



Updates in Diagnosis and Management of Ectopic Pregnancy

**Hesham Mohamed Hamad Morcy^{a*}, Luluah Maan Ramadan Abdullah^b,
Maryam Mohammed M. Alenezi^b, Almutairi, Fai Sultan F.^b,
Sama Abdulfattah M. Almadani^b and R. Alruwaili, Raghad Khalid^b**

^a Maternity and Children Hospital, Arar, Saudi Arabia.

^b Faculty of medicine, Northern Border University, Saudi Arabia.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Ectopic pregnancy (EP) occurs when the conceptus becomes embedded and matures beyond the endometrial cavity, resulting in the foetus' mortality.

Ectopic pregnancy can become a lifethreatening issue if it is not diagnosed and treated promptly. The most common symptoms of an unruptured ectopic pregnancy are first-haemorrhage and abdominal pain.

Although these symptoms can also occur in intrauterine pregnancy and spontaneous abortion, when a pregnant woman shows them, clinicians should suspect ectopic pregnancy. Methotrexate, a folic acid antagonist, has been extensively studied in medicine. Methotrexate inhibits dihydrofolate reductase, causing trophoblastic cells to divide rapidly and reducing tetrahydrofolate levels (a cofactor for deoxyribonucleic acid and ribonucleic acid formation).

Keywords: Ectopic pregnancy; foetus' mortality; abdominal pain.

[≡] Consultant of Ob &Gyn;

*Corresponding author: E-mail: morcy14@gmail.com;

1. INTRODUCTION

Ectopic pregnancy is a well-known pregnancy complication with a substantial risk of morbidity and mortality if not discovered and treated early. Because ectopic pregnancy might manifest with discomfort, vaginal bleeding, or more ambiguous indications like nausea and dissatisfaction, providers must maintain a high index of suspicion in their pregnant patients.

Fertilization and embryo implantation involve a complex combination of chemical, hormonal, and anatomical interactions and situations to allow for a safe intrauterine pregnancy. Although much of this system is beyond the scope of this page, the anatomical mechanisms most relevant to our understanding of the ovaries, fallopian tubes, uterus, egg, and sperm are summarised below.

The ovaries are female reproductive organs located on both lateral faces of the uterus in the lower pelvic area. One of the ovaries' functions is to release an egg each month in the hopes of fertilisation. The female egg is transferred from the ovaries to the uterus by the fallopian tubes, which are tubular structures. When sperm reaches the egg, it fertilises it, culminating in the development of an embryo. The embryo will next implant in the endometrial tissue of the uterus.

Ectopic pregnancy occurs when foetal tissue inserts outside of the uterus or connects to an abnormal or marked part of the uterus [1].

Ectopic pregnancy (EP) occurs when the foetus implants and matures outside of the endometrial cavity, eventually leading to the foetus' death.

EP can turn into a lifethreatening issue if it isn't diagnosed and treated quickly enough. The term refers to blastocyst implantation outside the endometrial cavity, with over 95.5 percent of blastocysts anchoring in the Fallopian tube, where the foetus or embryo is absent or stops growing. EP is a substantial health concern for women of reproductive age, accounting for 1.2–1.4% of all reported pregnancies.

Pelvic seditious illness, Chlamydia trachomatis infection, smoking, tubal surgery, induced conception cycle, and endometriosis are the most commonly mentioned risk factors. Its prevalence has progressively increased over the last 40 years, along with rising rates of sexually transmitted diseases (STDs) and salpingitis (irritation of the Fallopian tubes).

Around 15% of patients who arrive with infertility have unexplained infertility.

There is a lack of consensus among infertility specialists on the diagnostic tests that should be conducted, their predictive value, and normalcy standards. The basic diagnostics for diagnosing unexplained infertility appear to be serum progesterone for ovulation detection, hysterosalpingography and/or laparoscopy for tubal patency, and sperm testing [2,3].

For young people with a brief time of infertility, eager treatment is the best option.

In this group of patients, the rate of impulsive pregnancy is extremely high. Measured ovarian hyper stimulation and intrauterine impregnation (COH and IUI) has been shown in the literature to be an effective treatment for infertility that is unexplained.

This method could be limited to three trials based on the available data. Both COH and IUI appear to be key independent positive factors in getting a higher pregnancy rate in unexplained infertility. If the foregoing methods fail to produce a pregnancy, GIFT or IVF/ICSI may be used, as they have a high pregnancy rate [4].

Ectopic pregnancy is still a major cause of maternal morbidity and mortality around the world, despite the fact that the rate of occurrence has remained stable in affluent countries over the last decade.

This is due to a variety of circumstances, including misdiagnosis and a failure to provide prompt and adequate therapy aimed at preserving fertility and reducing related morbidity. The frequency of women presenting with a ruptured ectopic pregnancy has decreased as a result of recent breakthroughs in imaging and biomonitoring.

Any endeavour to reduce the effects of ectopic pregnancies must therefore focus on teaching people about the unruptured kind of ectopic pregnancy and providing evidence-based, cost-effective treatment.

The authors of this review examine the identification and treatment of this complication in light of recent evidence and what modifications might be made to lessen the risk [5].

2. ETIOLOGY

Ectopic pregnancy occurs when an embryo is implanted outside of the uterine cavity, most commonly in the fallopian tube. Within the fallopian tubes, smooth muscle contraction and ciliary beat aid in the transit of an egg and embryo. Tubal dysfunction is caused by damage to the fallopian tubes, which is commonly caused by swelling. Tubal dysfunction can result in the preservation of an egg or embryo. Swelling can be caused by a variety of local factors, including toxic, viral, immunologic, and hormonal factors. Following tubal injury, pro-inflammatory cytokines are upregulated, which promotes embryo implantation, invasion, and angiogenesis within the fallopian tube. Tubal epithelial cells produce interleukin 1 in response to *Chlamydia trachomatis* contamination, which is a crucial marker for embryo implantation within the endometrium. Interleukin 1 is also involved in downstream neutrophil recruitment, which contributes to tubal damage in the fallopian tubes. Smoldering and infection have a deleterious impact on the frequency of cilia beats. Hormonal changes during the menstrual cycle have also been shown to affect the frequency of cilia beats [6].

2.1 Risk Factors

Despite the fact that most women with ectopic pregnancy have no discernible risk factors, a prospective case-control study has found that increased awareness of ectopic pregnancy and knowledge of the associated risk factors aids in the identification of women at higher risk, allowing for earlier and more accurate diagnosis [7]. The majority of risk variables are linked to the possibility of previous Fallopian tube injury. Any previous pelvic or abdominal surgery, as well as a pelvic infection, are among these factors [7]. Ectopic pregnancies have been linked to *Chlamydia trachomatis* in 30–50% of cases [8]. The actual mechanism of this link has not been found, however it has been suggested that it could be owing to a result on the tubal microenvironment, in addition to misrepresentation of tubal architecture [9].

Despite the fact that various factors have been recognised as increasing the risk of ectopic pregnancy, almost half of those diagnosed with this condition have no known risk factors [10,11]. Ankum et al. summarised known risk variables in a meta-analysis that included 36 research, some of which are addressed here [12].

2.2 Infertility and Ectopic Pregnancy

Infertility affects 8-12 percent of couples over the world [13]. Infertility and EP have a complicated relationship since one might be a cause and the other can be a consequence at the same time [14,15]. There has been a surge in demand for assisted reproductive technologies (ART), such as intrauterine insemination and IVF-embryo transfer (IVF-ET) with or without intracytoplasmic sperm injection, since the birth of the first successful in vitro fertilisation (IVF) baby in 1978 [16,17]. EP/HP has been linked to a number of factors, including the aetiology of female infertility and the technical procedures used during IVF-ET [18].

2.3 Inflammation of the Pelvis Illness

Infection of the tubal epithelium by pathogens such as *Chlamydia trachomatis* compensates the ciliated epithelium, resulting in intraluminal unions that predispose to zygote trapping and ectopic blastocyst implantation. Westrom et al. evaluated 450 women with laparoscopically demonstrated pelvic inflammatory illness (case-control research) and found that the incidence of tubal impediment increased with subsequent episodes: 13% after the first episode, 35% after the second, and 79% after the third [19]. The proportion of ectopic to intrauterine pregnancy after one episode of laparoscopically proven acute salpingitis was 1:24, a sixfold increase compared to women with laparoscopically unsatisfactory outcomes. Only 50% of fallopian tubes removed for an ectopic pregnancy show signs of salpingitis on histology.

2.4 Tubal Surgery in the Past

Those who have had a previous ectopic pregnancy and those who have had tubal surgery, including sterilisation, setback, and tubal reconstructive surgery, fall into this category [12].

Following one previous ectopic pregnancy, the probability of recurrence is around 10%, and after two or more ectopic pregnancies, the risk rises to 25–30%. [20,21]. The size and location of previous ectopic pregnancy, the position of the contralateral adenexa, treatment approach, and a history of infertility all play a role in determining the probability of reappearance.

Due to differences in cultural and societal traits, the main risk factors for ectopic pregnancy vary by country. When the primary risk factors for

ectopic pregnancy are identified, it is easier to diagnose the condition and improve prevention methods. Past ectopic pregnancy, previous pelvic surgery, introduction of ovulation, intrauterine device (IUD) use, history of pelvic provocative disease (PID), and smoking at the time of conception are all risk factors for ectopic pregnancy. Smooth muscle contractions and ciliary beating control the transport of the inseminated ovum down the fallopian tube [22]. Ectopic pregnancy risk factors include conditions that compromise the tube's integrity and impede its activities.

2.5 Types of Ectopic Pregnancy

In most cases of tubal EP, the mutual site is the Fallopian tube. EPs are found in the ampullary region of the Fallopian tube, 10–15 percent in the isthmic portion, and around 5% in the fimbrial end. A transvaginal ultrasound scan (TVS) can detect the tubal EP, which indicates an intact Fallopian tube with a developing pregnancy and is visualised as an inhomogeneous mass that could be a collapsed sac containing trophoblastic tissue.

2.6 Physical Examination and Medical History

The majority of women who report with an ectopic pregnancy complain of pelvic pain; however, not all ectopic pregnancies cause pain. Pelvic pain/unease, abdominal pain/discomfort, nausea/vomiting, syncope, lightheadedness, vaginal bleeding, and other symptoms in women of childbearing age should be investigated for the possibility of pregnancy. Providers must determine when the patient's last menstrual period occurred and whether the patient has monthly menstrual cycles. Patients who have missed their last cycle or have atypical uterine bleeding while sexually active may be pregnant, necessitating additional testing with a pregnancy test. Wage-earners should be aware of any recognised ectopic pregnancy risk factors in their patient's history, such as if the patient has had a previous confirmed ectopic pregnancy, The fallopian tube has been damaged (history of pelvic inflammatory illness, tubal surgery, known occlusion), or a pregnancy has been achieved through infertility treatment [23].

Peritoneal symptoms such as rebound soreness and cervical motion tenderness, which indicate the likelihood of hemoperitoneum, should be detected during physical examination. In a

pregnant woman, abdominal discomfort with peritoneal symptoms would necessitate an early assessment by a gynaecologist to identify the necessity for alternative surgery.

The presence of flow and signs of products of conception in the vaginal canal can help distinguish impulsive abortion from ectopic pregnancy. To avoid misdiagnosing a decidual cast as starting products, pathologic examination of tissue obtained from the vagina is essential [24].

3. EVALUATION

The use of transvaginal ultrasound imaging in the diagnosis of a possible ectopic pregnancy is critical. To confirm the diagnosis, serial exams with transvaginal imaging, serum hCG level capabilities, or both are required. On ultrasound, a tiny sac curiously positioned within the decidua is the first sign of an intrauterine pregnancy. The "double decidual" sign is named after the two tissue rings that form around the sac. On abdominal ultrasound imaging, the double decidual sign normally converts detectable during the fifth week of pregnancy. The yolk sac will become visible during this period, although identification will require transvaginal ultrasound imaging. At roughly six weeks of pregnancy, an embryonic pole will be visible on transvaginal imaging [23].

4. TREATMENT / MANAGEMENT

In hemodynamically stable women with a non-ruptured ectopic pregnancy, intramuscular methotrexate or presentation of laparoscopic surgery are safe and effective behavioural methods. The patient's clinical picture, laboratory findings, and radiologic imaging, as well as the patient's well-informed choice after rereading the risks and benefits of each process, all influence which modality to pursue. The single-dose methotrexate regimen would be beneficial to patients with low hCG levels. Two-dose regimens may be required for those with high hCG levels. Methotrexate therapy does not appear to have any negative consequences on [25] ovarian fallback or fertility. (Post-methotrexate injection, hCG levels should be trended until they reach a non-pregnancy level [26]. When patients exhibit any of the following symptoms: intraperitoneal flow, symptoms suggestive of a continuing ruptured ectopic mass, or hemodynamic volatility, surgical care is required [26].

Ectopic pregnancy can be treated surgically, medically, or through pregnancy. It's crucial to understand the risks of a ruptured ectopic pregnancy in these days with growing outpatient diagnosis and running. It's crucial to have a clear certification of diagnostic and management procedures, including clinical, sonographic, and biological assessments of the patient. The best course of action is determined by continuing evaluation and a variety of clinical considerations. Individual patients are organised depending on their appearance and the severity of their ailment, as well as the applicability of treatment alternatives and patient preferences.

4.1 Surgery

In the case of a ruptured ectopic pregnancy, surgical care is the best option. In a patient who is haemodynamically stable, a laparoscopic method is preferable to an open approach. Shorter operative timeframes, less intraoperative blood loss, shorter hospital stays, and less analgesia are all related with laparoscopic operations [27,28].

4.2 Expectant Management

In the treatment of ectopic pregnancy, expectant management is effective in 47 to 82% of cases [29,30]. A strong candidate for hoping management has a beta-hCG level of less than 1,000 mIU per mL (1,000 IU per L) and declining, an ectopic mass of less than 3 cm, no foetal heartbeat, and has consented to follow-up criteria.

4.3 Medical Treatment

Methotrexate, a folic acid antagonist, has been extensively researched as a treatment option. Methotrexate inhibits dihydrofolate reductase, resulting in a reduction in tetrahydrofolate stages (a cofactor for deoxyribonucleic acid and ribonucleic acid synthesis), interrupting rapidly dividing trophoblastic cells [31]. Hyperosmolar glucose, prostaglandins, and mifepristone are some of the other treatment options (Mifeprex) [32].

4.4 Diagnoses

First-trimester bleeding and abdominal pain are the most prevalent signs of an unruptured ectopic pregnancy. Although these symptoms can also occur in intrauterine pregnancy and spontaneous abortion, doctors should suspect

ectopic pregnancy if a pregnant woman exhibits them. The clinical history should include the date of conception, the start and severity of symptoms, and an evaluation of ectopic pregnancy risk factors. These details help define the appropriate diagnostic path and the pace at which the test should be conducted. For example, a physician may want to conduct ultrasonography in a patient with a suspected ectopic pregnancy at eight to ten weeks' gestation in order to determine where the pregnancy is located. Ultrasonography is also less likely to be helpful in confirming the location of a pregnancy at four weeks' gestation. The severity of the symptoms should be monitored; with more straightforward bleeding, hemodynamic constancy is a concern, and surgical treatment may be necessary [24].

It's also worth remembering that a woman may experience abdominal pain without being aware of her pregnancy status. As a result, any woman of childbearing age who has abdominal pain or abnormal vaginal bleeding should be checked for pregnancy at the initial examination [24].

4.5 Prognosis

Patients with a low beta hCG level will almost certainly have a better prognosis. successful treatment with single-dose methotrexate [32]. The additional the ectopic pregnancy, the less possible single-dose methotrexate therapy will suffice. Patients who present in extremis or with hemodynamic instability are at a higher risk of complications, such as hemorrhagic shock or other perioperative problems. The prognosis will thus be determined by early detection and intervention. The fertility outcomes of tubal conservation procedures are still being debated, as some evidence suggests that there is no substantial difference in intrauterine pregnancy rates when comparing salpingectomy to traditional tubal management [33].

4.6 Follow Up

During treatment, doctors should check on patients at least once a week, if not everyday. After management, serial beta-hCG readings should be taken until the amount is undetectable. If the levels do not improve, the patient can be given a second dose of methotrexate or methotrexate after surgery. If beta-hCG levels rise, surgical intervention is required. Patients who receive appropriate treatment have a fair prognosis. With proper patient selection,

expectant management success rates approach 82 percent, medical management success rates near 90 percent, and surgical treatment success rates near 92 percent [34,35,36].

5. COMPLICATIONS

If Methotrexate was assumed, women who presented early in pregnancy and had analyses suggestive of an ectopic pregnancy would compromise the viability of an intrauterine pregnancy [37]. Women on the single-dose Methotrexate regimen are at significant risk of treatment failure if their hCG level does not drop by 15% from day 4 to day 7, necessitating the use of a second-dose regimen [32]. If the ectopic pregnancy is near the cervical os, women with vaginal bleeding and pelvic pain may be mistaken as having an abortion in progress. If a dilation and curettage procedure is performed, the woman may have a cervical ectopic pregnancy, putting her at risk of haemorrhage and possible hemodynamic instability [37]. Management complications can lead to treatment failure, as women may present with/or develop hemodynamic instability, which can lead to death despite early surgical treatments.

6. CONCLUSION

Ectopic pregnancy continues to be an significant cause of maternal morbidity and mortality. The main risk factors of ectopic pregnancy are diverse in various countries due to different cultural and social characteristics. Resolve of main risk factors of ectopic pregnancy leads to a rapid diagnosis and an enhancement in strategies for its prevention. physicians should inspect patients at least weekly and sometimes daily.

Any endeavour to reduce the effects of ectopic pregnancies must therefore focus on teaching people about the unruptured kind of ectopic pregnancy and providing evidence-based, cost-effective treatment. In more than half of the instances, the etiopathogenesis is unknown, and while there has been progress in our understanding of clinical performance and care, a tiny proportion of patients function atypically. We've talked about these nonconforming scenarios and how to deal with them in this review [5].

DISCLAIMER

The products used for this research are commonly and predominantly use products in our

area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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