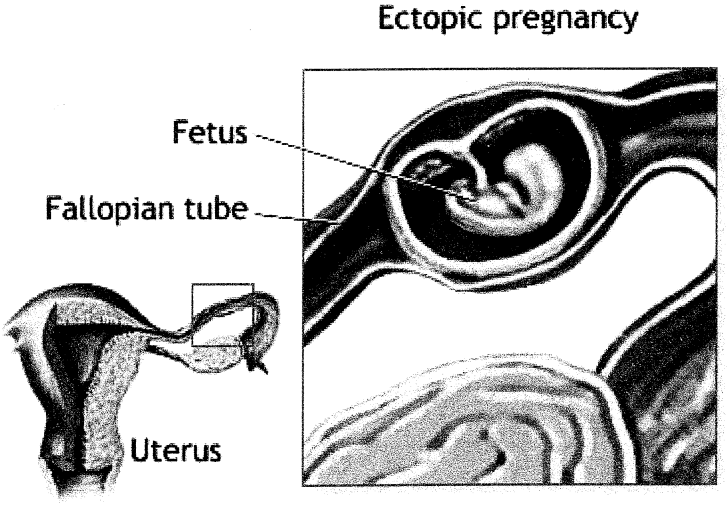
ECTOPIC PREGNANCY



A.D.A.M.

Diploma work by Marthe Østgaard Mohn
6th year, 2006

SUMMARY

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 death of the fetus. Without timely diagnosis and treatment, ectopic pregnancy can become a life-threatening situation. In this diploma, I will discuss the risk factors and treatment options, as well as diagnostic procedures and clinical symptoms and signs.

ECTOPIC PREGNANCY – A REVIEW

INTRODUCTION

Ectopic pregnancy was first described in the 11th century, and, until the middle of the 18th century, it was usually fatal. John Bard reported the first successful surgical intervention to treat an ectopic pregnancy in New York City in 1759.
In the beginning of the 20th century, great improvements in anesthesia, antibiotics, and blood transfusion contributed to the decrease in the maternal mortality rate. In the early half of the 20th century, 200-400 deaths per 10,000 cases of all pregnant women were attributed to ectopic pregnancy.

Ectopic pregnancy is derived from the Greek word *ektopos,* meaning out of place, and it refers to the implantation of a fertilized egg in a location outside of the uterine cavity, including the fallopian tubes, cervix, ovary, cornual region of the uterus, and the abdominal cavity. Ectopic pregnancy is caused by conditions that obstruct or slow the passage of a fertilized ovum (egg) through the fallopian tube to the uterus. This may be caused by a physical blockage in the tube. Ectopic pregnancy may also be caused by failure of the zygote (the cell formed after the egg is fertilized) to move down the tube and into the uterus. The abnormally implanted 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 and death.

Ectopic pregnancy currently is the leading cause of pregnancy-related death during the first trimester in the United States, accounting for 9% of all pregnancy-related deaths. In addition to the immediate morbidity caused by ectopic pregnancy, the woman's future ability to reproduce may be adversely affected as well.

1-2% of all pregnancies are ectopic, in Norway 1:60. 95% of ectopic pregnancies are in the tubes. The remaining are in ovaries, cervix, abdominal cavity or in mesosalpinx. Within the tube, 80% are in the ampulla, 12% in isthmus, and 6% in infundibulum.

ETIOLOGY

Multiple factors contribute to the relative risk of ectopic pregnancy. In theory, anything that hampers the migration of the embryo to the endometrial cavity could predispose women to ectopic gestation. The most logical explanation for the increasing frequency of ectopic pregnancy is previous pelvic infection; however, most patients presenting with an ectopic pregnancy have no identifiable risk factor. The following risk factors have been linked with ectopic pregnancy:

1. **Previous ectopic pregnancy:** After one ectopic pregnancy, a patient incurs a 7- to 13-fold increase in the likelihood of another ectopic pregnancy. Overall, a patient with prior ectopic pregnancy has a 50-80% chance of having a subsequent intrauterine gestation, and a 10-25% chance of a future tubal pregnancy.
2. **Pelvic inflammatory disease:** Pelvic inflammatory disease is usually caused by invasion of either gonorrhea or chlamydia from the cervix up to the uterus and tubes. The infection in these tissues causes an intense inflammatory response. Bacteria, white blood cells and other fluids (pus) fill the tubes as the body combats the infection. Eventually, the body wins and the bacteria are controlled and destroyed. However, during the healing process the delicate inner lining of the tubes (tubal mucosa) is permanently scarred. The end of the tube by the ovaries may become partially or completely blocked, and scar tissue often forms on the outside of the tubes and ovaries. All of these factors can impact ovarian or tubal function and the chances for conception in the future. If pelvic inflammatory disease

is treated very early and aggressively with IV antibiotics, the tubal damage might be minimized, and fertility maintained. The most common cause is antecedent infection caused by *Chlamydia trachomatis.* Patients with chlamydial infection have a range of clinical presentations, from asymptomatic cervicitis to salpingitis and florid pelvic inflammatory disease (PID). More than 50% of women who have been infected are unaware of the exposure. Other organisms causing PID, such as *Neisseria gonorrhoeae,* increase the risk of ectopic pregnancy. 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).

3. **Prior tubal surgery:** Prior 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 salpingostomy, neosalpingostomy, fimbrioplasty, tubal reanastomosis, and lysis of peritubal or periovarian adhesions. Conception after previous tubal ligation increases a women's risk of developing ectopic pregnancies. Thirty-five to 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 occlusion using suture, rings, or clips. Failure is attributed to fistula formation that allows sperm passage. 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.
4. **Cigarette smoking:** Cigarette smoking has been shown to be a risk factor for developing an ectopic pregnancy. Studies have demonstrated elevated risk ranging from 1.6-3.5 times that of nonsmokers. A dose-response effect also has 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, or altered immunity. To date, no study has supported a specific mechanism by which cigarette smoking affects the occurrence of ectopic pregnancy
5. **Vaginal douche**
6. **DES exposure:** Diethylstilbestrol. A synthetic form of estrogen once given to women to prevent miscarriage. Discovered in the late 1960s to have serious side effects, including cancer, infertility, and miscarriage.

7. **Advanced maternal age:** The highest rate of ectopic pregnancy occurs in women aged 35-44 years. A 3- to 4-fold increase in the risk for developing an ectopic pregnancy exists compared to women aged 15-24 years. One proposed explanation involves the myoelectrical activity in the fallopian tube, which is responsible for tubal motility. Aging may result in a progressive loss of myoelectrical activity along the fallopian tube.
8. **Infertility/ovulation induction:** Ovulation induction with clomiphene citrate or injectable gonadotropin therapy has been linked with 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 has demonstrated that infertility patients with luteal phase defects have a statistically higher ectopic pregnancy rate than patients whose infertility is caused by anovulation. 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 to conceive, such as in vitro fertilization (IVF) or gamete intrafallopian transfer (GIFT). Furthermore, studies have demonstrated that up to 1% of pregnancies achieved through IVF or GIFT can result in a heterotopic gestation, compared to an incidence of 1 in 30,000 pregnancies for spontaneous conceptions.
9. **Intrauterine device:** While anticontraceptives such as condoms and birth control pills prevent both intra- and extrauterine pregnancies, the IUDs are primarily protective against intrauterine pregnancies. Whether copper or hormone IUDs lead to an increase in ectopic pregnancies in general is controversial. However, if a woman gets pregnant with IUD in situ, there's a 10% chance that this is ectopic. Copper-containing IUDs have a higher probability of ectopic pregnancy than hormonal IUDs. The actual incidence of ectopic pregnancies with IUD use is 3-4%.
10. **Caecarean section, removal of ovarian cysts or fibrinoids, appendectomy**
11. **Salpingitis isthmica nodosum:** Salpingitis isthmica nodosa 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 histopathological sections of the fallopian tube have revealed that approximately 50% of patients treated with salpingectomy for ectopic pregnancy have evidence of salpingitis isthmica nodosa. The etiology of salpingitis isthmica nodosa is unclear, but proposed mechanisms include postinflammatory and congenital as well as acquired tubal changes such as observed with endometriosis.

12. **The administration of hormones**, specifically estrogen and progesterone, can slow the normal movement of the fertilized egg through the tubal epithelium and result in implantation in the tube. Women who become pregnant despite using progesterone-only oral contraceptives have a 5-fold increase in the ectopic pregnancy rate.

CLINICAL SYMPTOMS AND SIGNS

The symptoms of ectopic pregnancy can differ. Most cases present between the 4th and 10th week of pregnancy.

1. **intact ectopic pregnancy:**

- late period
- slight abdominal pain
- spotting
- non-specific signs of pregnancy
- positive pregnancy test

2. **rupture of the tube or "abortus tubarius":**

- signs of haemoperitoneum, eg shoulder-tip pain due to blood irritating the diaphragm
- strong abdominal pain, may not be on the side of the ectopic pregnancy
- signs of peritoneal irritation
- sometimes strong bleeding: unlike period, this bleeding is dark and watery, sometimes described as looking like a "prune juice"
- collapse or shock: The woman may feel light-headed or faint, and often this is accompanied by a feeling of something being very wrong. Other signs such as paleness, increasing pulse rate, sickness, diarrhoea and falling blood pressure may also be present.

Differential diagnosis: intrauterine pregnancy, spontaneous abortion, corpus luteum with bleeding, salpingitis.

DIAGNOSTIC PROCEDURES

To make the diagnosis, a thorough history and physical examination are essential. Inspection of cervix and bimanual palpation should be performed very carefully, as there is a risk of rupture of the tube and bleeding. Patients with early normal intrauterine pregnancies often present with signs and symptoms similar to those encountered in patients with ectopic pregnancies and other gynecological or gastrointestinal conditions. The availability of various biochemical, ultrasonographic, and surgical modalities can aid the health care provider today in establishing a definitive diagnosis and differentiating among various conditions.

In order to reduce the morbidity and mortality associated with ectopic pregnancy, a high index of suspicion is necessary to make a prompt and early diagnosis. Neither risk factors nor signs and symptoms of ectopic pregnancy are sensitive or specific enough to establish a definitive diagnosis. Hence, screen any female patient in the reproductive years presenting with abdominal pain, cramping, or vaginal bleeding for pregnancy. In recent years, serum and urine assays for the beta subunit of human chorionic gonadotropin (beta-hCG) have been developed to detect a pregnancy before the first missed period. While some commercial urine test kits are able to detect beta-hCG in early gestation, they are associated with varying false-negative rates. In addition, the need for a quantitative value makes serum beta-hCG the criterion standard for biochemical testing.

The basic diagnostic criteria are the dynamic changes in serum-HCG-level and transvaginal ultrasound examination. In emergency cases the gold standard for diagnosis is the diagnostic laparoscopy.

- *Beta–human chorionic gonadotropin*
    - In early healthy intrauterine pregnancies, serum levels of beta-hCG double approximately every 2 days.
    - Even though ectopic pregnancies have been established to have lower mean serum beta-hCG levels than healthy pregnancies, no single serum beta-hCG level is diagnostic of an ectopic pregnancy. In short, serial serum beta-hCG

levels are necessary to differentiate between normal and abnormal pregnancies and to monitor resolution of ectopic pregnancy once therapy has been initiated.

- The major disadvantage in relying on serial titers to distinguish between normal and abnormal pregnancies is the potential for delay in reaching the diagnosis. Furthermore, while serial beta-hCG titers may be used to differentiate between a normal and an abnormal gestation, the test does little to indicate the location of the pregnancy. Hence, additional diagnostic modalities, including US and other biochemical markers, are needed.

- *Progesterone*

  - A single serum progesterone level is another tool that is useful in differentiating abnormal gestations from healthy intrauterine pregnancies. Serum progesterone levels 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, and they do not correlate with beta-hCG levels. However, no consensus on a single value that differentiates between a normal and an abnormal pregnancy currently exists. A progesterone value of greater than 25 ng/mL excluded ectopic pregnancy with 97.4% certainty in one large study. Furthermore, levels of less than or equal to 5 ng/mL indicated a nonviable pregnancy, ectopic or intrauterine, and excluded normal pregnancy with 100% sensitivity.
  - Although inexpensive, the usefulness of serum progesterone is limited in that a significant number of results fall in the equivocal range of 5-25 ng/mL. Also, this test is unreliable in differentiating between normal and abnormal pregnancies in patients who conceive after IVF because of excessive progesterone production from multiple corpora lutea, as well as the practice of pharmacologic progesterone supplementation

- *Other markers*

  - Several other serum and urine markers are currently under investigation to help distinguish normal and abnormal pregnancies. These include serum estradiol, inhibin, pregnancy-associated plasma protein A, pregnanediol glucuronide,

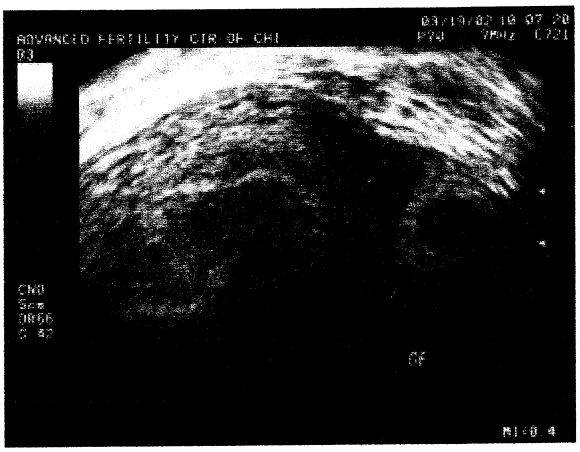
placental proteins, creatinine kinase, and a quadruple screen of serum progesterone, beta-hCG, estriol, and alfa-fetoprotein.

At present, use each of these markers only as a research tool until substantial clinical evidence proves their role in clinical medicine.

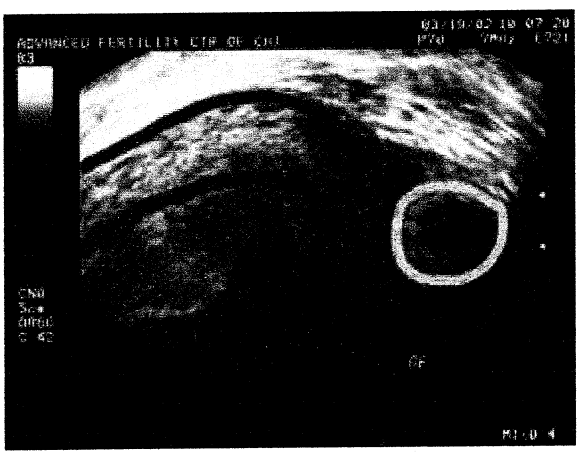
- *Ultrasonography*
    - US probably is the most important tool in diagnosing an extrauterine pregnancy. More frequently, it is used to confirm an intrauterine pregnancy. Visualization of an intrauterine sac, with or without fetal cardiac activity, often is adequate to exclude ectopic pregnancy. The exception to this is in the case of heterotropic pregnancies, which occur from 1 in 4000 to 1 in 30,000 spontaneous pregnancies. Screening the adnexa by US is mandatory despite visualization of an intrauterine pregnancy in patients undergoing ovarian stimulation and assisted reproduction because they have a 10-fold increased risk of heterotropic pregnancy.
    - Transvaginal US, with its greater resolution, can be used to visualize an intrauterine pregnancy by 24 days postovulation, or 38 days after last menstrual period, which is about 1 week earlier than transabdominal US. The gestational sac, which is a sonographic term and not an anatomic term, is the first structure that is recognizable on transvaginal US. 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.
    - A pseudosac is a collection of fluid within the endometrial cavity created by bleeding from the decidualized endometrium often associated with an extrauterine pregnancy and should not be mistaken for a normal early intrauterine pregnancy. The true gestational sac is located eccentrically within the uterus beneath the endometrial surface, whereas the pseudosac fills the endometrial cavity.
    - The yolk sac is the first visible structure within the gestational sac, and it resembles a distinct circular structure with a bright echogenic rim and a sonolucent center. It can first be recognized 3 weeks postconception, about 5 weeks after last menstrual period. The embryo is recognized first as a

thickening along the edge of the yolk sac, and embryonic cardiac motion can be observed 3.5-4 weeks postconception, about 5.5-6 weeks after the last menstrual period.

- In the absence of reliable menstrual and ovulatory history, a discriminatory zone of beta-hCG levels validates the US findings. The discriminatory zone is the level of beta-hCG, using the Third International Standard for quantitative beta-hCG, at which all intrauterine pregnancies should be visible on US. With abdominal US, that level is 6000-6500 mIU/mL, but high-resolution transvaginal US has reduced this level to 1500-1800 mIU/mL. If transvaginal US does not reveal an intrauterine pregnancy when the discriminatory beta-hCG levels are reached, the pregnancy generally can be considered extrauterine.
- An exception to this is multiple gestations. It has been reported that patients with normal multiple gestates were found to have levels of beta-hCG above the discriminatory zone before any US evidence of the gestation was apparent. They showed multiple gestations with beta-hCG levels of up to 2300 mIU/mL before transvaginal US recognition. Therefore, if a multiple gestation is suspected, as in pregnancies resulting from assisted reproduction, the beta-hCG discriminatory zone must be used cautiously. The coincidence of ectopic and intrauterine pregnancies, is called "heteroptropic pregnancy". It occurs 1:300 000 of all pregnancies
- The value of US is highlighted further in its ability to demonstrate free fluid in the cul-de-sac. While free fluid could represent hemoperitoneum, it is not specific for ruptured ectopic pregnancy. Free fluid on US can represent physiological peritoneal fluid or blood from retrograde menstruation and unruptured ectopic pregnancies. Furthermore, US can be used to detect the presence of other pathological conditions that may display the signs and symptoms of ectopic pregnancy.



Ultrasound showing uterus and tubal pregnancy



Same image. Uterus outlined in red, uterine lining in green, ectopic pregnancy yellow. Fluid in uterus at blue circle - sometimes called a "pseudosac"

- *Doppler US*
    - Color-flow Doppler US has been demonstrated to improve the diagnostic sensitivity and specificity of transvaginal US, especially in cases where a gestational sac is questionable or absent. A study of 304 patients at high risk for ectopic pregnancy found that the use of color-flow Doppler US, compared with transvaginal US alone, increases the diagnostic sensitivity from 71-87% for ectopic pregnancy, from 24-59% for failed intrauterine pregnancy, and from 90-99% for viable intrauterine pregnancy.

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

- *Dilatation and curettage*

  - A simple way to rule out an ectopic pregnancy is to establish an intrauterine pregnancy. Dilation and curettage is a rapid cost-effective method to diagnose ectopic pregnancy. Once an abnormal pregnancy is established by beta-hCG or progesterone levels, curettage can help differentiate between an intrauterine or ectopic pregnancy. If tissue obtained is positive for villi by floating in saline or by histological diagnosis on frozen or permanent section, then a nonviable intrauterine pregnancy has occurred. In the absence of villi, the diagnosis of ectopic pregnancy is probable. Laparoscopy should be performed at that time, or the case may be followed by serial serum beta-hCG levels and treated medically or surgically at a later time, depending on the clinical setting.
  - This method of diagnostic dilatation and curettage may only be used, of course, in cases where 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.
  - While dilatation and curettage is easy and effective, it can provide false reassurance in cases of heterotropic pregnancies where multiple gestations are present, with at least one being intrauterine and one being extrauterine.

- *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 nonclotting blood is found in conjunction with a suspected

ectopic pregnancy, operative intervention is indicated because the likelihood of a ruptured ectopic pregnancy is high. But negative finding doesn't exclude the diagnosis of ectopic pregnancy.

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

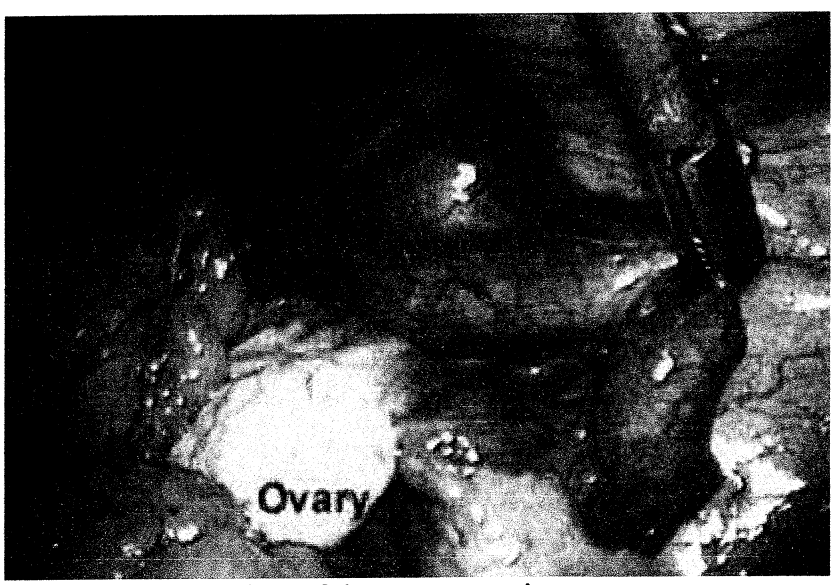
- *Laparoscopy*

  - Patients in pain and/or those who are hemodynamically unstable should proceed to laparoscopy. Laparoscopy allows assessment of the pelvic structures, size and exact location of ectopic pregnancy, presence of hemoperitoneum, and 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, and, as more ectopic pregnancies are diagnosed earlier in gestation, the rate of false-negative results with laparoscopy would be expected to rise.

A right tubal ectopic pregnancy as seen at laparoscopy.

The swollen right tube containing the ectopic pregnancy is on the right at E

The stump of the left tube is seen at L - this woman had a previous tubal ligation



Close view of the same ectopic pregnancy