

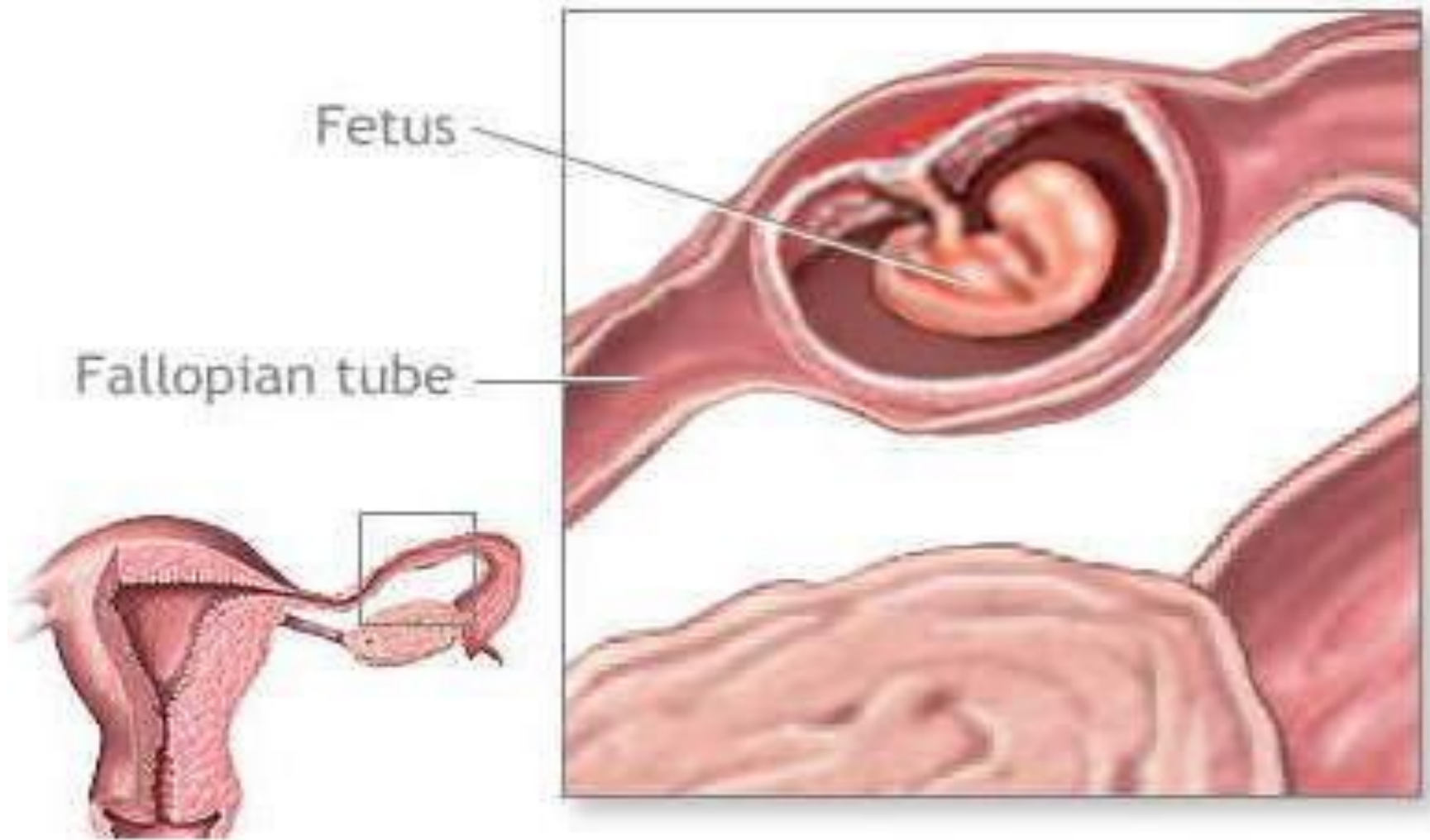
Ectopic Pregnancy

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Definition

- The implantation of the blastocyst (fertilized ovum) outside the endometrial lining of the uterine cavity

Blastocyst implanted in the fallopian tube



Etiology

- These are factors that lead to tubal damage or dysfunction and thus prevent, retard or delay passage of the fertilized ovum into the uterine cavity.
- May be due to:
 - Mechanical factors
 - Functional factors
 - Assisted reproduction
 - Failed contraception

Etiology

- Mechanical Factors
 1. Previous ectopic pregnancy
 2. Previous salpingitis
 - Agglutination of the mucosal aborescent folds with luminal narrowing or formation of blind pockets
 - Reduced ciliation
 3. Prior PID especially by Chlamydia trachomatis – **most common risk factor**
 4. Peritubal adhesions
 - Cause tubal kinking and narrowing of the lumen
 5. In utero exposure to DES
 - Developmental tubal abnormalities (diverticula, accessory ostia and hypoplasia)
 6. Previous CS delivery

Etiology

- Functional Factors
 1. OCP
 2. IUD
 3. Luteal phase defects
 4. Cigarette smoking
 5. Vaginal douching

Etiology

- Assisted Reproduction
 1. GIFT
 2. IVF
 3. Atypical implantations are more common (corneal, extratubal, abdominal, cervical and heterotypic)

Etiology

- Failed Contraception
 1. Tubal sterilization – ectopic pregnancy rate increased 9-fold
 2. Following laparoscopic fulguration – highest rate of ectopic pregnancy
 3. Following hysterectomy – sperm migrated from a fistulous communication in the vaginal vault

Risk Factors

	Factor	Risk
HIGH RISK	Tubal Corrective Surgery	21.0
	Tual Sterilization	9.3
	Previous Ectopic Pregnancy	8.3
	In Utero DES Exposure	5.6
	Intrauterine Device	4.2-45
	Documented Tubal Pathology	3.8-21
MODERATE RISK	Infertility	2.5-21
	Previous Genital Infection	2.5-3.7
	Multiple Partners	2.1
SLIGHT RISK	Previous Pelvic/Abdominal Surgery	0.93-3.8
	Smoking	2.3-2.5
	Douching	1.1-3.1
	Intercourse before 18 years of age	1.6

Risk Factors

- After one previous ectopic pregnancy, the chance of another is **7-15%**.
- An increased relative incidence of ectopic pregnancy has been reported with use of **progestin-only oral contraceptives, postovulatory high-dose estrogens to prevent pregnancy, and following ovulation induction**

Epidemiology

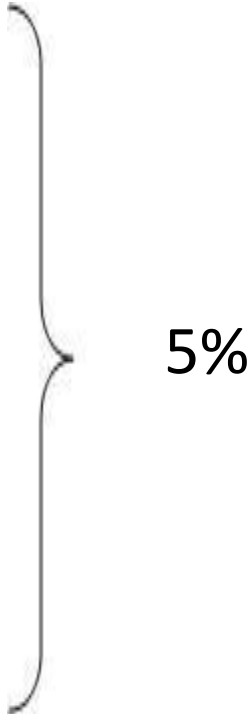
- There has been a marked increase in the number and rate of ectopic pregnancy in the past two decades.
- Increasing ectopic pregnancy rates due to:
 1. Prevalence of sexually transmitted tubal infection and damage
 2. Ascertainment through earlier diagnosis of some ectopic pregnancies otherwise defined to resorb spontaneously
 3. Popularity of contraception that predisposes failures to be ectopic

Epidemiology

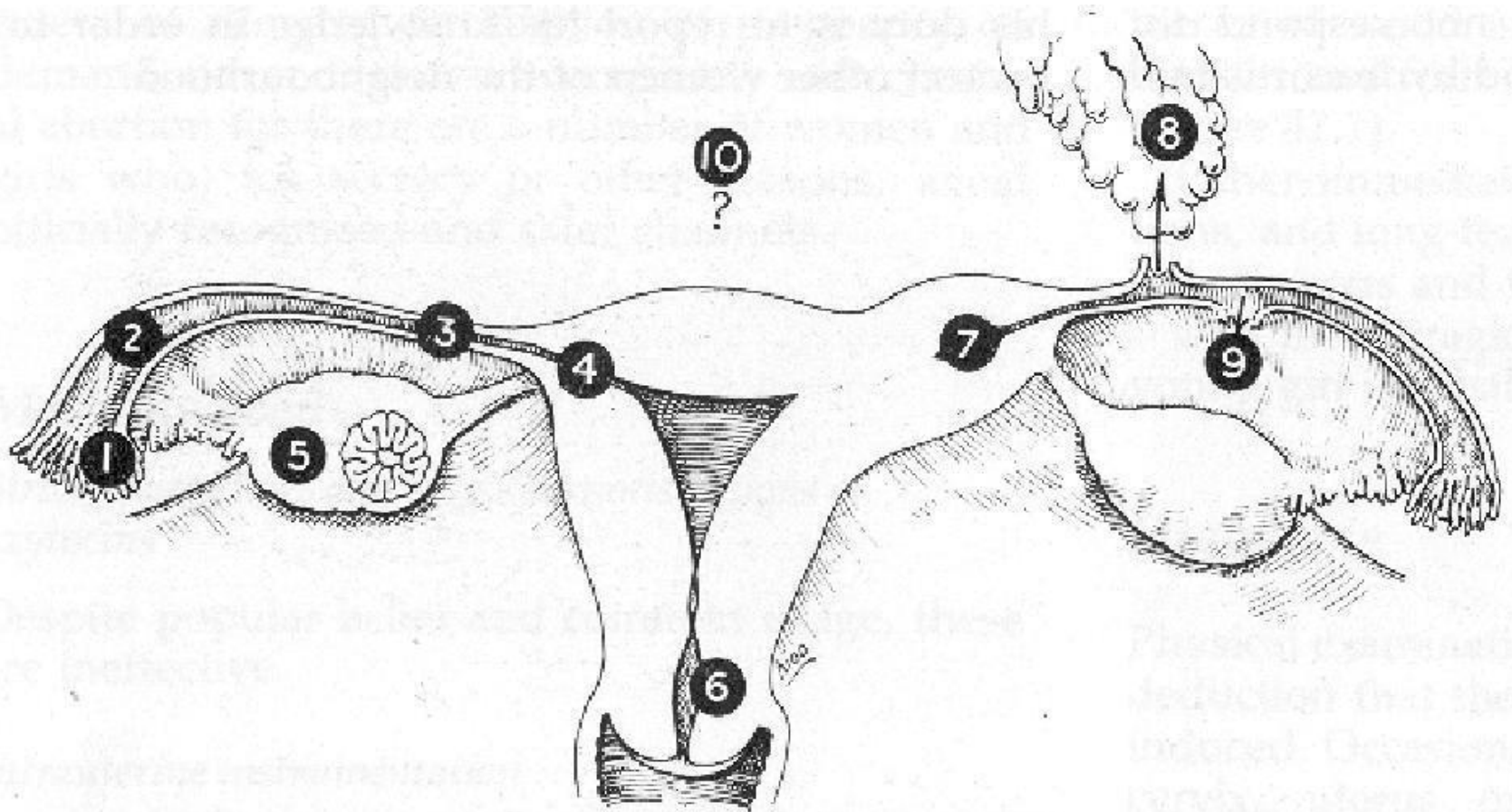
- Increasing ectopic pregnancy rates due to:
 4. Use of tubal sterilization techniques that increase the likelihood of ectopic pregnancy
 5. Use of assisted reproductive techniques
 6. Use of tubal surgery, including salpingotomy for tubal pregnancy and tuboplasty for infertility

Pathogenesis

- Sites of Implantation

- Fallopian tube – **most common** site (ampulla) – 95%
 - Ovary
 - Uterine cornu
 - Cervix
 - Broad ligament
 - Spleen
 - Liver
 - Retroperitoneum
 - Diaphragm
 - Cesarean scar
- 

Pathogenesis



Uterine Changes in Ectopic Pregnancy

- The uterus undergoes some of the changes associated with early normal pregnancy, including increase in size and softening of the cervix and isthmus.
- Lack of uterine changes does not exclude an ectopic pregnancy.
- The finding of uterine decidua without trophoblast suggests ectopic pregnancy but is not absolute.
- *Arias-Stella reaction*
 - Endometrial changes characterized by hypertrophic, hyperchromatic, lobular and irregularly shaped nuclei, and vacuolated, foamy cytoplasm with occasional mitoses
 - Not specific for ectopic and may occur with normal implantation
- External bleeding – from degeneration and sloughing of uterine deciduas

Outcome of Ectopic Pregnancy

- Tubal Pregnancy
 - The fertilized ovum may lodge in any portion of the oviduct
- Tubal Abortion
 - The frequency of tubal abortion depends in part on the implantation site (common in *ampullary*).
 - If placental separation is complete, all of the products of conception may be extruded through the fimbriated end into the peritoneal cavity.

Outcome of Ectopic Pregnancy

- Tubal Rupture
 - in first few weeks = isthmus
 - up to 16 weeks = interstitial
 - may be spontaneous or caused by trauma associated with coitus or bimanual examination
 - If an early conceptus is expelled into the peritoneal cavity it may be resorbed, or if larger, may remain in the cul-de-sac for years as an encapsulated mass or even become calcified to form a *lithopedion*

Outcome of Ectopic Pregnancy

- Heterotypic ectopic pregnancy – Tubal pregnancy accompanied by a coexisting uterine gestation. One should consider
 - After assisted reproductive techniques
 - With persistent or rising chorionic gonadotropin levels after dilatation and curettage for an induced or spontaneous abortion
 - When the uterine fundus is larger than menstrual dates
 - With more than one corpus luteum
 - With absence of vaginal bleeding in the presence of signs and symptoms of an ectopic pregnancy
 - When there is ultrasonographic evidence of uterine and extrauterine pregnancy

CLINICAL FEATURES OF ECTOPIC PREGNANCY

Signs & Symptoms

- Often **subtle**, or even **absent**

1. *Pain*

- Pelvic and abdominal pain – sharp, stabbing or tearing in character
- Pleuritic chest pain – from diaphragmatic irritation caused by the hemorrhage

2. *Abnormal Menstruation*

- Amenorrhea
- Vaginal bleeding – may be scanty, dark brown, intermittent or continuous

3. *Abdominal and pelvic Tenderness*

- Tenderness on abdominal and vaginal examination especially on motion of the cervix – ruptured or rupturing tubal pregnancies

Signs & Symptoms

4. *Uterine changes*

- In 25% of women, the uterus enlarges due to hormonal stimulation of pregnancy.

5. *Blood pressure and pulse*

- Before rupture vital signs are generally normal.
- Hypotension and tachycardia – if bleeding continues and hypovolemia becomes significant

6. *Pelvic Mass*

- Almost always either posterior or lateral to the uterus, and typically soft and elastic
- The mass may be firm with extensive infiltration of blood into the tubal wall.

Culdocentesis

- This simple technique is used to identify hemoperitoneum
- The cervix is pulled toward the symphysis with a tenaculum, and a long 16- or 18-gauge needle is inserted through the posterior fornix into the cul-de-sac
- Fluid containing fragments of old clots, or bloody fluid that does not clot, is compatible with the diagnosis of hemoperitoneum resulting from an ectopic pregnancy

Laboratory Tests

1. Hemogram

- After hemorrhage, depleted blood volume is restored toward normal by hemodilution over the course of a day or longer.
- In about half of women with ruptured ectopic pregnancies, varying degrees of leukocytosis up to 30,000/ μ L may be documented.

2. Chorionic Gonadotropin Assays

- Current serum and urine pregnancy tests that use enzyme-linked immunosorbent assays (ELISAs) are sensitive to levels of 10 to 20 mIU/mL, and are positive in over 99% of ectopic pregnancies

3. Serum Progesterone Levels

- A value exceeding 25ng/mL excludes ectopic pregnancy.
- Values below 5ng/mL suggest either an intrauterine pregnancy with a dead fetus or an ectopic pregnancy.

Ultrasound Imaging

- Abdominal Sonography
 - Identification of pregnancy products in the fallopian tube is difficult using abdominal sonography
 - A uterine pregnancy usually is not recognized using abdominal ultrasound until 5 to 6 menstrual weeks or 28 days after timed ovulation

Ultrasound Imaging

- Vaginal Sonography
 - Allows ultrasonic detection of a uterine gestation as early as 1 week after missed menses
 - Used to detect adnexal masses
 - An ectopic pregnancy may be missed, when a tubal mass is small or obscured by bowel
 - The reported sensitivity of vaginal sonography for the diagnosis of ectopic pregnancy ranges widely (20-80%)

DIAGNOSIS OF ECTOPIC PREGNANCY

Multi-Modality Diagnosis

1. Vaginal sonography
 - If the uterus is empty, an ectopic pregnancy can be diagnosed based on visualization of an adnexal mass separate from the ovaries
2. Serum β -hCG – both the initial level and the pattern of subsequent rise or decline
 - An **empty uterus** with a serum β -hCG concentration of **1500 mIU/mL** (*discriminatory level*) or higher is 100% accurate in excluding a live intrauterine pregnancy (dead fetus vs ectopic pregnancy).
 - Mean doubling time for β -hCG in serum is approximately 48 hours, and the lowest normal value for this increase is 66%.
 - Failure to maintain this rate of increased β -hCG production along with an empty uterus is suggestive for an ectopic pregnancy.

Multi-Modality Diagnosis

3. Serum progesterone

- Serum levels of at least **25ng/mL** after spontaneous conception provide reassurance that an ectopic pregnancy is *unlikely*.

4. Uterine curettage

- Used to differentiate between incomplete abortion and ectopic pregnancy

Multi-Modality Diagnosis

5. Laparoscopy and, less frequently, laparotomy

– Laparoscopy

- Offers a reliable diagnosis in most cases of suspected ectopic pregnancy, and a ready transition to definitive operative therapy
- More cost-effective and shorter postoperative recovery

– Laparotomy

- Preferred when the woman is hemodynamically unstable, or when laparoscopy is not feasible

Multi-Modality Diagnosis

- The choice of diagnostic algorithm applies only to hemodynamically stable women; those with presumed rupture should undergo prompt surgical therapy

TREATMENT & PROGNOSIS

Anti-D Immunoglobulin

- D-negative women with an ectopic pregnancy who are not sensitized to D-antigen should be given anti-D immunoglobulin

Surgical Management: CONSERVATIVE

- Salpingostomy
 - Used to remove a small pregnancy usually $<2\text{ cm}$ in length and located in the *distal third* of the fallopian tube
 - A 10-15 mm linear incision is made on the antimesenteric border immediately over the ectopic pregnancy, and is *left unsutured* to heal by secondary intention
 - Readily performed through a laparoscope
 - **Gold standard** surgical method used for unruptured ectopic pregnancy

Surgical Management: CONSERVATIVE

- Salpingotomy
 - Procedure is the same as salpingostomy except that the incision is closed with a suture
- Surgical Resection & Anastomosis
 - Sometimes used for an unruptured isthmic pregnancy

Surgical Management: RADICAL

- Salpingectomy
 - Tubal resection
 - May be used for both ruptured and unruptured ectopic pregnancies
 - Performed if the fallopian tube is extensively diseased or damaged
 - *Cornual resection* – a wedge of the outer third (or less) of the interstitial portion of the tube is excised to minimize the rare recurrence of pregnancy in the tubal stump

Persistent Trophoblast

- Factors that increase the risk of persistent ectopic pregnancy
 1. Small pregnancies, less than 2 cm
 2. Early therapy, before 42 menstrual days
 3. B-hCG serum levels exceeding 3000mIU/mL
 4. Implantation medial to the salpingostomy site

Medical Management: METHOTREXATE

- An anti-neoplastic drug that acts as a folic acid antagonist, and is highly effective against rapidly proliferating trophoblasts
- Success is greatest if
 - The gestation is <6 weeks
 - The tubal mass should be <3.5 cm in diameter
 - The fetus is dead
 - B-hCG is <15,000 mIU/mL

Medical Management:

METHOTREXATE

- Contraindications:
 - Intra-abdominal hemorrhage
 - Breast feeding
 - Immunodeficiency
 - Alcoholism
 - Liver or renal disease
 - Blood dyscrasias
 - Active pulmonary disease
 - Peptic ulcer

Methotrexate Therapy for Primary Treatment of Ectopic Pregnancy

Regimen	Follow-up
Single Dose Methotrexate, 50 mg/m ² IM	Measure β -hCG levels days 4 and 7: ➤ If difference is $\geq 15\%$, repeat weekly until undetectable ➤ If difference $< 15\%$, repeat methotrexate dose and begin new day 1 ➤ If fetal cardiac activity present day 7, repeat Methotrexate dose, begin new day 1 ➤ Surgical treatment if β-hCG levels not decreasing or fetal cardiac activity persists after three doses of methotrexate
Variable Dose Methotrexate, 1mg/kg IM, days 1, 3, 5, 7 Leukovorin, 0.1 mg/kg IM, days 2, 4, 6, 8	➤ Continue alternate-day injections until β-hCG levels decrease 15% in 48 hr, or four doses methotrexate given ➤ Then, weekly β-hCG until undetectable

Medical Management: METHOTREXATE

- Monitoring Efficacy of Therapy
 - For single dose therapy repeat serum β -hCG is done at 4 and 7 days
 - For variable dose methotrexate, serum β -hCG concentrations are measured at 48-hour intervals until they fall $> 15\%$
 - After successful treatment, weekly determinations are done until β -hCG is undetectable

Expectant Management

- Criteria:
 1. Decreasing serial β -hCG levels
 2. Tubal pregnancies only
 3. No evidence of intra-abdominal bleeding or rupture as assessed by vaginal sonography
 4. Diameter of the ectopic mass not greater than 3.5 cm

ABDOMINAL PREGNANCY

Pathogenesis

- Almost all cases follow early rupture or abortion of a tubal pregnancy into the peritoneal cavity
- The growing placenta, after penetrating the oviduct wall, maintains its tubal attachment but gradually encroaches upon and implants in the neighboring serosa. Meanwhile, the fetus continues to grow within the peritoneal cavity
- The incidence is increased after gamete intrafallopian transfer, in vitro fertilization, induced abortion, endometriosis, tuberculosis and intrauterine devices

Fetal Outcome

- Fetal malformation and deformations – facial or cranial asymmetry, or both, various joint abnormalities, limb deficiency and CNS anomalies
- If the fetus dies after reaching a size too large to be resorbed, it may undergo
 - Suppuration
 - Mummification/ *Lithopedian* formation
 - Calcification

Diagnosis

- Laboratory tests - An **unexplained increase in the serum alpha-fetoprotein** value sometimes is found
- *Sonographic Criteria suggestive of an abdominal pregnancy*
 1. Visualization of the fetus separate from the uterus
 2. Failure to visualize uterine wall between the fetus and urinary bladder
 3. Close approximation of fetal parts to the maternal abdominal wall
 4. Eccentric position (relation of fetus to uterus) or abnormal fetal attitude (relation of fetal parts to one another) and visualization of extrauterine placental tissue
- MRI – used to confirm abdominal pregnancy following a suspicious sonographic examination
- CT – superior to MRI but its use is limited because of the concern for fetal radiation

Management

- In-hospital expectant management if pregnancy is diagnosed after 24 weeks
- Surgery may precipitate torrential hemorrhage due to the lack of constriction of hypertrophied blood vessels after placental separation
- Adequate blood must be immediately available and techniques for monitoring the adequacy of the circulation should be employed
- The infant should be delivered, and the cord severed close to the placenta

Management

- Leaving the placenta inside the abdominal cavity may cause infection, abscess, adhesion, intestinal obstruction, and wound dehiscence, but it may be less grave than the hemorrhage that sometimes result from placental removal during surgery
- Methotrexate has been recommended to hasten placental involution, however its use is controversial.

OVARIAN PREGNANCY

Spiegelberg Criteria

1. The tube on the affected side must be intact
2. The fetal sac must occupy the position of the ovary
3. The ovary must be connected to the uterus by the ovarian ligament
4. Definite ovarian tissue must be found in the sac wall

Diagnosis

- Findings are likely to mimic those of a tubal pregnancy or a bleeding corpus luteum
- The increased use of vaginal ultrasound has resulted in the more frequent diagnosis of unruptured ovarian pregnancies

Management

- Classical management: Surgical
 - Laparotomy with ovarian wedge resection or cystectomy, ovariectomy
- Methotrexate, for unruptured ovarian pregnancy
- Laparoscopic resection or laser ablation

CERVICAL PREGNANCY

Rubin's Criteria

- Cervical glands Cervical must be present opposite placental attachment
- Attachment of placenta to cervix must be intimate
- The placenta must be below the entrance of the uterine vessels or below the peritoneal reflection on the anteroposterior uterine surfaces
- Fetal elements must not be present in the uterine corpus

Diagnosis

- Cervical pregnancy rarely extends beyond 20 weeks, and is usually surgically terminated because of bleeding
- High degree of clinical suspicion coupled with sonography
 - Sonographic findings of an empty uterus and a gestation filling the cervical canal

Management

- Cerclage
- Curettage and tamponade – suction curettage followed by insertion of foley catheter and vaginal pack
- Uterine artery embolization with gelfoam
- Methotrexate – first line therapy in stable women
- Hysterectomy – if other interventions fail