

ECTOPIC PREGNANCY

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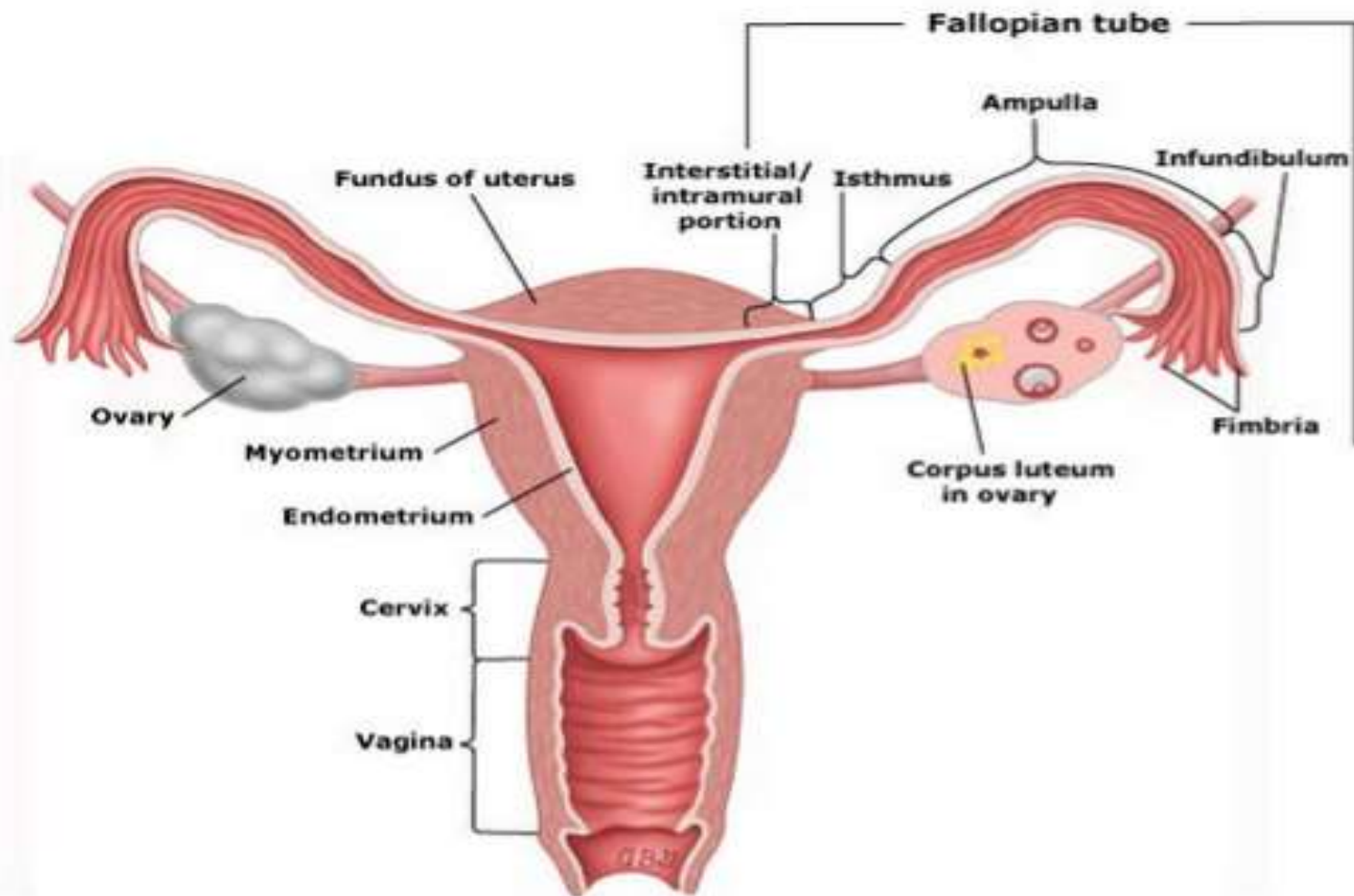
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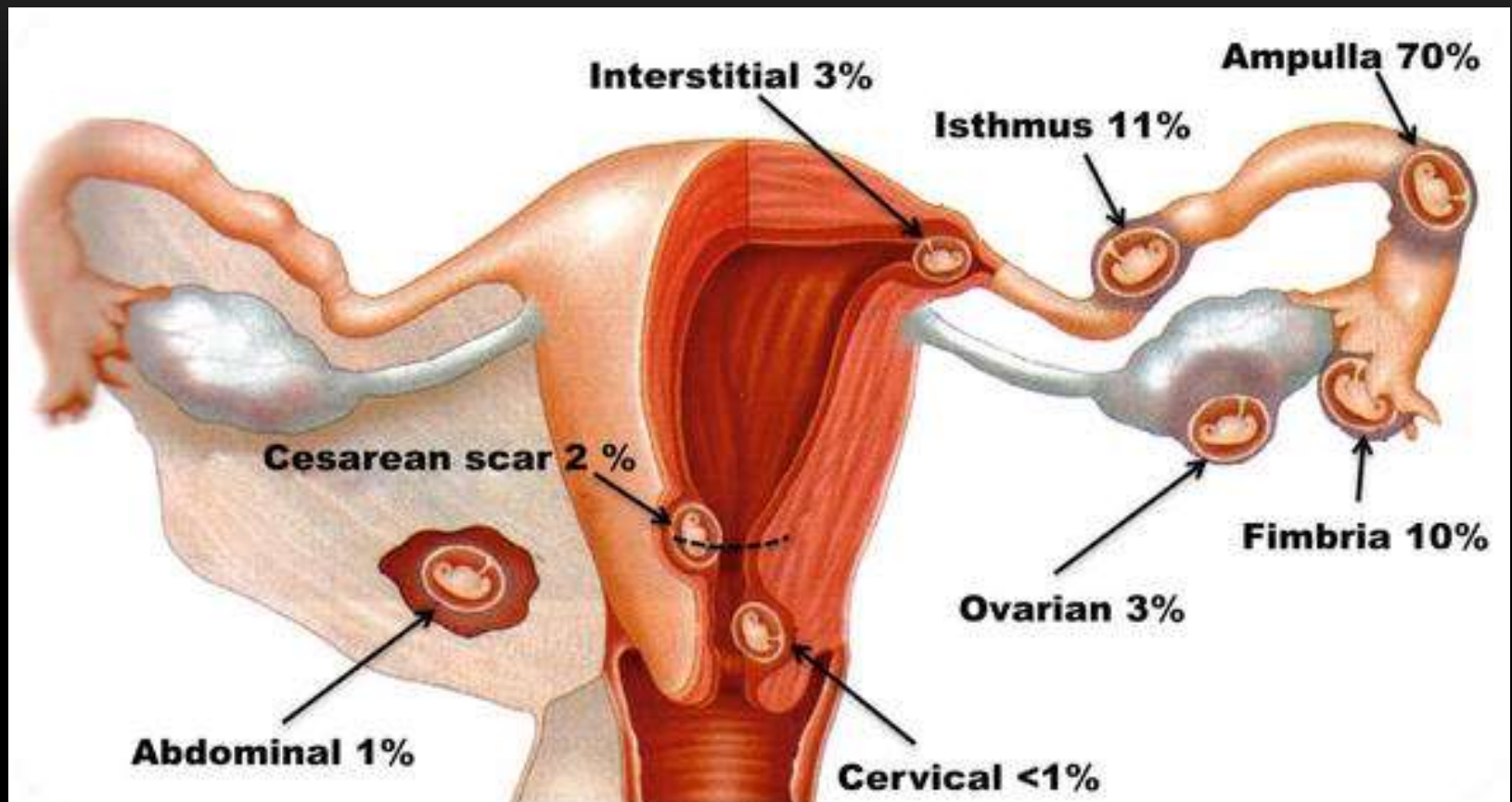
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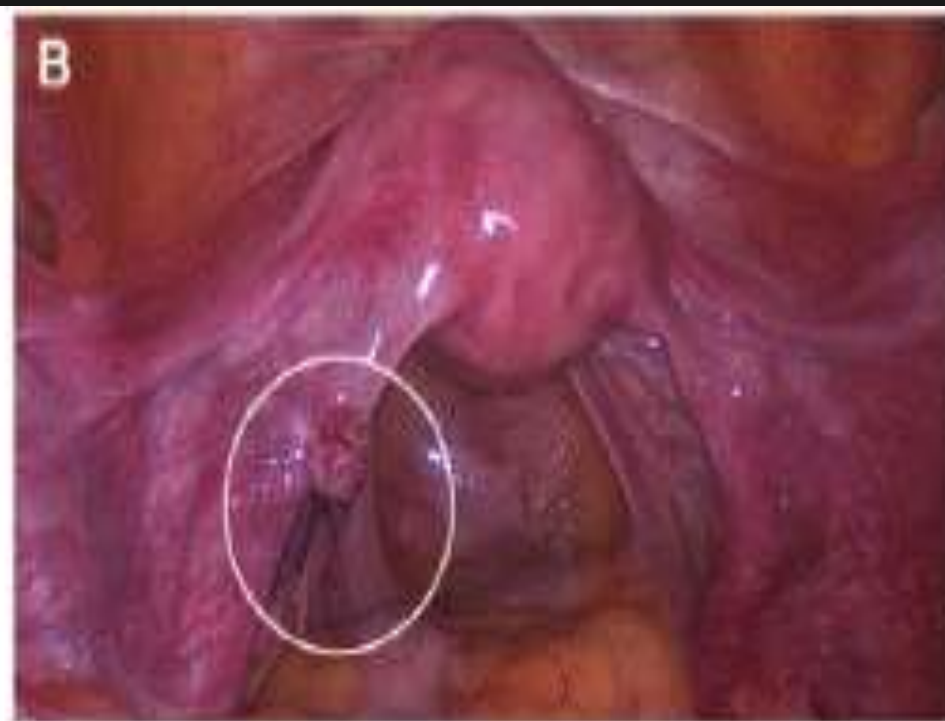
DEFINITION

- Ectopic pregnancy is a pregnancy in which the developing blastocyst becomes implanted at a site other than the endometrium of the uterine cavity.

Normal female reproductive anatomy







Six week ectopic pregnancy



EPIDEMIOLOGY

- The reported incidence of ectopic pregnancy has varied across time and patient populations. Estimated rate of 15-20 per 1000 pregnancies.(2%)
- Ectopic pregnancy mortality ratio is 0.48 deaths per 100,000 live births in developed countries, and higher ratio in developing countries.

ANATOMIC SITES

The great majority of ectopic pregnancies occur in **the fallopian tube (96 percent)**.

- Ampullary (70 percent)
- Isthmic (12 percent)
- Fimbrial (11.1 percent)
- Ovarian (3.2 percent),
- Interstitial or cornual pregnancy (2.4 percent)
- Abdominal (1.3 percent)
- Cervical
- Rare types
- Rudimentary uterine horn pregnancy
- Hysterotomy scar pregnancy
- Heterotopic pregnancy (both intrauterine and ectopic pregnancy)

PATHOLOGY

- Tubal pregnancy — Several factors may be involved in the pathogenesis of tubal pregnancies, but they are generally believed to be the result of (1) conditions that delay or prevent passage of the fertilized oocyte into the uterine cavity or (2) factors inherent in the embryo that result in premature implantation.
- Tubal pathology, particularly chronic salpingitis, is observed in up to 90 percent of surgical specimens of tubal pregnancies. The histologic features of chronic salpingitis are infiltration of the tubal wall by plasma cells and lymphocytes.
- Serum or extracellular factors – A number of factors (eg, lectin, integrin, matrix-degrading cumulus, prostaglandins, growth factors, cytokines, and modulator proteins) may cause premature implantation in the tube.

RISK FACTORS

The major cause of ectopic pregnancy is **disruption of normal tubal anatomy** from factors such as infection, surgery, congenital anomalies, or tumors. Anatomic distortion can be accompanied by functional impairment due to damaged ciliary activity.

1) Previous ectopic pregnancy, especially if history of salpingostomy. The risk of repeat ectopic pregnancy in patients with a prior ectopic gestation is approximately three- to eightfold higher compared with other pregnant patients

2) Pelvic inflammatory disease and other genital infections — Pelvic infection (eg, nonspecific salpingitis, chlamydia, gonorrhea), especially recurrent infection, is a major cause of tubal pathology and, therefore, increases the risk of ectopic pregnancy. Pelvic infection may alter tubal function and may also cause tubal obstruction and pelvic adhesive disease. Patients with a history of PID have an approximately threefold increased risk of ectopic pregnancy.

3) Previous pelvic surgeries.

- 4) Infertility — The incidence of ectopic pregnancy is approximately two- to threefold higher in patients with infertility, although this could reflect the increased incidence of tubal abnormality in this group of patients, which may also be an etiology of infertility.
- 5) In vitro fertilization — IVF has been associated with an increased risk of tubal ectopic pregnancy. Especially if day-three embryo transfer compared to day-five embryo transfer, and with higher risk with a fresh embryo transfer cycles compared to frozen embryo transfer cycles.
- 6) Other assisted reproduction methods — Several reports have also suggested an association between fertility drugs and ectopic pregnancy, which may be related to altered tubal function secondary to hormonal fluctuation.
- 7) Contraceptive methods — Patients using hormonal contraception or an intrauterine device (IUD) are at very low risk of conceiving any pregnancy, either intrauterine or ectopic. However, if they conceive, the probability of an ectopic pregnancy is generally higher than in those not using contraception. Among IUD users with contraceptive failure, the risk of ectopic pregnancy is high (1 in 2 pregnancies for the LNG IUD and 1 in 16 pregnancies for the copper IUD versus 1 in 50 pregnancies among noncontraceptors).
- Estrogen/progestin contraceptives — Similarly, estrogen/progestin oral contraceptives are highly effective and the overall risk of ectopic pregnancy is low, since conception is prevented. However, in patients who do become pregnant while on these contraceptives, the risk of ectopic pregnancy appears to be increased two- to fivefold compared with other pregnant patients.

8) Smoking — Cigarette smoking in the periconceptional period is associated with an increased risk of ectopic pregnancy. A history of smoking is associated with a two- to threefold increase in ectopic pregnancy risk and current use is associated with a two- to fourfold risk; the risk may be dose-dependent. A possible explanation for this finding may be impaired tubal motility in smokers or impaired immunity, thus predisposing them to pelvic inflammatory disease.

9) In utero DES exposure — Patients with a history of in utero diethylstilbestrol (DES) exposure have a fourfold increased risk of ectopic pregnancy due to abnormal tubal morphology and, possibly, impaired fimbrial function. There was a 3.7-fold increase in risk associated with DES exposure compared with no exposure.

10) Vaginal douching — Regular vaginal douching is associated with an up to threefold increased risk of ectopic pregnancy.

11) Increasing age — There is an increasing proportion of ectopic pregnancies among patients in the older age groups. This high incidence in older patients may be a reflection of cumulative risk factors over time.

12) Endometriosis

Other — Other factors, such as blood pressure, body mass index, low density lipoprotein cholesterol, and alcohol consumption do not appear to be associated with an increased risk of ectopic pregnancy.

CLINICAL MANIFESTATIONS

The most common clinical presentation of ectopic pregnancy is **first trimester vaginal bleeding and/or abdominal pain**, typically appear six to eight weeks after the last normal menstrual period (**amenorrhea**) but may occur later, especially if the ectopic pregnancy is at a non tubal site.

- Ectopic pregnancy may also be asymptomatic.
- Ectopic pregnancy may be unruptured or ruptured at the time of presentation to medical care. Tubal rupture can result in life threatening intraabdominal hemorrhage, present with severe or persistent abdominal pain or symptoms suggestive of ongoing blood loss(feeling faint or loss of consciousness).
- Normal early pregnancy symptoms (e.g breast tenderness, frequent urination, nausea) are sometimes present and may be absent because hormones levels (estradiol, progesterone, hCG) may be lower than in normal pregnancy.

The vaginal bleeding in patient with tubal ectopic pregnancy---

- There is no bleeding pattern or volume that is pathognomonic for ectopic pregnancy. Bleeding may range from scant brown staining to hemorrhage.
- The vaginal bleeding is usually intermittent but may occur as a single episode or continuously.
- The vaginal bleeding is typically preceded by amenorrhea. However, some patients may misinterpret bleeding as normal menses and may not realize they are pregnant prior to developing symptoms associated with ectopic pregnancy. This is particularly true in patients who have irregular menses or who do not keep track of menstrual cycles.
- The presumptive source of such bleeding is sloughing of the decidualized endometrium rather than bleeding from the tube itself.

The abdominal pain in patient with tubal ectopic pregnancy ---

- The timing, character and severity of abdominal pain vary, and there is no pain pattern that is pathognomonic for ectopic pregnancy.
- Usually located in the pelvis and may be diffuse or localized to one side, mild or severe, continuous or intermittent, dull or sharp.
- Tubal rupture may be associated with an abrupt onset of severe pain (acute abdomen+surgical abdomen). Referred pain may be felt in the shoulder. Blood pooling in pouch of douglas may cause an urge to defecate.

- **Physical examination**

-Is often unremarkable or may reveal adnexal, cervical motion, and/or abdominal tenderness, an adnexal mass, and mild uterine enlargement.

-If ruptured ectopic pregnancy: hemodynamic unstable (feeling faint, hypotension, tachycardia....shock), surgical abdomen (distended, diffused or localized tenderness)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of bleeding with or without pain early in pregnancy includes :

- Ectopic pregnancy
- Physiologic (eg, implantation bleeding)
- Spontaneous abortion (miscarriage)
- Cervical, vaginal, or uterine pathology (eg, cervical polyp)
- Subchorionic hematoma (threatened miscarriage)
- Gestational trophoblastic disease (human chorionic gonadotropin concentration is unusually high for the gestational age)

INVESTIGATIONS

- 1) Transvaginal ultrasound (TVUS)
- 2) Serum human chorionic gonadotropin (hCG)

Other (laparoscopy, serum progesterone level, endometrial curettage, MRI)

Transvaginal Ultrasound (TVUS)

Is the most useful imaging test for determining the location of a pregnancy. TVUS should be performed at the time of presentation of a suspected ectopic pregnancy and may need to be repeated, depending on the findings and the hCG level.

- Diagnose an IUP (intrauterine pregnancy): Findings diagnostic of an IUP include a gestational sac with a yolk sac or embryo (with or without a heartbeat) in the uterus.
- Diagnose an ectopic pregnancy: The most specific signs of an ectopic pregnancy include a gestational sac with a yolk sac or embryo (with or without a heartbeat) outside of the uterus. With empty uterus.
- Detect findings that are suggestive, but not diagnostic, of ectopic pregnancy: A complex inhomogenous extraovarian adnexal mass. This is the most common ultrasound finding in ectopic pregnancy and is present in 89 percent or more of cases.
- Detect findings suggestive of ectopic rupture: A finding of fluid with debris (consistent with blood) in the pelvic cul-de-sac and/or abdomen may be consistent with rupture of an ectopic pregnancy. Blood clot may also surround the uterus and adnexa on the side of the patient's pain.

If TVUS is nondiagnostic, it may be because the gestation is too early to be visualized on ultrasound. If so, the patient has a pregnancy of unknown location. For follow up by serum hCG level every 2 days and repeat TVUS.

Human chorionic gonadotropin

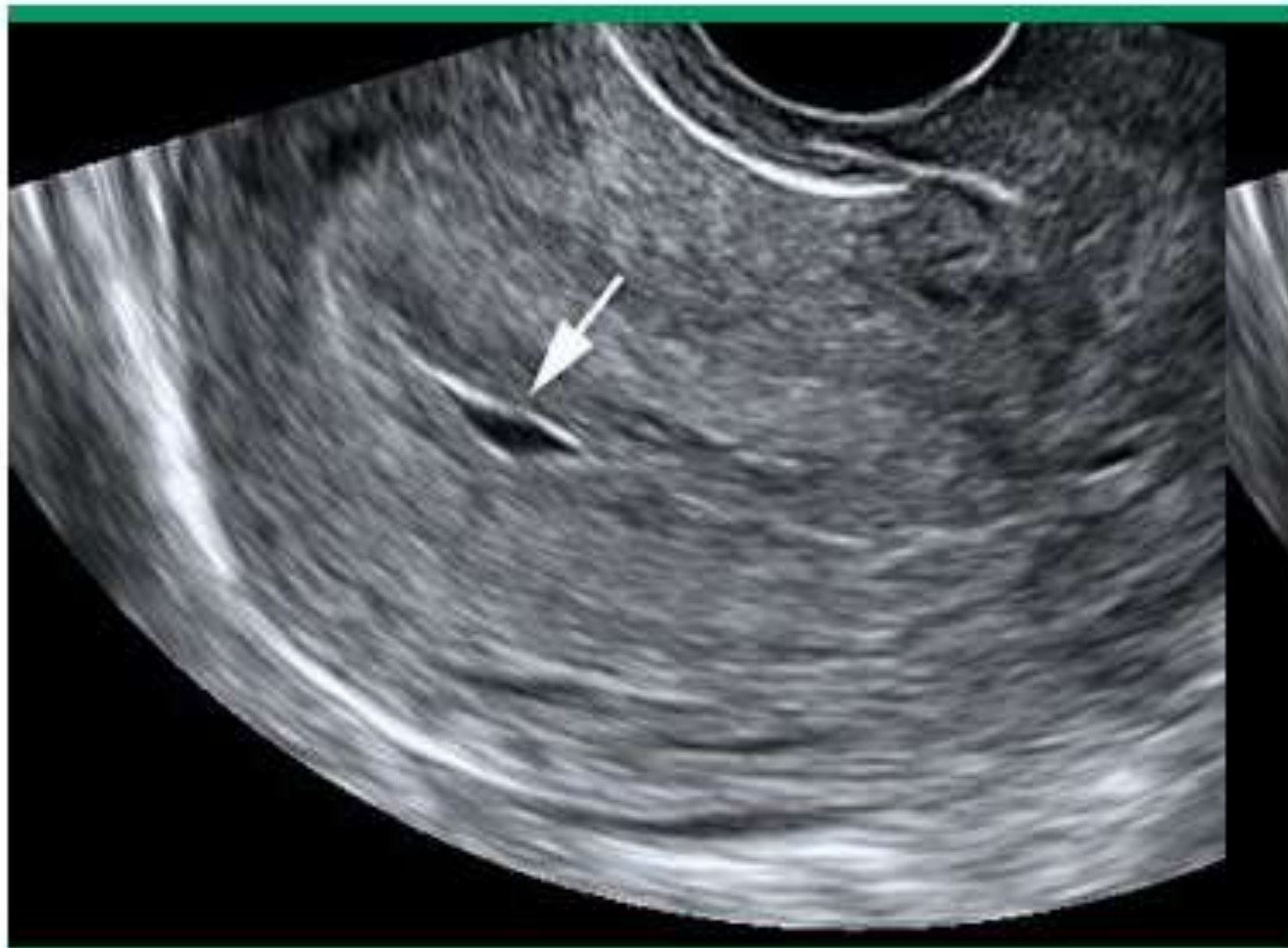
- Serum, rather than urine, hCG is the preferred test for a pregnant patient with pain and/or bleeding. It is not possible to determine whether a pregnancy is normal from a single hCG level because there is a wide range of normal levels at each week of pregnancy.
- In pregnant patients, hCG can be detected in serum as early as six days after the luteinizing hormone surge (approximately 21 to 22 days after the first day of the last menstrual period in patients with 28-day cycles).The hCG concentration in a normal IUP rises in a curvilinear fashion until approximately 41 days of gestation, after which it rises more slowly until approximately 10 weeks, and then declines until reaching a plateau in the second and third trimesters.
- hCG discriminatory zone — The discriminatory zone is the serum hCG level above which a gestational sac should be visualized when an IUP is present. For TVUS, discriminatory zone vary by laboratory and institution, and some institutions set the discriminatory zone at 2000 mIU/MI [[1500 mIU/mL (80 percent had a gestational sac visualized), 2000 mIU/mL (91 percent), and 3510 mIU/mL (99 percent)]].
- In ectopic pregnancy there is abnormal rising or plateauing of serum hCG. we generally define an abnormal rise as <50 percent over two days

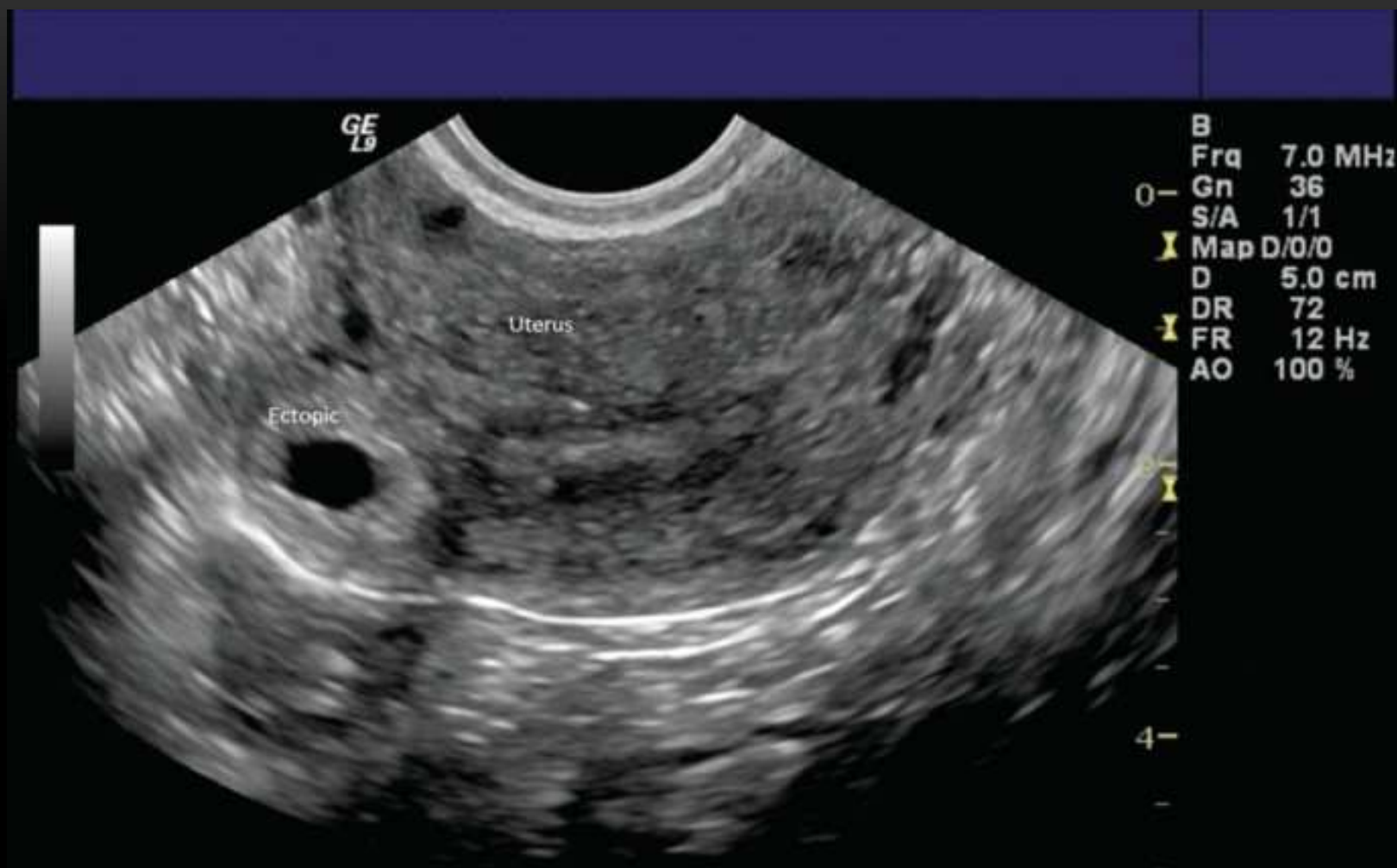
Double decidual sign



Transvaginal image demonstrating the double decidual sac sign in the endometrium.
G: gestational sac.

Endometrial pseudosac





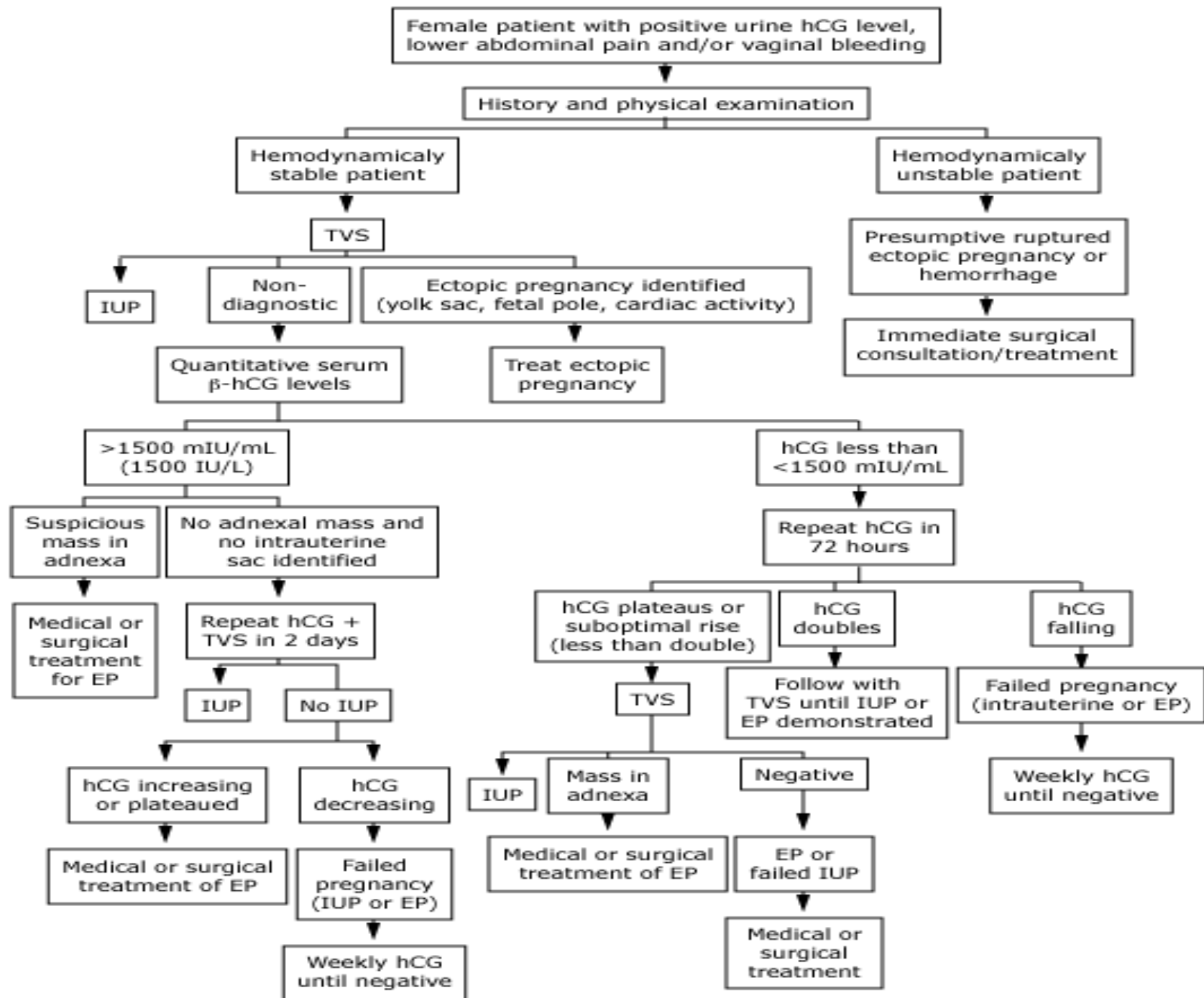
Definitive Intrauterine Pregnancy
Yolk Sac Inside Gestational Sac



Yolk Sac Seen at 5.0-5.5 Weeks on TVS
1 Week Later on TAS

Progesterone

-Serum progesterone concentrations are higher in viable intrauterine pregnancies than in ectopic pregnancies and intrauterine pregnancies that are destined to abort.



MANAGEMENT

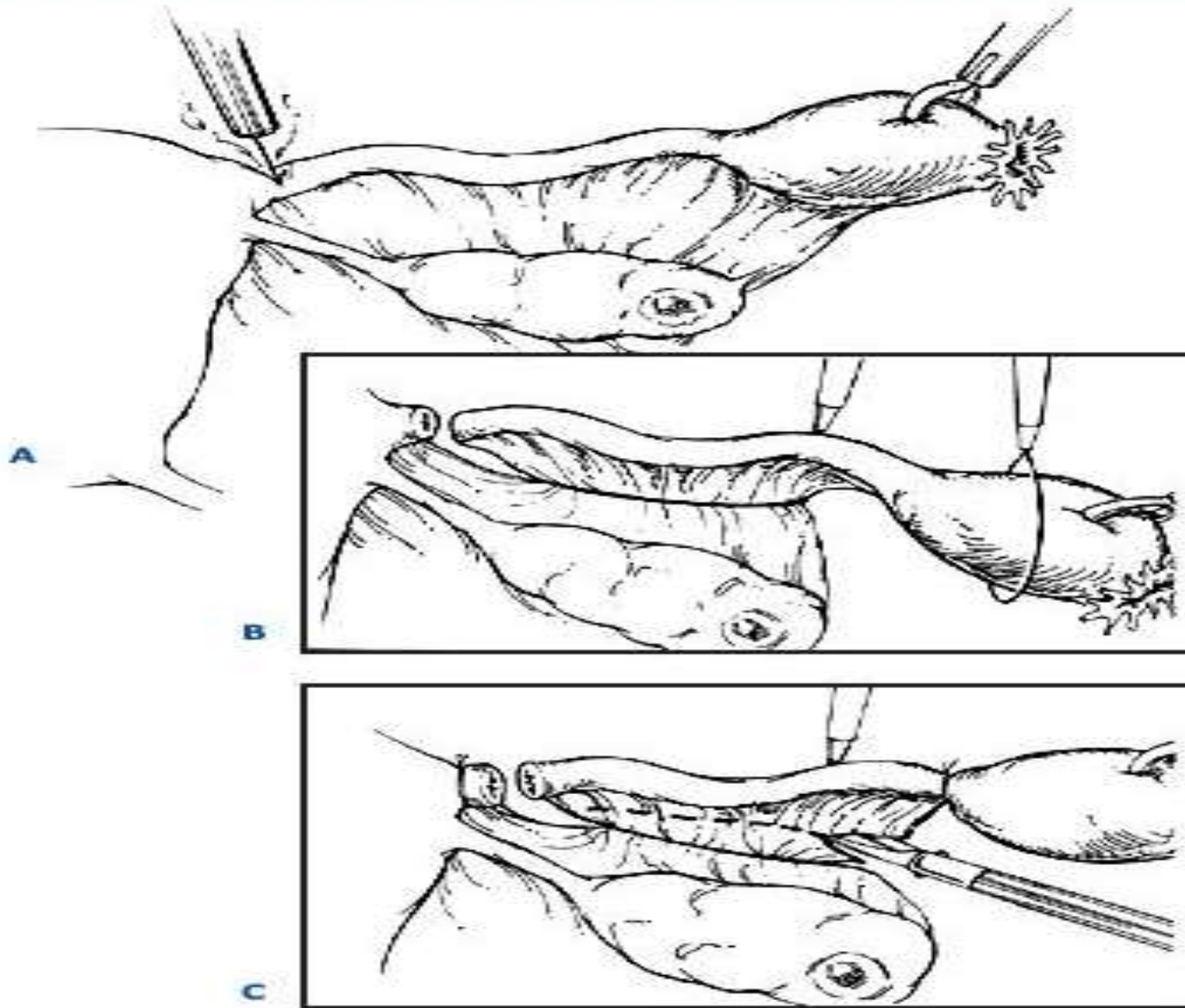
- Surgical
- Medical
- Expectant

- **INDICATIONS FOR SURGICAL TREATMENT**

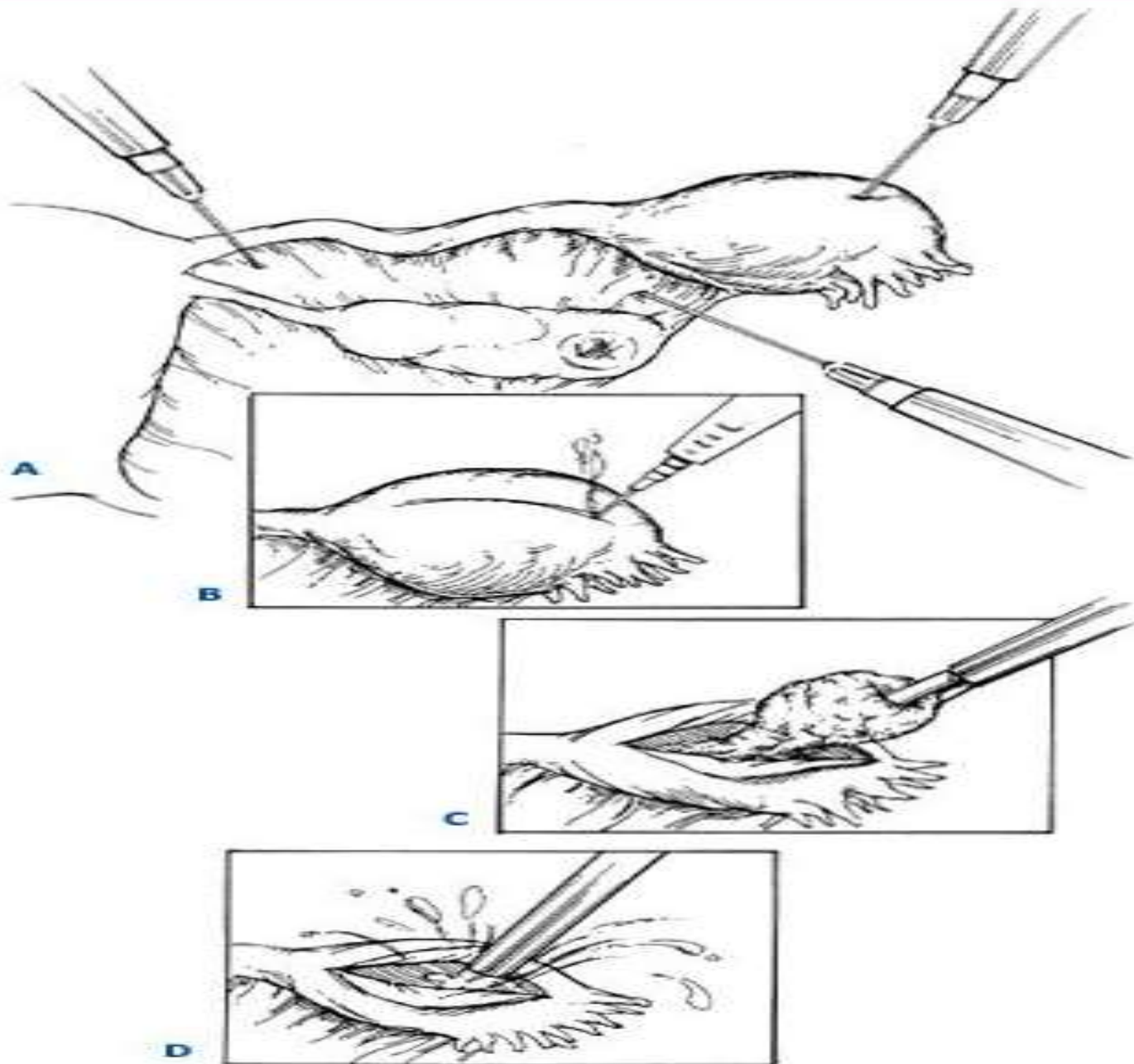
- Hemodynamic instability
- Impending or ongoing rupture of ectopic mass
- Contraindications to methotrexate
- Coexisting intrauterine pregnancy
- Not able or willing to comply with medical therapy post-treatment follow-up
- Lack of timely access to a medical institution for management of tubal rupture
- Desire for permanent contraception
- Known tubal disease with planned in vitro fertilization for future pregnancy (only in patients who are otherwise good candidates for surgical therapy)
- Failed medical therapy

- A laparoscopic surgical approach is preferable to an open approach.
- In the presence of a healthy contralateral tube, salpingectomy should be performed in preference to salpingostomy.
- In women with a history of fertility-reducing factors (previous ectopic pregnancy, contralateral tubal damage, previous abdominal surgery, previous pelvic inflammatory disease), salpingostomy should be considered.
- If a salpingostomy is performed, women should be informed about the risk of persistent trophoblast with the need for serum B-hCG level follow-up. They should also be counselled that there is a small risk that they may need further treatment in the form of systemic methotrexate or salpingectomy.

Technique of laparoscopic total salpingectomy



Linear salpingostomy



MEDICAL TREATMENT

- Methotrexate (MTX) is a folic acid antagonist widely used for treatment of neoplasia, severe psoriasis, and rheumatoid arthritis. It inhibits deoxynucleic acid (DNA) synthesis and cell reproduction, primarily in actively proliferating cells such as malignant cells, trophoblasts, and fetal cells. MTX is rapidly cleared by the kidneys.
- The dose of MTX used to treat ectopic pregnancy (50 mg/m^2 or 1 mg/kg)
- MTX can be given systemically (ie, intravenously, intramuscularly [IM], or orally) or by direct local injection into the ectopic pregnancy sac with either a transvaginal or transabdominal (eg, laparoscopic) approach. **IM administration is the most common route for treatment of tubal pregnancy.** Local injection is used in some cases of rare ectopic gestation locations (eg, cervical ectopic pregnancy).
- With early diagnosis, most patients with ectopic pregnancy may be treated medically with MTX.

- MTX is the preferred treatment option when all of the following characteristics are present:

- 1) Hemodynamic stability.
- 2) Serum beta-human chorionic gonadotropin (hCG) concentration ≤ 5000 U/L.
- 3) No fetal cardiac activity detected on transvaginal ultrasound (TVUS). Ectopic mass size less than 3 to 4 cm.
- 4) Patients are willing and able to comply with post-treatment follow-up and have access to emergency medical services within a reasonable time frame in case of a ruptured fallopian tube.

- MTX is contraindicated and surgery is required when the following are present:

- 1) Hemodynamic instability.
- 2) Intrauterine pregnancy, including a heterotopic pregnancy with coexisting viable intrauterine pregnancy.
- 3) Signs or symptoms of impending or ongoing rupture of ectopic mass (eg, pelvic or abdominal pain or evidence of intraperitoneal bleeding suggestive of rupture).
- 4) Clinically important abnormalities in baseline hematologic, kidney, or hepatic laboratory values.
- 5) Medical conditions such as immunodeficiency, active pulmonary disease (eg, tuberculosis), and peptic ulcer disease.
- 6) Hypersensitivity to MTX.
- 7) Breastfeeding.

EXPECTANT MANAGEMENT

- **CANDIDATES FOR EXPECTANT MANAGEMENT**

- Transvaginal ultrasound (TVUS) does not show a gestational sac or demonstrate an extrauterine mass suspicious for an ectopic pregnancy and
- The beta-human chorionic gonadotropin (hCG) concentration is low (≤ 200 mIU/mL) and declining.