

New advances in the causes and treatment of ectopic pregnancy: A review

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Abstract: In recent years, the incidence of ectopic pregnancy has significantly increased, making it one of the common acute abdominal conditions in obstetrics and gynecology and a leading cause of maternal mortality. The etiology of ectopic pregnancy [1-4] is diverse, with inflammation being identified as a primary causative factor based on clinical statistics. Chronic salpingitis, particularly, is the most prevalent form of inflammation associated with ectopic pregnancy. Additionally, there is a close correlation with factors such as intrauterine devices, surgical history, and hormone levels. Therefore, effective measures should be taken to promote menstrual and antenatal hygiene, rigorously adhere to the surgical indications in obstetrics and gynecology, ensure aseptic procedures during surgery, and postoperatively focus on infection prevention to reduce the incidence. The current discussions on the treatment options for ectopic pregnancy include medical and surgical interventions. Notably, laparoscopic surgery [13] for treating ectopic pregnancy is characterized by its minimal invasiveness, high success rates, rapid postoperative recovery, fewer complications, and the preservation of patients' fertility. Hence, it is worthy of extensive clinical promotion.

1. Introduction

Ectopic pregnancy (EP) refers to the implantation of a fertilized egg outside the uterine cavity (commonly known as ectopic gestation). EP includes tubal pregnancy, ovarian pregnancy, interstitial pregnancy within the uterine wall, abdominal pregnancy, broad ligament pregnancy, and cervical pregnancy. Ectopic pregnancy specifically refers to pregnancies outside the uterus, excluding cervical pregnancies and cornual pregnancies (interstitial pregnancies within the uterine wall). Among them, tubal pregnancy is the most common, accounting for approximately 95% of EP cases. EP is a common acute abdominal condition in obstetrics and gynecology, with a current incidence rate of about 2% of total pregnancies [5]. However, its mortality rate accounts for approximately 9% to 10% of total maternal deaths. Major clinical symptoms of ectopic pregnancy include amenorrhea, abdominal pain, vaginal bleeding, shock and syncope, and abdominal mass.

2. Causes

2.1 Pelvic Inflammation and Ectopic Pregnancy

Chronic salpingitis is the most common factor disrupting the normal passage of fertilized eggs, making it a common and major cause of tubal pregnancy. Parazzini et al. reported that pelvic inflammatory diseases could increase the risk of ectopic pregnancy by 2.7 times. The pathogens causing tubal inflammation are mainly those associated with sexually transmitted diseases, with common culprits being gonococci and *Chlamydia trachomatis*. Early-stage infections of *Chlamydia trachomatis* and gonococci can manifest as urethritis, vestibular gland inflammation, and cervical inflammation. The pathogenic bacteria travel from the cervical canal mucosa to the uterine cavity, ultimately causing ascending infection into the fallopian tubes. In severe cases of tubal endometritis, complete occlusion of the tube lumen may occur, while mild cases can lead to adhesions of the tubal mucosal folds [6]. Following antibiotic treatment to control inflammation, incomplete destruction of the tubal epithelium may result in irregular and narrowed tubal passages, hindering the normal passage of fertilized eggs and leading to infertility and ectopic pregnancy. Miscarriages and postpartum bacterial infections can spread through lymph and blood circulation, causing inflammation in the tissues surrounding the fallopian tubes. Lesions in the serosal or muscular layers around the tubes, resulting in adhesions, torsion of the tubes, narrowing of the tube lumen, and weakened muscular peristalsis, can impede the normal passage of fertilized eggs. Consequently, the fertilized egg may become arrested in the fallopian tube, undergo local development, and lead to ectopic pregnancy.

2.2 Abdominal Surgery and Ectopic Pregnancy

2.2.1 Abdominal Surgical Procedures

Hanyu et al. conducted a case-control study involving 337 cases of tubal pregnancy and 893 control subjects, revealing that perforated appendicitis is a significant risk factor for ectopic pregnancy, with a relative risk (RR) of 1.8. Unperforated appendicitis poses a relatively small risk, with an RR of 1.2. This elevated risk may be attributed to the formation of peri-appendiceal abscesses following appendiceal perforation, leading to inflammatory exudation and/or damage that obstructs the fallopian tubes. Another study by Michalas et al. indicated that an appendectomy increases the risk of ectopic pregnancy by 1.8 times. Other abdominal surgeries have minimal impact on the occurrence of tubal pregnancy.

2.2.2 Pelvic Surgery

Michalas et al. reported that with an increasing number of pelvic surgeries, the risk of ectopic pregnancy significantly rises. The type of pelvic surgery also slightly influences the risk of ectopic pregnancy, with the removal of ovarian cysts and tuboplasty increasing the risk by 2.9 times and 5.9 times, respectively. This suggests that procedures involving the fallopian tubes and their postoperative management directly affect the anatomical structure of the tubes.

2.2.3 Cesarean Section

As the frequency of cesarean section surgeries rises, the incidence of ectopic pregnancy also increases in parallel. However, no correlation has been found between cesarean section and the occurrence of ectopic pregnancy.

2.2.4 Recurrent Ectopic Pregnancy

Following one episode of ectopic pregnancy, there is a higher probability of experiencing a subsequent ectopic pregnancy. After the first ectopic pregnancy, approximately one-third of patients are prone to recurrence. The rate of recurrent ectopic pregnancy has not been reported to date.

2.3 Insertion of Intrauterine Devices (IUDs) and Ectopic Pregnancy

According to the classical theory, the placement of an intrauterine device (IUD) within the uterus induces a non-bacterial inflammatory response due to a foreign body reaction. This response leads to the accumulation of white blood cells and macrophages within the uterus, altering the intrauterine environment and hindering the implantation of the fertilized egg. Additionally, white blood cells and macrophages have sperm phagocytic activity, reducing the number of sperm reaching the fallopian tubes, thereby decreasing the chances of fertilization. However, this mechanism does not completely prevent fertilization and implantation of the egg within the fallopian tubes. Consequently, women using an IUD have a relatively increased risk of ectopic pregnancy. Recent research suggests that the contraceptive effect of IUDs is not limited to the uterine cavity; it may also alter the fluid within the uterus and fallopian tubes, impairing gamete survival and reducing the chances of sperm-egg binding and fertilization. In 1994, Wollen et al. reported that IUDs activate the immune system in the fallopian tubes and may interfere with their immune function, affecting their role in the fertilization process. This multifaceted contraceptive mechanism confirms that IUDs do not increase the risk of ectopic pregnancy.

2.4 Tubal Maldevelopment or Dysfunction

Tubal maldevelopment or dysfunction, including conditions such as elongated fallopian tubes, inadequate muscle layer development, lack of ciliary epithelium, bilateral fallopian tubes, diverticula, or pseudoumbrella, can result in tubal pregnancy. Tubal function is regulated by estrogen and progesterone, and failure of this regulation can affect the normal movement of the fertilized egg. Additionally, psychological factors may induce spasm and abnormal peristalsis of the fallopian tubes, disrupting the implantation of the fertilized egg.

2.5 Other Factors

Uterine fibroids or ovarian tumors pressing on the fallopian tubes can impede the patency of the tubal lumen, obstructing the passage of the fertilized egg. Endometriosis may increase the likelihood of implantation of the fertilized egg within the fallopian tubes. In summary, the causes of ectopic pregnancy are complex and often involve a combination of factors. Therefore, women with high-risk factors who suspect pregnancy should be highly vigilant for ectopic pregnancy to facilitate more effective and early diagnosis.

3. Treatment

Treatment options for ectopic pregnancy include non-surgical pharmacological treatment and surgical intervention, with the choice depending largely on the type and severity of the ectopic pregnancy.

3.1 Non-surgical Treatment (Pharmacological Treatment)

Non-surgical treatment, specifically pharmacological treatment, is primarily indicated for early

tubal pregnancies, especially in young patients who wish to preserve fertility. This approach is suitable under the following conditions: no contraindications to drug therapy; absence of signs of tubal rupture or acute internal bleeding; ultrasound confirmation of an abnormal mass in the adnexal region with a diameter less than 4 cm and no apparent fetal heartbeat, with blood β -HCG levels below 2,000 U/L; normal liver function; and normal blood routine.

3.1.1 Systemic Medication

(1) Methotrexate (MTX)

Single-dose regimen: MTX 50 mg/m² administered as a single intramuscular injection. No folinic acid (CF) rescue is required. Patients are advised to abstain from alcohol, sexual activity, and the consumption of folate-containing vitamin preparations during treatment. Blood β -HCG levels are monitored regularly, and if a 15% reduction is observed 4–7 days after administration, a repeat dose may be given. The success rate ranges from 87% to 92%.

(2) Low-dose MTX multiple-dose regimen: MTX 0.4 mg/(kg day) administered intramuscularly for 5 days per course. If there is no significant reduction in blood β -HCG after one course, the second course begins after a one-week interval.

(3) MTX-CF regimen: MTX 1 mg/(kg day) administered intramuscularly on alternate days (days 1, 3, 5, 7), and CF 0.1 mg/(kg day) administered intramuscularly on alternate days (days 2, 4, 6, 8). Medication is discontinued if a >15% reduction in blood β -HCG is observed 48 hours after administration.

3.1.2 Local Medication

Under ultrasound guidance, MTX can be directly injected into the embryo implantation site or administered via catheterization into the fallopian tube.

3.2 Surgical Treatment

Surgical treatment is divided into conservative surgery and definitive (radical) surgery. Conservative surgery involves preserving the affected fallopian tube, while definitive surgery entails removing the affected fallopian tube. Surgical treatment is indicated for patients who exhibit unstable vital signs or signs of intra-abdominal bleeding, those with unclear diagnoses, cases where ectopic pregnancy progresses, unreliable follow-up, and individuals with contraindications to drug therapy.

3.2.1 Definitive Surgical Treatment

The removal of the affected fallopian tube is suitable for cases where conservative treatment has failed, and fertility preservation is not a priority. It is also recommended for severe pelvic adhesions and critically ill patients with internal bleeding, especially when laparoscopic surgery has failed. For critically ill patients, active correction of shock should be initiated, followed by open exploration, clamping the bleeding site with ovum forceps to stop bleeding, accelerating fluid and blood transfusion. After blood pressure stabilization, the affected fallopian tube can be excised. For interstitial tubal pregnancies, efforts should be made to perform a wedge-shaped excision of the uterine horn before rupture, along with excision of the affected fallopian tube, and if necessary, removal of the uterus.

3.2.2 Conservative Surgery

Conservative surgery is suitable for young women with fertility requirements, especially those with the contralateral fallopian tube already removed or showing significant lesions. In recent years,

with the increased early diagnosis of ectopic pregnancy, there has been a noticeable rise in the use of conservative surgery. The choice of procedure depends on the implantation site of the fertilized egg and the condition of the fallopian tube. For ampullary pregnancies, the ectopic products can be expelled by squeezing. For isthmic pregnancies, segmental excision and anastomosis are performed. The use of microsurgical techniques during surgery can enhance future pregnancy rates.

3.2.3 Laparoscopic Surgery [7-10]

The application of laparoscopy in the treatment of tubal pregnancy is one of the earliest and most mature procedures in gynecological surgery. It has a strong tendency to replace open surgery and has become a primary method for treating ectopic pregnancies in recent years. In most cases of tubal pregnancy, the ectopic sac within the fallopian tube can be punctured under direct vision through laparoscopy. After aspirating part of the sac fluid, medication can be injected. Alternatively, under laparoscopy, the fallopian tube can be incised to remove the embryo, followed by the injection of medication or tubal excision [13-20]. Laser or electrocoagulation can also be performed under laparoscopy to induce necrosis of the embryonic tissue, although this is rarely used due to the risk of postoperative tubal adhesions. Previously, ectopic pregnancy with bleeding and shock was considered a contraindication for laparoscopic surgery. However, some studies suggest that rupture and active bleeding in ectopic pregnancies do not necessarily contraindicate laparoscopic surgery, as long as appropriate intraoperative management is applied, successful completion of the procedure is feasible. Research indicates that laparoscopic surgery is a safe and effective approach for treating low-volume ectopic pregnancies [10-12].

Various studies report that ectopic pregnancies often occur in women of childbearing age, with a significant portion being nulliparous or having no healthy surviving children. Therefore, during the treatment process, consideration should be given to preserving the patient's fertility, increasing the chances of future pregnancies, and reducing adverse factors affecting pregnancy after the disease.

4. Conclusion

Drawing on recent research and clinical experience, the incidence of ectopic pregnancy has significantly increased, making it a common acute abdominal emergency in obstetrics and a major cause of maternal mortality. The etiology is multifaceted, with inflammation playing a pivotal role, particularly chronic salpingitis being a prominent factor in the occurrence of ectopic pregnancies. Additionally, factors such as intrauterine device usage, surgical history, and hormonal levels are closely associated with ectopic pregnancies. To reduce the incidence of ectopic pregnancies, there is a need to enhance hygiene awareness during menstrual and gestational periods, rigorously adhere to the indications for obstetric and gynecologic surgery, emphasize aseptic techniques during procedures, and focus on postoperative infection prevention. In terms of treatment options, there is ongoing debate between pharmaceutical and surgical interventions. Notably, laparoscopic surgery, with its minimal invasiveness, high success rates, rapid postoperative recovery, and reduced complications, stands out as a compelling choice. Furthermore, it preserves the patient's fertility, making it a valuable and widely applicable approach in clinical practice. By implementing these comprehensive measures, it is anticipated that the challenges posed by ectopic pregnancies can be more effectively addressed, thereby improving treatment outcomes and postpartum health for affected individuals.

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