Consensus Guideline: Ectopic Pregnancy For Maternity Hospitals In Afghanistan

CG011

General Directorate of Curative Medicine
Ministry of Public Health, Kabul, Afghanistan

2017
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<tr>
<td>AFP</td>
<td>Alpha Feto Protein</td>
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<tr>
<td>AST</td>
<td>Aspartate Amino Trans Ferase</td>
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<tr>
<td>BUN</td>
<td>Blood Urea Nitrogen</td>
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<tr>
<td>CSEP</td>
<td>Caesarian Scar ectopic Pregnancy</td>
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<td>DES</td>
<td>Diethyl Still Besterol</td>
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<tr>
<td>DNA</td>
<td>De Oxyrebo nucleic acid</td>
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<tr>
<td>EP</td>
<td>Ectopic Pregnancy</td>
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<tr>
<td>GIFT</td>
<td>Glutamic intra fallopian Transfer</td>
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<tr>
<td>HCG</td>
<td>Hormone Chorionic Gonadotropin</td>
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<tr>
<td>IUD</td>
<td>Intra Uterine Device</td>
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<td>IVF</td>
<td>In vitro fertilization</td>
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<td>PID</td>
<td>Pelvic Inflammatory Disease</td>
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<tr>
<td>SGOT</td>
<td>Serum Glutamic-Oxaloacetic Transaminase</td>
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<td>SGPT</td>
<td>Serum Glutamic-Pyruvic Transaminase</td>
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Forward

Ectopic pregnancy is a life threatening condition and is the leading cause of death in the first trimester of pregnancy requiring a quality emergency intervention.

We believe clinical decisions based on a systematic approach to translate evidence into practice results in better patient care and clinical effectiveness. Therefore, we are encouraging a culture of healthcare practice based on evidence in our hospitals and healthcare facilities. However, the reality of our society for the time being is that access to definitive evidence and knowledge is not easy for some of our clinicians, especially for those who practice in remote areas of the country.

Clinical guidelines and standards are proven to improve patient care. Therefore, Clinical guideline development department of GDCM decided to develop guideline on Ectopic pregnancy. This Guideline has been extract from evidence base and reliable resources and was prepared by distinguished OBGYN experts from Kabul Maternity hospitals through regular weekly core group meetings.

I would like to take this opportunity to thank the OBGYN core group members, peer reviewers and all those who contributed in the development of this Valuable document.

I am pleased that a dedicated Work group under the Clinical Guideline Development Department managed to compile this guideline for the management of Ectopic Pregnancy that fulfills the said requirements. This guideline describes good clinical practice and setting standards of care at pre-hospital and hospital levels for on time diagnosis and management and follows up of Ectopic Pregnancy.

Dr Feda Muhammad Paikan MD, MPH
Deputy Minister of Health Care Service Provision
1- **Aim of the Guideline**

This guideline covers diagnosing and managing Ectopic Pregnancy. It aims to raise knowledge of health care professionals, and to provide clear advice on what action to take when women with signs and symptoms first present in healthcare settings (public and private). It also provides advice on the range of treatments available on Ectopic Pregnancy.

2- **Introduction**

In a normal pregnancy, the egg is fertilized by the sperm in a fallopian tube, and then it travels into the womb and implants itself in the lining. The embryo develops into a fetus and remains in the uterus until the baby is born. ¹

In ectopic pregnancy (the term ectopic is derived from the Greek word *ektopos*, meaning out of place), the gestation grows and draws its blood supply from the site of abnormal implantation. As the gestation enlarges, it creates the potential for organ rupture, because only the uterine cavity is designed to expand and accommodate fetal development. Ectopic pregnancy can lead to massive hemorrhage, infertility, or death.

Ectopic pregnancy is a common life-threatening emergency in the developing world and its frequency is still high. As many as 1 in 100 pregnancies is an ectopic. ²

Pregnancy Ectopic pregnancy is the commonest cause of maternal morbidity and mortality in the first trimester of pregnancy; Complications of early pregnancy are common clinical conditions that often require emergency care. The patient may or may not be aware that she is pregnant at the time of evaluation at the emergency, Diagnosis is frequently missed and should be considered in any woman in the reproductive age group presenting with abdominal pain or vaginal bleeding especially when combined with an episode of collapse, Ectopic pregnancy is a

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¹ (Nordqvist, Last reviewed: Wed 1 June 2016)
² (ectopic pregnancy foundation 2017)
condition that occurs in all races, in all countries and in any socio-economic class of women during the reproductive years.³

Ectopic pregnancy refers to the implantation of a fertilized egg in a location outside of the uterine cavity, including the fallopian tubes (approximately 97.7%), cervix, ovary, corneal region of the uterus, and abdominal cavity, the ampulla is the most common site of implantation (80%), followed by the isthmus (12%), fimbria (5%), cornua (2%), and interstitia (2-3%). (See the image below.)

The increased incidence of ectopic pregnancy has been partially attributed to improved ability in making an earlier diagnosis. Ectopic pregnancies that previously would have resulted in tubal abortion or complete, spontaneous reabsorption and remained clinically undiagnosed are now detected.

3-Implantation:
The faulty implantation that occurs in ectopic pregnancy occurs because of a defect in the anatomy or normal function of either the fallopian tube (as can result from surgical or infectious scarring), the ovary (as can occur in women

³ (Anon, Published in print edition October, 2011)
undergoing fertility treatments), or the uterus (as in cases of bi coronate uterus or cesarean delivery scar). Reflecting this, most ectopic pregnancies are located in the fallopian tube; the most common site is the ampullary portion of the tube, where over 80% of ectopic pregnancies occur. (See Etiology.)

No tubal ectopic pregnancies are a rare occurrence, with abdominal pregnancies accounting for 1.4% of ectopic pregnancies and ovarian and cervical sites accounting for 0.2% each. Some ectopic pregnancies implant in the cervix (<1%), in previous cesarean delivery scars, or in a rudimentary uterine horn; although these may be technically in the uterus, they are not considered normal intrauterine pregnancies.

About 80% of ectopic pregnancies are found on the same side as the corpus luteum (the old, ruptured follicle), when present. In the absence of modern prenatal care, abdominal pregnancies can present at an advanced stage (>28 wk) and have the potential for catastrophic rupture and bleeding.

4- Etiology
An ectopic pregnancy requires the occurrence of 2 events: fertilization of the ovum and abnormal implantation. Many risk factors affect both events; for example, a history of major tubal infection decreases fertility and increases abnormal implantation.

Multiple factors contribute to the relative risk of ectopic pregnancy. In theory, anything that hampers or delays the migration of the fertilized ovum (blastocyst) to the endometrial cavity can predispose a woman to ectopic gestation. The following risk factors have been linked to ectopic pregnancy:

- Pelvic inflammatory diseases and Salpingitis isthmic nodosum
- History of previous ectopic pregnancy
- History of tubal surgery and conception after tubal ligation
- Smoking
✓ Use of oral contraceptives or an intrauterine device
✓ Use of fertility drugs or assisted reproductive technology
✓ Increasing age
✓ Diethylstilbestrol (DES) exposure
✓ Others

Other risk factors associated with increased incidence of ectopic pregnancy include anatomic abnormalities of the uterus such as a T-shaped or bicornuate uterus, fibroids or other uterine tumors, previous abdominal surgery, failure with progestin-only contraception, and ruptured appendix

4:1- Pelvic Inflammatory Diseases

The most common cause of PID is an antecedent infection caused by *Chlamydia trachomatis*. Patients with chlamydial infection have a range of clinical presentations, from asymptomatic cervicitis to salpingitis and florid PID. More than 50% of women who have been infected are unaware of the exposure.

Other organisms that cause PID, such as *Neisseria gonorrhoeae*, also increase the risk of ectopic pregnancy, and a history of salpingitis increases the risk of ectopic pregnancy 4-fold. The incidence of tubal damage increases after successive episodes of PID (ie, 13% after 1 episode, 35% after 2 episodes, 75% after 3 episodes).

4:2- History of Previous Ectopic Pregnancy

After 1 ectopic pregnancy, a patient incurs a 7- to 13-fold increase in the likelihood of another ectopic pregnancy. Overall, a patient with a previous ectopic pregnancy has a 50-80% chance of having a subsequent intrauterine gestation and a 10-25% chance of a future tubal pregnancy.

4:3- History of Tubal Surgery and Conception after Tubal Ligation

Previous tubal surgery has been demonstrated to increase the risk of developing ectopic pregnancy. The increase depends on the degree of damage and the extent of anatomic alteration. Surgeries carrying higher risk of subsequent ectopic
pregnancy include salpingectomy, neosalpingostomy, fimbrio plasty, tubal anastomosis, and lysis of peritubal or peri ovarian adhesions. Conception after previous tubal ligation also increases a women's risk of having an ectopic pregnancy; 35-50\% of patients who conceive after a tubal ligation are reported to experience an ectopic pregnancy. Failure after bipolar tubal cautery is more likely to result in ectopic pregnancy than is occlusion using suture, rings, or clips. This failure is attributed to fistula formation that allows sperm passage. In one study, 33\% of pregnancies occurring after tubal ligation were ectopic; those who underwent electrocautery and women younger than 35 years were at higher risk. Ectopic pregnancies following tubal sterilizations usually occur 2 or more years after sterilization rather than immediately after. In the first year, only about 6\% of sterilization failures result in ectopic pregnancy (Anon., June 2016).

4:4- SMOKING
Cigarette smoking has been shown to be a risk factor for ectopic pregnancy development. Studies have demonstrated an elevated risk ranging from 1.6 to 3.5 times that of nonsmokers. A dose-response effect has also been suggested. Based on laboratory studies in humans and animals, researchers have postulated several mechanisms by which cigarette smoking might play a role in ectopic pregnancies. These mechanisms include one or more of the following: delayed ovulation, altered tubal and uterine motility, and altered immunity. To date, however, no study has supported a specific mechanism by which cigarette smoking affects the occurrence of ectopic pregnancy.

4:5- USE OF ORAL CONTRACEPTIVES OR AN INTRAUTERINE DEVICE
All contraceptive methods lead to an overall lower risk of pregnancy and therefore to an overall lower risk of ectopic pregnancy. However, among cases of contraceptive failure, women at increased risk of ectopic pregnancy compared with pregnant controls included those using progestin-only oral contraceptives, progestin-only implants, or IUDs and those with a history of tubal ligation.

The presence of an inert, copper-containing or progesterone IUD traditionally has been thought to be a risk factor for ectopic pregnancy. Data from the
Contraceptive CHOICE Project demonstrated a relative risk of 3.16 for ectopic pregnancy in women not using any form of contraception as compared with women using the progesterone IUD. Nevertheless, if a woman ultimately conceives with an IUD in place, it is more likely to be an ectopic pregnancy.

Emergency contraception (levonorgestrel, or Plan B) does not appear to lead to a higher-than-expected rate of ectopic pregnancy.

4:5- **Use of Fertility Drugs or Assisted Reproductive Technology**

Ovulation induction with clomiphene citrate or injectable gonadotropin therapy has been linked to a 4-fold increase in the risk of ectopic pregnancy in a case-control study. This finding suggests that multiple eggs and high hormone levels may be significant factors.

One study demonstrated that infertility patients with luteal phase defects have a statistically higher ectopic pregnancy rate than do patients whose infertility is caused by anovulation. In addition, the risk of ectopic pregnancy and heterotopic pregnancy (ie, pregnancies occurring simultaneously in different body sites) dramatically increases when a patient has used assisted reproductive techniques—such as in vitro fertilization (IVF) or gamete intra fallopian transfer (GIFT)—to conceive.

4:6- **Increasing Age**

The highest rate of ectopic pregnancy occurs in women aged 35-44 years. A 3- to 4-fold increase in the risk of developing an ectopic pregnancy exists compared with women aged 15-24 years. One proposed explanation suggests that aging may result in a progressive loss of myoelectrical activity in the fallopian tube; myoelectrical activity is responsible for tubal motility.

4:7- **Salpingitis Isthmica Nodosum**

Salpingitis isthmica nodosum is defined as the microscopic presence of tubal epithelium in the myosalpinx or beneath the tubal serosa. These pockets of epithelium protrude through the tube, similar to small diverticula. Studies of serial
histopathologic sections of the fallopian tube have revealed that approximately 50% of patients treated with salpingectomy for ectopic pregnancy have evidence of salpingitis isthmica nodosum. The etiology of salpingitis isthmica nodosum is unclear, but proposed mechanisms include post inflammatory and congenital changes, as well as acquired tubal changes, such as those observed with endometriosis.

**4:8- DES EXPOSURE**

Before 1971, several million women were exposed in utero to DES (Di Ethyl Stelbesterol), which was given to their mothers to prevent pregnancy complications. In utero exposure of women to DES is associated with a high lifetime risk of a broad spectrum of adverse health outcomes, including infertility, spontaneous abortion, and ectopic pregnancy.

**4.9- OTHER**

Other risk factors associated with increased incidence of ectopic pregnancy include anatomic abnormalities of the uterus such as a T-shaped or bicornuate uterus, fibroids or other uterine tumors, previous abdominal surgery, failure with progestin-only contraception, and ruptured appendix.

**5-DEFERENTIAL DIAGNOSIS**

Only 50% of patients with an ectopic pregnancy present with the classic triad of pain, amenorrhea, and vaginal bleeding. Numerous conditions may have a presentation similar to an extra uterine pregnancy. The most common of these include the following:

- Appendicitis
- Salpingitis
- Ruptured corpus luteum cyst or ovarian follicle
- Ovarian torsion
- Urinary tract disease

Intrauterine pregnancies with other abdominal or pelvic problems, such as degenerating fibroids, must also be included in the differential diagnosis.
The following conditions should also be considered in the differential diagnosis

- Post abortion bleeding, Retained products of abortion, Abortion Complications, Spontaneous abortion or threatened abortion
- Molar pregnancy
- Cornual myoma or abscess
- Ovarian tumor
- Endometrioma
- Cervical Cancer
- Dysmenorrhea
- Hypovolemic shock (Hemorrhagic Shock)

6- **Clinical Manifestation:**

Earlier patient presentation and more precise diagnostic technology typically allow identification before rupture. In this case symptoms and sign of ectopic pregnancy and assumes that she has a normal early pregnancy or is having a miscarriage.

With later diagnosis, a “classic “presentation is characterized by the tired of delayed menstruation, pain and vaginal bleeding or spotting. With tubal rupture, there is usually severe lower abdominal and pelvic pain that is frequently described as sharp, stabbing or tearing .there is tenderness during abdominal palpation. Bimanual pelvic examination, especially cervical motion, causes exquisite pain. The posterior vaginal fornix may bulge from blood in the recto uterine cul-de-sac or attender boggy mass may be felt to one side of the uterus. Although minimal early, later the uterus may be pushed to one side by an ectopic mass. The uterus may also be slightly enlarged due to the hormonal stimulation. Symptoms of diaphragmatic irritation, characterized by pain in the neck or shoulder especially on inspiration developed in perhaps half of women with sizable hem peritoneum.

Some degree of vaginal spotting or bleeding is reported by60 to 80 percent of women with tubal pregnancy. Although profuse virginal bleeding is suggestive of an incomplete abortion, such bleeding occasionally is seen with tubal gestations. Moreover, tubal pregnancy can lead to significant intera abdominal hemorrhage. Responses to moderate bleeding include no change in vital sign,
a slight rise in blood pressure, or a vasovagal response with bradycardia and hypotension. Birkhahn and colleagues (2003) noted that 25 women with ruptured ectopic pregnancy, most at presentation had a heart rate<100 beats /min and a systolic BP> 100mmHG.BP will fall and pulls will rise only if bleeding continues and hypovalemia becomes significant. Vasomotor disturbances developed ranging from vertigo to syncope

Even after substantive hemorrhage, hemoglobin or hematocrit readings may at first show only a slight reduction.Hence, after an acute hemorrhage, a decline in HB or hematocrit level over several hours is more valuable index of blood lose than is initial level.In approximately half of women with a ruptured ectopic pregnancy, varying degree of leukocytosis up to 30,000 micro letters may be documented.

Decidua is endometrium that is hormonally prepared for pregnancy, and the degree to which the endometrium is converted with EP is variable. Tus, in addition to bleeding women with ectopic tubal pregnancy may pass a decidual cast, which is the entire sloughed endometrium that takes the form of endometrium cavity impartially decidual sloughing may also occur with uterine abortion.tus tissue should be carefully evaluated visually and then histologically for evidence of a conceptuse.It no clear gestational sac is visually seen or if no villi are identified histologically within the cast, then the possibility of ectopic pregnancy must still be considered.

In summary the following 4 symptoms independently contributed to the diagnosis of tubal rupture.

- Vomiting during pain
- Diffuse abdominal pain
- Acute pain for longer than 30 minutes
- Flashing pain (if blood from ruptured ectopic pregnancy builds up an irritate certain nerve)
6.1- PHYSICAL EXAMINATION

Some physical findings that have been found to be predictive (although not diagnostic) for ectopic pregnancy include the following:

- Presence of peritoneal signs
- Cervical motion tenderness

Unilateral or bilateral abdominal or pelvic tenderness Usually much worse on the affected side

Abdominal rigidity, involuntary guarding, and severe tenderness, as well as evidence of hypovolemic shock, such as orthostatic blood pressure changes and tachycardia, should alert the clinician to a surgical emergency; this may occur in up to 20% of cases. However, midline abdominal tenderness or a uterine size of greater than 8 weeks on pelvic examination decreases the risk of ectopic pregnancy.

On pelvic examination, the uterus may be slightly enlarged and soft, and uterine or cervical motion tenderness may suggest peritoneal inflammation. An adnexal mass may be palpated but is usually difficult to differentiate from the ipsilateral ovary.

The presence of uterine contents in the vagina, which can be caused by shedding of endometrial lining stimulated by an ectopic pregnancy, may lead to a misdiagnosis of an incomplete or complete abortion and therefore a delayed or missed diagnosis of ectopic pregnancy.

6:2- BETA–HUMAN CHORIONIC GONADOTROPIN LEVELS

Serum and urine assays for the beta subunit of human chorionic gonadotropin (β-HCG) have been developed to detect a pregnancy before the first missed period. Although some commercial urine test kits are able to detect β-HCG in early gestation, they are associated with varying false-negative rates. In addition, the need for a quantitative value makes serum β-HCG the criterion standard for biochemical testing. Serum β-HCG levels correlate with the size and gestational age in normal embryonic growth. In a normal pregnancy, the β-HCG level doubles every 48-72 hours until it reaches 10,000-20,000mIU/mL. In ectopic pregnancies, β-HCG levels usually increase less.
Furthermore, even though ectopic pregnancies have been established to have lower mean serum β-HCG levels than healthy pregnancies, no single serum β-HCG level is diagnostic of an ectopic pregnancy. In short, serial serum β-HCG levels are necessary to differentiate between normal and abnormal pregnancies and to monitor resolution of ectopic pregnancy once therapy has been initiated.

6:3- PROGESTERONE LEVELS
A single serum progesterone level is another tool that is useful in differentiating abnormal gestations from healthy intrauterine pregnancies. Serum progesterone levels have the following characteristics:

- They are not gestational age–dependent
- They remain relatively constant during the first trimester of normal and abnormal pregnancies
- They do not return to the reference range if initially abnormal
- They do not correlate with beta–human chorionic gonadotropin (β-HCG) levels

However, no consensus on a single progesterone value that differentiates between a normal and an abnormal pregnancy currently exists.

6:4- OTHER MARKERS
Several other serum and urine markers are under investigation to help distinguish normal and abnormal pregnancies. These include serum estradiol, inhibin, pregnancy–associated plasma protein A, pregnanediol glucuronide, placental proteins, creatinine kinase, and a quadruple screen of serum progesterone, beta–human chorionic gonadotropin (β-HCG), estriol, and Alfa-fetoprotein (AFP). These markers are usually either early pregnancy proteins or signs of inflammation and damage in smooth muscles and have not been sufficiently sensitive to be useful in clinical medicine.

6:4:1- Ultrasonography
Ultrasonography is probably the most important tool for diagnosing an extrauterine pregnancy, although it is more frequently used to confirm an intrauterine pregnancy.
Visualization of an intrauterine sac, with or without fetal cardiac activity, is often adequate to exclude ectopic pregnancy. The exception to this is in cases of heterotopic pregnancies, which occur in between 1 in 4000 and 1 in 30,000 spontaneous pregnancies.

In patients undergoing ovarian stimulation and assisted reproduction, screening the adnexa by ultrasonography is mandatory even when an intrauterine pregnancy has been visualized, because these patients have a 10-fold increased risk of heterotopic pregnancy. Heterotopic pregnancy is a combined intrauterine and ectopic pregnancy, and it may occur in approximately 1 in 30,000.

The value of ultrasonography is highlighted further by its ability to demonstrate free fluid in the cul-de-sac. However, although free fluid can represent hemothorax, it is not specific for ruptured ectopic pregnancy. Free fluid on ultrasonographic images can represent physiologic peritoneal fluid or blood from retrograde menstruation and unruptured ectopic pregnancies.

Ultrasonography can also be used to detect the presence of other pathologic conditions that may display the signs and symptoms of ectopic pregnancy. For example, although cesarean scar ectopic pregnancy (CSEP) is a rare occurrence, its frequency appears to be increasing with the increasing number of cesarean sections being performed. Early endovaginal ultrasonography may be used to detect CSEPs, thereby helping to minimize maternal complications, maintain treatment options, and potentially preserve future fertility.

Transvaginal ultrasonography, or endovaginal ultrasonography, with its greater resolution, can be used to visualize an intrauterine pregnancy by 24 days post ovulation or 38 days after the last menstrual period (which is about 1 week earlier than trans abdominal ultrasonography can be used for this). This imaging technique can be performed in the outpatient clinic or emergency department.

6:4:2- Gestational sac
The gestational sac, which is an ultrasonographic term and not an anatomic term, is the first structure that is recognizable on Transvaginal ultrasonographic images. It has a thick, echogenic rim surrounding a sonolucent center corresponding to the
trophoblastic decidual reaction surrounding the chorionic sac. Structures that represent a developing embryo cannot be recognized until a later time.

An endovaginal sonogram reveals an intrauterine pregnancy at approximately 6 weeks. A yolk sac (ys), gestational sac (gs), and fetal pole (fp) are depicted.

### 6:4:3-Other ultrasonography findings in ectopic pregnancy
Findings such as an adnexal mass (usually a corpus luteum, occasionally hematoma), free cul-de-sac fluid, and/or severe adnexal tenderness with probe palpation may be present. Patients with no definite intrauterine pregnancy and the above-mentioned findings may be at high risk for an ectopic pregnancy.

An appreciation for the spectrum of ultrasonographic findings in ectopic pregnancy, discussed below, may allow physicians to recognize an early ectopic pregnancy.

**a- Tubal ring**
A tubal ring is an echogenic, ring like structure found outside of the uterus that represents an early ectopic pregnancy.

**b- Extrauterine mass**
The presence of a tender adnexal mass on ultrasonographic images suggests an ectopic pregnancy. One study suggested that the presence of any adnexal mass other than a simple cyst was the most significant ultrasonographic finding for the diagnosis of ectopic pregnancy.
c- Interstitial ectopic pregnancy
An interstitial ectopic pregnancy implants at the highly vascular region of the uterus near the insertion of the fallopian tube. These types can grow larger than those within the fallopian tube, because the endometrial tissue is more expandable. Owing to the increased size and partial endometrial implantation, these advanced ectopic pregnancies can be misdiagnosed as intrauterine pregnancies.

An aid in the diagnosis of an interstitial ectopic pregnancy is the eccentric location of the gestational sac. Evaluating the amount of uterine myometrium surrounding the gestational sac and echogenic decidual layer is important. This is termed the myometrial mantle. At least 5 mm of myometrium should be present. The presence of less than 5mm suggests the diagnosis. Another ultrasonographic finding is the interstitial line sign.

d- Hemosalpinx and ruptured ectopic pregnancy
A hemosalpinx is a condition in which the fallopian tubes may fill with blood or free fluid. Findings of a ruptured ectopic pregnancy on ultrasonography images include free fluid or clotted blood in the cul-de-sac or in the intraperitoneal gutters, such as the Morrison pouch.

6:5- Doppler ultrasonography
Color-flow Doppler ultrasonography has been demonstrated to improve the diagnostic sensitivity and specificity of transvaginal ultrasonography, especially in cases in which a gestational sac is questionable or absent.

The addition of color-flow Doppler ultrasonography may expedite earlier diagnosis and eliminate delays caused by using levels of β-HCG for diagnosis. Furthermore, color-flow Doppler ultrasonography can potentially be used to identify involuting ectopic pregnancies that may be candidates for expectant management.

The absence of the ‘sliding sign’ and blood flow around the gestational sac using color Doppler

4 BJOG and international journal
Royal college of Obstetrics and Gynecology
Green-top Guideline No. 21
6.6-Dilatation and Curettage

A simple way to rule out an ectopic pregnancy is to establish the presence of an intrauterine pregnancy. Once the presence of an abnormal pregnancy has been established by assessing beta–human chorionic gonadotropin (β-HCG) or progesterone levels, dilatation and curettage can provide a rapid, cost-effective method to help differentiate between an intrauterine and an ectopic pregnancy.

If the tissue obtained is positive for villi by floating in saline or by histologic diagnosis on frozen or permanent section, then a nonviable intrauterine pregnancy has occurred. In the absence of villi, the diagnosis of ectopic pregnancy is made. Laparoscopy can be performed at that time, or the case may be followed using serial serum β-HCG levels and be treated medically or surgically at a later time, depending on the clinical setting.

This method of diagnostic dilatation and curettage may be used, of course, only in cases in which continuation of a pregnancy is not desired even if it were an intrauterine gestation.

In a patient undergoing a dilatation and curettage for the diagnosis of ectopic pregnancy, obtaining consent for a diagnostic, and possibly operative, laparoscopy is also necessary in case the diagnosis of ectopic pregnancy is made; this spares the patient exposure to an additional operative procedure.

Although dilatation and curettage is easy and effective, it can provide false reassurance in cases of heterotopic pregnancies, in which multiple gestations are present, with at least 1 being intrauterine and 1 being extra uterine.

6:7-Culdocentesis

Culdocentesis is another rapid and inexpensive method of evaluation for ruptured ectopic pregnancy. It is performed by inserting a needle through the posterior fornix of the vagina into the cul-de-sac and attempting to aspirate blood. When non clotting blood is found in conjunction with a suspected ectopic pregnancy,
operative intervention is indicated, because the likelihood of a ruptured ectopic pregnancy is high.

Although culdocentesis is of historic interest, its use today is rare. This procedure is associated with a high false-negative rate (10-14%), usually reflecting blood from an unruptured ectopic pregnancy, a ruptured corpus luteum, an incomplete abortion, or retrograde menstruation. Furthermore, the improved technology with ultrasonographic and hormonal assays is far superior in sensitivity and specificity in reaching the correct diagnosis.

6:8-Laparoscopy
Patients in pain and/or those who are hemodynamically unstable should proceed to laparoscopy. Laparoscopy allows assessment of the pelvic structures, the size and exact location of the ectopic pregnancy, the presence of hemoperitoneum (see the image below), and the presence of other conditions, such as ovarian cysts and endometriosis, which, when present with an intrauterine pregnancy, can mimic an ectopic pregnancy. Furthermore, laparoscopy provides the option to treat once the diagnosis is established.

Laparoscopy remains the criterion standard for diagnosis; however, its routine use on all patients suspected of ectopic pregnancy may lead to unnecessary risks, morbidity, and costs. Moreover, laparoscopy can miss up to 4% of early ectopic pregnancies; as more ectopic pregnancies are diagnosed earlier in gestation, the rate of false-negative results with laparoscopy would be expected to rise.

7-Other Diagnostic Imaging Modalities
7:1-Magnetic resonance imaging
Although most emergency departments (EDs) have more ready access to ultrasonography than to magnetic resonance imaging (MRI), the latter’s lack of ionizing radiation may give it a role to play in the broader workup of pregnant women with abdominal pain (eg, ruling out appendicitis). MRI could also be indicated in those rare cases where ultrasonography results are inconclusive as to whether a visualized pregnancy is intrauterine or interstitial.
7:2- **Computed tomography**
Computed tomography (CT) scanning involves the use of a substantial amount of ionizing radiation. Accordingly, it is, at best, a third-line choice of diagnostic study for pregnant patients.

8- **Other Laboratory Studies**

- Complete blood count, if significant hemorrhage is suspected
- Metabolic panel to rule out electrolyte imbalances and also to rule out hepatic or renal abnormalities in case methotrexate therapy is being considered
- Serum lactate level in cases of suspected shock
- Urinalysis to eliminate urinary tract infection as a cause of pelvic pain
- Blood type and Rh factor, if transfusion is required or if RhoGAM will be provided for Rh-negative patients with vaginal bleeding

9- **Methotrexate Therapy**
Before initiating therapy, draw blood to determine baseline laboratory values for renal, hepatic, and bone marrow function, as well as a baseline β-HCG level. Determine blood type, Rh factor, and the presence of antibodies. Patients who are Rh negative should receive Rh immunoglobulin.

Methotrexate is an antimetabolite chemotherapeutic agent that binds to the enzyme dihydrofolate reductase, which is involved in the synthesis of purine nucleotides. This interferes with deoxyribonucleic acid (DNA) synthesis and disrupts cell multiplication.

Methotrexate has long been known to be effective in the treatment of leukemias, lymphomas, and carcinomas of the head, neck, breast, ovary, and bladder. It has also been used as an immunosuppressive agent in the prevention of graft versus host disease and in the treatment of severe psoriasis and rheumatoid arthritis.

The effectiveness of methotrexate on trophoblastic tissue has been well established and is derived from experience gained in using this agent in the treatment of hydatiform moles and choriocarcinomas. As used in the treatment of
ectopic pregnancy, methotrexate is administered in a single or in multiple intramuscular (IM) injections.

Treatment with methotrexate is an especially attractive option when the pregnancy is located on the cervix or ovary or in the interstitial or the cornual portion of the tube. Surgical treatment in these cases is often associated with increased risk of hemorrhage, often resulting in hysterectomy or oophorectomy.

9:1- Indications
Medical therapy for ectopic pregnancy involving methotrexate may be indicated in certain patients. To determine acceptable candidates for methotrexate therapy, first establish the diagnosis by one of the following criteria:

- Abnormal doubling rate of the beta–human chorionic gonadotropin (β-HCG) level and ultrasonographic identification of a gestational sac outside of the uterus
- Abnormal doubling rate of the β-HCG level, an empty uterus, and menstrual aspiration with no chorionic villi

A number of other factors must also be considered once the diagnosis is established, as follows:

- The patient must be hemodynamically stable, with no signs or symptoms of active bleeding or hemoperitoneum (must be met by every patient)
- The patient must be reliable, compliant, and able to return for follow-up care (must be met by every patient)
- The size of the gestation should not exceed 4cm at its greatest dimension (or exceed 3.5 cm with cardiac activity) on ultrasonographic measurement. Exceeding this size is a relative, but not absolute, contraindication to medical therapy
- Absence of fetal cardiac activity on ultrasonographic findings. The presence of fetal cardiac activity is a relative contraindication
- No evidence of tubal rupture. Evidence of tubal rupture is an absolute contraindication
- β-HCG level less than 5000 mIU/mL. Higher levels are a relative contraindication
9:2- **Contraindications**
A β-HCG level of greater than 5,000 IU/L, fetal cardiac activity, and free fluid in the cul-de-sac on ultrasonographic images (presumably representing tubal rupture) are contraindications to medical therapy with methotrexate.

Although patients with β-HCG levels above 5,000 IU/L and fetal cardiac activity have been treated successfully with methotrexate, these patients require much greater surveillance and carry a higher risk of subsequent operative intervention. There is an inverse association between β-HCG levels and successful medical management of an ectopic pregnancy..

Other contraindications to the use of methotrexate include the following:

- Documented hypersensitivity to methotrexate
- Breastfeeding
- Immunodeficiency
- Alcoholism
- Alcoholic liver disease
- Any other type of liver disease
- Blood dyscrasias
- Leukopenia
- Thrombocytopenia
- Anemia
- Active pulmonary disease
- Peptic ulcer disease
- Renal, hepatic, or hematologic dysfunction

9:3- **Adverse effects and mandatory patient counseling**
Adverse effects associated with the use of methotrexate can be divided into adverse drug effects and treatment effects. Adverse drug effects include the following:

- Nausea
- Vomiting
- Stomatitis
- Diarrhea
• Gastric distress
• Dizziness

**9:4- Methotrexate Treatment Protocols**

**Multiple-dose regimen**

Initial experience used multiple doses of methotrexate with leucovorin to minimize adverse effects. Leucovorin is folinic acid that is the end product of the reaction catalyzed by dihydrofolate reductase, the same enzyme inhibited by methotrexate. Normal dividing cells preferentially absorb leucovorin; hence, it decreases the action of methotrexate, thereby decreasing methotrexate’s adverse systemic effects.

This regimen involves administration of methotrexate as 1 mg/kg IM on days 0, 2, 4, and 6, followed by 4 doses of leucovorin as 0.1 mg/kg on days 1, 3, 5, and 7. Because of a higher incidence of adverse effects and the increased need for patient motivation and compliance, the multiple dosage regimen has fallen out of favor in the United States.

**Single-dose regimen**

The more popular regimen today is the single-dose injection, which involves injection of methotrexate as 50 mg/m2 IM in a single injection or as a divided dose injected into each buttock. Studies comparing the multiple methotrexate dosage regimens with the single dosage regimen have demonstrated that the 2 methods have similar efficacy. With smaller dosing and fewer injections, fewer adverse effects are anticipated, and the use of leucovorin can be abandoned.

**Day 0**

Obtain β-HCG level, ultrasonography

**Day 1**

Obtain levels of the following:

• β-HCG
• Liver function Eg, aspartate aminotransferase (AST or serum glutamic-oxaloacetic transaminase [SGOT]), alanine aminotransferase (ALT or serum glutamic-pyruvic transaminase [SGPT])
• Blood urea nitrogen (BUN)
• Creatinine

Evidence of hepatic or renal compromise is a contraindication to methotrexate therapy. Blood type, Rh status, and antibody screening are also performed, and all Rh-negative patients are given Rh immunoglobulin. Methotrexate (50 mg/m2) is administered by IM injection. Advise patients not to take vitamins with folic acid until complete resolution of the ectopic pregnancy. They should also refrain from alcohol consumption and intercourse for the same period.

Day 4
The patient returns for measurement of her β-HCG level. The level may be higher than the pretreatment level. The day-4 hCG level is the baseline level against which subsequent levels are measured.

Day 7
Draw β-HCG and AST levels and perform a complete blood count (CBC). If the β-HCG level has dropped 15% or more since day 4, obtain weekly β-HCG levels until they have reached the negative level for the lab. If the weekly levels plateau or increase, a second course of methotrexate may be administered.

If the β-HCG level has not dropped at least 15% from the day-4 level, administer a second IM dose of methotrexate (50 mg/m2) on day 7, and observe the patient similarly. If no drop has occurred by day 14, surgical therapy is indicated.

If the patient develops increasing abdominal pain after methotrexate therapy, repeat a transvaginal ultrasonographic scan to evaluate for possible rupture.

Vitamins
Vitamins are used to correct folic acid deficiency resulting from use of folic acid antagonists after methotrexate regime.

SURGICAL MANAGEMENT

10 - Salpingostomy and Salpingectomy
Within the last 2 decades, a more conservative surgical approach to unruptured ectopic pregnancy using minimally invasive surgery has been advocated to preserve tubal function. The conservative approaches include linear salpingostomy and milking the pregnancy out of the distal ampulla. The more radical approach includes resecting the segment of the fallopian tube that contains the gestation, with or without reanastomosis. Laparoscopy has become the recommended approach in most cases. Laparotomy is usually reserved for patients who are hemodynamically unstable or for patients with cornual ectopic pregnancies; it also is a preferred method for surgeons inexperienced in laparoscopy and in patients in whom a laparoscopic approach is difficult (eg, secondary to the presence of multiple dense adhesions, obesity, or massive hemoperitoneum).

Linear salpingostomy along the antimesenteric border to remove the products of conception is the procedure of choice for unruptured ectopic pregnancies in the ampullary portion of the tube. Ectopic pregnancies in the ampulla are usually located between the lumen and the serosa and, thus, are ideal candidates for linear salpingostomy. Several studies have demonstrated no benefit of primary closure (salpingotomy) over healing by secondary intention (salpingostomy).

Coagulation of oozing areas may be necessary and can be accomplished using microbipolar forceps. Some ampullary pregnancies can be teased out and expressed through the fimbrial end (milking of the tube) by using digital expression, suction, or aqua-dissection. However, this approach carries with it a higher rate of bleeding, persistent trophoblastic tissue, tubal damage, and recurrent ectopic pregnancy.

11 - Segmental Tubal Resection and Total Salpingectomy

In some cases, resection of the tubal segment containing the gestation or a total salpingectomy is preferred over salpingostomy. This is true for isthmic pregnancies, in which the endosalpinx is usually damaged. These patients do poorly with linear salpingostomy, with a high rate of recurrent ectopic pregnancy occurring.
Segmental tubal resection is performed by grasping the tube at the proximal and
distal borders of the segment of the tube containing the gestation and coagulating
thoroughly from the antimesenteric border to the mesosalpinx. This portion of the
tube is then excised. The underlying mesosalpinx is also coagulated and excised,
with particular attention to minimize the damage to the surrounding vasculature.

Total salpingectomy can be achieved by progressively coagulating and cutting the
mesosalpinx, starting from the fimbriated end and advancing toward the proximal
isthmic portion of the tube. At this point, the tube is separated from the uterus by
coagulating and excising with scissors or laser.

Salpingectomy should be the treatment of choice in women with intact
contralateral tubes, because conservative treatment provides no additional benefit
and incurs the additional costs and morbidity associated with persistent ectopic
pregnancy and recurrent ectopic pregnancy in the already damaged tube.

11:1 - Preoperative details
The optimal surgical management for a patient with an ectopic pregnancy
depends on several factors, including the following:

- Patient's age, history, and desire for future fertility
- History of previous ectopic pregnancy or pelvic inflammatory disease (PID)
- Condition of the ipsilateral tube - Ie, ruptured or unruptured
- Condition of the contralateral tube - Eg, adhesions, tubal occlusion
- Location of the pregnancy - Ie, interstitium, ampulla, isthmus
- Size of the pregnancy
- Presence of confounding complications
- In a patient who has completed childbearing and no longer desires fertility,
in a patient with a history of an ectopic pregnancy in the same tube, or in a
patient with severely damaged tubes, total salpingectomy is the procedure
of choice. The presence of uncontrolled bleeding and hemodynamic
instability warrants radical surgery over conservative methods. The
preferred approach based on the location of the pregnancy varies, as
previously discussed. In all instances, regardless of desired fertility, fully inform the patient of the possibility of a laparotomy with bilateral salpingectomy.

11:2- Intraoperative details
Throughout the procedure, take care to minimize blood loss and reduce the potential for retained trophoblastic tissue, which can reimplant and persist. Remove large gestations in an endoscopic bag, and perform copious irrigation and suctioning to remove any remaining fragments. Inspect the peritoneal cavity and remove any detected residual trophoblastic tissue.

Note the condition of the contralateral tube, the presence of adhesions, or other pathologic processes because this helps in the postoperative counseling of the patient with regard to future fertility potential.

11:3- Postoperative details
Proper pain control and hemodynamic stability are important postoperative considerations. Most often, patients treated with laparoscopy are discharged on the same day of surgery; however, overnight admission may be necessary for some patients in order to monitor postoperative bleeding and achieve adequate pain control. Patients treated by laparotomy are usually hospitalized for a few days.

11- Prognosis
Ectopic pregnancy presents a major health problem for women of childbearing age. It is the result of a flaw in human reproductive physiology that allows the conceptus to implant and mature outside the endometrial cavity, which ultimately ends in the death of the fetus. Without timely diagnosis and treatment, ectopic pregnancy can become a life-threatening situation.

The evidence in the literature reporting on the treatment of ectopic pregnancy with subsequent reproductive outcome is limited mostly to observational data and a few randomized trials comparing treatment options.
Assessment of successful treatment and future reproductive outcome with various treatment options is often skewed by selection bias. For example, comparing a patient who was managed expectantly with a patient who received methotrexate or with a patient who had a laparoscopic salpingectomy is difficult.

A patient with spotting, no abdominal pain, and a low initial beta–human chorionic gonadotropin (β-HCG) level that is falling may be managed expectantly, whereas a patient who presents with hemodynamic instability, an acute abdomen, and high initial β-HCG levels must be managed surgically. These 2 patients probably represent different degrees of tubal damage; thus, comparing the future reproductive outcomes of the 2 cases would be flawed.

12-Complications
Complications of ectopic pregnancy can be secondary to misdiagnosis, late diagnosis, or treatment approach. Failure to make the prompt and correct diagnosis of ectopic pregnancy can result in tubal or uterine rupture (depending on the location of the pregnancy), which in turn can lead to massive hemorrhage, shock, disseminated intravascular coagulopathy (DIC), and death. Ectopic pregnancy is the leading cause of maternal death in the first trimester, accounting for 9-13% of all pregnancy-related deaths. In the United States, an estimated 30-40 women die each year from ectopic pregnancy.

Any time a surgical approach is chosen as the treatment of choice, consider the complications attributable to the surgery, whether it is laparotomy or laparoscopy. These include bleeding, infection, and damage to surrounding organs, such as the bowel, bladder, and ureters, and to the major vessels nearby. Infertility may also result secondary to loss of reproductive organs after surgery. Also consider the risks and complications secondary to anesthesia. Make the patient aware of these complications, and obtain the appropriate written consents. Mortality

Virtually all ectopic pregnancies are considered nonviable and are at risk of eventual rupture and resulting hemorrhage. In addition to the immediate morbidity caused by ectopic pregnancy, the woman's future ability to reproduce may be adversely affected as well. However, patients who are diagnosed with
ectopic pregnancy before rupture have a low mortality rate and also have a chance at preserved fertility.

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