

Diagnosis and Management of Tubal Pregnancy

El Gamal H, MD* and Abdel-Aziz A, MSc**

Introduction

Ectopic pregnancy (EP) is a pregnancy in which the fertilized ovum implants outside the uterine cavity. It is a potentially fatal condition accounting for 10% of all maternal mortalities and remained a leading cause of pregnancy – related death in the first trimester. During the past 30 years, there has been an alarming increase in the incidence of ectopic pregnancy, with a 2% incidence of tubal pregnancies in some parts of the world¹.

The technologic advances in the past two decades, availability of sensitive and specific quantitative human chorionic gonadotrophin (hCG) assays, and high-resolution transvaginal ultrasonography have radically changed the management of tubal pregnancy due to earlier diagnosis treatment has shifted from the classical open surgical approach to a more conservative, minimally invasive laparoscopic intervention to even medical treatment and expectant management in selected patients, with successful results exceeding 85% in many trials².

Diagnosis

The diagnosis of ectopic pregnancy is complicated by the wide spectrum of clinical presentations. With patients presenting earlier in the disease process, the number of those who are asymptomatic or who have minimal symptoms has increased. Therefore, there must be a high degree of suspicion of ectopic pregnancy, especially in areas of high prevalence. History and physical examination will identify patients at risk, improving the probability of detection of ectopic pregnancy prior to rupture².

History

Patients who have an ectopic pregnancy generally gave an abnormal menstrual pattern or the perception of a spontaneous pregnancy loss.

*Assistant Professor, Department of Obstetrics and Gynecology, Ain Shams University.

**Assistant Lecturer, Department of Obstetrics and Gynecology, Ain Shams University.

Correspondence to: Dr. Hatem El-Gamal, Department of Obstetrics and Gynecology, Ain Shams University.

Table 1. Risk Factor Assessment

Non Mechanical Factors	Mechanical Factors
<ol style="list-style-type: none"> 1. <i>Endometriosis.</i> 2. <i>Fallopian Tube Disorders</i> <ul style="list-style-type: none"> – Diverticuli. – Motility disorders. 3. <i>Progestin-only contraceptives.</i> 4. <i>Postcoital estrogen.</i> 5. <i>Diethyl stilbestrol exposure.</i> 6. <i>Prior history of infertility.</i> 7. <i>Use of fertility – inducing agents.</i> 8. <i>History of prior ectopic pregnancy.</i> 	<ol style="list-style-type: none"> 1. <i>Previous History of Pelvic inflammatory Disease</i> <ul style="list-style-type: none"> – Gonococcal. – Chlamydial. – Tuberculous. – Other. 2. <i>Intrauterine contraceptive device use.</i> 3. <i>Bilateral tubal ligation.</i> 4. <i>Previous abdominal surgery.</i>

Pertinent history includes the menstrual history, previous pregnancy, history of infertility, current contraceptive status, risk factor assessment (table 1) and current symptoms.

Physical Examination

The physical examination should include measurements of vital signs and examination of the abdomen and pelvis. Frequently, the findings prior to rupture and hemorrhage are normal. The abdomen may be non-tender or mildly tender, with or without rebound. The uterus may be slightly enlarged, with findings similar to a normal pregnancy. Cervical motion tenderness may or may not be present. An adnexal mass may be palpable in up to 50% of cases, but the mass may be the corpus luteum and not the ectopic pregnancy².

Investigations

1- Serial Quantitative Human Chorionic Gonadotropin (hCG) Assay

Quantitative β -hCG measurements are the diagnostic cornerstone for ectopic pregnancy. The hCG enzyme immunoassay, with a sensitivity of 25 mIU/ml, is an accurate screening test for detection of ectopic pregnancy. The assay is

positive in virtually all documented ectopic pregnancies.

In normal intrauterine pregnancies, the chorionic gonadotrophin levels rise in a curvilinear fashion until they plateau at approximately 100,000 mIU per milliliters. However, because the increase is essentially linear early in pregnancy, the rate of increase can be used to assess the viability of pregnancy.

The mean doubling time of serum chorionic gonadotrophin levels in viable singleton intrauterine pregnancies is 48 hours³. With ectopic pregnancies, the levels typically increase at much slower rates. Studies of doubling time indicate that in 85 percent of viable intrauterine pregnancies, serum chorionic gonadotrophin levels rise by at least 66 percent every 48 hours during the first 40 days of gestation. Conversely, in 15 percent of viable intrauterine pregnancies the increase is less than 66 percent in a 48-hour period.

Among women with chorionic gonadotropin level of at least 2000 mIU/ml, transvaginal ultrasonography should be able to identify an intrauterine sac in those with viable intrauterine pregnancies². Women who have chorionic gonadotrophin levels of less than 2000 mIU per millimeter and who have a subnormal rise in chorionic gonadotrophin levels (less than 50 percent in 48-hour period) or levels that have plateaued (changed by 15 percent or less) may undergo suction curettage with minimal fear of interrupting a viable pregnancy³.

2- Ultrasonography

The earliest ultrasonographic finding of an intrauterine pregnancy is a small fluid space and the gestational sac, surrounded by a thick echogenic ring during the located eccentrically within the endometrial cavity. The earliest normal gestation sac is seen at 6 weeks of gestation with transabdominal ultrasonography and at 5 weeks of gestation with transvaginal ultrasonography. As the gestational sac grows, a yolk sac is seen within it, followed by an embryo with cardiac activity.

The appearance of a normal gestational sac may be simulated by intrauterine fluid collection, the pseudogestational sac, which occurs in 8-29% of patients with ectopic pregnancy. This ultrasonographic lucency, centrally located probably represents bleeding into the endometrial cavity by the decidual cast. Clots within this lucency may mimic a fetal pole.

The demonstration of an adnexal gestational sac with a fetal pole and cardiac cavity is the most specific but least sensitive sign of ectopic

pregnancy, occurring in only 10-17% of cases². The recognition of other characteristics of ectopic pregnancy has improved ultrasonographic sensitivity. Adnexal rings (fluid sac with thick echogenic rings) that have a yolk sac or nonliving embryo are accepted as specific ultrasonographic signs of ectopic pregnancy. Adnexal rings are visualized in 22% of ectopic pregnancies using transabdominal ultrasonography and 38% using transvaginal sonography⁴. The adnexal ring may not always be apparent, because bleeding around the sac results in the appearance of a nonspecific adnexal mass. Although the discriminatory zone for intrauterine pregnancy is well established, there is no such zone for ectopic pregnancy. Levels of hCG have not been shown to be correlated with the size of ectopic pregnancy. Regardless of how high the hCG level may be, nonvisualization does not exclude ectopic pregnancy. An ectopic pregnancy may be present anywhere in the abdominal cavity, making ultrasonographic visualization difficult².

Diagnostic Laparoscopy

In contemporary gynecologic practice, laparoscopy remains the standard for the diagnosis of an ectopic pregnancy. It is the best invasive procedure because it misses the diagnosis of an ectopic pregnancy in fewer than 3% of cases and then typically only in extremely early gestations. This approach also allows for therapy to be incorporated at one operative setting. The likelihood of an ectopic pregnancy being missed increases as the diagnosis of pregnancy is made at increasingly earlier gestational ages. For patients who are hemodynamically stable, diagnostic laparoscopy is the single best operation for both diagnosis and therapy.

The diagnostic capabilities improve attempts are being made to move away from laparoscopy for diagnosis, thus leaving it as a treatment modality only. If the need for diagnosis with laparoscopy is eliminated, the risks, complications and morbidity of medical therapy as an alternative to surgery become more appealing. False negative laparoscopy results can be avoided when hormonal markers and ultrasound are used in conjunction with the diagnostic procedure. In addition, false positive laparoscopy findings i.e. tubal discoloration or dilation can be misinterpreted as ectopic gestations. These are factors that will have to be considered as the role of the laparoscopy in the diagnosis of ectopic pregnancy is further defined in the future⁴.

Management

Laparoscopy versus Laparotomy

Three prospective randomized trials have shown definitively that laparoscopic surgery is superior to laparotomy in hemodynamically stable patients. All three studies demonstrated lower cost shorter hospital stay, less operative time less blood loss less analgesia required, and shorter convalescence in the laparoscopic group. The rates of subsequent intrauterine pregnancy were 61% after laparotomy and 53% after laparoscopy, and the rates of ectopic pregnancy were 7% and 14% respectively. There was no difference in the reproductive outcome after salpingostomy by laparotomy. In another study, the rate of elimination of serum β -hCG was similar in the two groups and there was no statistical difference in the rate of persistent ectopic pregnancy⁵. Yao and Tulandi⁶ reviewed fertility outcome after linear salpingostomy by laparoscopy and laparotomy. Among 811 patients attempting to conceive after the laparotomy approach, the intrauterine pregnancy rate was 61.4% and the recurrent ectopic pregnancy rates was 15.4% very similar intrauterine and recurrent ectopic pregnancy rates (61.0% and 15.5% respectively) were obtained in 703 patients attempting to conceive after the same surgery by laparoscopy.

In a retrospective review of 374 patients, the reproductive outcome after salpingectomy was also not different between laparoscopy and the laparotomy⁷. Because of the general advantages of laparoscopy, most surgical treatment of ectopic pregnancy should be done using the procedure.

Conservative versus Radical Surgery

Among 2,635 patients, 528 patients in the conservative group and 1,246 patients in the radical group designed to preserve fertility. The rate of subsequent intrauterine pregnancy was 53.0% in the conservative group and 49.3% in the salpingectomy group (statistically non-significant). The recurrent ectopic pregnancy rates were 14.8% and 9.9% respectively⁸ (statistically significant).

In a study that compared prospective cohorts of 86 patients, the intrauterine pregnancy rates were 60% and 53.8% and recurrent ectopic rates were 18.3% and 7.7% in the conservative and the radical groups, respectively⁸. There has been no randomized study comparing the fertility outcome after conservative and radical surgery for tubal pregnancy, studies to date have suggested that conservative surgery may provide a subsequent intrauterine pregnancy rate comparable or greater than that after radical surgery, but the recurrence

rate of ectopic pregnancy also may be higher. In women who wish to preserve their fertility, conservative treatment is a logical option, mainly if the contralateral tube is thought to be unhealthy. There are some conditions, however that require salpingectomy. These include uncontrolled bleeding, recurrent ectopic pregnancy in the same tube, a severely damaged tube, a large tubal pregnancy of ≥ 5 cm and in women who have completed their family. Salpingectomy also is advisable by the royal college of obstetricians and gynaecologists (RCOG) guidelines to reduce the recurrence rate since the fertility rate appears to be similar among patients who undergo radical or conservative surgery⁴.

Linear Salpingostomy

In women who wish to preserve their fertility, conservative surgery by linear salpingostomy is considered the gold standard for the management of ectopic pregnancy. The presence of hemoperitoneum should not prevent laparoscopic treatment of ectopic pregnancy. Using a suction irrigator, the blood can be evacuated and the pelvic organs are irrigated with crystalloid solution⁷. The ectopic pregnancy is identified and the tube is immobilized with laparoscopic forceps. Using a 22-gauge injection needle inserted through a 5-mm portal a solution of vasopressin in (0.2 IU/ml of physiologic saline) is injected into the wall of the tube at the area of maximal distention. This will allow surgery with minimal bleeding. A 10-15 mm longitudinal incision is made on the maximally distended antemesosalpinx wall of the tube. Laser, unipolar needle electrocautery or scissors can be used. The product of conception is flushed out of the tube with high pressure of irrigating solution using a combination of hydrodissection and gentle blunt dissection with a section irrigator, the entire product of conception is removed from outside.

The specimen is grasped with 10 mm claw; forceps and then removed from the abdominal cavity. A laparoscopic pouch may be useful for the removal of large fragments of placental tissue. The tube is irrigated carefully and inspected under water for hemostasis. Bleeding points can be controlled by pressure or coagulated with light application of bipolar coagulation. If bleeding persists, ligation of the vessels in the mesosalpinx with 6-0 polyglactin suture is needed. This requires surgeon's expertise in laparoscopic suturing. The tubal incision is left open to heal by secondary intention. There is no difference in subsequent fertility and adhesion formation between salpingotomy with and without tubal

suturing⁴.

Non Surgical Treatment

Methotrexate

Methotrexate is an antimetabolite that interferes with the synthesis of DNA by inhibiting the action of dihydrofolate reductase in the conversion of dihydrofolic acid to tetrahydrofolic acid. It interrupts the synthesis of the purine nucleotide thymidilate and the amino acids serine and methionine. The safety of methotrexate in women of the reproductive age group with respect to future pregnancies has been proven is a study from the 1970s involving methotrexate as a treatment of gestational trophoblastic disease. There was no increase in the rate of subsequent spontaneous abortions or the rate of congenital anomalies after its use.

Table 2. Criteria for the use of Methotrexate in patients with ectopic pregnancy⁴

- Hemodynamic stability.
- β-subunit hCG level that does not exceed 5000 mIU/L (some researchers proved benefit with levels up to 10 and 15,000).
- Unruptured ectopic mass less than 3 cm in greatest dimension.
- No fetal cardiac motion detected.
- No contraindications to methotrexate therapy.
- Patient compliance.

Systemic Methotrexate

Kooi and kock⁹ reviewed 24 studies on the use of methotrexate in EP and found that only 15 of 284 cases (5%) required further surgery for methotrexate failure. Their review included studies using parenteral and local administration of methotrexate. Slaughter and Grimes reviewed

Table 3. Ectopic pregnancy protocol for outpatient multidose administration of Methotrexate

Day	Therapy*
1	CBC, SGOT, MTX, hCG, blood type+Rh, BUN, creatinine.
2	CF, hCG.
3	MTX, hCG.
4	CF, hCG.
5	MTX, hCG.
6	CF, hCG.
7	MTX, hCG.
8	CF, hCG.

17 studies on 400 patients treated with parenteral methotrexate and found the success rate to be 92% contrary to the multiple dose schedules that

Table 4. Single Dose Methotrexate Protocol for Ectopic Pregnancy Treatment¹⁰

Day	Therapy*
0**	HCG, D&C, CBC, SGOT, BUN, C reatinine, blood type + Rh.
1	MTX, hCG.
7	HCG.
7***	HCG.

were prevalent in older studies (table 3), recent studies used more unified single dose methotrexate (1mg/kg body weight or 50 mg/m² body surface area) (table 4).

*CBC = complete blood count with differential and platelet count, SGOT= serum glutamic oxaloacetic transaminase, MTX= intramuscular methotrexate 1.0 mg/kg,. BUN = blood area nitrogen, CG= intramuscular citrovorum U mg/kg. BUN = blood urea nitrogen, MTX = intramuscular methotrexate 50 mg/m².

**In those patients not requiring D & C before MTX intitration (hCG < 2000 mLU/mL and no gestational sac on transvaginal ultrasound) day 0 and day 1 are combined.

***If < 15% decline in hCG titer between days 4 and 7 give a second dose of methotrexate, 50 mg/m² on day 7 if > 15% decline in hCG titer between days 4, and 7 follow weekly until hCG ≥ 15 mIU/mL.

****The use of citrovorum rescue has been shown to be unnecessary.

Local Methotrexate

The success rate of local injection of methotrexate under U/S guidance ranged from 70% to 95% in a total of 177 patients treated¹¹. Among 79 patients desiring fertility, the over all IUP rate was 48% and the recurrent EP rate was 6%. The duration to reach undetectable serum β-hCG levels was 26,5 to 35 days. Hysterosalpingogram demonstrated ipsilateral tubal patency in 81% to 90% of patients¹¹.

Administration of methotrexate into the gestational site under laparoscopic guidance was performed with varying dosages ranging from 5 to 100 mg and the amount of normal saline as diluent ranged from 9.8 to 10 ml. the success rate ranges between 13% and 100%. Of 72 patients who attempted to conceive, the overall intrauterine and recurrent pregnancy rates were 58% and 10% respectively. Laparoscopic injection of methotnexasate still requires surgery, and if it fails, another surgery may be needed.

Therefore, local injection under ULS is preferable for local treatment¹¹.

Laparoscopic Surgery Vs Methotrexate⁵

There are currently several randomized studies confirming that medical treatment in selected cases of EP is as effective as laparoscopic treatment. Both treatments are also equal in preserving tubal patency. As expected, the duration of time for hCG concentrations to

decrease to undetectable level is faster after laparoscopic surgery. A recent meta-analysis revealed that the success rate of methotrexate treatment (87%, range 75-900%) is similar to that of laparoscopic salpingostomy (91%, range 72-100%).

Table 5. Three RCTs of Laparoscopic Versus Open Surgery for Ectopic Pregnancy⁶

	No. in Study	Hospital Stay	Time to Normal	Persistent Ectopic	% of Subsequent Intrauterine Pregnancies	% of Subsequent Ectopic Pregnancies
Laparotomy	123	3.8 days	43 days	1.7%	55%	16.6%
Laparoscopy	108	1.6 days	14 days	12.2%	70%	5%

Table 6. Persistent Pregnancy Outcomes in 11 Comparative Studies of Laparoscopic Versus Open Surgery for Ectopic Pregnancy⁶

	No. of Ectopics in Study	No. with Persistent Ectopics	% of Persistent Ectopics
Laparotomy	23	9	3.9%
Laparoscopy	699	58	8.3

Table 7. Subsequent pregnancy outcomes in 30 non-comparative studies of laparoscopic versus laparotomy salpingotomy⁶

	No attempting further pregnancy	No of IUPs	No of ectopics
Laparotomy	811	498(6.14%)	125 (15.4%)
Laparoscopy	703	429 (61.0%)	109 (15.5%)

Table 8. Subsequent Pregnancy Outcomes in Nine Comparative Studies of Salpingectomy for Ectopic Pregnancy⁶

	No attempting further pregnancy	No of IUPs	No of ectopics
Salpingotomy	528	280 (53.0%)	68 (12.9%)
Salpingectomy	1246	614 (49.3%)	128 (10.3%)

However, medical treatment has a more negative impact on patients' health-related quality of life than surgical treatment.

The possible risk of tubal rupture after medical treatment, combined with a prolonged follow up and a frequent initial rise in the serum hCG concentration, are likely to cause distress.

Abdominal pain several days after medical treatment also contributes to the patient's concern. A detailed informed consent before the administration of the treatment is important, and the ramifications of both treatments should be fully discussed.

Several studies evaluated the role of Shock Index (heart rate/systolic blood pressure) to diagnose

rupture of an ectopic pregnancy as compared to the traditional vital data.

The later proved to be poorer predictors of ruptured ectopic pregnancy; shock index (SI) correlated best with the quantity of intraperitoneal hemorrhage. A SI > 0.85 made the diagnosis of ruptured EP 15.0 (95% CI = 5.6 to 40.4) times more likely.¹²

It is important to note that the surgical approach can be universally done for all patient with ectopic pregnancy, whereas methotrexate treatment is given only to a selected group of patients. The two treatments can complement each other. The advantages of single systemic methotrexate compared with laparoscopic salpingostomy are noninvasiveness, shorter hospital stay, lower cost and avoidance of risk of general anesthesia or surgery.

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