

Ectopic Pregnancy

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Relevance

- Potential for rupture and acute hemorrhage
- Ruptured ectopic pregnancy is a true medical emergency
 - Leading cause of maternal mortality in 1st trimester
 - (12/10,000 women)
 - Accounts for 10-15% of all maternal deaths

Definition

- Any pregnancy where fertilized ovum implants outside the uterine cavity
 - 95% occur in fallopian tubes
 - 2.5% in cornua of uterus
 - 2.5% in ovary, cervix, abdomen

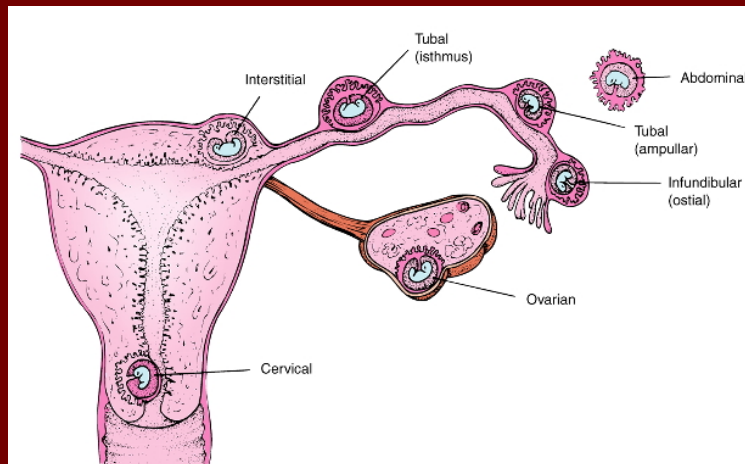
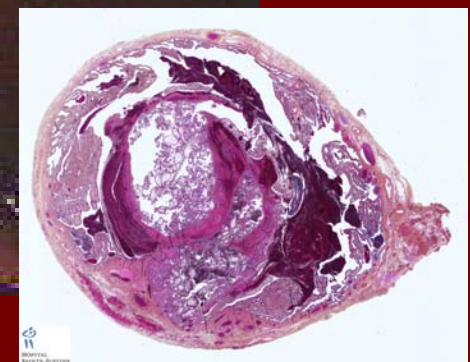
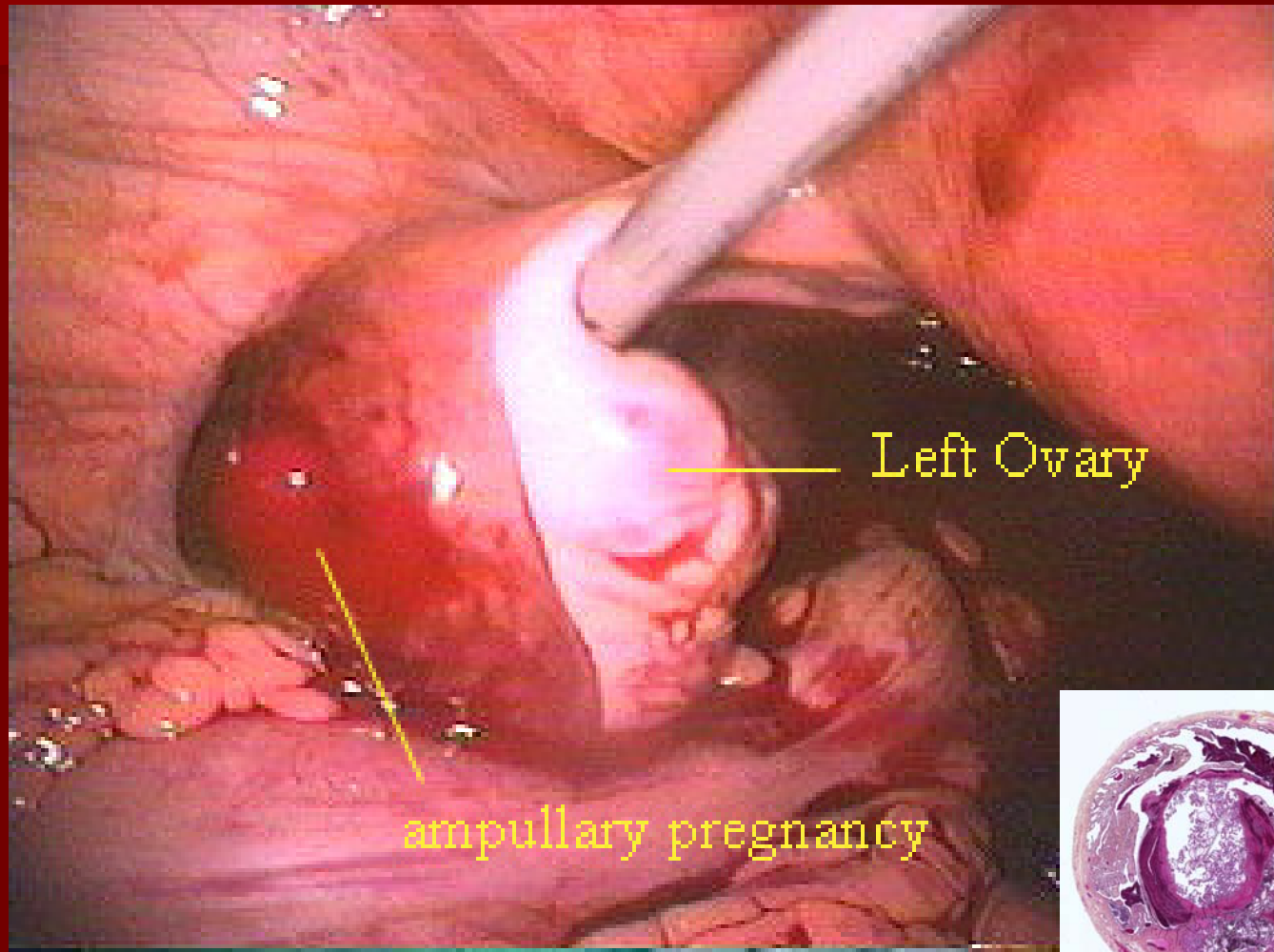


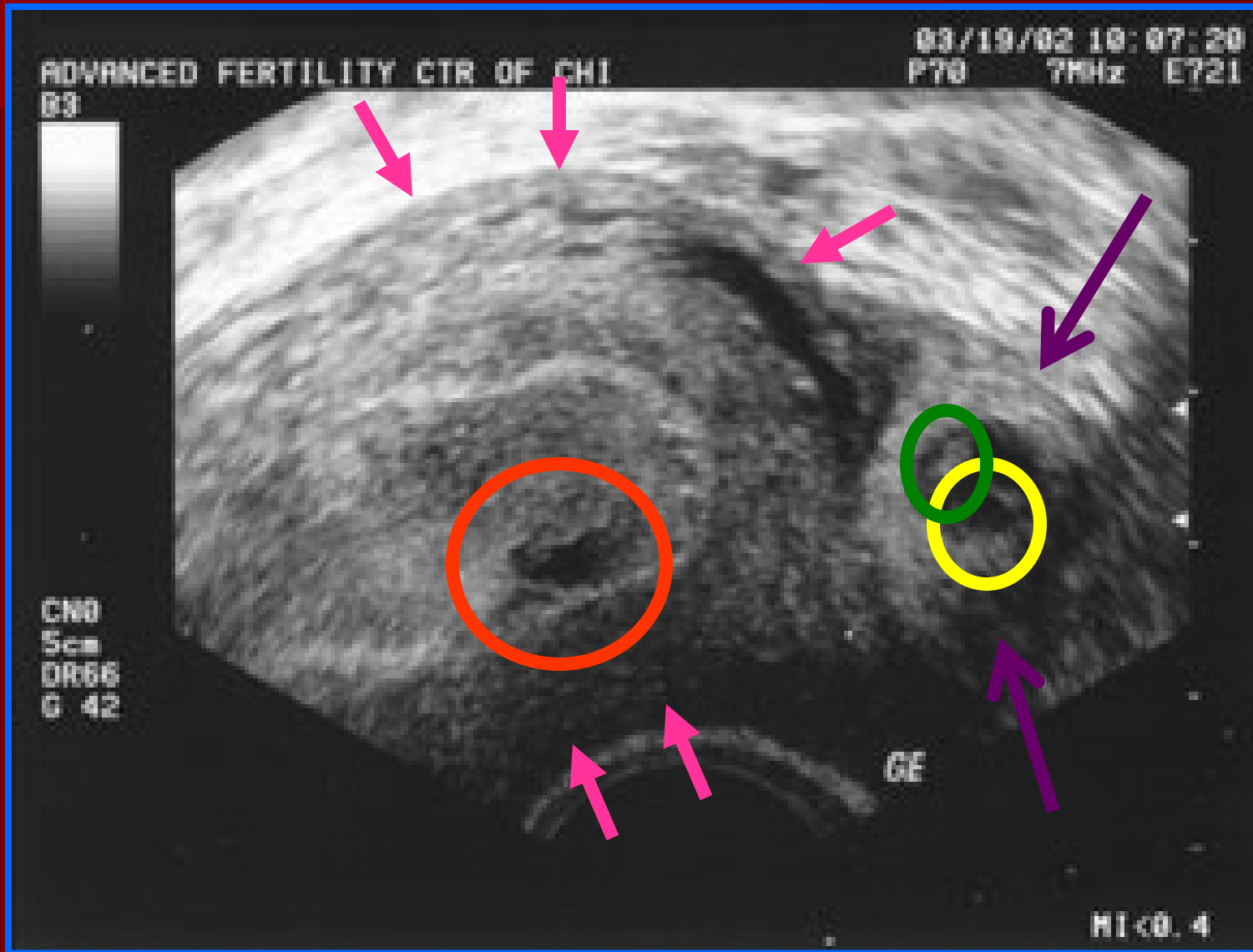
Figure 46-9 Sites of ectopic pregnancy.

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Tubal Ectopic



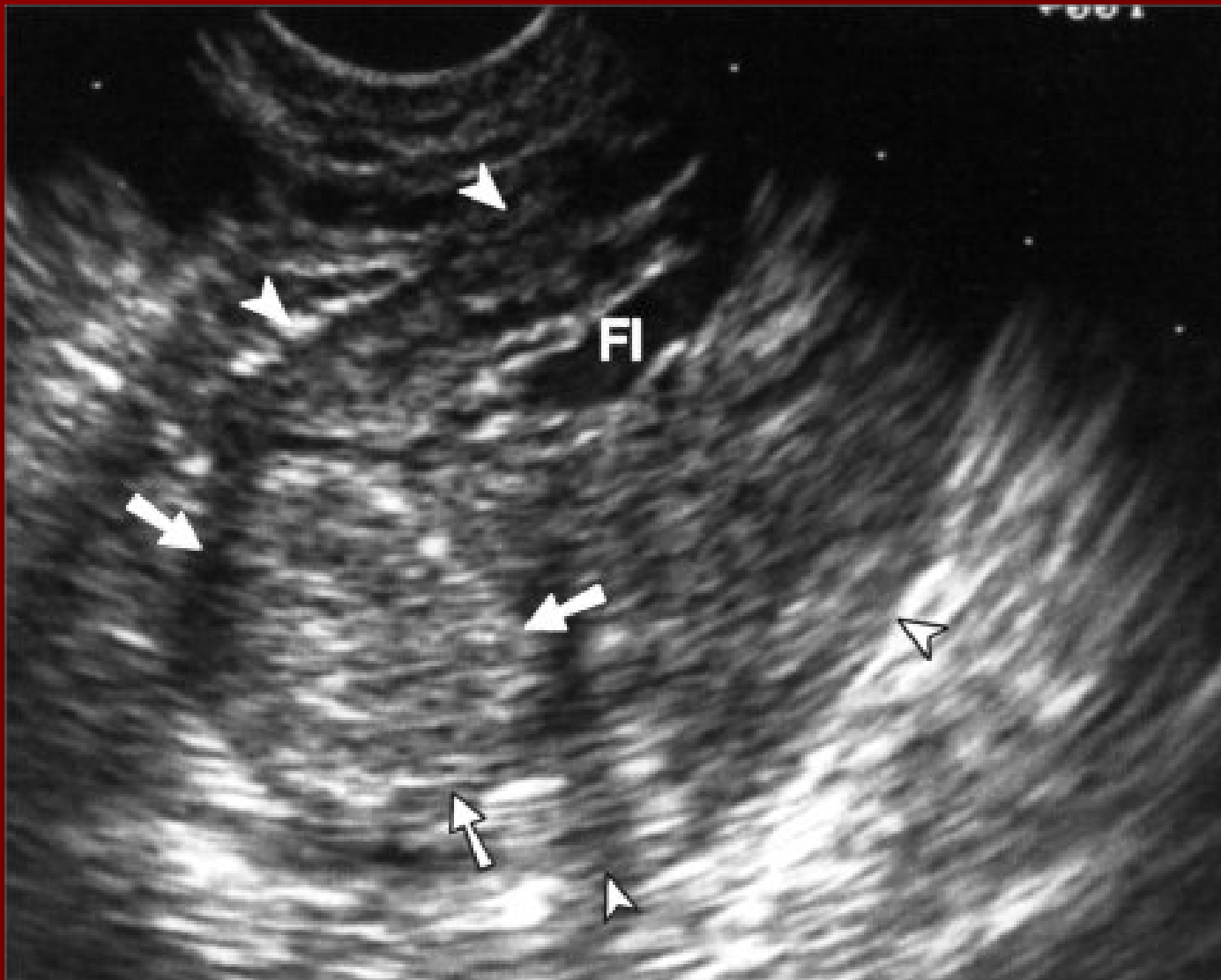
Tubal Ectopic



Tubal Ectopic



Cornual Ectopic



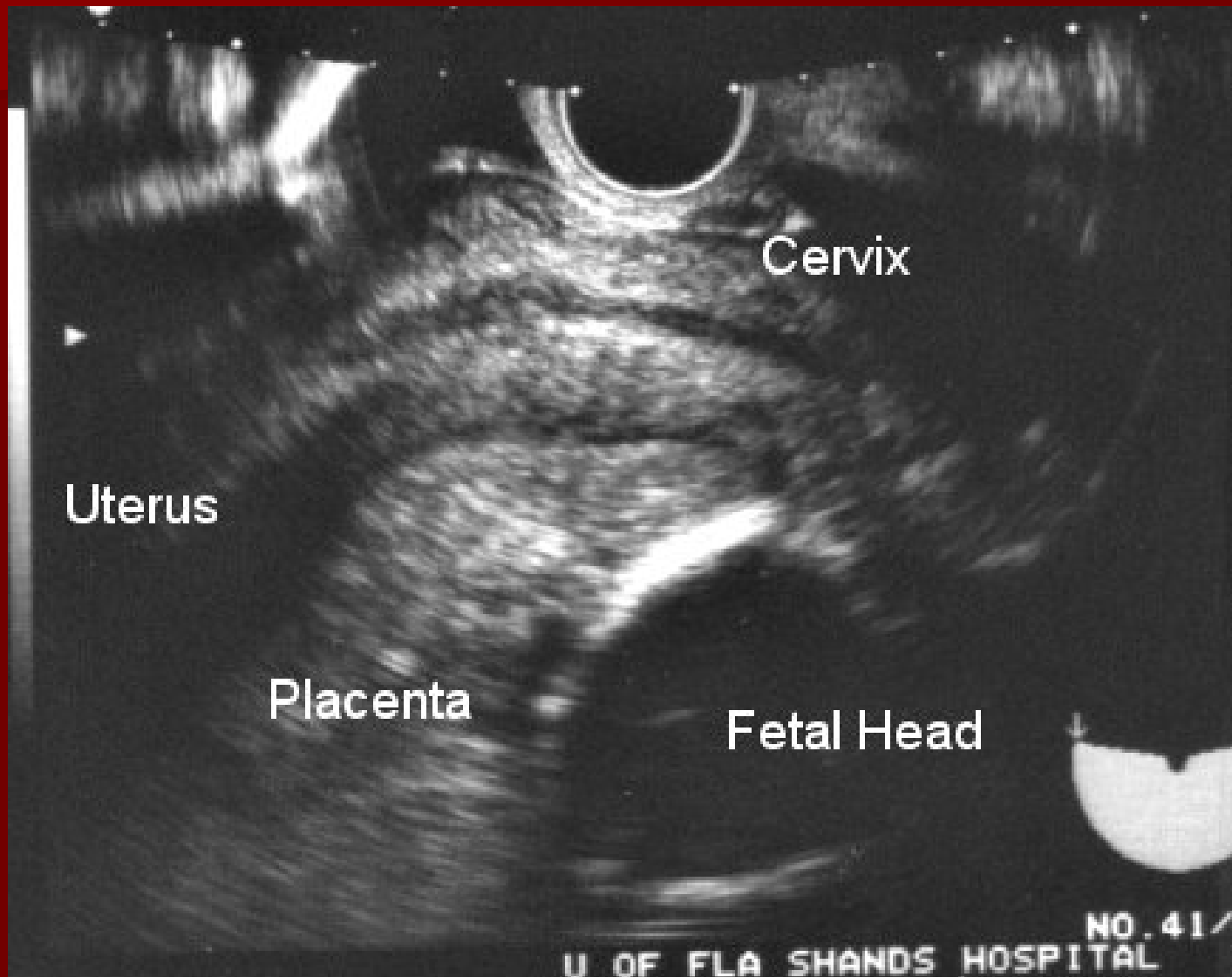
Cornual Ectopic



Cervical Ectopic



Abdominal Ectopic



Epidemiology

- Incidence is increasing
 - 4.5 / 1000 pregnancies in 1970
 - 19.7 / 1000 pregnancies in 1992
 - (2% of all pregnancies)
- Case-fatality rate declining
 - 35.5 deaths / 10,000 ectopics in 1970
 - 3.8 deaths / 10,000 ectopics in 1989
- More common
 - >35 years old
 - Non-Caucasian

Risk Factors

- Strong evidence for association
 - PID (6-9%)
 - Previous ectopic
 - Recurrence risk 15-20% if treated with linear salpingostomy
 - 2 previous ectopics, recurrent risk 32%
 - Endometriosis
 - Previous tubal surgery
 - Post-partum Sterilization – 15%
 - Tubal cauterization – 50-75%
 - Infertility and infertility treatment (5%)
 - History of DES exposure (4-5%)
 - Smoking
 - Affects ciliary action of nasopharynx, respiratory tract and fallopian tubes

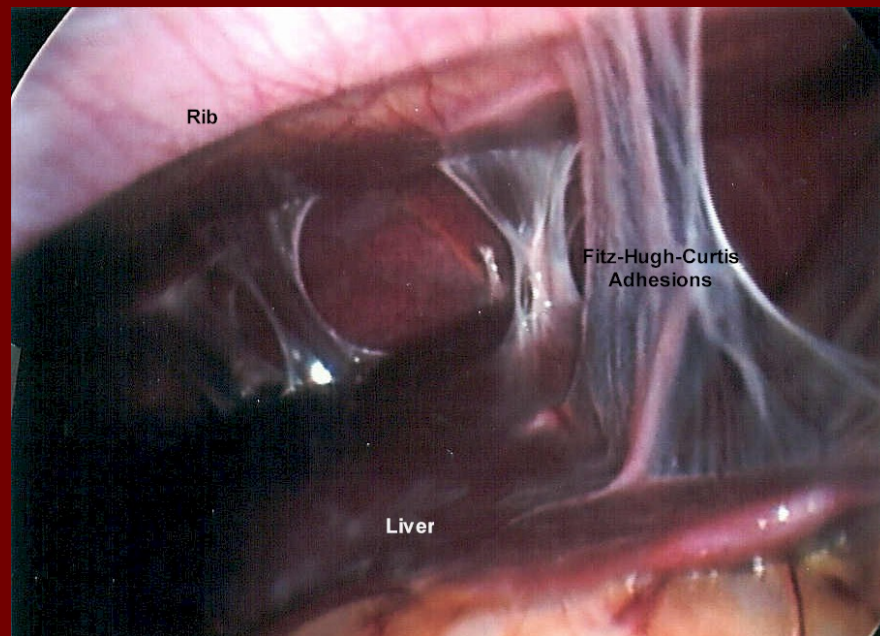
Risk Factors

- Weaker evidence for association
 - Multiple sexual partners
 - Early age at first intercourse
 - Vaginal douching

Identification of risk factors can raise the index of suspicion and lend significance to otherwise minor physical findings

PID

- *N. gonorrhoeae* and *C. trachomatis*
 - Preferentially attack the fallopian tubes
 - Can produce silent infections
 - Early treatment does not necessarily prevent tubal damage



IUDs

- Do not increase risk of ectopic
 - Mistaken association comes from
 - IUDs more effective in preventing IUP than ectopic
 - when an IUD is present, ectopic occurs more often than an intrauterine pregnancy
- No evidence to suggest they cause PID

Presentation

- Classic Triad of Symptoms
 - Abdominal pain – 91%
 - Spotting - 79%
 - + BHCG
 - Usually 6-8 weeks after normal LMP
- Other presentations
 - Shoulder pain
 - Vaginal bleeding
 - Syncope
 - Hypovolemic Shock
 - Asymptomatic

Presentation

- Possible clinical findings
 - Normal or slightly enlarged uterus
 - Pelvic pain with movement of cervix
 - Adenexal mass
 - Hypoactive bowel sounds
 - Hypotension
 - Acute abdomen

Differential Diagnosis

- Missed abortion
- Threatened abortion
- Normal early IUP
- False positive HCG

- Appendicitis
- Ruptured ovarian cyst
- PID
- Ovarian Torsion

Diagnosis

- Serial quantitative BHCG
- Transvaginal US
- Serum progesterone measurements
- Suction D&C
- Culdocentesis

Beta HCG

■ Glycoprotein Hormone

– Produced by

- Normal trophoblast cells of the placenta
- Trophoblast cells of molar pregnancy
- Choriocarcinoma
- Germ Cell Tumors

– Structure: α and β

- α subunit identical to α subunit of other pituitary hormones (LH, FSH, TSH)
- β subunit – unique to HCG

BHCG in a normal Pregnancy

- Enters maternal circulation immediately after implantation (day 21)
- Concentration rises exponentially in the first 10 weeks
 - Doubles every 2 days
 - Day 28: 100 mIU/ml (5 - 450)
 - Week 10: 60K mIU/ml (5K - 150K)
 - Weeks 10-20: 12K mIU/ml (2K - 50K)

BHCG in an Abnormal Pregnancy

- Higher than normal
 - Downs Syndrome
 - Molar pregnancy

- Lower than normal
 - Impending SAB
 - Ectopic pregnancy

Serial quantitative BHCG level

- Serial BHCG testing at 48 hour intervals
 - Normal IUP
 - 66% or greater increase in 48hrs
 - Shephard Obstet Gynecol 1990
 - Prospective study of asymptomatic patients described a 36% sensitivity and 63-71% specificity for serial testing
- Limitations of testing
 - Inherent 48 hour delay
 - Cannot distinguish between failing IUP and ectopic
 - 15% of normal IUPs will have < 66% rise
 - 17% of ectopics will have normal doubling times

Ultrasound findings of early IUPs

- Ultrasound finding in normal pregnancy:
 - @ 4 wks: gestational sac
 - @ 5 wks: gestational sac + yolk sac
 - @ 6 wks: fetal pole with cardiac activity
- By BHCG levels
 - >1,500 mIU/ml: Should see gestational sac
 - >7,000 mIU/ml: should see yolk sac
- Quick Estimates
 - Gestational Sac diameter (in mm) +30 = # days of gestation
 - Crown Rump Length (in mm) + 42 = # days of gestation
 - Range +/- 3 days

Ultrasound findings of early IUPs



Note the Double Ring sign!!

GS in mm + 30 = days of gestation



GS diam (mm)	GA in weeks	GA in days
2	5.0	32
3	5.1	33
4	5.2	34
5	5.4	35
6	5.5	36
7	5.6	37
8	5.7	38
9	5.9	39
10	6.0	40
11	6.1	41
12	6.2	42
13	6.4	43
14	6.5	44
15	6.6	45
16	6.7	46
17	6.9	47
18	7.0	48

•Daya, Can Med Assoc J 1991

CRL in mm + 42 = days of gestation



CRL (mm)	GA in weeks	GA in days
2	6.3	44
3	6.4	45
4	6.6	46
5	6.7	47
6	6.9	48
7	7.0	49
8	7.1	50
9	7.3	51
10	7.4	52
11	7.6	53
12	7.7	54
13	7.9	55
14	8.0	56

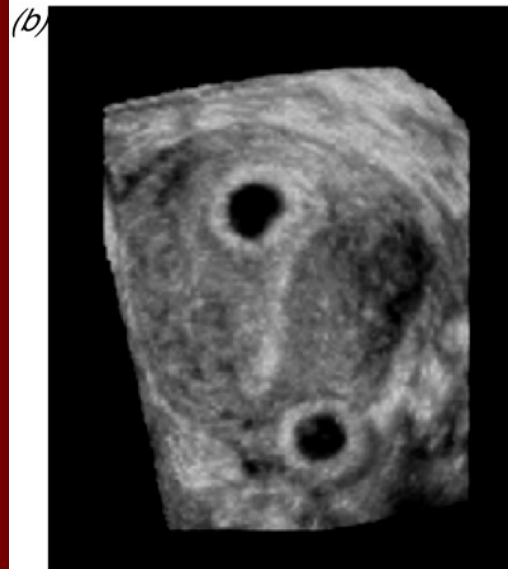


•Daya, Can Med Assoc J 1991

TVUS diagnosis of Ectopic

- Identification of an ectopic gestational sac
 - Not seen in all cases
 - Sensitivity 20% – 84%
 - Varies according to specific criteria used for diagnosis
- Free Fluid (71% sensitivity)
- Heterotopic Pregnancy
 - Coexistence of IUP and ectopic pregnancies
 - Historically, an IUP led to the presumptive exclusion of ectopic
 - Based on 50 year old calculation of incidence of heterotopic pregnancy of 1/30,000
 - Calculated by multiplying incidence of ectopic with dizygotic twinning
 - Incidence is increasing with ART
 - Some studies report as high as 1%

Heterotopic Pregnancy



Serum Progesterone

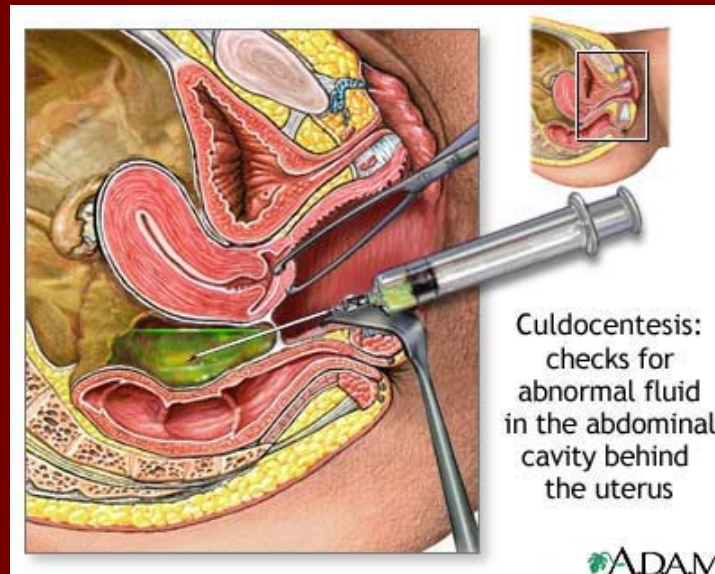
- In pregnant patients
 - Less than 5 ng/mL
 - 85% SAB
 - 0.16% viable IUP
 - 14% ectopics
 - Level 20.4 – 24.9 ng/mL
 - 4% ectopics
 - Level >25 ng/mL
 - 2% ectopics
- 52% of ectopic pregnancies are associated with Serum Progesterone level of 10 – 20 mg/mL

Suction D&C

- To evaluate the presence or absence of chorionic villi in the uterus
 - To aid in narrowing the differential diagnosis

Culdocentesis

- Spinal needle inserted behind uterus into abdominal cavity and fluid is aspirated
- Performed rarely
 - if ultrasound not available
- If Positive for non-clotting blood – strongly suggests ruptured ectopic
 - If straw colored fluid – consistent with ruptured ovarian cyst



Treatment

- Surgical
 - Laparoscopy vs laparotomy

- Medical
 - Methotrexate

Surgery

- General anesthetic
- Laparotomy vs. Laparoscopy
 - X-lap if patient is hemodynamically unstable
 - X-lap large hemoperitoneum
- Salpingostomy in ampullary ectopic
 - Remove ectopic tissue through longitudinal incision of tube
 - May leave incision to heal by secondary intent – surgical repair associated with higher rate of recurrent ectopic
 - If ectopic located at fimbria, can attempt a “milking” technique to allow the trophoblastic tissue to pass without incision
- Salpingectomy
 - Tube is beyond repair
 - Uncontrolled bleeding
 - Patient desires surgical sterilization
- Hysterectomy
 - May be necessary if Cornual or Cervical ectopic

Medical Management

■ Advantages

- Avoidance of surgery
- Preservation of tubal patency
- Lower cost

■ Chemical Agents

- Previously studied
 - Hyperosmolar glucose, urea, prostaglandins, mifepristone (RU486), actinomycin,
- Most commonly used
 - Methotrexate (MTX)

Methotrexate

- Folinic acid antagonist
 - Inhibits dihydrofolic acid reductase
 - Inhibits synthesis of purines and pyrimidines
 - Interferes with DNA synthesis, repair, and cellular replication
 - Actively growing tissue is more sensitive
 - Malignant cells, bone marrow, fetal cells, buccal and intestinal mucosa
 - Toxic effects are related to dose and duration of therapy

Criteria for receiving MTX

- Hemodynamically stable patient
 - No active bleeding or signs of hemoperitoneum
- Patient desires future fertility
- Patient is reliable and able to return for follow-up care
- Patient has no contraindications to MTX
- Unruptured mass <3.5cm at greatest dimension
- No Fetal Cardiac motion detected
- BHCG <10,000 mIU/mL
 - Some advocate for BHCG <5,000 mIU/mL

Contraindications to MTX

- Breastfeeding
- Evidence of Immunodeficiency
- Alcoholism, or chronic liver disease
- Pre-existing blood dyscrasias
- Active Pulmonary disease
- Peptic Ulcer disease
- Hepatic or Renal dysfunction
- Known sensitivity to MTX
- Gestational sac > 3.5cm
- Embryonic cardiac motion

Dosing of MTX

- Calculated according to Estimated BSA (Body Surface Area):

50 mg/m²

www.halls.md/body-surface-area/bsa.htm

www.globalrph.com/bsa.cgi

- Single Dose given IM

Follow up care

- Recheck BHCG on Day 4 and Day 7
 - BHCG level usually increases in the first few days following treatment
 - peaks at Day 4
 - Appropriate response is a 15% decline in BHCG level between Day 4 and Day 7
 - If drop <15% - consider surgery vs. second dose of MTX
- Recheck BHCG weekly until < 10 x 2 weeks
 - It typically takes 4-6 weeks for the ectopic to be resorbed
 - If BHCG plateaus or increases – consider surgery vs. rescue dose of MTX

Success Rates of MTX

- Success is defined by resolution without surgical intervention
- Success rates: 67% - 94%
 - Stovall, Am J Obstet Gynecol 1993
 - Largest study: involving 120 women
 - Overall success 94%
 - 71% success with single dose
- 25% required more than 1 dose of MTX

MTX success by starting Serum BHCG level

Serum BHCG Level	Success Rate
0 – 1,000	98%
1,000 – 1,999	93%
2,000 – 4,999	92%
5,000 – 9,999	87%
10,000 – 14,999	82%
> 15,000	68%

Presented at ACOG annual clinical meeting 1999

Potential Problems with MTX

- Drug-related Side effects
 - N/V, Stomatitis, GI distress, Dizziness,
 - Rare: neutropenia, reversible alopecia,
- Treatment-related effects
 - Increased abdominal pain (2/3rds of patients)
 - Increased BHCG in first 1-3 days
 - Vaginal bleeding or spotting
- Treatment failure
 - Significantly worse abdominal pain
 - Hemodynamic instability
 - BHCG doesn't decline by >15% between Day 4 and Day 7
 - BHCG plateaus or increases after the 1st week of treatment

Patient information/counseling

- Expect some pelvic discomfort
 - common for increased discomfort 3 days after injection
 - DO NOT take Aspirin or Motrin
- Until the ectopic pregnancy has resolved ...
 - Avoid Folic Acid
 - Do not take Prenatal Vitamins, or folic acid supplements
 - Avoid orange juice, green veggies, beans, peas, “fortified” breakfast cereals or “enriched” whole wheat bread
 - No Alcohol
 - No Sexual Intercourse
 - No vigorous athletic activity

Patient information/counseling

- Side Effects occur in 1%
 - mouth sores, N/V, heartburn, GI Distress, diarrhea, fatigue, Dizziness
- Call or go to ER if ...
 - Severe pain
 - Heavy bleeding (more than 1 pad per hour)
 - Significant dizziness or lightheadedness

MTX Protocol

- Obtain baseline labs
 - Serum BHCG
 - CBC
 - CMP (must have normal LFT's and Creatinine)
 - Blood Type
 - accurate Height and Weight
- Treatment Day 0
 - Inject Methotrexate IM (50mg/m²)
 - RhoGAM 300 micrograms IM (if Rh negative)
 - Discontinue folic acid supplements
 - Counsel patient about activity, side effects and need for follow up

MTX Protocol

- Day 4
 - Repeat serum BHCG
- Day 7
 - Repeat serum BHCG
 - Transvaginal US
 - Give 2nd Dose of Methotrexate if decline in BHCG is < 25% of Day 0 level
- Weekly thereafter
 - Serum HCG until negative
 - Transvaginal US
- LAPAROSCOPY if acute abdomen or US evidence of hemoperitoneum