Management of Undisturbed Ectopic Pregnancy: A comprehensive Review.

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Ectopic pregnancy occurs when a fertilized ovum implants outside of the uterine cavity. In the United States, the estimated prevalence of ectopic pregnancy is 1% to 2%, and ruptured ectopic pregnancy accounts for 2.7% of pregnancy-related deaths. Risk factors include a history of pelvic inflammatory disease, cigarette smoking, fallopian tube surgery, previous ectopic pregnancy, and infertility. Ectopic pregnancy should be considered in any patient presenting early in pregnancy with vaginal bleeding or lower abdominal pain in whom intrauterine pregnancy has not yet been established. The definitive diagnosis of ectopic pregnancy can be made with ultrasound visualization of a yolk sac and/or embryo in the adnexa. However, most ectopic pregnancies do not reach this stage. More often, patient symptoms combined with serial ultrasonography and trends in beta human chorionic gonadotropin levels are used to make the diagnosis. Pregnancy of unknown location refers to a transient state in which a pregnancy test is positive, but ultrasonography shows neither intrauterine nor ectopic pregnancy. Serial beta human chorionic gonadotropin levels, serial ultrasonography, and, at times, uterine aspiration can be used to arrive at a definitive diagnosis. Treatment of diagnosed ectopic pregnancy includes medical management with intramuscular methotrexate, surgical management via salpingostomy or salpingectomy, and, in rare cases, expectant management. A patient with diagnosed ectopic pregnancy should be immediately transferred for surgery if she has peritoneal signs or hemodynamic instability, if the initial beta human chorionic gonadotropin level is high, if fetal cardiac activity is detected outside of the uterus on ultrasonography, or if there is a contraindication to medical management

1. Introduction

Ectopic pregnancy affects approximately 1% of pregnancies and is a leading cause of maternal mortality in the first trimester **[1]**. Timely and appropriate treatment of ectopic pregnancy is critical. Ectopic pregnancy may be managed surgically, medically, or expectantly. Surgical treatment with salpingectomy or salpingostomy is required typically for advanced or ruptured ectopic pregnancy, whereas methotrexate is the first-line medical treatment for early un ruptured ectopic pregnancy. Methotrexate can be administered as single or multidose regimens, with success rates reaching 93% **[2].**

Methotrexate is a folic acid antagonist that inhibits the enzyme dihydrofolate

reductase, which converts folic acid to tetrahydrofolate, a cofactor needed in DNA and RNA synthesis. By inhibiting dihydrofolate reductase, methotrexate interrupts trophoblast proliferation and induces abortion. Methotrexate is as effective as salpingostomy for ectopic pregnancy and does not appear to affect future fertility **[3].**

Methotrexate is a chemotherapeutic agent that can have adverse consequences, including nausea, vomiting, conjunctivitis, stomatitis, gastritis, impaired liver function, bone marrow suppression, and photosensitivity. Methotrexate is not indicated for patients with ruptured ectopic pregnancy, hemodynamic instability, or b-human chorionic gonadotropin (HCG) levels >5,000 mIU/mL, all signs of more advanced ectopic pregnancy. Other contraindications include immunodeficiency, anemia, thrombocytopenia, pulmonary disease, peptic ulcer, hepatic or renal dysfunction, and breastfeeding. Thus, alternate medical treatments are needed **[4]**

Methotrexate is associated with: Long interval until resolution of the ectopic pregnancy, the need to wait for several weeks before another attempt at pregnancy and future fertility potential are not unexpected **[5].**

In this issue of Fertility and Sterility, **Mitwally et al., (2020)[6]** assessed the use of letrozole for treatment of ectopic pregnancy. Letrozole is a third-generation aromatase inhibitor that suppresses estrogen production. Aromatase is an enzyme involved in estrogen biosynthesis that converts androstenedione to estrone and testosterone to estradiol. Letrozole blocks the action of aromatase, preventing a critical step in the production of estrogens. Letrozole is used for estrogen dependent breast cancer in postmenopausal women and ovulation induction in women with polycystic ovary syndrome. Because progesterone is considered more essential than estrogen to establish and maintain pregnancy, it is not immediately evident why letrozole would interrupt ectopic pregnancy.

Mitwally et al. [6] designed a nonrandomized trial of 42 women with tubal ectopic pregnancy. Women selected their treatment and were divided into three arms of 14 patients administered letrozole, methotrexate, or salpingectomy. The letrozole arm received 5 mg daily for 10 days, whereas the methotrexate arm received a single intramuscular injection at a dose of 50 mg/m2. b-human chorionic gonadotropin levels were measured on treatment day and 4, 7, and 14 days later. Undetectable b-hCG levels indicated resolution of ectopic pregnancy. The authors monitored hemoglobin levels, blood platelet counts, liver enzymes, renal function, and antimuellerian hormone**[6]**.

According to their results, letrozole was as effective as methotrexate, with success rates of 86% for both treatment arms. b-human chorionic gonadotropin levels even appeared to decrease more rapidly for women treated with letrozole than methotrexate, although the difference was statistically non-significant. Letrozole did not affect hematologic parameters, whereas methotrexate was associated with an increase in liver enzymes and a decrease in hemoglobin and platelet count. Letrozole had no impact on antimuellerian hormone levels 3 months after treatment. The results are promising,

although letrozole was compared with single-dose methotrexate, which is somewhat less effective than the multidose regimen **[7]**.

1. Risk Factors

Factors conferring a high risk [odds ratio (OR) > 4.0]

Prior tubal surgery or a prior tubal pregnancy are the most important risk factors for tubal pregnancy (Table 1). Sterilization is a very effective method of contraception; nevertheless, if a woman becomes pregnant despite having undergone a putatively sterilizing procedure, extrauterine pregnancy must be considered as a possibility, as about 30% of pregnancies after sterilization are extrauterine. The cumulative 15-year risk of tubal pregnancy is 2.9 per 1000 sterilizations. The risk of tubal pregnancy is higher after electrocoagulation of the fallopian tubes, because of tubal recanalization and/or the formation of a utero-/tuboperitoneal fistula **[9].**

Factors conferring a moderately elevated risk (OR > 2.0)

Elevated rates of extrauterine pregnancy have been found among women taking hormones (clomifene) to treat infertility, although the increased prevalence of tubal pathology and prior surgical treatments in this population are obvious confounding variables. Assisted reproductive technology (ART) has also been reported to elevate the risk of an extrauterine pregnancy from 0.025% (the value in the general population) to 1% among women who have undergone in vitro fertilization. The incidence of extrauterine pregnancy after ART seems to have fallen somewhat in recent years **[10].**

Women with an active or prior ascending infection with *Chlamydia trachomatis* or *Neisseria gonorrhoeae* are at an elevated risk of extrauterine pregnancy. Other types of intra-abdominal infection, e.g., appendicitis, can also raise the risk.

Factors conferring a mildly elevated risk (OR < 2.0)

The highest incidence of extrauterine pregnancy is between the ages of 35 and 45, perhaps because of the cumulative effect of multiple risk factors over time **[11].**

Factors conferring a high risk of extrauterine pregnancy

Prior tubal surgery and prior tubal pregnancy are the main risk factors for tubal pregnancy.

2. Differential Diagnosis

One should begin to formulate a differential diagnosis when taking into account the patient's history and physical exam findings. Important differential diagnoses to consider with ectopic pregnancies are ovarian torsion, tuba-ovarian abscess,

appendicitis, hemorrhagic corpus luteum, ovarian cyst rupture, threatened miscarriage, incomplete miscarriage, pelvic inflammatory disease, and ureteral calculi. The patient's history and hemodynamic status on clinical presentation will influence the order of these differentials, as well as the testing necessary to rule out said differentials **[12].**

3. Prognosis

Patients with a relatively low beta hCG level will likely have a better prognosis regarding treatment success with single-dose methotrexate. The further the ectopic pregnancy has advanced; the less likely single-dose methotrexate therapy will suffice. The patients that present in extremis or with hemodynamically instability have more risk of deterioration such as from hemorrhagic shock or other perioperative complications. Prognosis will thus hinge on early recognition and timely intervention. Fertility outcomes with tubal conservation surgeries remain debatable as some data suggests no significant difference in intrauterine pregnancy rates when comparing salpingectomy versus conservative tubal management **[13].**

4. Complications

Women who present early in pregnancy and have testing suggestive of an ectopic pregnancy would jeopardize the viability of an intrauterine pregnancy if given Methotrexate. Women who receive the single-dose Methotrexate regimen are at high risk of treatment failure if the hCGlevel does not decrease by 15% from day 4 to day 7 thus prompting second-dose regimen. Women presenting with vaginal bleeding and pelvic pain may be misdiagnosed as an abortion in progress if the ectopic pregnancy is at the cervical os. The patient may have a cervical ectopic pregnancy and would thus run the risk of hemorrhage and potential hemodynamic instability if a dilation and curettage are performed. Complications from management extend to treatment failure, in that women may present with/or develop hemodynamic instability which can result in death despite early operative interventions **[13].**

5. Clinical manifestations and diagnosis

The clinical diagnosis of ectopic pregnancy is based on a combination of serum quantitative human chorionic gonadotropin levels and transvaginal ultrasound findings. The clinical manifestations and diagnosis of ectopic pregnancy are reviewed here with a focus on tubal pregnancy. The medical and surgical treatment of ectopic pregnancy are reviewed elsewhere. Related topics regarding ectopic pregnancy are discussed in detail separately, including:

6. Clinical Presentation

The most common clinical presentation of ectopic pregnancy is first-trimester vaginal bleeding and/or abdominal pain **[14].** Ectopic pregnancy may also be asymptomatic. Clinicians should consider ectopic pregnancy as a diagnosis in any patient of

reproductive age with vaginal bleeding and/or abdominal pain who has the following characteristics:

- Pregnant but does not have a confirmed intrauterine pregnancy.

- Pregnant and conceived with in vitro fertilization.

- Pregnancy status uncertain, particularly if amenorrhea of >4 weeks preceded the current vaginal bleeding.

- In rare cases, a patient who presents with hemodynamic instability and an acute abdomen that is not explained by another diagnosis.

Clinical manifestations of ectopic pregnancy typically appear six to eight weeks after the last normal menstrual period but may occur later, especially if the pregnancy is at an extrauterine site other than the fallopian tube. Normal pregnancy discomforts (eg, breast tenderness, frequent urination, nausea) are sometimes present. Early pregnancy symptoms may be less common in patients with ectopic pregnancy because progesterone, estradiol, and human chorionic gonadotropin levels may be lower than in normal pregnancy **[15].**

7. Diagnosis

- The diagnosis of ectopic pregnancy should be **suspected** in a pregnant patient with no evidence of an intrauterine pregnancy on transvaginal ultrasound (TVUS) and any of the following:

o Visualization of a complex inhomogenous extraovarian adnexal mass, an extraovarian adnexal mass containing an empty gestational sac, or intraperitoneal bleeding on TVUS.

o A serum human chorionic gonadotropin (hCG) that is rising abnormally. In our practice, we generally define an abnormal rise as <35 percent over two days. Historically, this number was <50 percent over two days; however, this was based on a limited number of patients. The actual expected rate of rise is dependent on initial hCG level; the expected rate of increase is 49 percent for an initial hCG level of <1500 mIU/mL, 40 percent for an initial hCG level of 1500 to 3000 mIU/mL, and 33 percent for an initial hCG level of >3000 mIU/mL **[16].**

o Abdominal pain and/or vaginal bleeding, especially in those patients with risk factors for ectopic pregnancy.

- The diagnosis of ectopic pregnancy can be **confirmed** when any of the following are present:

o Visualization of an extrauterine gestational sac with a yolk sac or embryo (with or without a heartbeat) on TVUS.

o A positive serum hCG and no products of conception on uterine aspiration with subsequent rising or plateauing hCG levels.

o Visualization at surgery (usually performed for patients with hemodynamic instability) with histologic confirmation following resection of ectopic pregnancy tissue.

8. Diagnose an ectopic pregnancy

Findings diagnostic of an ectopic pregnancy include a gestational sac with a yolk sac or embryo (with or without a heartbeat) outside of the uterus **[12].**

As above, a gestational sac alone (without a yolk sac or embryo) is insufficient for diagnosis. The reported sensitivity and specificity of TVUS for the detection of an ectopic pregnancy at a serum hCG of >2000 milli-international units/mL are 10.9 and 95.2 percent, respectively.

Detect findings that are suggestive, but not diagnostic, of ectopic pregnancy. These findings include **[14]:**

• A complex inhomogenous extraovarian adnexal mass. This is the most common ultrasound finding in ectopic pregnancy and is present in 89 percent or more of cases.

• An extraovarian adnexal mass containing an empty gestational sac (sometimes referred to as a "tubal ring").

If TVUS is nondiagnostic, it may be because the gestation is too early to be visualized on ultrasound. If so, serial measurements of the serum hCG concentration should be taken until the hCG discriminatory zone is reached.

Detect findings suggestive of ectopic rupture

• A finding of echogenic fluid (consistent with blood) in the pelvic cul-de-sac and/or abdomen may be consistent with rupture of an ectopic pregnancy. However, a small amount of fluid is present in many patients, and blood may be present in other conditions (eg, spontaneous abortion or ruptured ovarian cyst).

Human chorionic gonadotropin — Serum, rather than urine, hCG is the preferred test for a pregnant patient with pain and/or bleeding. It is not possible to determine whether a pregnancy is normal from a single hCG level because there is a wide range of normal levels at each week of pregnancy **[17].**

In pregnant patients, hCG can be detected in serum as early as six days after the luteinizing hormone surge (approximately 21 to 22 days after the first day of the last menstrual period in patients with 28-day cycles).

The hCG concentration in a normal IUP rises in a curvilinear fashion until approximately 41 days of gestation, after which it rises more slowly until approximately 10 weeks, and then declines until reaching a plateau in the second and third trimesters [18].

hCG discriminatory zone

The discriminatory zone is the serum hCG level above which a **gestational sac** should be visualized when an IUP is present. It is important to emphasize that a patient should not be diagnosed or treated for an ectopic pregnancy based on a single serum hCG level. This is discussed in more detail below.

- For **TVUS**, we use a discriminatory zone of **3510 milli-international units/mL**. However, results and discriminatory zone vary by laboratory and institution, and some institutions set the discriminatory zone at 2000 milli-international units/mL [23].

Setting the discriminatory zone at 3510 milli-international units/mL increases the ability to diagnose a live IUP on TVUS, if present, but also increases the risk of delaying a diagnosis of an ectopic pregnancy. In a study of 651 patients with first-trimester bleeding or pain, among live IUPs, a gestational sac was seen at differing hCG levels in the following proportion of pregnancies: 1500 milli-international units/mL (80 percent had a gestational sac visualized), 2000 milli-international units/mL (91 percent), and 3510 milli-international units/mL (99 percent) [24]; 1 percent of IUPs will not be visualized on TVUS when the discriminatory zone is set at 3510 milli-international units/mL.

- For **transabdominal ultrasound**, the discriminatory zone is higher (approximately **6500 milli-international units/mL**).

It is important to note that there is a variation in the level of hCG across pregnancies for each gestational age, and the discriminatory levels are not always reliable. In addition, other factors can affect the early detection of a gestational sac, including the skill of the ultrasonographer, the quality of the ultrasound equipment, and the presence of physical factors (eg, fibroids, multiple gestation, obesity).

9. Other testing

Pretreatment laboratory tests

Patients with a suspected ectopic pregnancy may require treatment with methotrexate. Although treatment decisions will be made later in the course of the evaluation,

methotrexate pretreatment blood tests are typically ordered with the initial blood draw. In addition to a complete blood count, these also include renal and liver function tests**[25].**

Ancillary diagnostic tests

Additional diagnostic tests have been used in patients with suspected ectopic pregnancy. Except in selected cases, such tests do **not** provide additional clinically useful information**[26]**.

Serum progesterone – Serum progesterone concentrations are higher in viable IUPs than in ectopic pregnancies and IUPs that are destined to abort **[20]**, and measurement of serum progesterone may be useful in a patient with abdominal pain and bleeding who has a serum hCG level below that expected for the gestational age. However, the definition of low progesterone is unclear, and in our experience, progesterone measurements merely confirm diagnostic impressions already obtained by hCG measurements and TVUS. Therefore, we do not routinely measure serum progesterone.

10.   Ectopic Pregnancy: Treatment Options

Administration of intramuscular methotrexate or performance of laparoscopic surgery is safe and effective treatment modalities in hemodynamically stable women with a non-ruptured ectopic pregnancy. The decision of which modality to pursue is guided by the patient's clinical picture, their laboratory findings, and radiologic imaging as well as the patient's well-informed choice after having reviewed the risks and benefits with each procedure. Patients with relatively low hCG levels would benefit from the single-dose methotrexate protocol. Patients with higher hCG levels may necessitate two-dose regimens. There is literature suggestive that methotrexate treatment does not have adverse effects on ovarian reserve or fertility. hCG levels should be trended until a non-pregnancy level exists post-methotrexate administration. Surgical management is necessary when the patients demonstrate any of the following: an indication of intraperitoneal bleeding, symptoms suggestive of ongoing ruptured ectopic mass, or hemodynamically instability **[21]**.

Surgical management including salpingostomy or salpingectomy should be guided by clinical status, the extent of fallopian tube compromise, and desire for future fertility. In simplest form salpingectomy involves removing the fallopian tube partially or in full. Salpingostomy, or salpingotomy, involves removal of the ectopic pregnancy via tubal incision while leaving the fallopian tube in situ **[22].**

Once the decision has been made to treat a pregnancy as an ectopic (or a nonviable intrauterine pregnancy) the physician will attempt to eliminate the potentially dangerous pregnancy to minimize maternal risk. The physician will also try to preserve as much future fertility as possible.

Three primary types of treatment are available for an ectopic pregnancy. These include **surgical** management, **medical** management,and **expectant** management. The most common treatment is surgical.

Surgery allows a rapid and usually definite resolution of the pregnancy;however, the woman does assume the usual surgical risks. Medical management primarily involves the use of methotrexate, which has gained popularity as a way of avoiding surgical risk. Methotrexate management results in destruction of the growing pregnancy but is comparatively slow-- often taking 4-6 weeks for complete resolution of the ectopic pregnancy. Medical management risks rupture of the ectopic over this relatively long course of management. Expectant management is essentially observation and monitoring without active treatment, understanding that up to 25% of ectopic pregnancies will resolve on their own. The risk of expectant management is rupture of the ectopic pregnancy during the observation period[27].

TABLE 3

The surgical and medical treatment*[1,2] of extrauterine pregnancy, modified from Pisarska et al. (8)

Surgical treatment	Medical treatment (methotrexate)*
Indications – rupture – hemodynamic instability – symptoms (eg., pain) – diagnostic laparoscopy – suspected heterotopic pregnancy	**Indications** – hCG < 5000 IU/L – rising hCG level in 48 hours – normal: hemoglobin, leukocytes, platelets, liver enzymes – diameter of gestational sac < 4 cm
	Absolute contraindications – intrauterine pregnancy – immune suppression – hypersensitivity to methotrexate – active lung disease – active peptic ulcer disease – clinically significant renal or hepatic dysfunction – breastfeeding – ruptured extrauterine pregnancy – hemodynamic instability
	Relative contraindications – hCG > 5000 IU/L – objection to blood transfusions – follow-up not possible
Surgical procedure **organ- (tube-) preserving surgery** – salpingotomy – segmental resection (partial salpingectomy) – transampullary expression ("milk-out") **indications for an ablative procedure (salpingectomy)** – uncontrollable bleeding – marked tubal destruction – ipsilateral recurrence – prior ipsilateral sterilization	

Follow-up
– weekly hCG measurement until normalization
– persistent extrauterine pregnancy/trophoblastic tissue:
  – re-laparoscopy
  – drug therapy (methotrexate) when indicated
	Follow-up
	– weekly hCG measurement until normalization
	– persistent extrauterine pregnancy/trophoblastic tissue:
	  – repeat methotrexate administration
	  – surgery when indicated

*[1] Used in: persistent tubal pregnancy or trophoblastic tissue, non-tubal extrauterine pregnancy/heterotopic pregnancies—combined approach: surgery and local drug application.
*[2] Whatever treatment is given, all non-sensitized Rh-negative patients must be given post-treatment anti-D prophylaxis, as after an intrauterine abortion.
hCG, human chorionic gonadotropin

11. **(1)** *Surgery is the most common management of an ectopic pregnancy*[13]:

(2) *Methotrexate has become popular in selected cases of ectopic pregnancy*[13]**.** Unruptured tubal ectopic pregnancies in women who elect conservative (saving the tube) management may be able to be treated with methotrexate. The current (somewhat limited) factual data suggests that methotrexate management and conservative surgical management have similar success in terms of subsequent tubal patency, fertility, ectopic pregnancy and intrauterine pregnancy.

- **mean time to resolution** (negative pregnancy test) was 36 days, and as high as 7 weeks

- **post treatment** hysterosalpingograms demonstrated **tubal patency** on the side of the ectopic in 83% of those treated with methotrexate

- **subsequent fertility** in the methotrexate group of women was 80%

- of those achieving pregnancy following methotrexate treatment, **87% were intrauterine** and **13% were ectopic**

The first experience with methotrexate was in Japan (Dr. Tanaka) in 1982 and the first use of methotrexate in the USA (with Dr. Steven Ory) was in 1986. Ectopic pregnancy is **not an approved FDA indication** for methotrexate. FDA approved uses of methotrexate include **cancer** treatment (including trophoblast disease, breast cancers and leukemia), **psoriasis**, and **rheumatoid arthritis**.

Methotrexate is a mixture containing at least 85% of "4-amino-10-methylfolic acid," is a folic acid antagonist (reversibly inhibiting dihydrofolate reductase which normally reduces folic acid to tetrahydro folic acid), and consequently interferes with DNA synthesis and cell reproduction. Leucovorum calcium is a derivative of tetrahydro folic acid which replaces the missing active form of folic acid to block the effects of methotrexate (the so called "rescue").

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