatment does not increase the risk of EP compared to surgical treatments.

Additionally, studies have also compared the recurrence rate of EP after treatment with salpingostomy and salpingectomy. van Mello et al.[8] reported similar rates of recurrent EP (RR, 1.30, 95% CI, 0.72- 2.38) and intrauterine pregnancy (RR, 1.04; 95% CI, 0.899–1.21) between the two. In contrast, results of a cohort study demonstrated that salpingostomy is associated with higher rate of intrauterine pregnancy (RR, 1.24; 95% CI, 1.08–1.42) and higher risk of recurrent EP (10% versus 4%; RR, 2.27; 95% CI, 1.12–4.58) compared to salpingectomy[8]. Similar findings were reported in the ESEP study[32] indicating that even though salpingostomy is used for fertility preservation, it might be associated with a higher risk of recurrent EP than salpingectomy.

Implications of management of EP and subsequent IVF treatment

It is important to consider the potential effects of different treatments for EP on a subsequent cycle of IVF treatment. For example, it has been proposed that the potential impact of ovarian reserve could impact ART outcomes. MTX, as a cytotoxic agent, could affect the ovarian response during COH by affecting the primordial ovarian follicles[14]. However, studies have shown that MTX therapy has no harmful effect on the ovarian reserve[35,36]. A systematic review demonstrated no difference in the mean number of oocytes retrieved in women undergoing fertility treatment, before and after MTX therapy[37].

Salpingectomy may impact adnexal blood supply[6]. Branches from the ovarian and uterine arteries could be damaged disturbing the ovarian vascular supply and subsequently leading to decreased ovarian reserve and ovarian steroid production[6,38,39,40]. There are conflicting findings concerning its impact on ovarian reserve[6]. Several studies report that salpingectomy decrease the ovarian response during COH and affects the ovarian reserve[38,39,40]. However, a number of studies also showed no significant difference between patients who underwent ovarian induction pre- and post- salpingectomy by comparing the following ovarian parameters: basal FSH levels, estrogen concentration, length of stimulation, number of follicles, number of retrieved and fertilized oocytes and embryo quality[41,42,43]. These authors concluded that salpingectomy did not have a negative impact on ovarian reserve[41,42,43]. Furthermore, recent studies suggest that salpingectomy and salpingostomy do not affect the ovarian function as there was no statistical difference in the follicular number between the ipsilateral and the contralateral ovary to the surgical side in each patient[34].

Similar results have been reported by Irani et al.[6] examining the recurrence rate of EP in IVF patients with history of EPs after MTX treatment (2.8%) and post salpingectomy (3.6%). The authors postulated that an underlying pathology is the most common explanation, like pelvic inflammatory disease, affecting both tubes simultaneously. Therefore, removing one of the tubes will not minimize the risk of a future EP occurring in the contralateral salpinx[6]. Few studies have investigated the success rate of IVF after management of EP. Xu et al.[34] by comparing the three different treatment approaches of EP, namely, conservative treatment, salpingostomy and salpingectomy in patients with previous EP examined their effect on IVF outcome. Their findings showed no significant difference in the rate of delivery (37.17%, 35.87%,31.74%), clinical pregnancy (45.03%, 45.14%, 40.73%), miscarriage (16.28%, 17.00%, 12.61%), EP (5.81%, 4.87%, 4.50%) and implantation (31.91%, 32.66%, 30.02%) among the three groups. They also reported that the basal follicular number

and the follicular number on the day of hCG did not differ between the groups, suggesting that none of the three treatments affects the ovarian function. Since both these studies showed no overall difference in outcome based on treatment approach, it appears that the treatment modality should be based solely on the clinical scenario.

Conclusion

EP is a medical emergency and its incidence is increased in IVF patients. Therefore, it is important that the best treatment option is provided to patients based on their clinical status and their future fertility requirements. It appears that MTX has similar recurrence rate of EP with salpingectomy and salpingostomy both in pregnancies after natural conception and pregnancies that resulted from IVF. In addition, the available findings show no difference between them. However, additional studies are required to support these findings. Based in the available evidence, MTX may be considered as the first-line therapy of EP in patients with an early, unruptured EP, even for patient undergoing IVF treatment.

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