Ectopic Pregnancy

Tubal, Interstitial (cornual), Cervical, CS scar pregnancy

Lecture for the Academic Year 2018 – 2019
Defined Learning Objectives

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Ectopic Pregnancy
Presentation & Learning Objectives

- Epidemiology
- Clinical manifestations (pain, bleeding, risk in ART)
- Beta hCG flactuation and Progesterone (pathognomonic signs)
- US findings (importance of early diagnosis)
- Comparison between Tubal, cornual and CE
- Treatments (Methotrexate (Cytotoxic and Cytostatic medical treatment, combination of medical and/ or surgical treatments)
- US guided treatments (injection of MTX, combination of medical and surgical tx)
- Fertility sparing surgery (reassure future eutopic pregnancy

Epidemiology of Ectopic Pregnancy

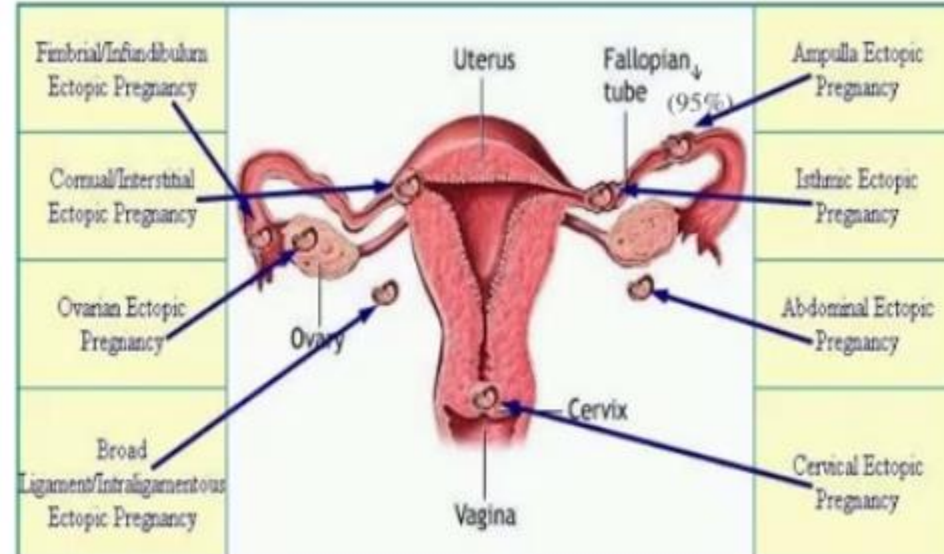
- 6% of all maternal deaths : CDC
- Leading cause of maternal death in 1st trimester
- Increasing incidence x 5 due to PID, modern antibiotics, ↑Dg
  - USA 4.5 – 19.7 / 1000
  - Norway 12.5 – 18 / 1000

- Maternal mortality decreased by 90% due to
  - Awareness and knowledge
  - Availability for diagnosis (beta hCG, Progesterone, TVU)
  - Prompt medical and surgical treatment (MTX + MIGS)

Sites of ectopic pregnancy

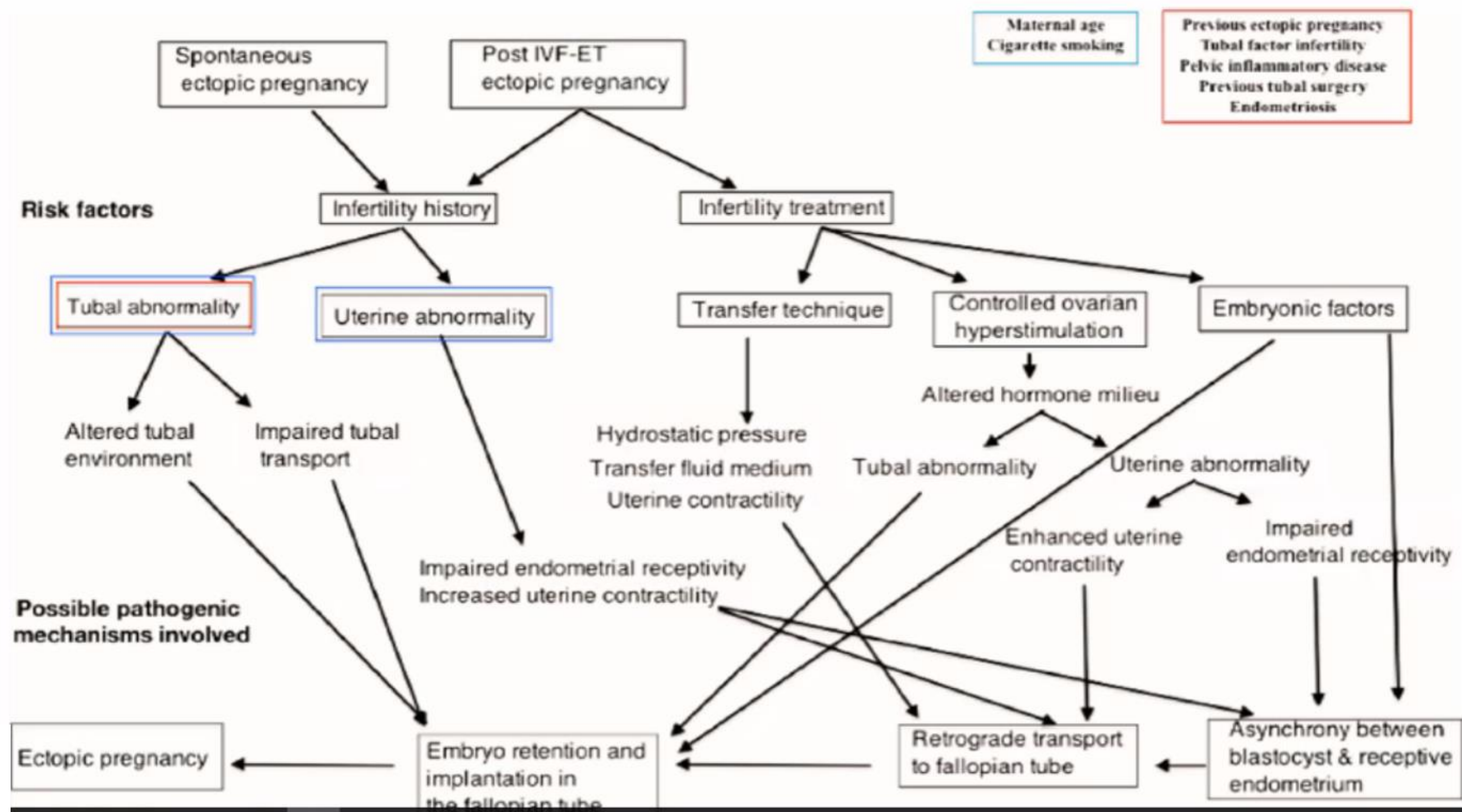
95% in the oviduct

- 55% in the ampulla
- 20-25% Isthmic portion
- 17% Infundibulum and fibria
- 2% Cornua



16% of ectopic resulted from contralateral ovulation

Potential mechanisms involved in the pathogenesis of tubal pregnancy after natural conception in relation to established risk factors



Risk factors for EP during IVF-ET

Maternal	IVF-ET Technique

Definite risks

Maternal
- PID
- History of tubal surgery
- Previous EP
- Cigarette smoking
- Endometriosis

IVF-ET Technique
- Tubal infertility
- High volume of transfer media
- Multiple embryo transfer

Inconclusive risks

Maternal
- Maternal age
- Uterine abnormalities

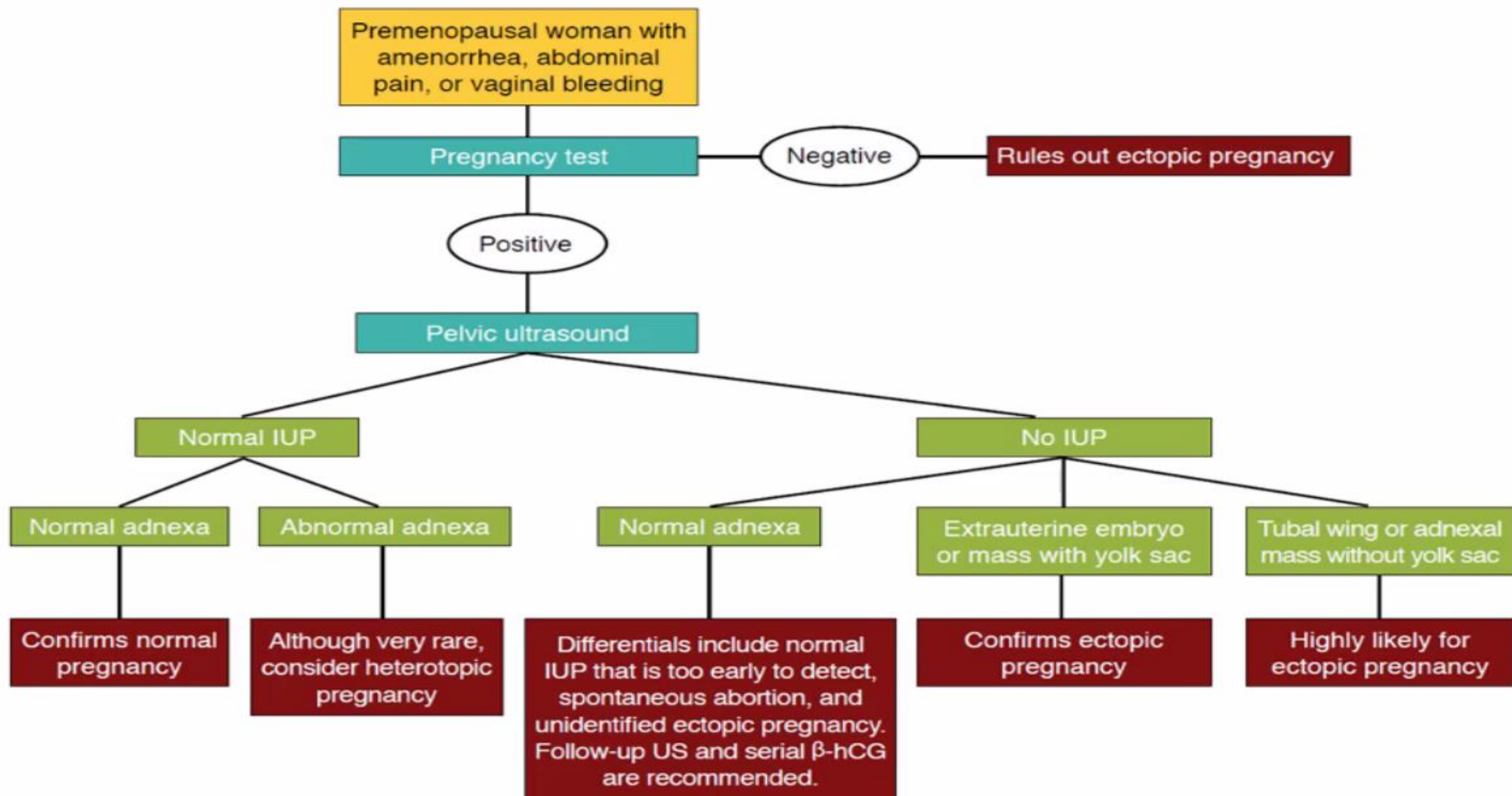
IVF-ET Technique
- Controlled ovarian stimulation
- Triggering oocyte maturation
- Luteal phase support
- IVF / maturation / Assisted hatching
- Embryonic stage at transfer
- Fresh vs. Frozen embryo
- ET technique

RB&E REPRODUCTIVE BIOLOGY AND ENDOCRINOLOGY Refaat B, Dalton E, Ledger WL, 2015

Risk factors for Ectopic pregnancy

Factors	Mechanism and statistics
Chronic PID	x 6, 1 ectopic per 25 gestations
Prior tubal surgery	even Surgical sterilization
Use of an IUD	4% ectopic with an IUD in place due to subtle tubal damages
Previous ectopic	Tubal damage
Progestin only oc	Affects mainly the normal tubal and endometrial function
ART and Infertility	2.1% after IVF, but CDC 0.7%, ET affects uterine contractility Tubal disease 3.65 % without tubal disease 1.19%
Multiple sex partners	Due to PID, salpingitis
Early age at first intercourse	Higher risk for PID, decreased local vaginal and Cx immunity
Cigarette smooking	Negatively affects cervical local immune system
Vaginal douching	Suspects that provokes and disturb normal uterine contractility

Lee R, Dupuis C, Chen B, Smith A, Kim YH.
Diagnosing ectopic pregnancy in the emergency setting. Ultrasonography 2018;37:78-87



β-hCG discriminatory level and TVU findings

- Gestational sac can be consistently identified by TVS at a cut-off level of serum β-hCG is 1500 - 2000 IU/L

[Chen ZY, et al. J Int Med Res. 2012, Desai D et al. Fertil Steril. 2014]

- When β-hCG is
  - above the predetermined threshold & no sac in US
  - or stabilises
  - or fails to increase normally

  EP should be considered

[Kirk E. Clin Obstet Gynecol. 2012 Talbot K, J Obstet Gynaecol. 2011]

A discriminatory tool for EP
β-hCG immunoassay

- detects serum levels as low as 5 IU/L
- with <0.2% incidence of false negative results
- detected as early as 7-8 days after ovulation
- or 1 day after blastocyst implantation
- β-hCG doubling serum levels every 2nd day

- in 87% of women with EP and
  15% of women with normal IUP
  β-hCG doubling *is more than 2.7 days*
  when the β-*hCG <6000 IU/L* *(Kadar et al.)*

A discriminatory tool for EP serum Progesterone levels

- in normal IUP > 20ng/ml
- in Ectopic Pregn. < 1.5ng/ml

- 1000 1st trimester pregnancies

- patients with Progesterone < 5ng/ml

  (had non-viable pregnancy by 100%)

- when Progesterone was > 25ng/ml

  97% had viable IUP

(Stoval et al.)

Progesterone as a discriminatory marker for EP

- normal intrauterine pregnancy usually Progesterone > 20ng/ml
- **< 15 ng /ml suspected for an ectopic pregnancy**

Progesterone levels 10-20ng/ml (Gelder et al.)

- 31% of viable intrauterine pregnancies
- 23% of abnormal intrauterine pregnancies
- 51% of ectopic pregnancies

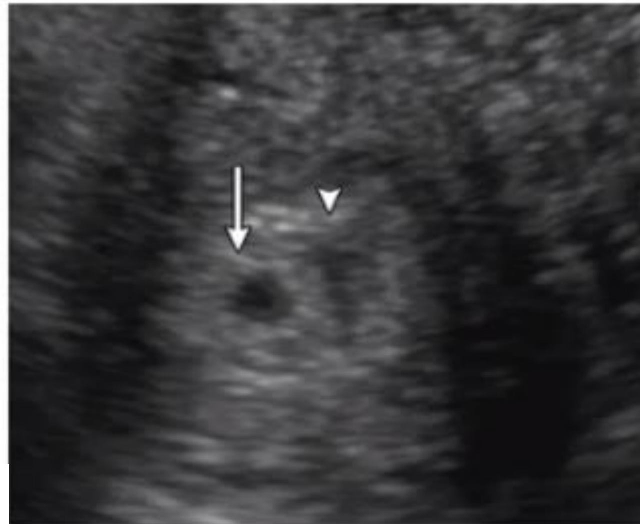
In 1000 early pregnancies follow up When Progesterone

- <5.1ng/ml detected a non viable pregnancy by 100%
- >25ng/ml detected a viable intrauterine pregnancy by 97%

(Stoval et al 1992)

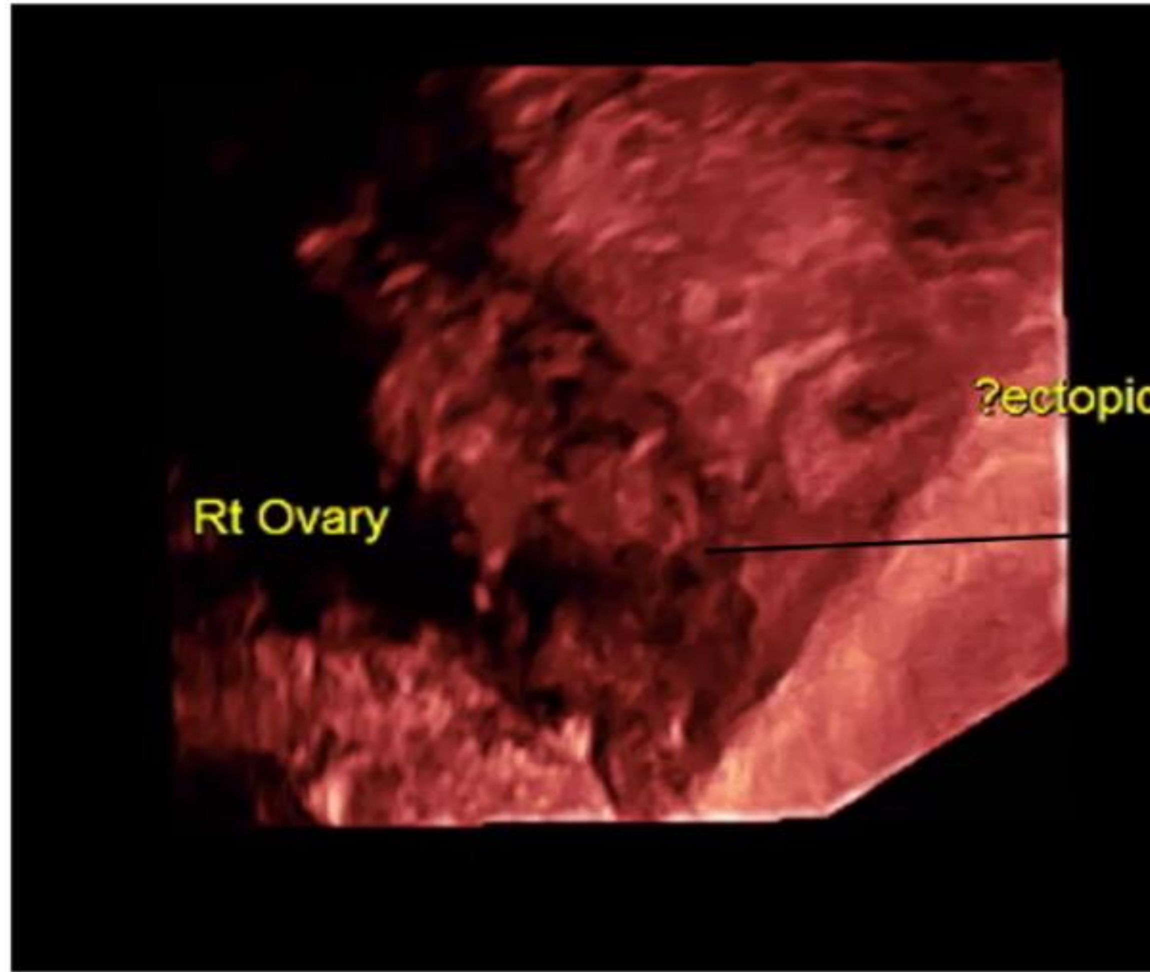
Trans Vaginal Sonography

- Revolutionized the diagnoses of ectopic
- Identify the masses in the adnexa as small as 10mm
- "Double line" image formed by the fainted hypoechoic decidual lining of the uterus and the hyperechogenic rim of the trophoblast surrounding the gestational sac



Tubal pregnancy

- 15% of tubal pregnancies rupture before the first missed menstrual period (especially if irregular cycle)
- Some form of vaginal bleeding occurs around the expected time of menses in more than 50% of women with EP
- Clinical symptoms usually appear 6-10 w after the LMP

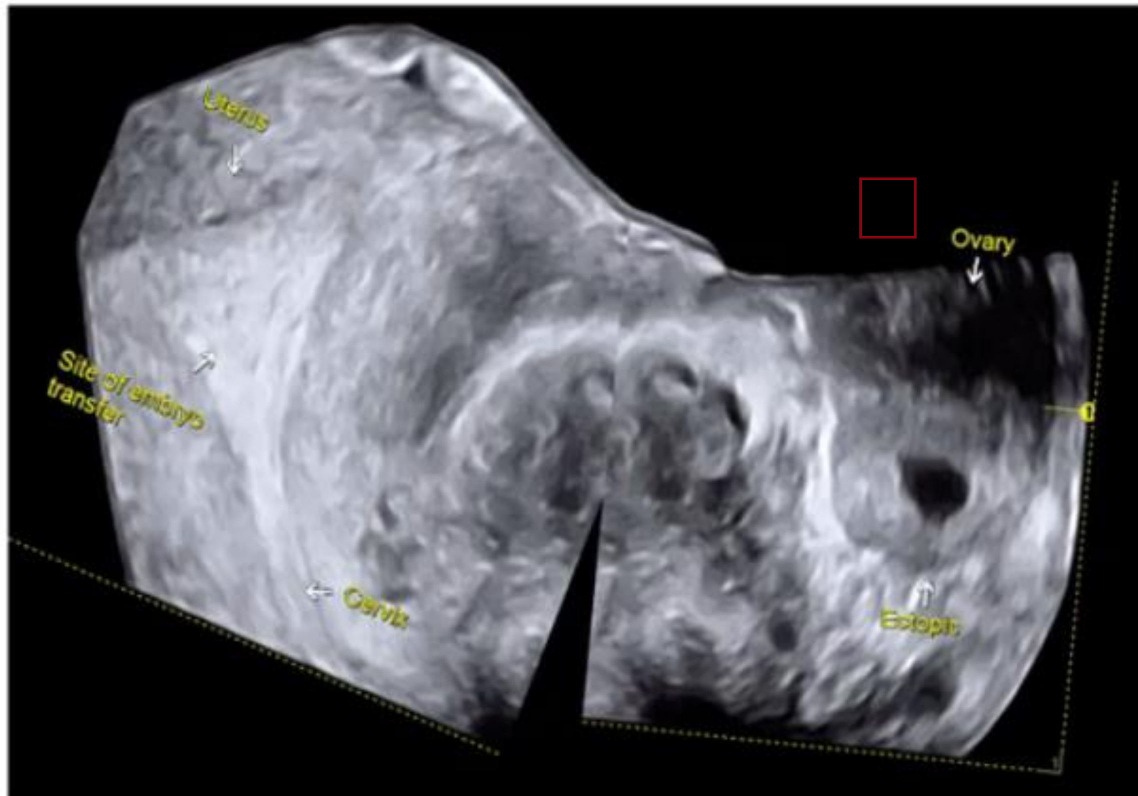


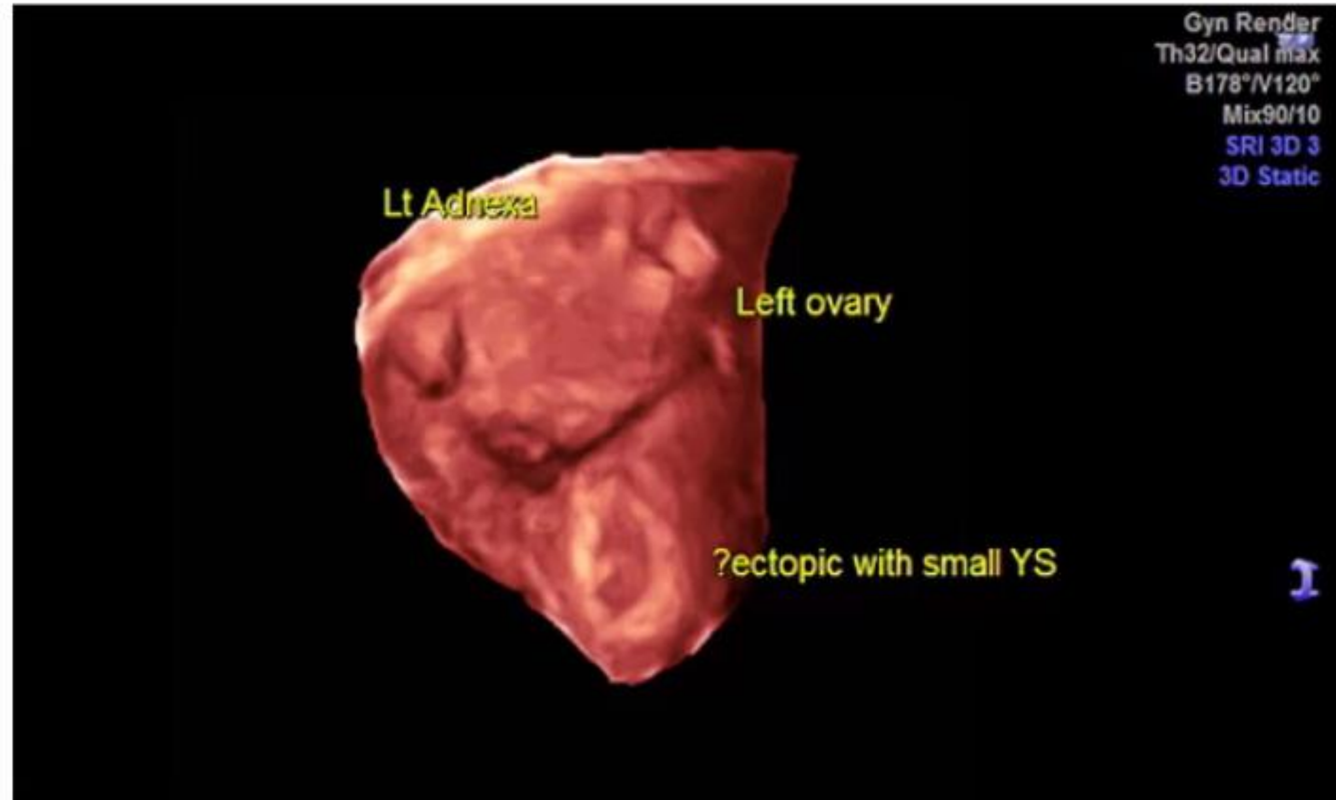
'Swollen' Fallopian tube with blood

Small tubal ectopic

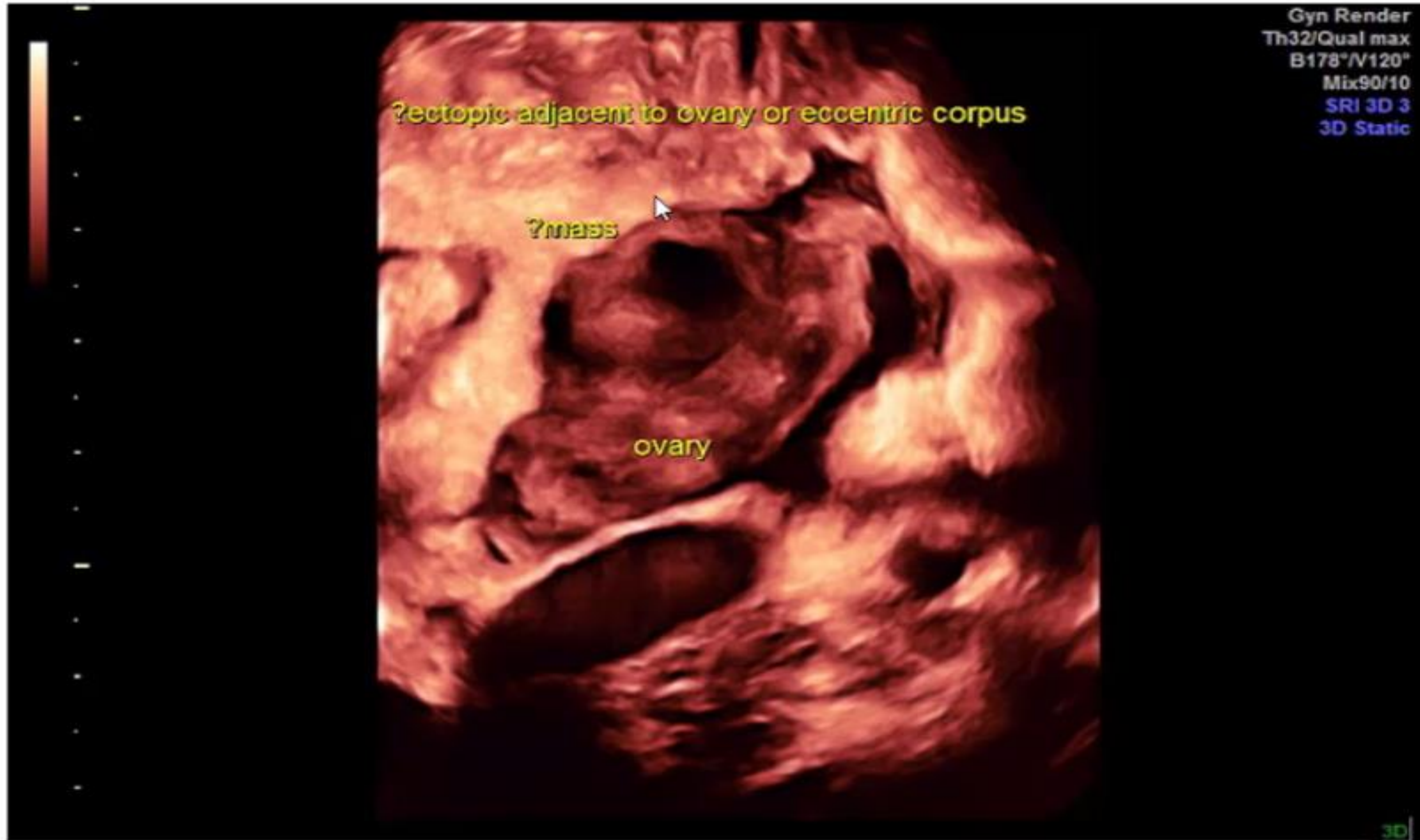
Diagnosis of EP is made
by suspicion of an EP + B-hCG / Progesterone + TVU 2D / 3D

Left tubal ectopic





Tubal ectopic stuck to the ovary



Curtesy Dr Soterios Saravelos 2018

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TVU for early detection of EP in asymptomatic patients

- β-hCG ≥ 1000 – 1500 IU/L and empty uterine cavity
- accuracy to detect the ectopic is 100%

(Barnes et al.)

- peritrophoblastic flow associated with an adnexal mass by color Doppler technique

(Kurjiak et al.)

- Color Doppler flow analyses of the tubal arteries can help to localize the side of the tubal EP
- increased tubal blood flow of 20 - 45% seen to the side of the EP

(Kirchler et al.)

Trans vaginal ultrasonography

Technical aspects

- 5MHz transducer allows deeper penetration of the pelvis than
- 7.5MHz provides better near resolution at the cost of shallower penetration

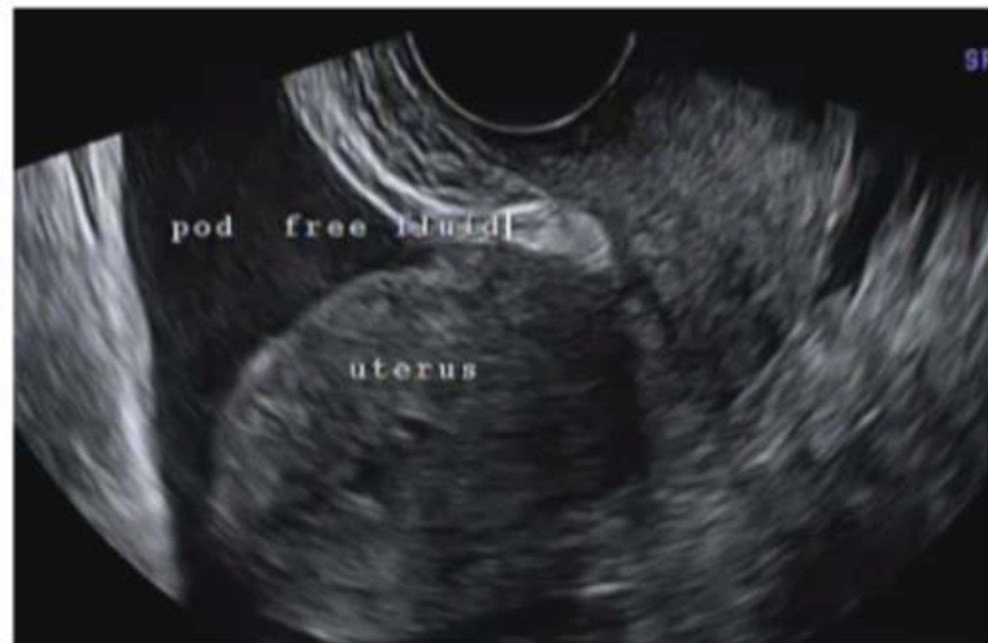
- Can detect masses, small as 10mm in diameter
- Reliably detects an IUP as early as 1w after missed menses
- when β-hCG is 1000 - 1500IU/L at 5-6w of GA

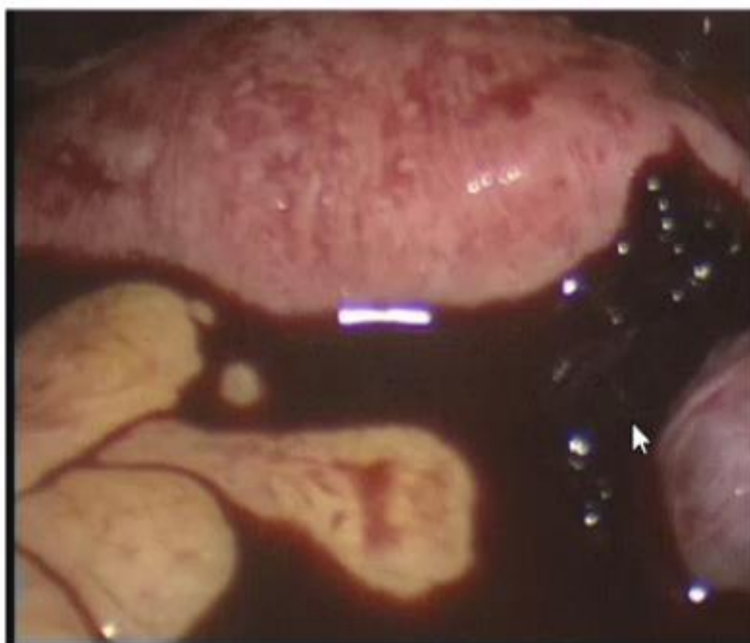
First-trimester study of ultrasound features for diagnosis of ectopic pregnancy

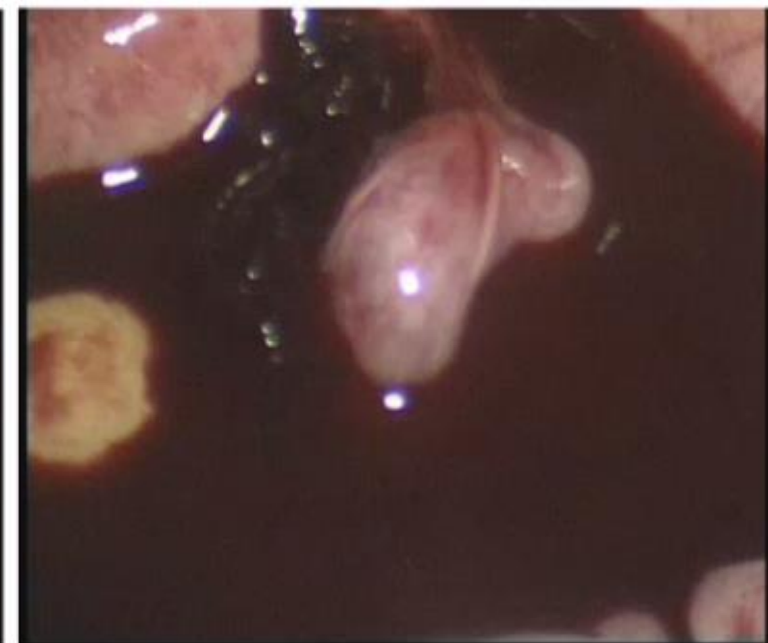
Potential of the parameter to predict an EP

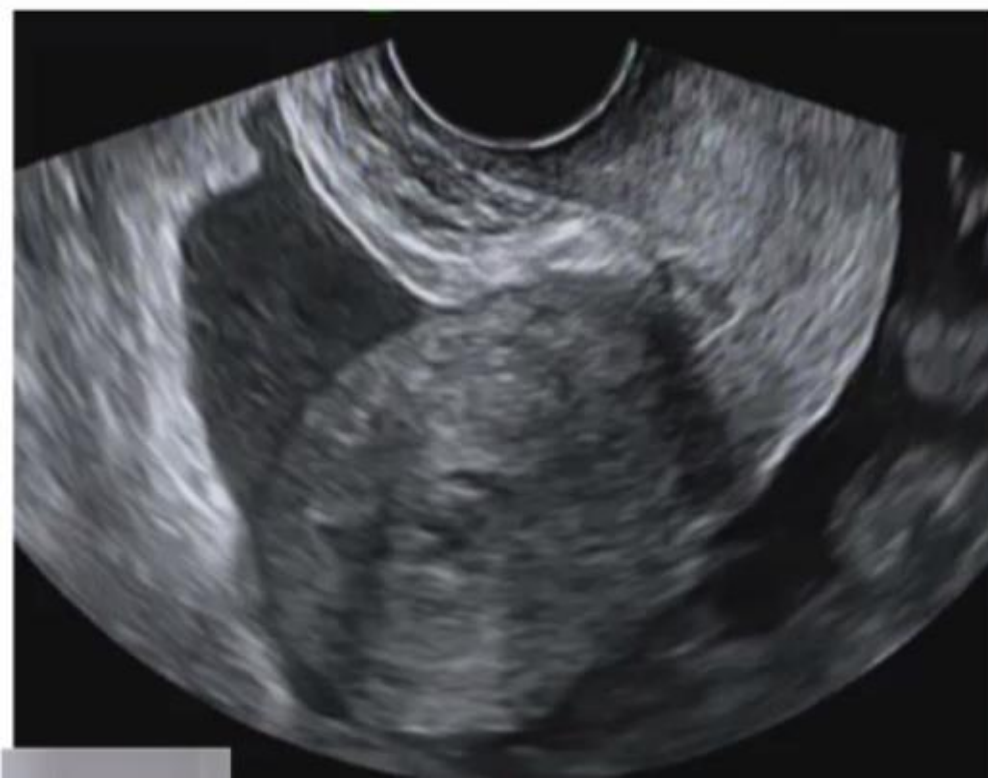
Parameter	Sensitivity %	Specificity %
empty uterus	81.1	79.5
pseudosac	5.5	94.2
adnexal mass	63.5	91.4
free fluid	47.2	92.3

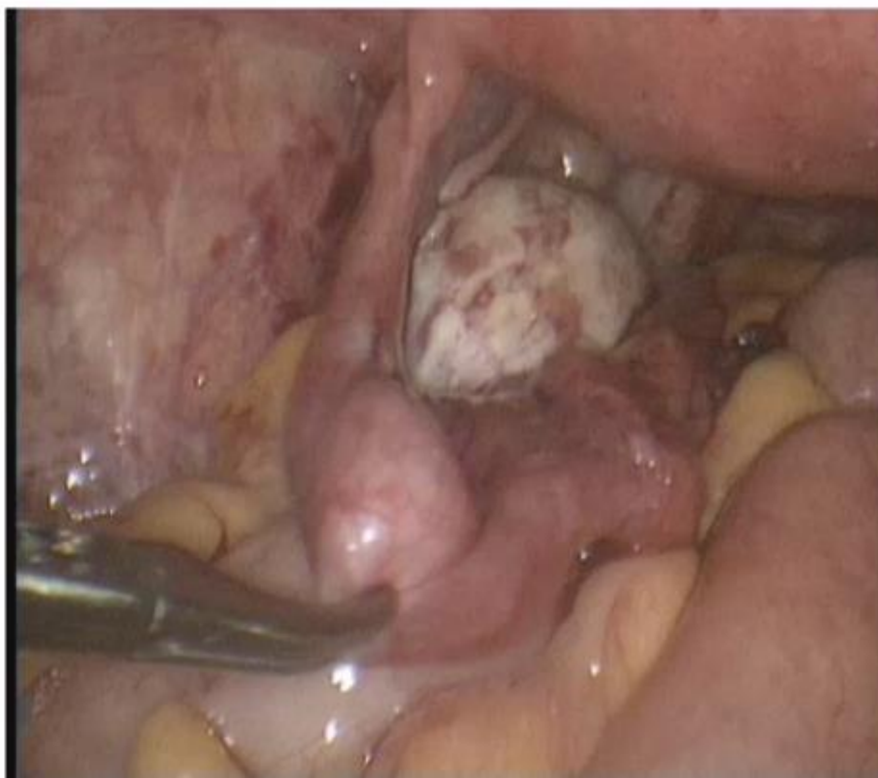
- Early diagnosis can reduce morbidity and mortality.
- Diagnosis before tubal rupture can prevent life-threatening hemorrhage
- Increases the chances for medical treatment and MIGS preserving the tube

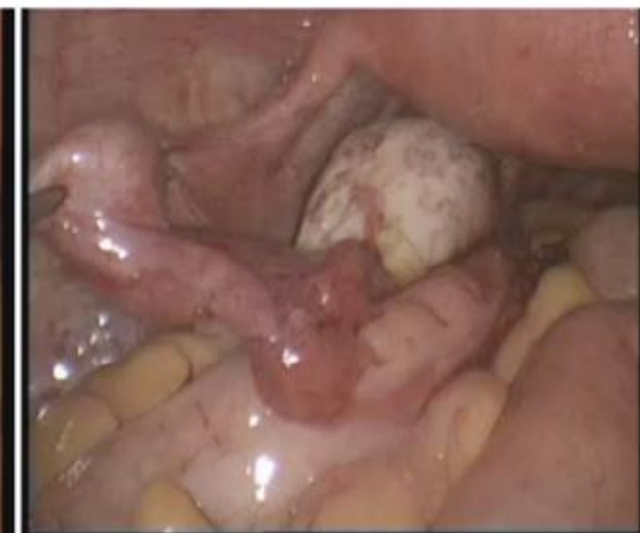












Left Tubal ectopic pregnancy
Life threatening condition
Emergency surgical treatment

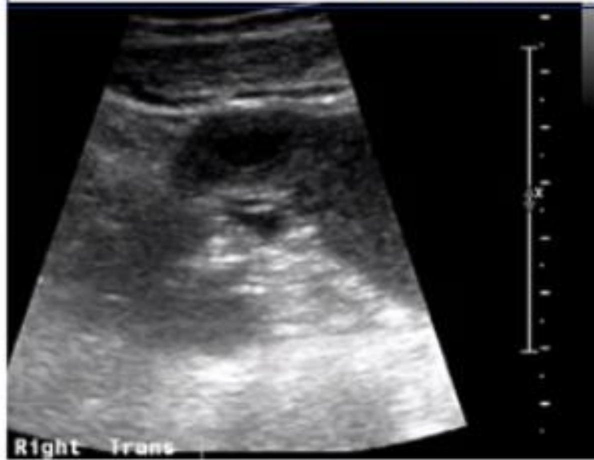
Indeterminate US findings

are neither diagnostic nor highly suggestive of an IUP or EP

- empty uterus,
- abnormal gestational sac (with an irregular border or an MSD large enough that a secondary structure such as a yolk sac would be expected),
- a normal gestational sac without a yolk sac or embryo
- a nonspecific intrauterine fluid collection
- ill-defined echogenic material within the endometrial cavity

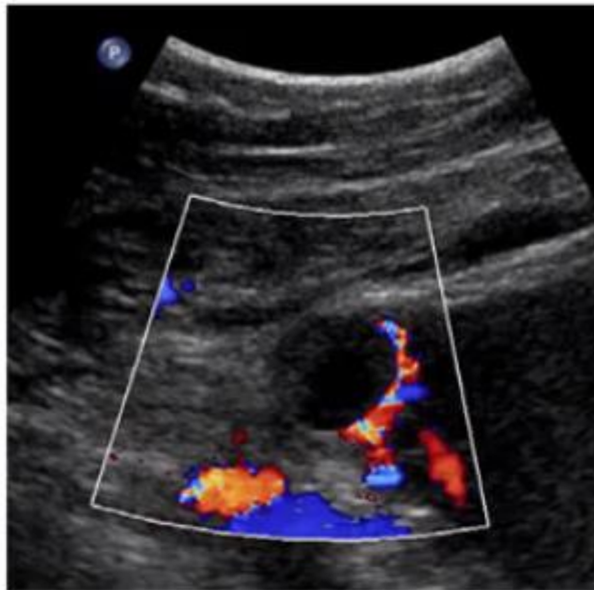
monitor with serial β-HCG testing and clinical assessments, as about 10-25% of such patients have normal pregnancies

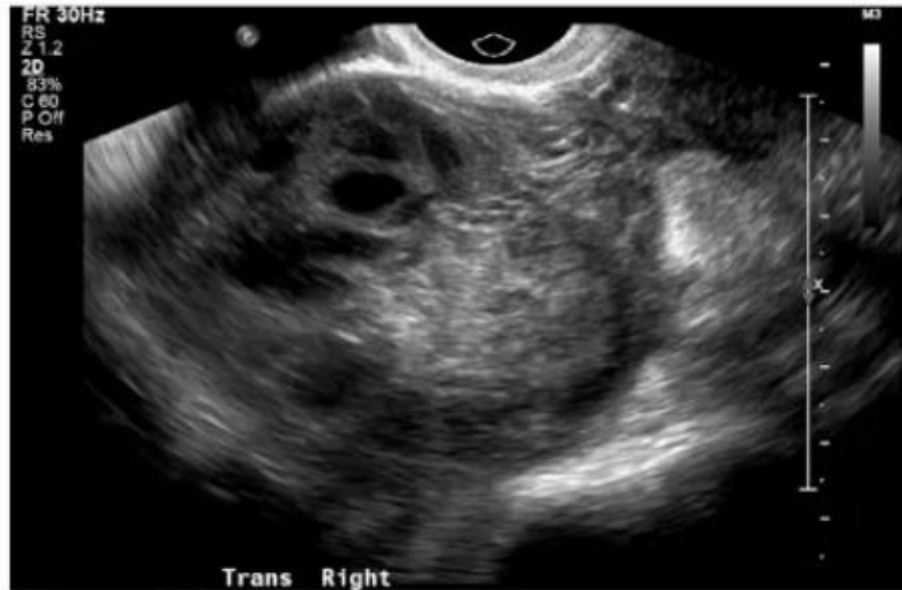
Tubal ring sign



21-year-old, with positive serum beta hCG and vaginal bleeding

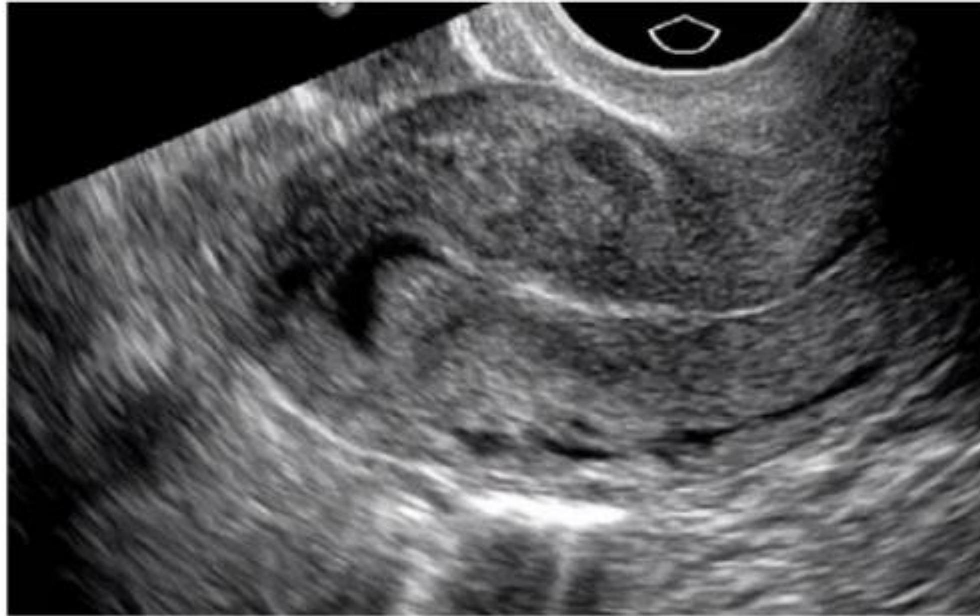
Ectopic pregnancy seen as a hematoma Rt adnexal mass separated from the rt ovary (arrow)

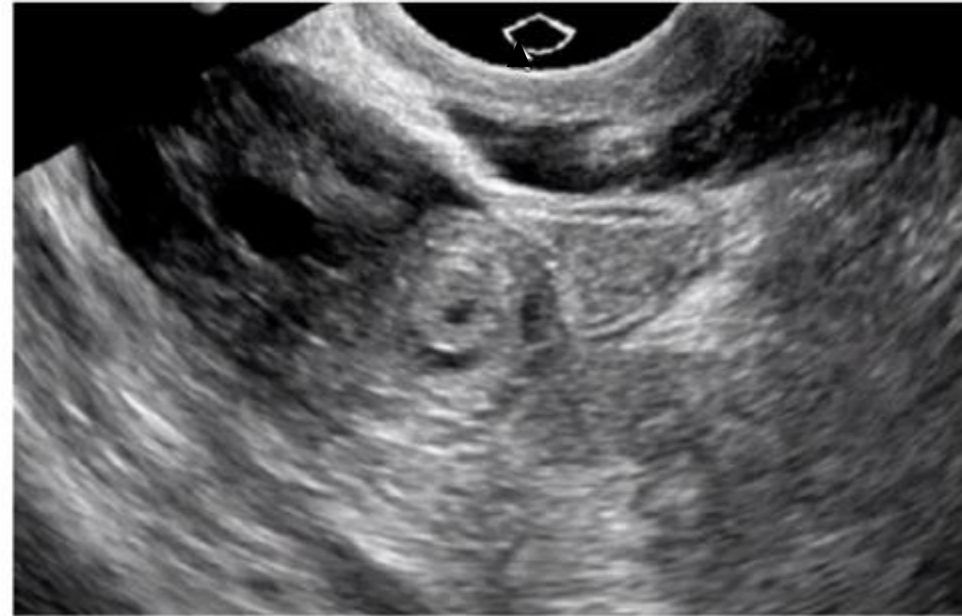




28 y, old woman at emergency room
c/o right lower quadrant pain
TVU: pseudogestational sac - irregular-shape
absent yolk sac or embryo, +ve β-hCG

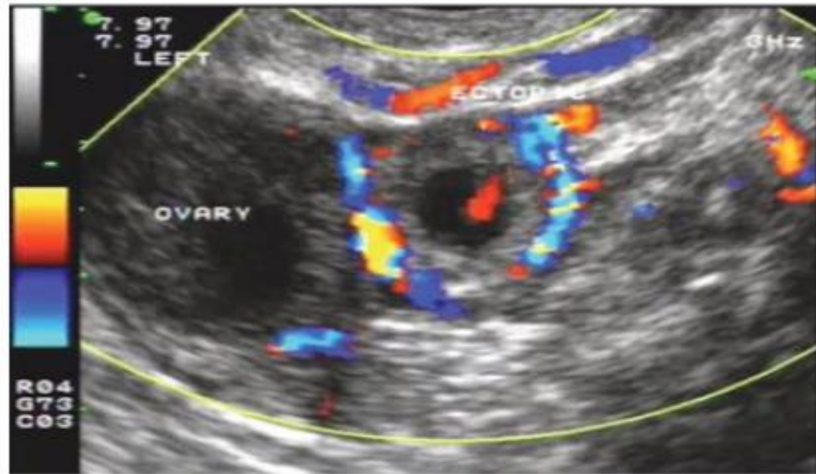
There is a right adnexal mass with an echogenic ring
suspicious for ectopic pregnancy



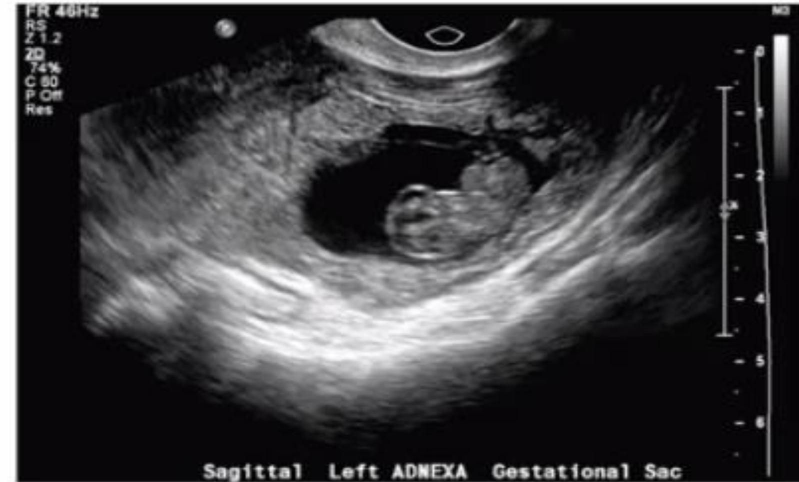


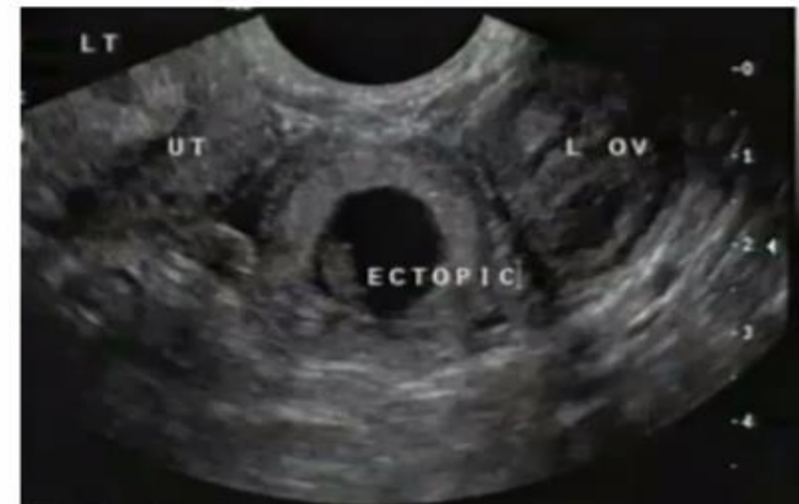
Gestational sac with an embryonic pole and positive cardiac activity

peritrophoblastic flow



Live tubal ectopic pregnancy Embryo with 170bpm and sac

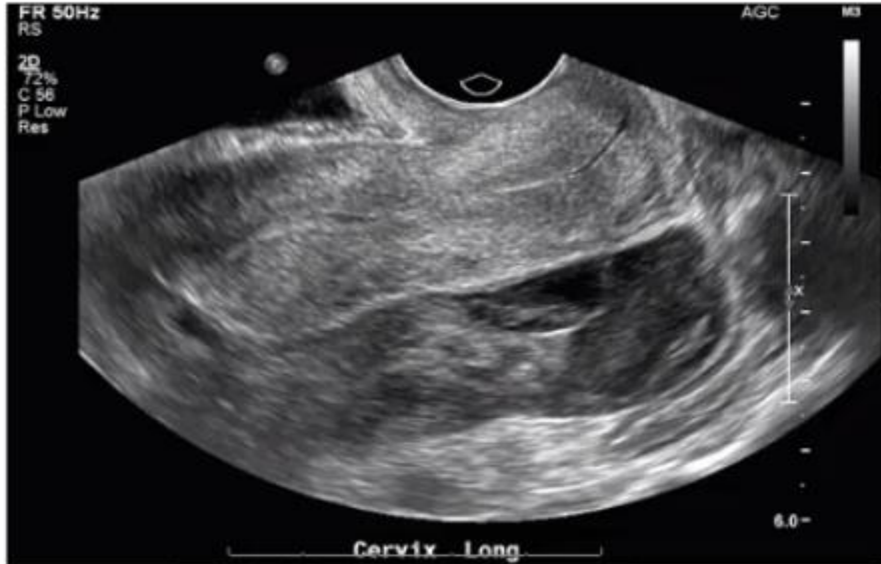


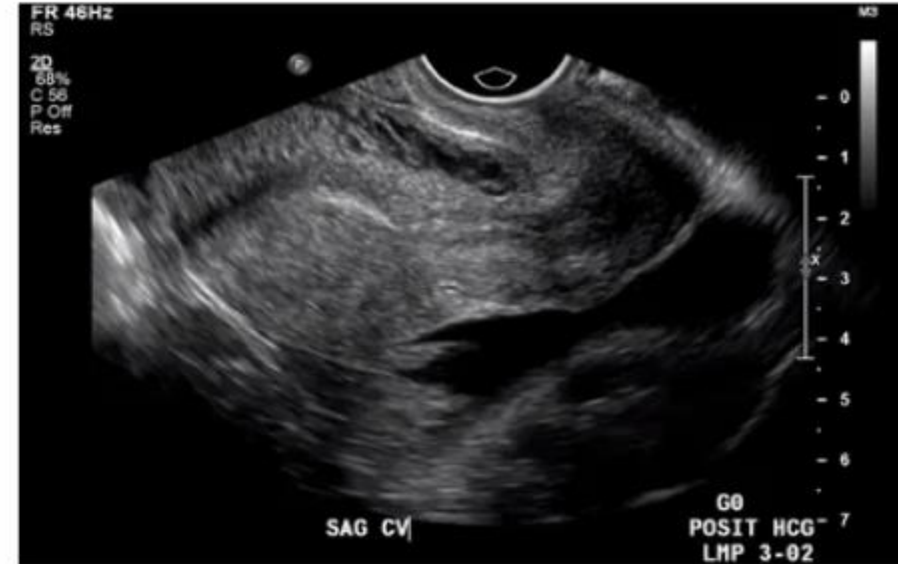


Differential Diagnosis
EP sac can be confused with

Hemoperitoneum
Ruptured Corpus Luteum

Free fluid in PoD
Ruptured simple cyst
PID, appendicitis





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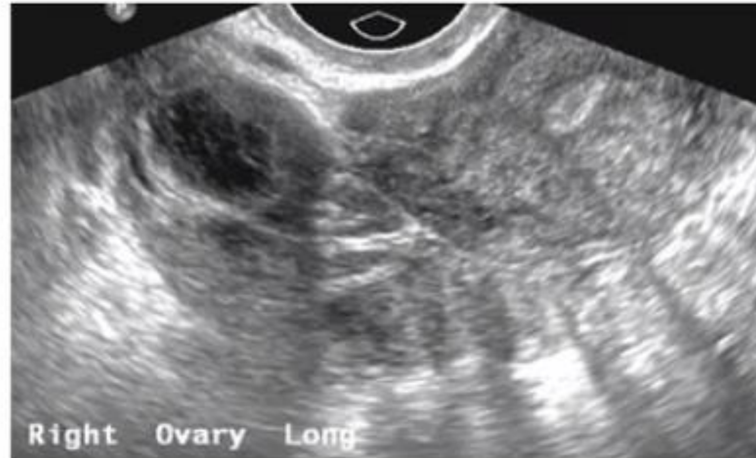
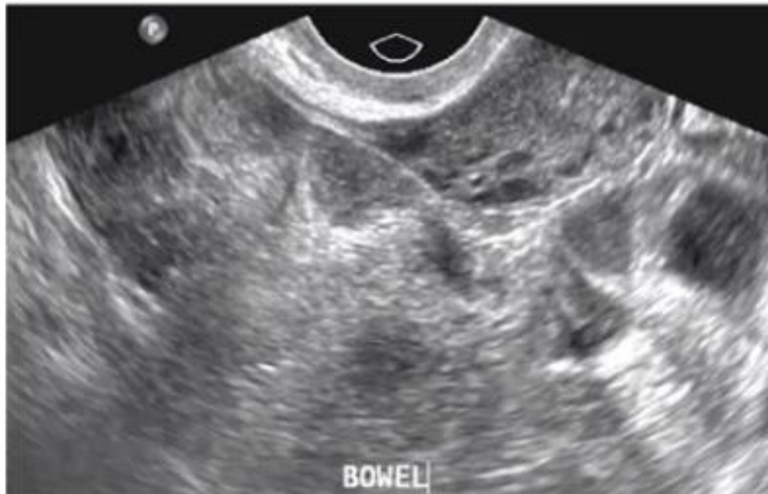
A young patient appears in emergency room for an abdominal and pelvic pain
LMP ended 4 days ago
The surgeon r/o appendicitis
Suspect enteritis
Gynaecologist performed US

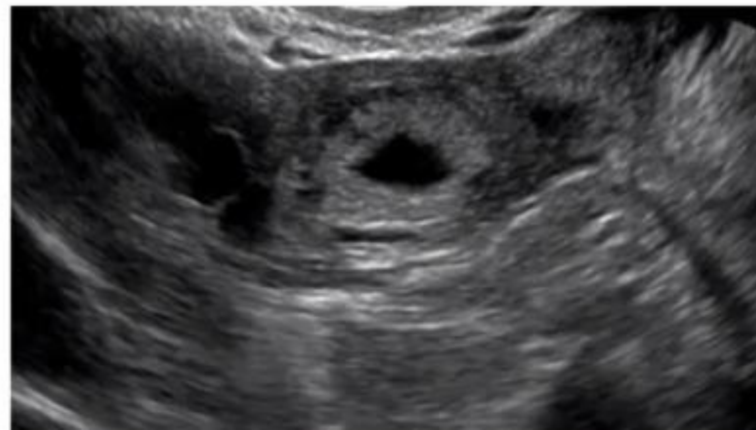
The sagittal view of the right adnexa right ovarian hemorrhagic cyst no adnexal mass can be seen



A transverse view of the RT adnexa nonspecific echogenicity in the right adnexa was interpreted as bowel loop

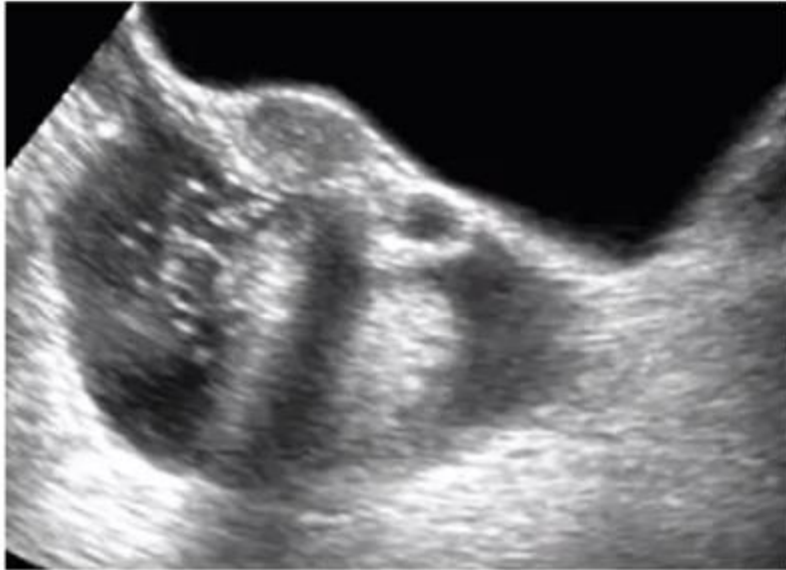


3 days after, pelvic pain deteriorates and in TVU a mass with a thick, echogenic ring in the right adnexa, is highly suspicious for EP

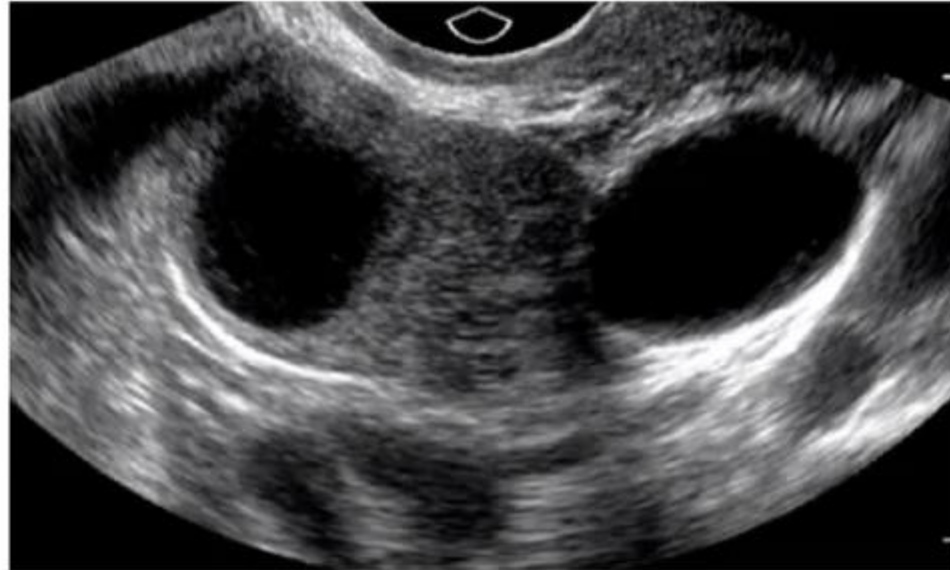


Differential Diagnosis
an EP sac can be confused with

DERMOID CYST



PARAOVARIAN CYST

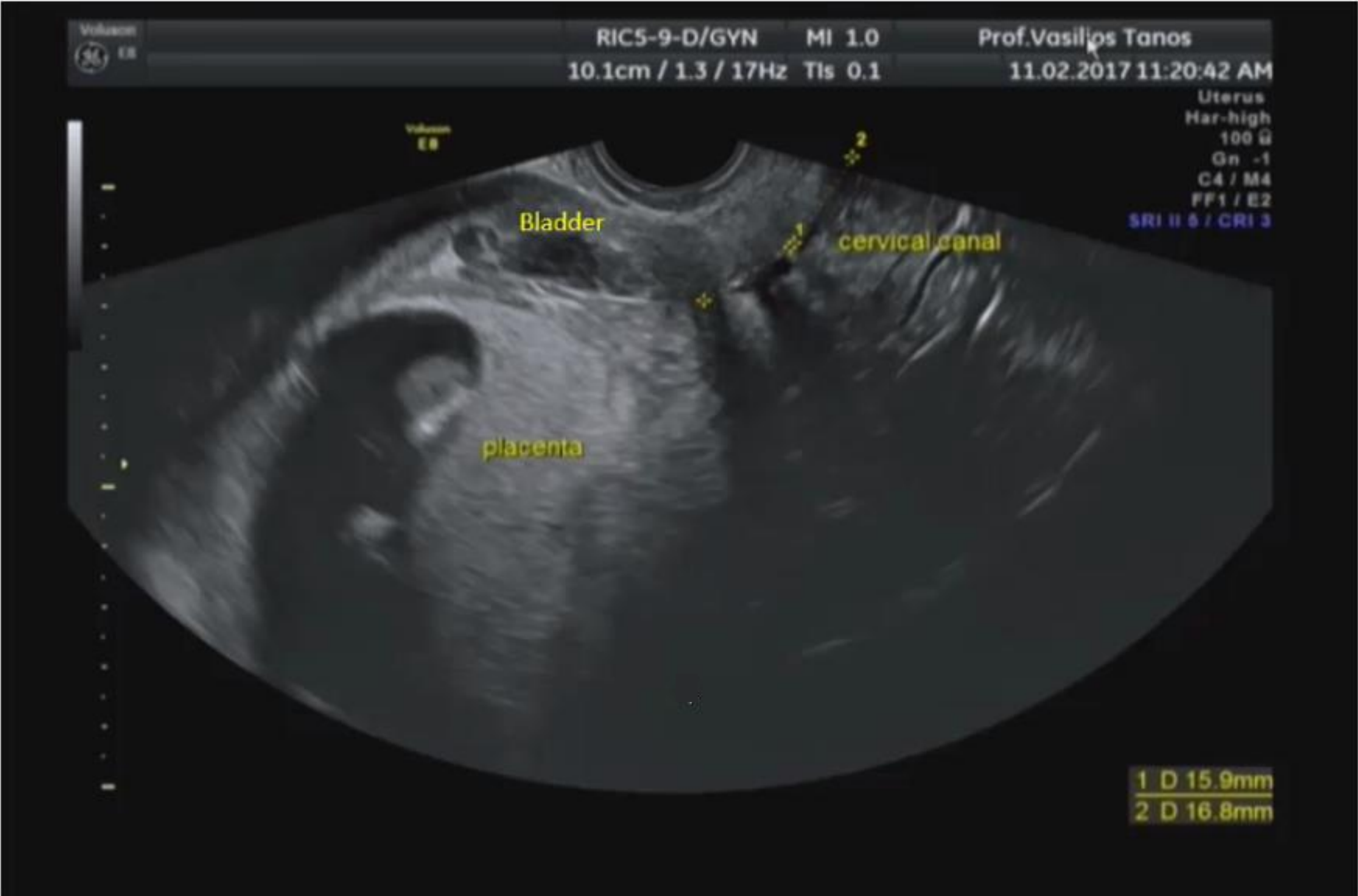


Management of EP

Tubal pregnancy

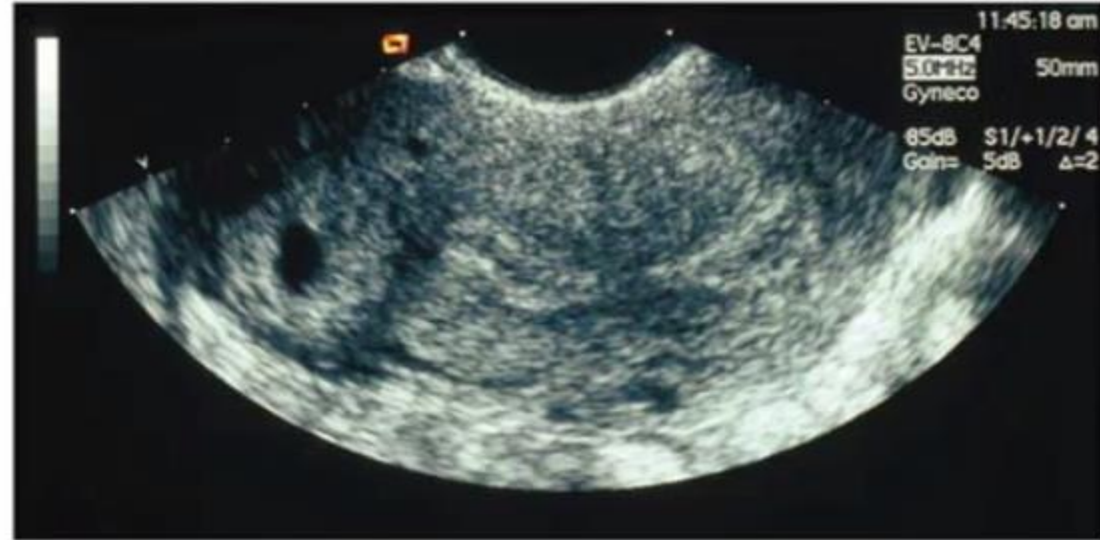
- Conservative management
  - Expectant (spontaneously resolved) close follow up needed
  - Methotrexate treatment
- Surgery (laparoscopy or laparotomy)
  - salpingectomy, salpingostomy

Ectopic placentation - placenta praevia

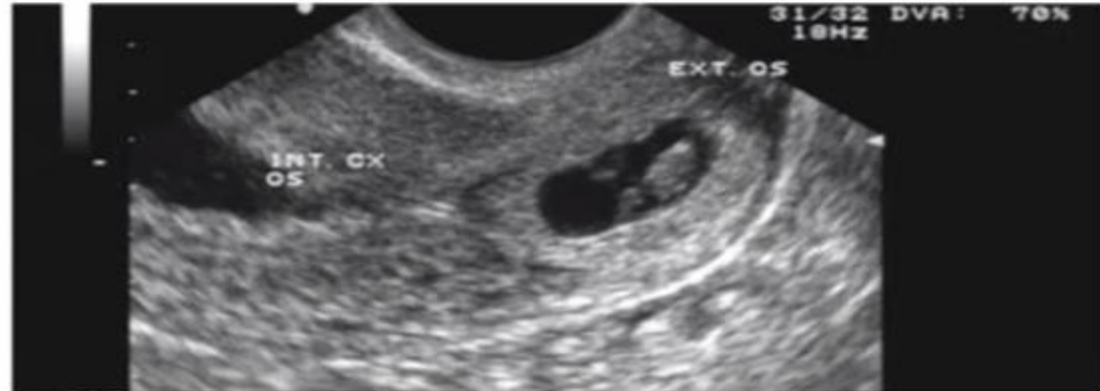


Rare sites of ectopic pregnancy

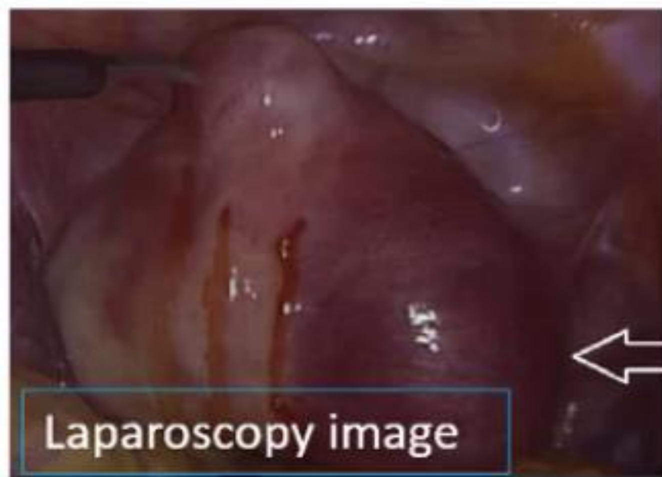
Interstitial pregnancy gestational sac is located 1 cm lateral to the endometrium in a woman with an incomplete septum



Cervical pregnancy: Sac is located below the level of the cervical internal os. Absence of the "sliding sign" clinches the US diagnosis



Interstitial pregnancy US diagnosis - 2D versus 3D


Laparoscopy image

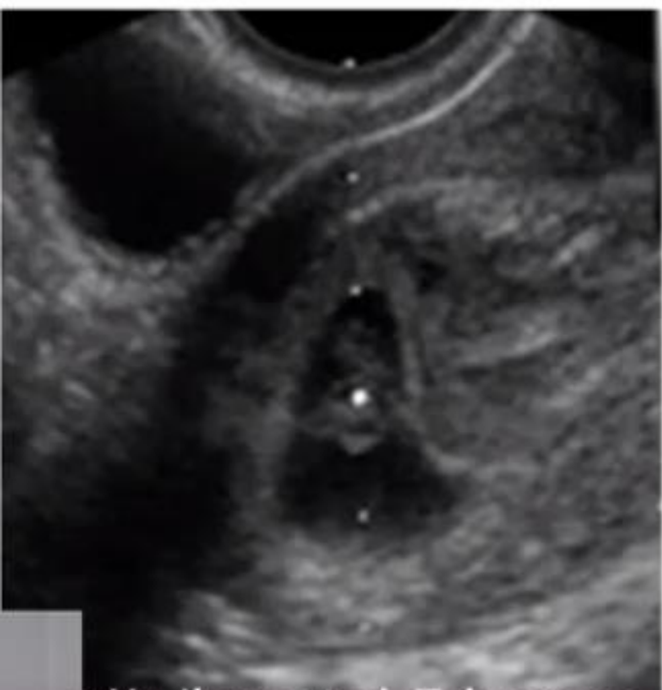
Gest.Sac surrounded by thin <5mm myometrium, close to the uterine serosa

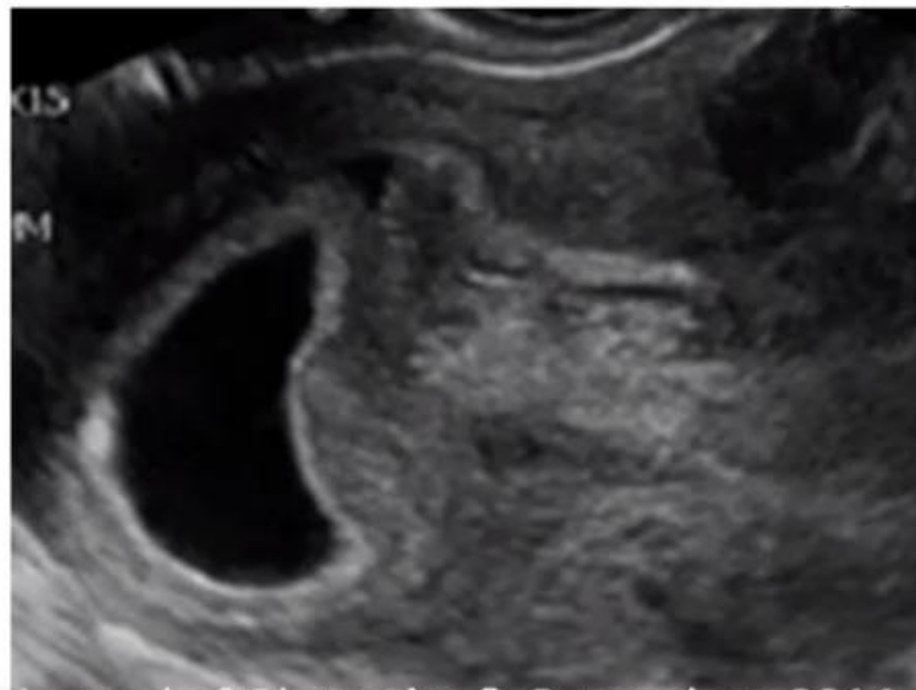
The interstitial line is more useful than an eccentric sac location or myometrial thinning

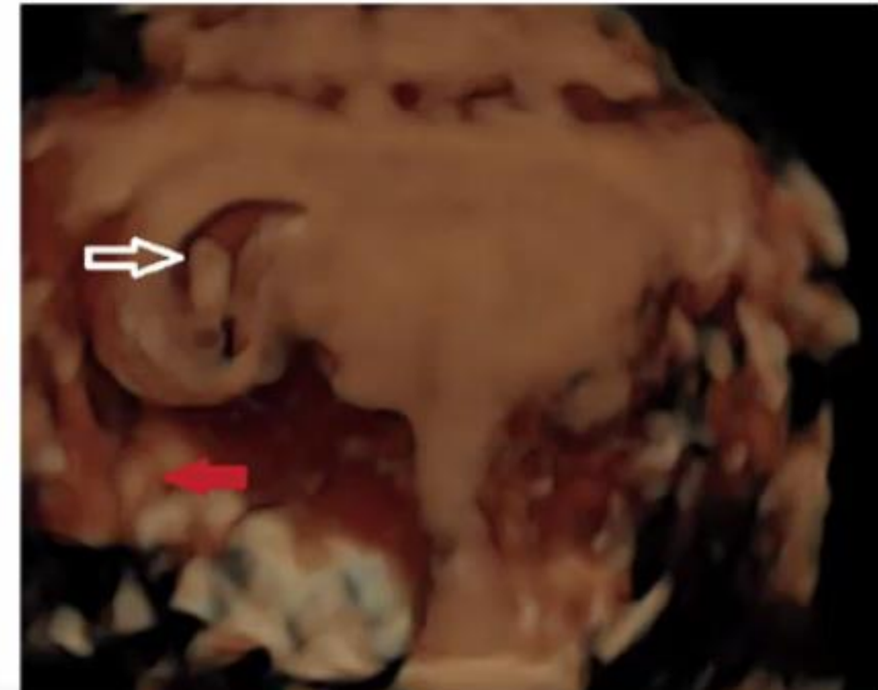
(Ackerman TE et al. Interstitial line: sono finding in interstitial pregnancy Radiology 1993)

2D US images

3D HD live rendering image

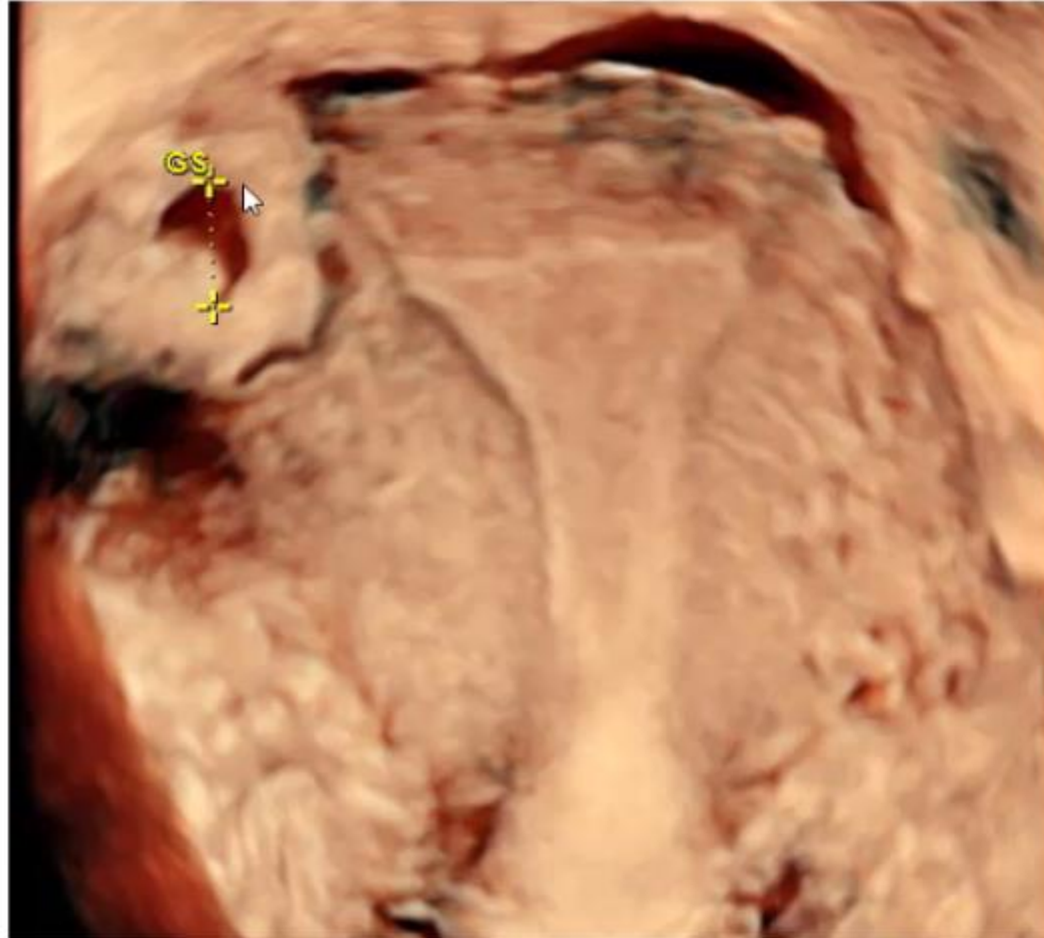




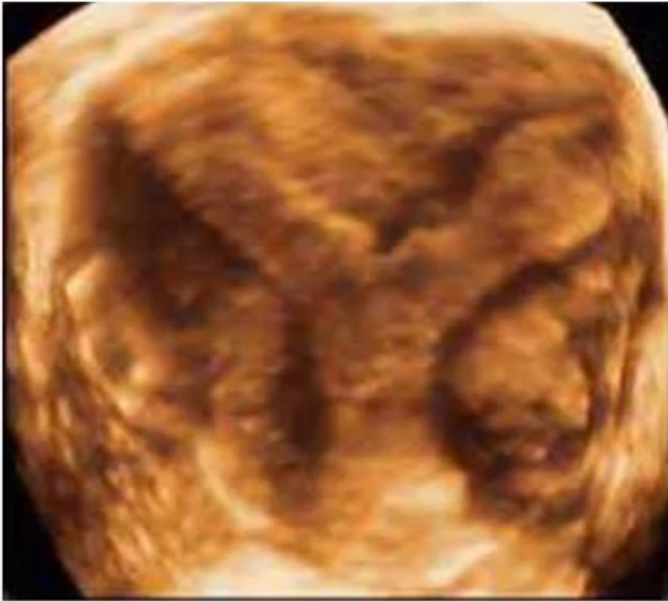


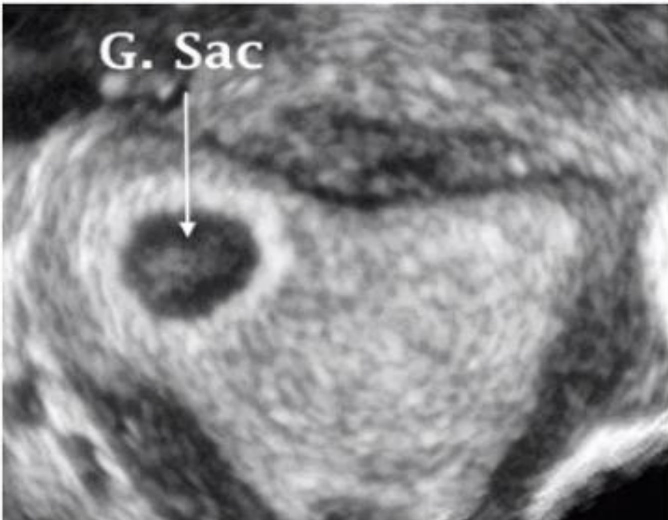
-Yu Jiang et al. Taiwanese Journal of Obstetrics & Gynecology 2014

Interstitial pregnancy



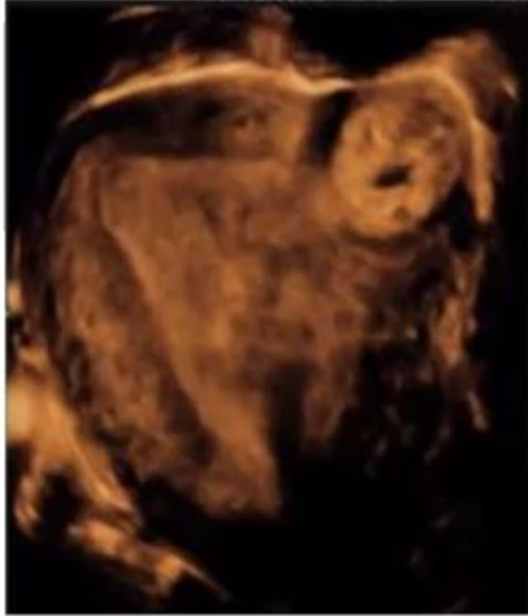
Clinical Diagnosis of IP

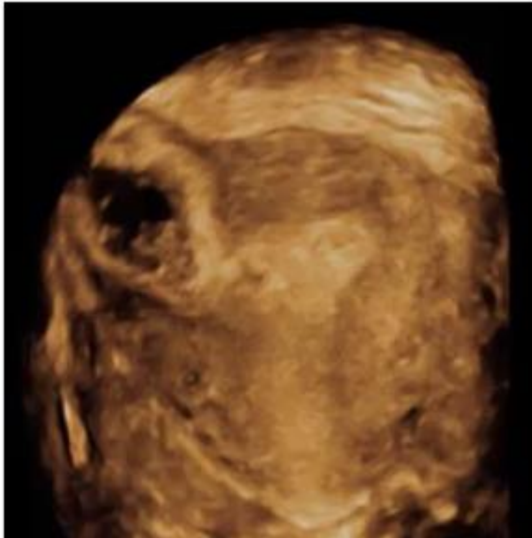




- Criteria like other types of tubal pregnancy
- Acute abdominal pain
- Intraperitoneal bleeding
- Low haematocrit
- Positive serum or urine pregnancy test

Vaginal ultrasonography and IP





- Dg of interstitial pregnancy. Asymmetry of the uterus-indicative of IP
- DD or misinterpreted as a pregnancy. In a bicorporated uterus or a myoma in a pregnant uterus
- Knowledge of the previous shape of the uterus. Confirms or exclude the existence of conuta or myomatous uterus
- Firm protrusion on the uterus suggests a myoma soft, tender asymmetric enlargement = IP

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Pathophysiology of cornual pregnancy

- Occurs at the most vascularized area of female pelvis
- Junction of the uterine and ovarian vessels
- Developing chorionic villi into the cornua may cause severe haemorrhage
- Rupture usually causes profound and sudden shock

A unique risk factors for interstitial pregnancy

- Ipsilateral salpingectomy
- Occurring in 37.5% of patients *(SRS Interstitial Pregnancy Registry Canadian Study)*

Symptoms

- Pelvic pain and vaginal spotting are common early symptoms

  later...> 12 gestational weeks is disputed

  (Tulandi and AL-Jaroudi Ob Gyn 2004)

- Gestational sac does not grow asymptomatic in the interstitial than in other portions of the tube

- 14 cases (43.7%) of rupture of interstitial pregnancy all at the time of initial diagnosis

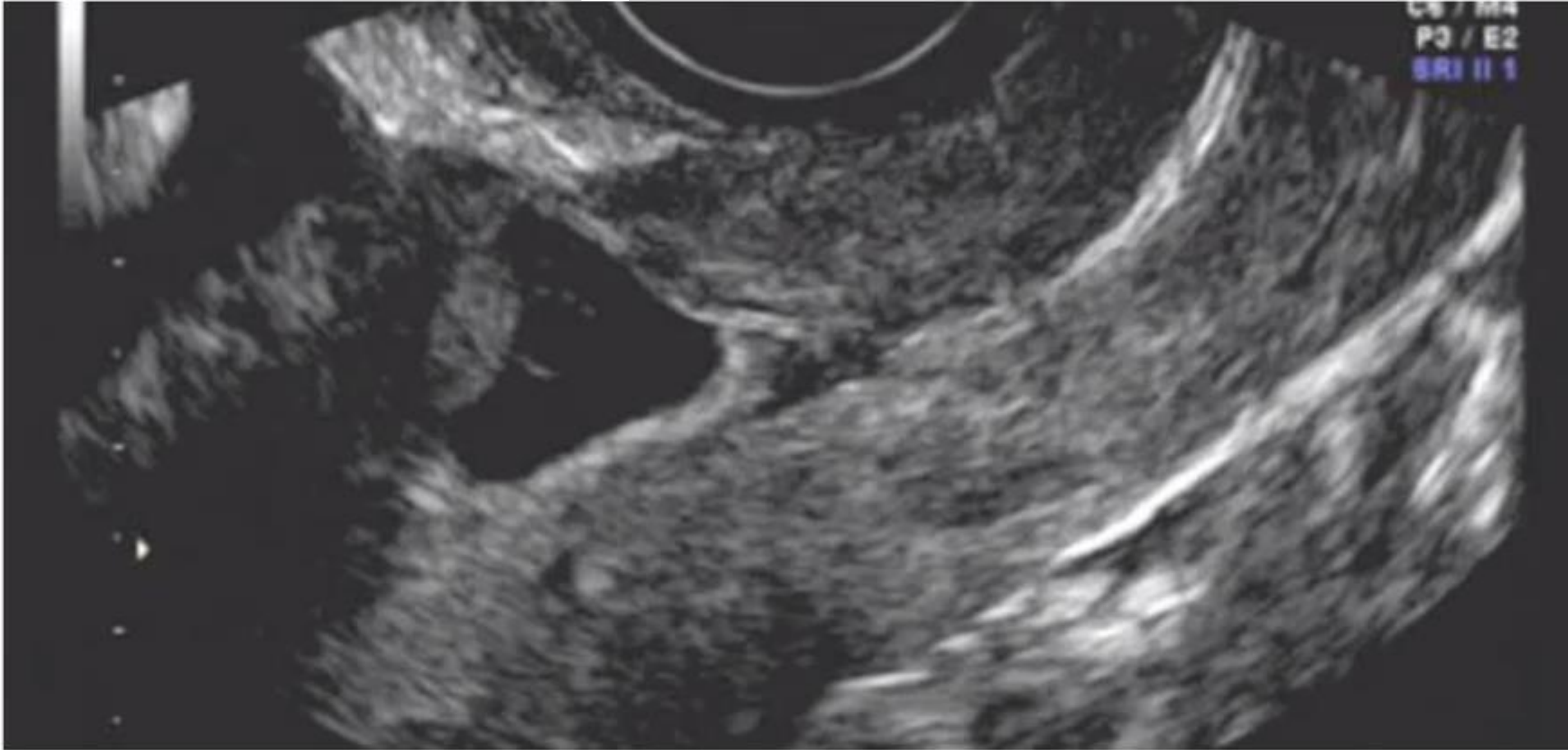
[Interstitial Pregnancy Registry by the Society of Reproductive Surgeons (SRS)]

Clinical Diagnosis of IP

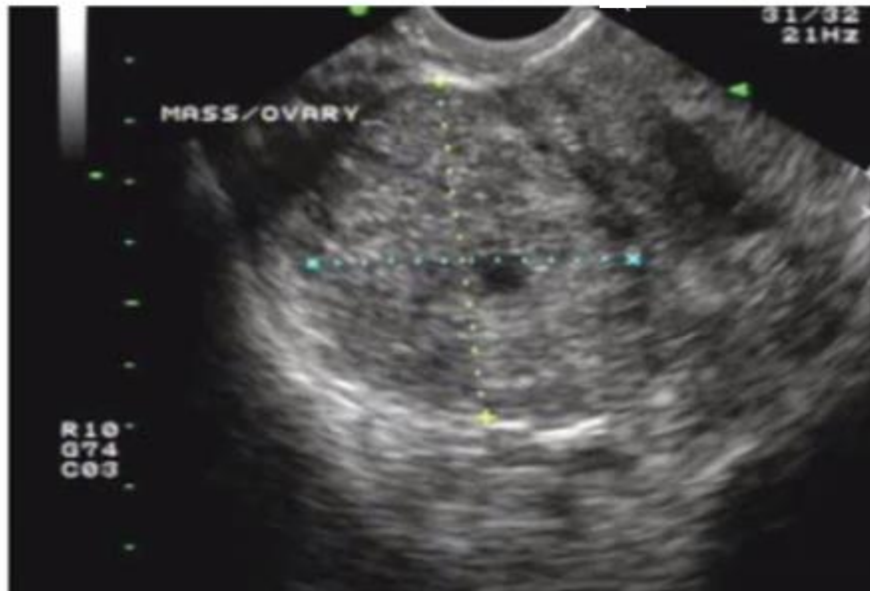
- Criteria like other types of tubal pregnancy
- Acute abdominal pain
- Intraperitoneal bleeding
- Low haematocrit
- Positive serum or urine pregnancy test

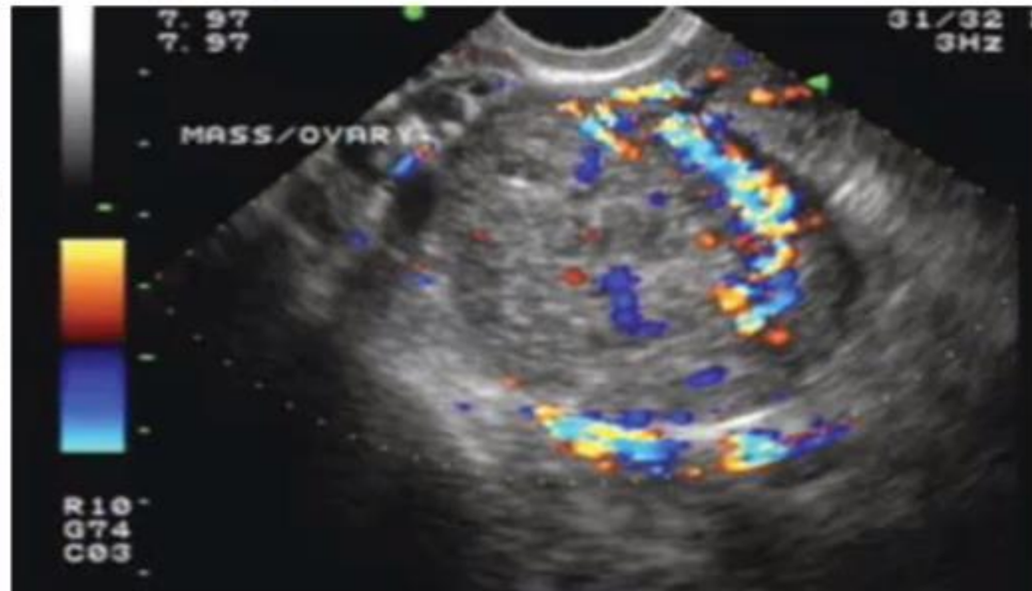
Caesarean section scar ectopic pregnancy

Niche or Isthmocelle

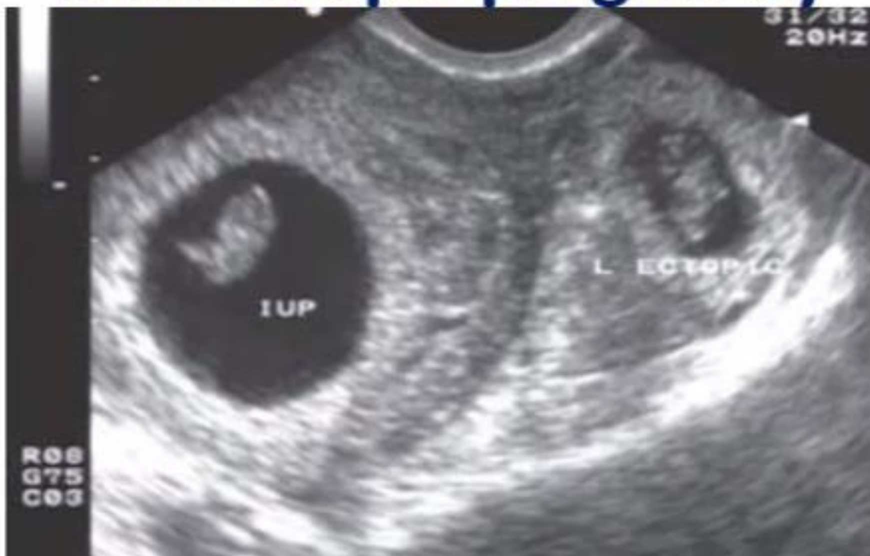


Ovarian ectopic pregnancy highly vascular

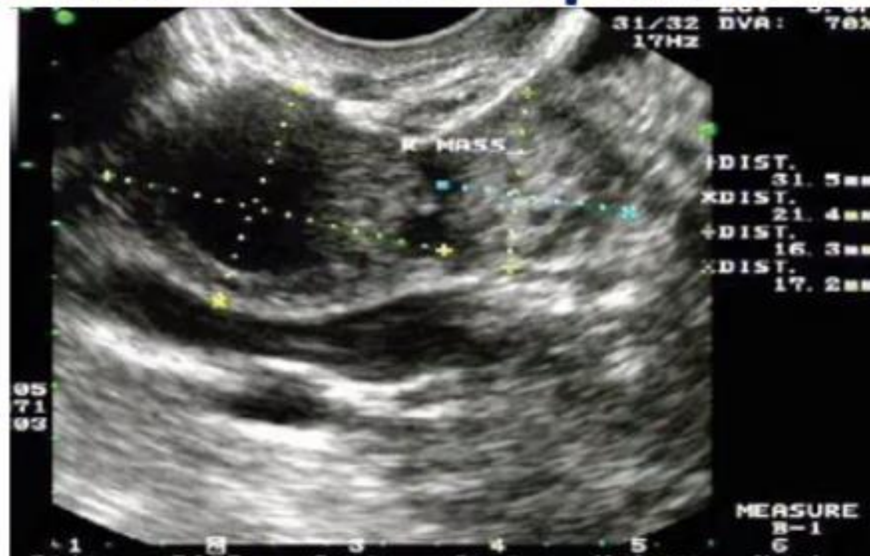




Heterotopic pregnancy



Mass in the Fallopian tube



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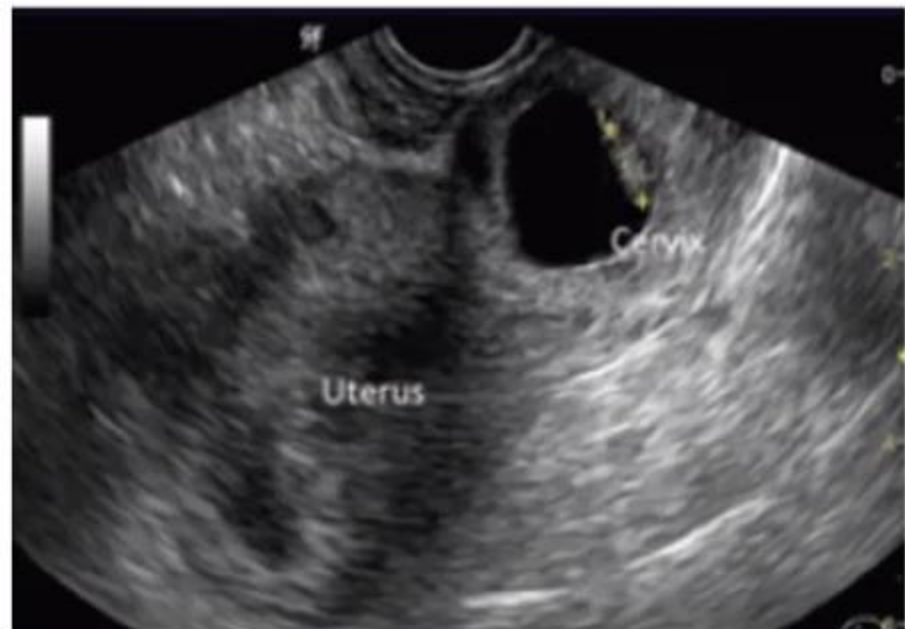
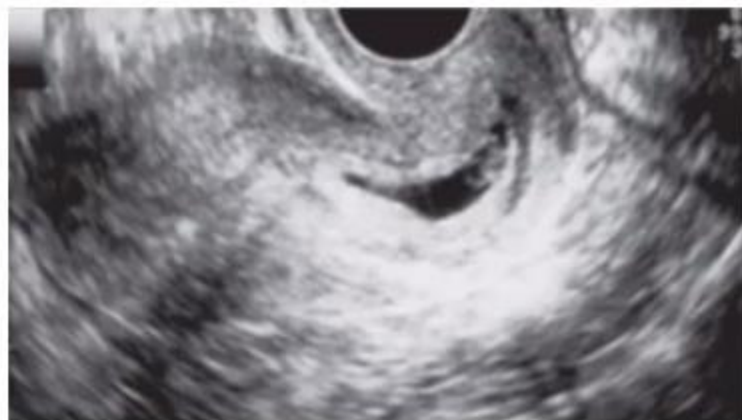
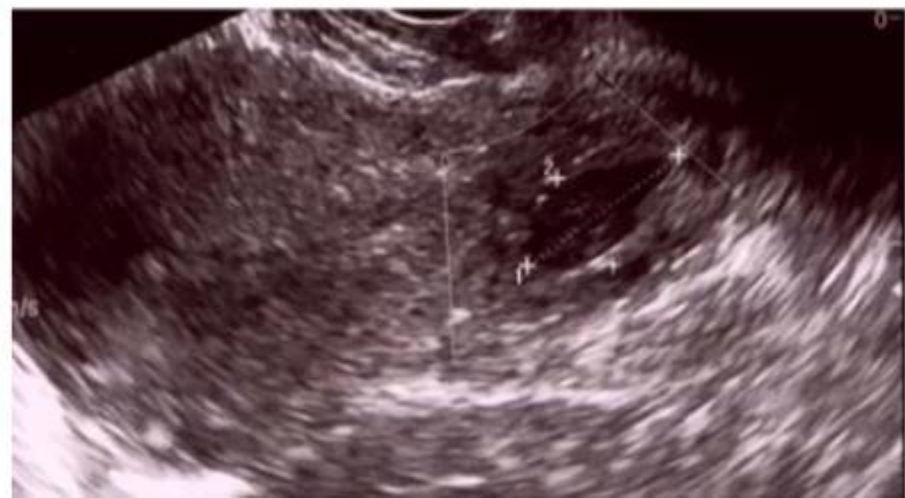
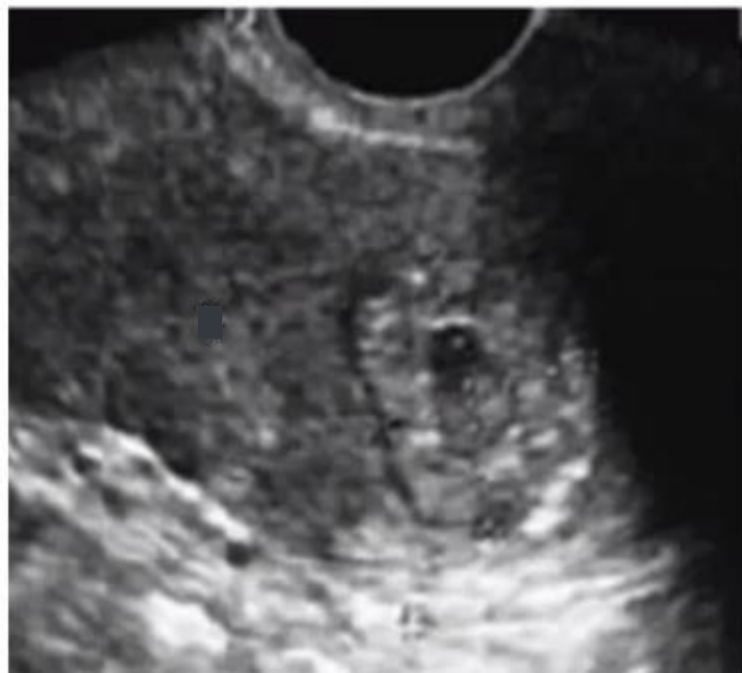
US images of Cervical Pregnancy





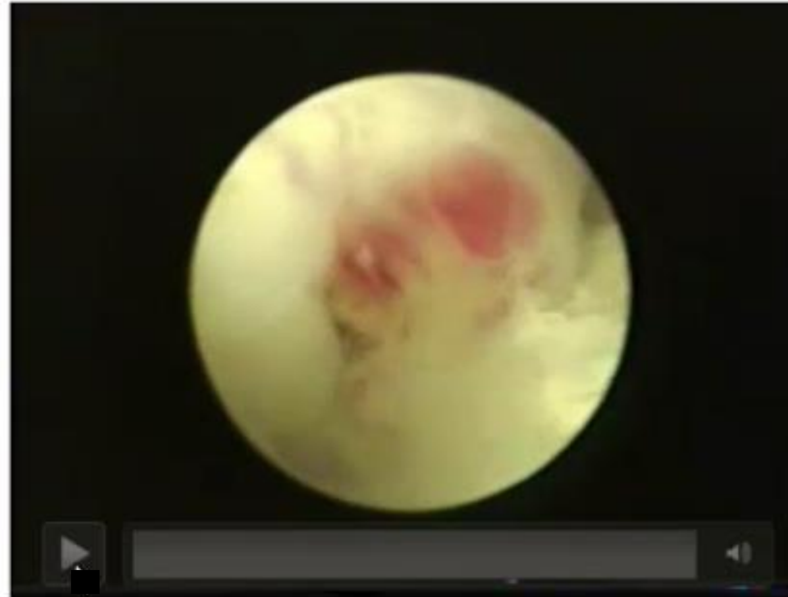




Sonographic Characteristics of CP

- Empty sac
- Barrel-shaped cervix
- Gestational sac present below the level of the uterine arteries
- Absence of the sliding sign

  (when pressure is applied to the Cx by the US probe the GS slides against the endocervical canal in a miscarriage but not in the CP)
- Blood flow in color Doppler around the gestational sac



Tanos et al. Journal Obst Gyn and Human Reproduction 2018

Kirk E et al US ObGyn 2006

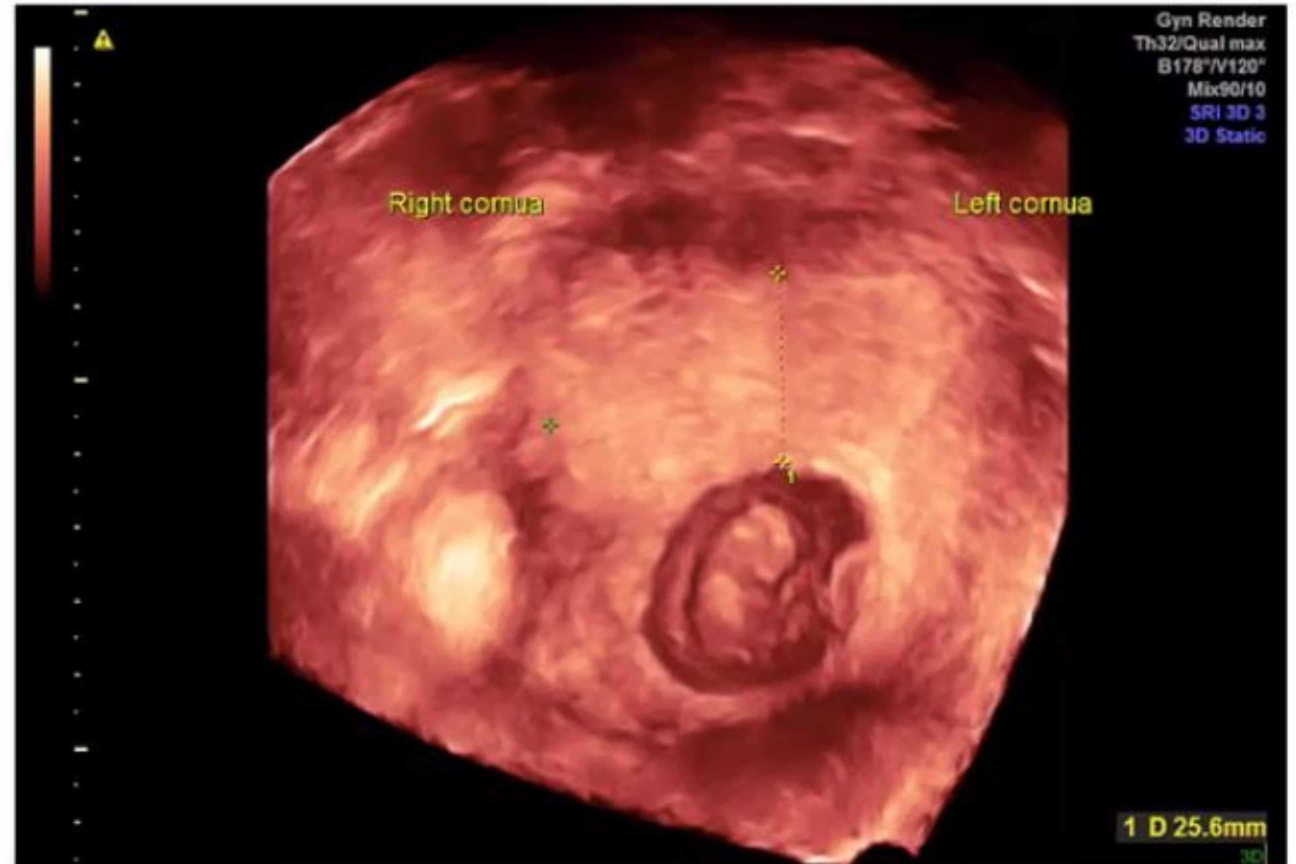
Caesarean scar ectopic

Increasing frequency of CS

Expected to see an increase the number of CSE

Methotrexate treatment

Laparoscopic excision



Cervical ectopic

Sonographic Characteristics

- Empty sac
- Barrel-shaped cervix
- Gestational sac present below the level of the uterine arteries
- Absence of the sliding sign (when pressure is applied to the Cx by the US probe the GS slides against the endocervical canal in in a miscarriage but not in the CP)
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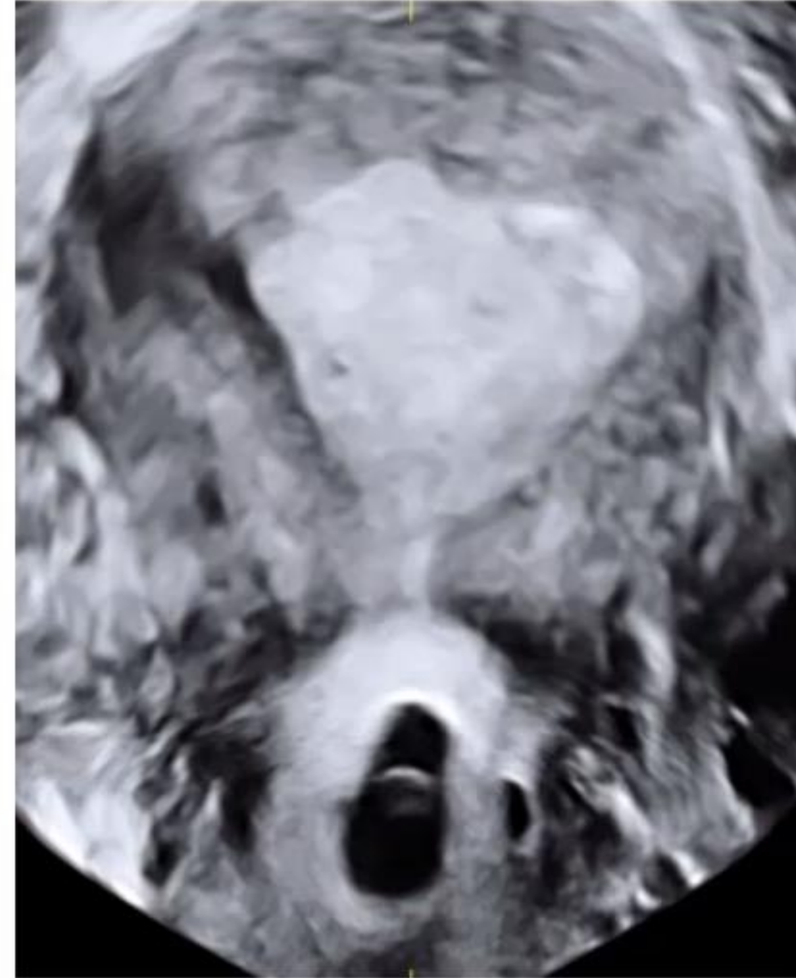
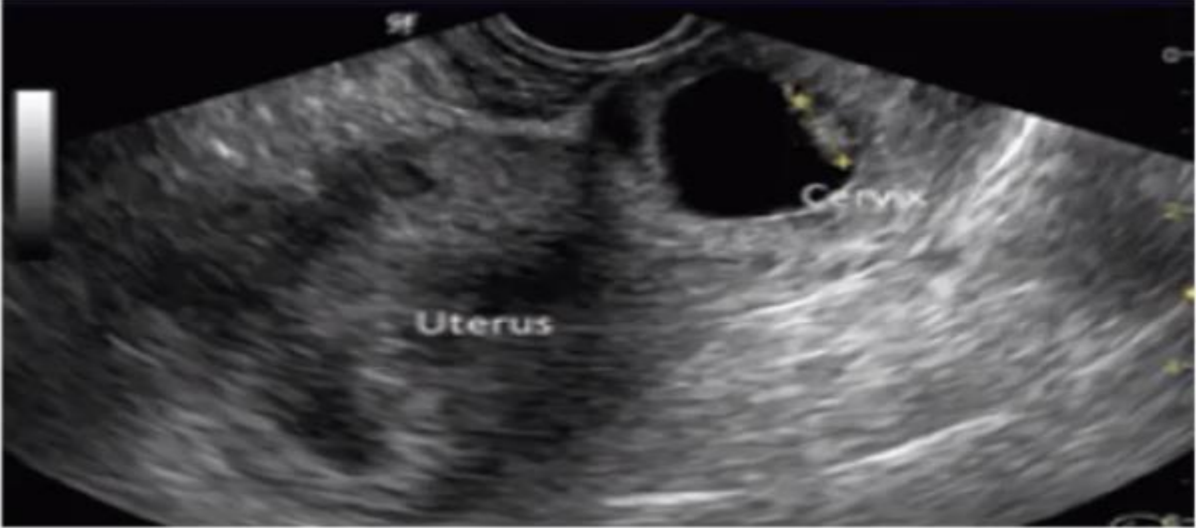
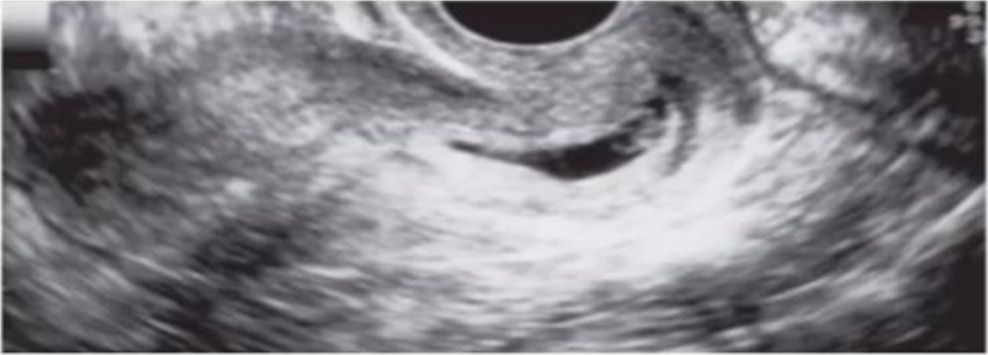
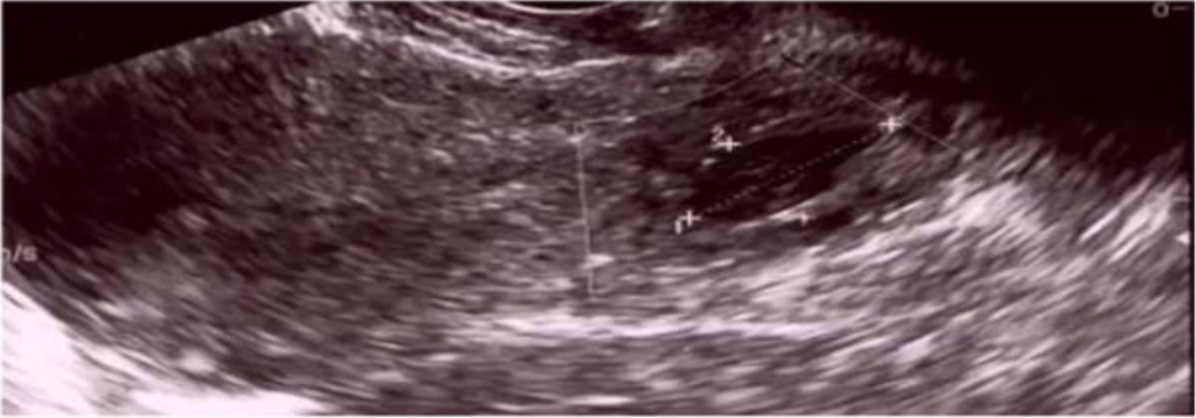
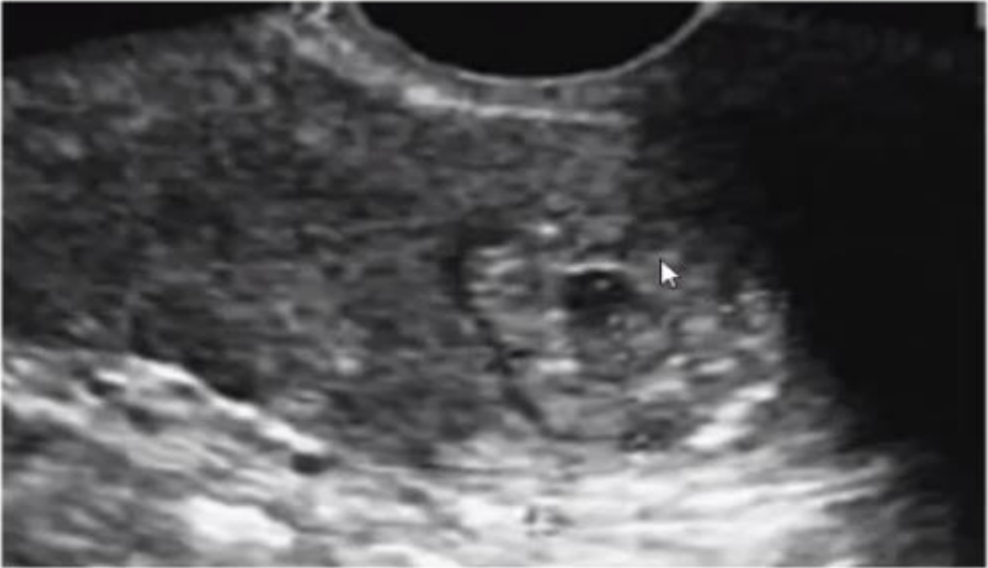


US images of Cervical Pregnancy









Cervical pregnancy clinical manifestations

- associated with significant morbidity
- life-threatening hemorrhage
- may require hysterectomy to prevent maternal death
- conservative and fertility-sparing management strategies are poorly described in the literature
- there is no clear standard of care
- conservative/fertility-sparing management can be successful

Kofinas JD, Purisch SE, Brandt JS, Montes M J Gyn Surgery, Vol. 28, No 5, 2012

Cervical Pregnancy Dgs & treatment

- high-resolution US assist to implement conservative treatment methods of cervical pregnancies
- decrease hysterectomies from 90% to some 15%

[Rubin IC. *Am J Obstet Gynecol* 1911; 13: 625-633]

- systemic or local administration of cytotoxic drugs (methotrexate, actinomycin D, cyclophosphamide)
- application of PGF2-alpha to the cervical canal in order to prevent severe bleeding

Raba G, Baran P, Szczupak K Journal of ObGyn of India 2015, 65(2):122–124

MTX and CP

- 10-18.7% of cervical pregnancies do not respond well to MTX treatment

Usually accompanied by:

- cervical evacuation
- dilatation and curettage
- with or without balloon tamponade

Grimbizis G, et al. *Reprod Biomed Online* 2006

Tinelli A, et al *Eur J Contracept Reprod Health Care* 2007

Indications for MTX treatment for EP

Indications

- Haemodynamically stable patients
- Minimal or no symptoms
- Serum hCG is < 5000 IU/L
- Ectopic mass < 3.5 cm
- No embryonic cardiac activity
- Confirmed diagnosis of ectopic pregnancy
- Able to comply with the follow-up

Contraindications

- Hemodynamically unstable
- Suspected ruptured EP
- Heterotopic pregnancy
- Pregnancy of unknown location
- Breastfeeding
- Chronic liver disease
- Renal disease
- Active peptic ulcer or colitis
- Active pulmonary disease
- Immunodeficiency
- Haematological disease
- Sensitivity to MTX
- Unable to comply w visits,follow-up