

## Pregnancy of Unknown Location and Ectopic Pregnancy

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## Pregnancy of Unknown Location and Ectopic Pregnancy

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Disclosures: None

## Learning Objectives

- Nomenclature regarding pregnancy of unknown location (PUL)
- Alternative approaches the diagnostic dilemma of evaluating a patient with a possible ectopic pregnancy.
- Understand the value of various diagnostic tests.
- Gain insight into the ultrasound findings in patients with an ectopic pregnancy

## Consensus Nomenclature

1. Definite ectopic pregnancy (EP)
2. Probable EP
3. PUL
4. Probable intrauterine pregnancy
5. Definite IUP

Barnhart et al. Fertil Steril 2011; 95: 857-866

## Consensus Nomenclature

- Definite ectopic pregnancy (EP)
  - Extrauterine gestational sac with yolk sac and/or embryo (with or without cardiac activity)
- Probable EP
  - Inhomogeneous adnexal mass or extrauterine sac-like structure

Barnhart et al. Fertil Steril 2011; 95: 857-866

## Consensus Nomenclature

- Probable intrauterine pregnancy
  - Intrauterine echogenic sac-like structure
- Definite IUP
  - Intrauterine gestational sac with yolk sac and/or embryo (with or without cardiac activity)

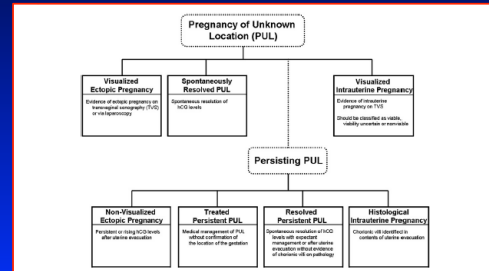
Barnhart et al. Fertil Steril 2011; 95: 857-866

## Consensus Nomenclature

- PUL
  - no signs of either EP or IUP

Barnhart et al. Fertil Steril 2011; 95: 857-866

## Pregnancy of Unknown Location



Barnhart et al. Fertil Steril 2011; 95: 857-866

CP 1

## Case Presentation

- 28 y.o. G1P0 presents with pelvic pain and scant vaginal spotting.
- LMP ~ 4-5 weeks ago
- + UPT at home
- Exam: VSS
  - Uterus AV, NT, TNS
  - Adnexa: NT, without masses
- hCG = 874 IU/L

## Increase in hCG in early pregnancy

Sampling Interval (days)	% Increase
1	29
2	66
3	114
4	175
5	255

Kadar et. al. Obstet Gynecol 1981; 58: 162 (Yale)

## Increase in hCG in early pregnancy

- Doubling time = 2.98 days
- 15% of normal pregnancies had abnormal  $\beta$ -hCG increases

Kadar et. al. Obstet Gynecol 1981; 58: 162 (Yale)

## Increase in hCG in early pregnancy

Days	Range	Median
1	1.24 – 1.81	1.50
2	1.53 – 3.28	2.24
3	1.88 – 5.94	3.35
4	2.33 – 10.76	5.00
7	4.38 – 63.88	16.73

Barnhart et al. Obstet Gynecol 2004; 104: 50-55.

## Case Presentation

Day 1	hCG = 874 IU/ml
Day 3	hCG = 1,056 IU/ml
Day 5	hCG = 1,110 IU/ml

## Threshold vs. Discriminatory Levels

### Threshold level

- Lowest  $\beta$ -hCG level at which a normal intrauterine pregnancy can be detected

### Discriminatory level

- The level of  $\beta$ -hCG above which all normal intrauterine pregnancies should be seen

## Threshold vs. Discriminatory Levels

### Threshold level

- $\beta$ -hCG = 400-500 mIU/mL (1st IRP)

### Discriminatory level

- $\beta$ -hCG = 1000-1500 mIU/mL (1st IRP)

### Dependencies

- Transducer frequency, uterine position, body habitus, operator experience/ability

## Evidence Against the hCG Discriminatory Level

- January 1, 2000 - December 31, 2010
- TVS and  $\beta$ -hCG on same day
- No intrauterine fluid collection
- Subsequent embryonic or fetal cardiac activity

Doubilet and Benson, J Ultrasound Med 2011; 30:1637-1642

## Evidence Against the hCG Discriminatory Level

hCG (3-4 <sup>th</sup> IS)	# (202)	%
<1000	162	80.2
1000-1499	19	9.4
1500-1999	12	5.9
2000	9	4.5

Doubilet and Benson, J Ultrasound Med 2011; 30:1637-1642

## Reevaluation of Discriminatory and Threshold Levels

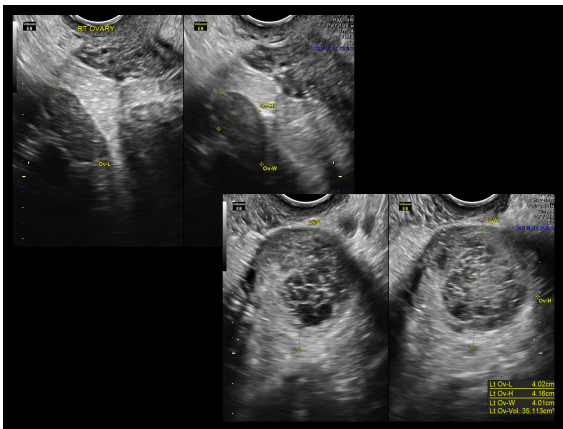
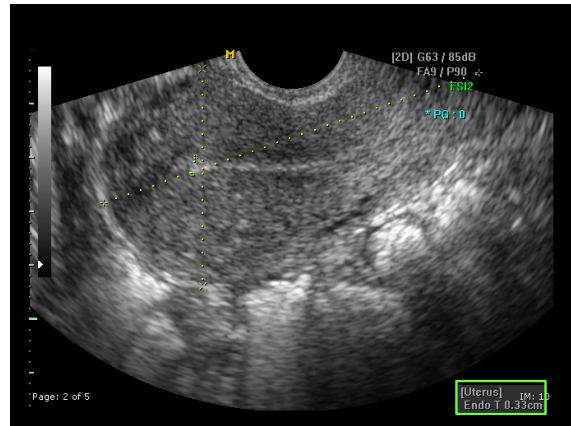
- 651 patients
- TVS and  $\beta$ -hCG within 6 hours of each other
- Known intrauterine pregnancies
- Findings visualized 99% of the time
- 1<sup>st</sup>, 3<sup>rd</sup>, or 4<sup>th</sup> International Standard
  - 2<sup>nd</sup> I.S. ~ 1/2 that of others

Connolly et al. Obstet Gynecol 2013;121:65-70.

## Reevaluation of Discriminatory and Threshold Levels

hCG = mIU/mL	Gestational Sac	Yolk Sac	Embryo
Threshold level	390	1094	1394
Discriminatory level	3510	17,716	47,685

Connolly et al. Obstet Gynecol 2013;121:65-70.



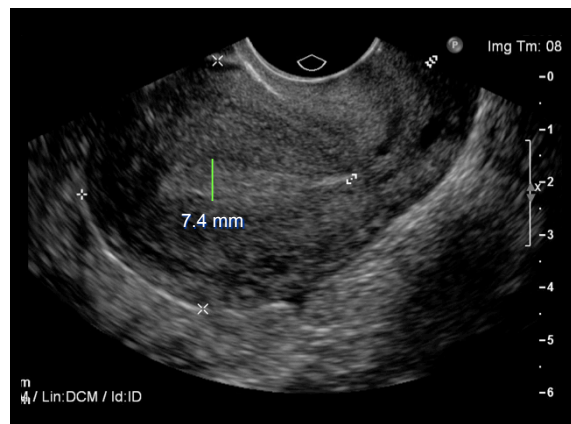
CP 1

## Case Presentation

- TVS
  - Uterus
    - No evidence of IUP
  - Ovaries
    - Corpus luteum - left
  - Adnexa
    - No definite adnexal pathology
- Current terminology PUL
- Treatment MTX 50 mg/m<sup>2</sup>

## Case Presentation

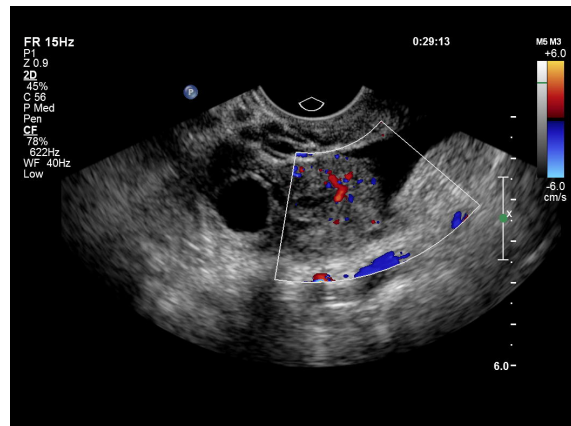
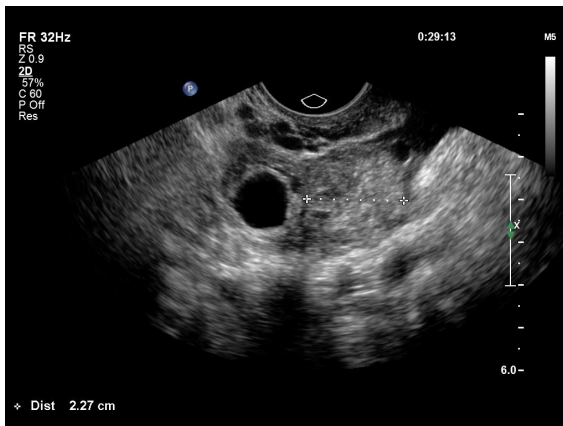
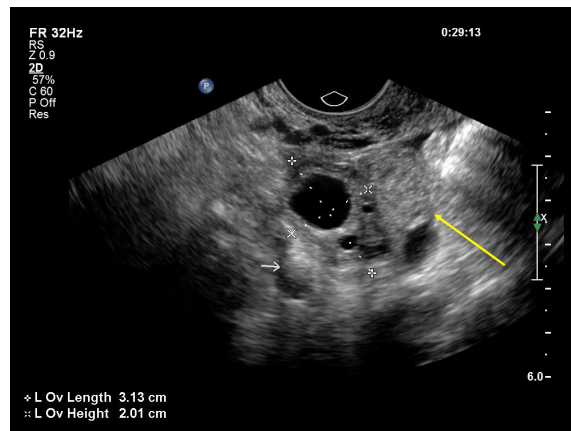
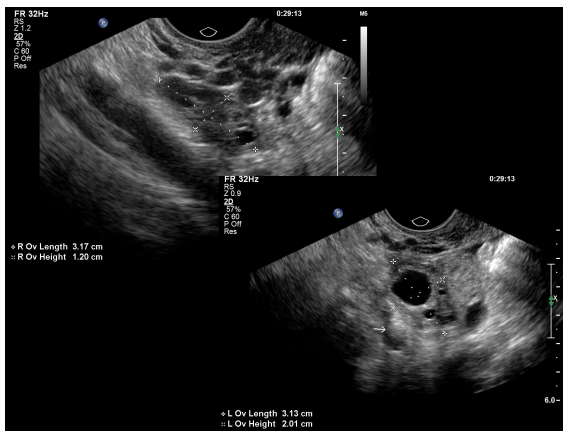
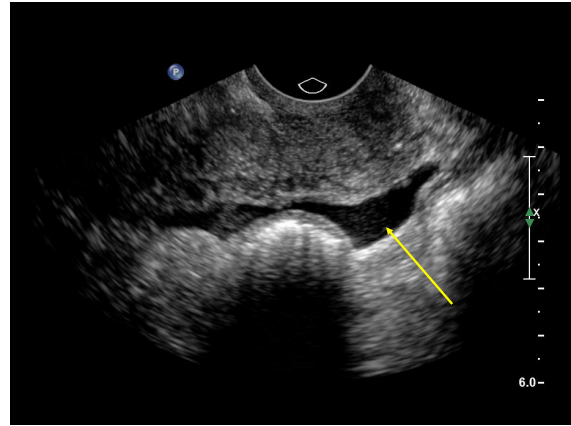
- 24 y.o. G2P0010 presents with scant vaginal spotting and pain
- LMP ~ 5 weeks ago
- Exam: VSS
  - Uterus NSSC, NT; Adnexa: NT
- Initial: hCG = 710 IU/L
- Repeat in 2 days: hCG = 980 IU/L

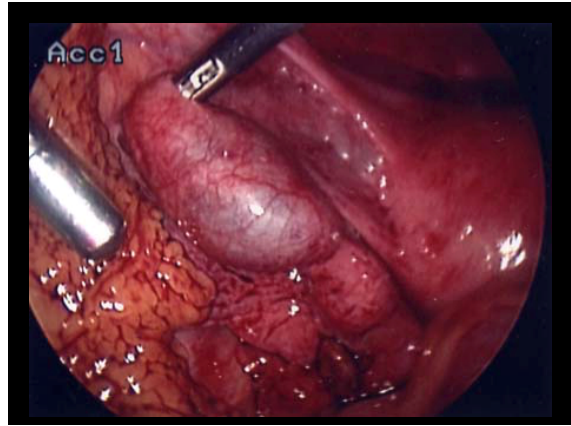
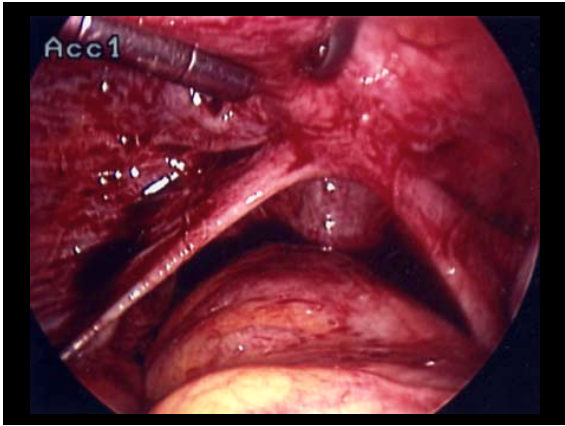


## Endometrial Thickness in Ectopic Pregnancy when hCG < Discriminatory Zone

Outcome	Mean (mm)	Range (mm)
Intrauterine pregnancy	13.42	$\pm 0.68$
Spontaneous abortion	9.28	$\pm 0.88$
Ectopic pregnancy	5.95	$\pm 0.35$
Abnormal pregnancy (97%)	$\leq 8$	

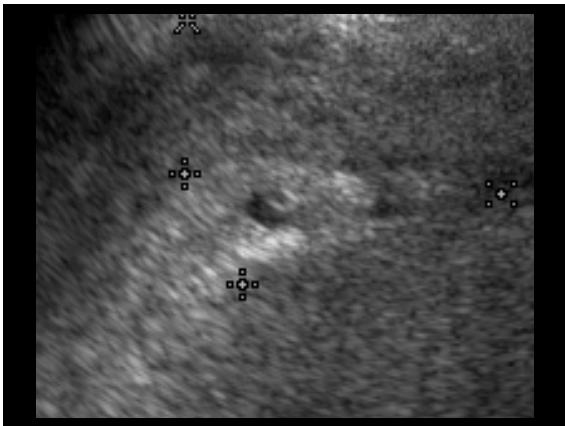
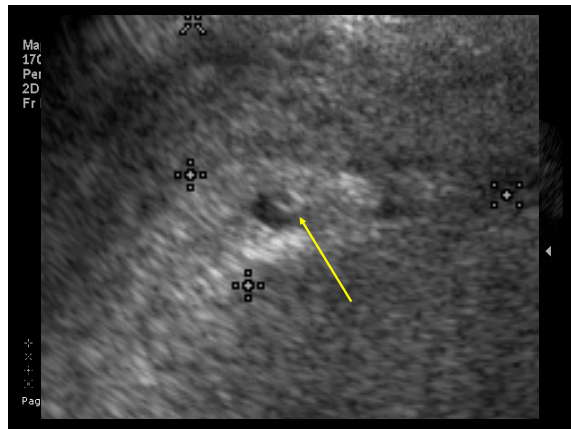
Spandorfer and Barnhart. Fertil Steril 1996; 474-47.





**Case Presentation - #3**

- 28 y.o. G1P0 presents with pelvic pain and scant vaginal spotting.
- LMP ~ 7 weeks ago
- Exam: VSS  
     Uterus TNS;  
     Mild adnexal discomfort
- hCG = 4,634 IU/L



## Intrauterine Fluid with Ectopic Pregnancy

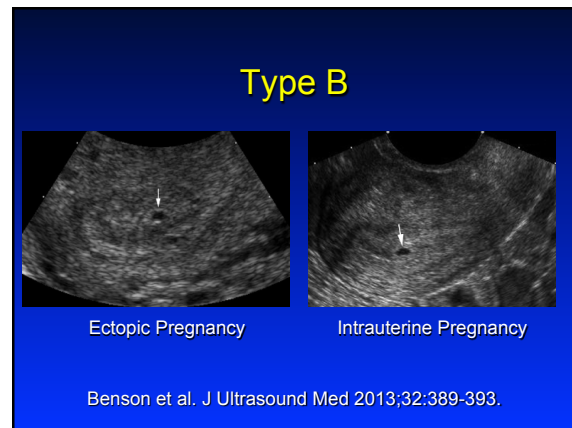
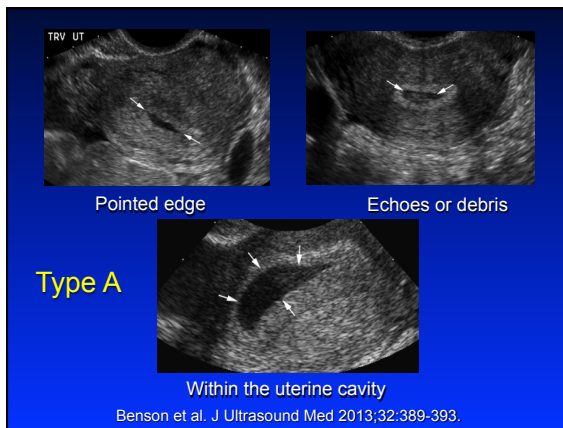
229 patients with ectopic	#	%
• No intrauterine fluid	191	83.4
• Intrauterine fluid	38	16.6
– Adnexal mass	33	86.8

Benson et al. J Ultrasound Med 2013;32:389-393.

## Intrauterine Fluid with Ectopic Pregnancy

38 patients	#	%
• Type A	31	81.6
– Pointy edged	30	78.9
– Echoes	28	73.7
– Located with the cavity	21	55.3
• Type B	7	18.4
– Smooth walled		
– Located in decidua or uncertain		

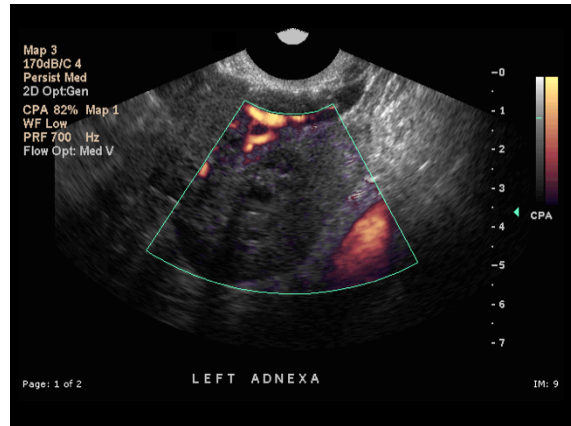
Benson et al. J Ultrasound Med 2013;32:389-393.



## Conclusions

- Findings
  - A smooth-walled anechoic intrauterine cystic structure
  - No adnexal mass
- Probability
  - Intrauterine pregnancy 99.8%
  - Ectopic pregnancy 0.02%





\*

## TVS for Diagnosing Ectopics

**Reviewed 10 studies**

- 2216 patients
- Ectopic = 565    25.5%
- No ectopic = 1651    74.5%

Brown and Doubilet, J Ultrasound Med 1994; 13: 259 (Harvard)

## TVS for Diagnosing Ectopics

**Inclusion criteria**

- Clinical suspicion of ectopic pregnancy
- All patients underwent TVS
- All cases of EP were surgically confirmed
- No adnexal masses were excluded, except simple cysts

Brown and Doubilet, J Ultrasound Med 1994; 13: 259 (Harvard)

## TVS for Diagnosing Ectopics

**Criteria for ectopic pregnancy**

- A: Adnexal embryo with heartbeat
- B: Adnexal mass containing yolk sac or embryo
- C: Adnexal mass with central anechoic area and hyperechoic rim ("tubal ring")
- D: Any adnexal mass other than a simple cyst or an intraovarian lesion

Brown and Doubilet, J Ultrasound Med 1994; 13: 259

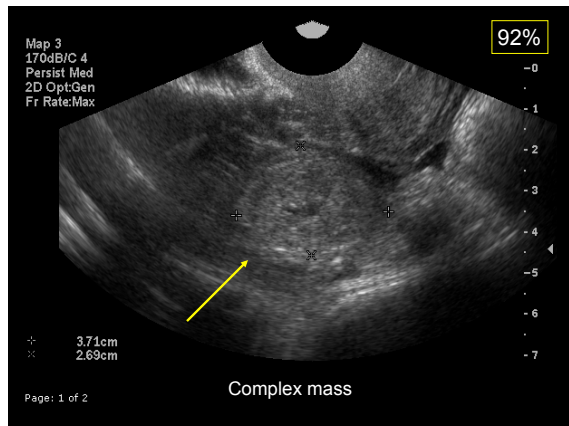
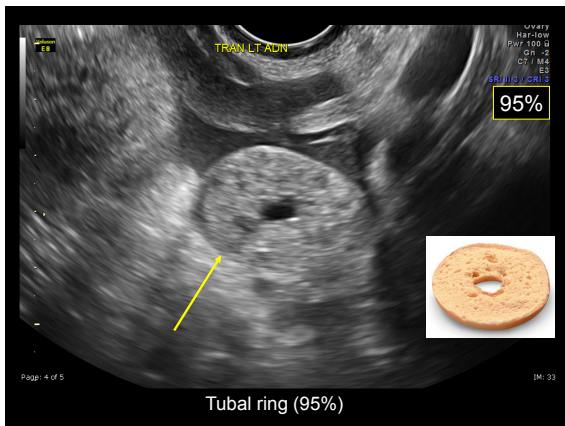
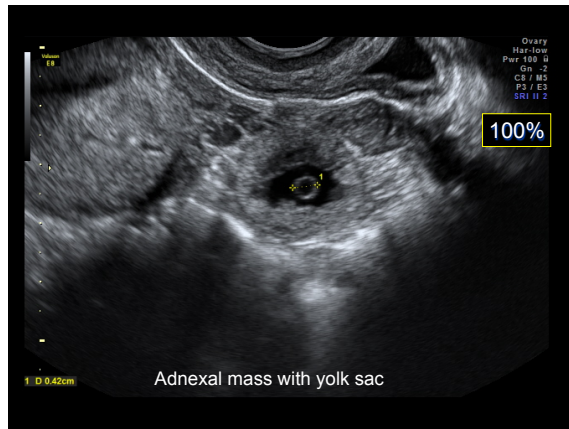
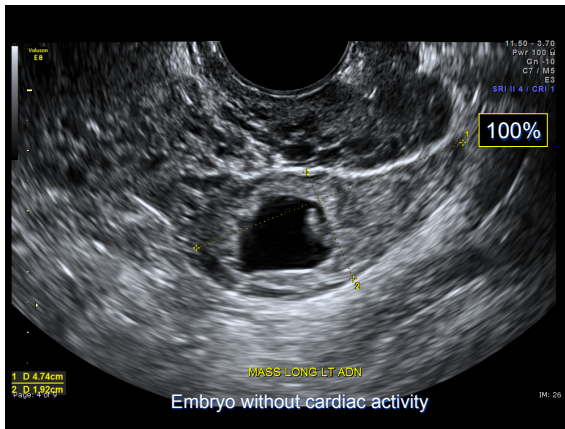


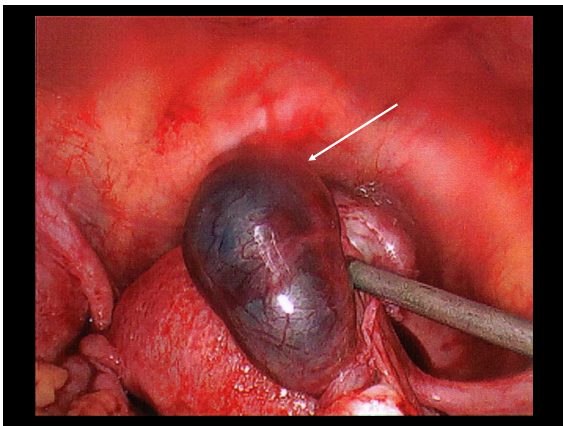
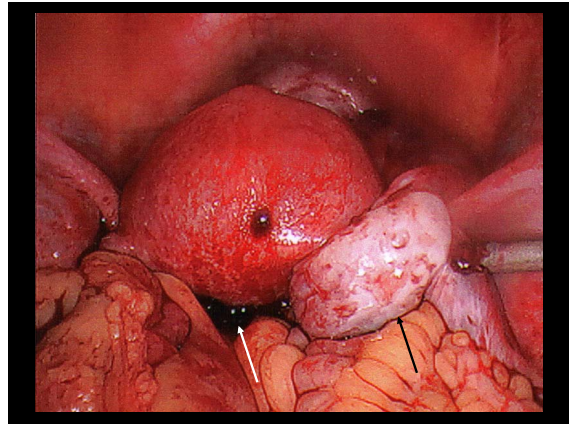
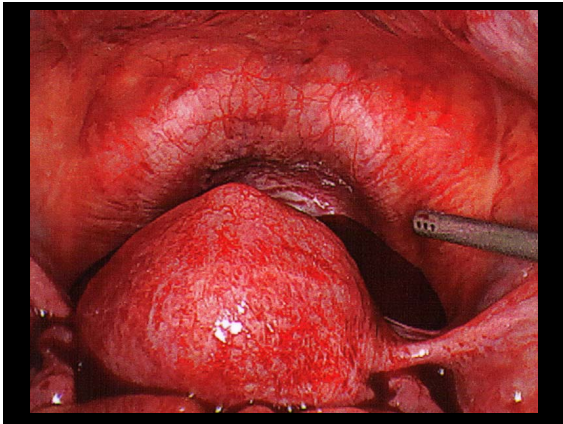
Adnexal Findings

TVS Criteria for Ectopic Pregnancy

TVS Finding	Likelihood of Ectopic
Extrauterine embryo + heartbeat	100%
Adnexal mass with yolk sac or embryo without heartbeat	100%
Tubal ring	95%
Complex or solid adnexal mass No tubal ring, yolk sac, embryo	92%

Brown and Doubilet, J Ultrasound Med 1994; 13: 259





### Diagnosing Ectopic Pregnancy Six Strategies

- Ultrasound followed by quantitative hCG
- Quantitative hCG followed by ultrasound
- Progesterone followed by ultrasound and quantitative hCG
- Progesterone followed by quantitative hCG and ultrasound
- Ultrasound followed by repeat ultrasound
- Clinical examination

Garcia and Barnhart. Obstet Gynecol 2001; 97: 464-70 (U. of Penn)

### Diagnosing Ectopic Pregnancy Six Strategies-Outcomes

Strategy	Missed EP/ 10,000	Interrupted IUP/10,000
US → hCG	0	70
hCG → US	0	122
P → US → hCG	24	25
P → hCG → US	24	39
US → US	0	121
Clinical Exam	940	0

Garcia and Barnhart. Obstet Gynecol 2001; 97: 464-70

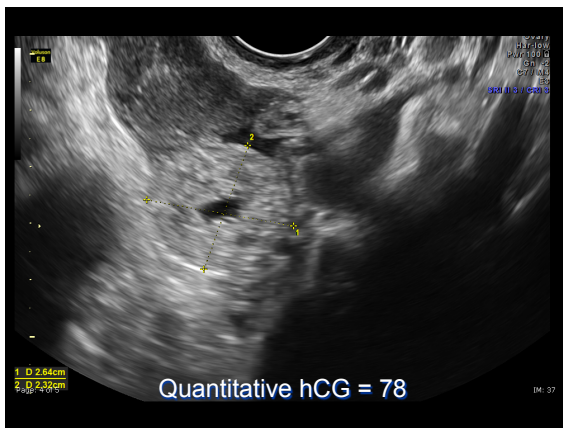
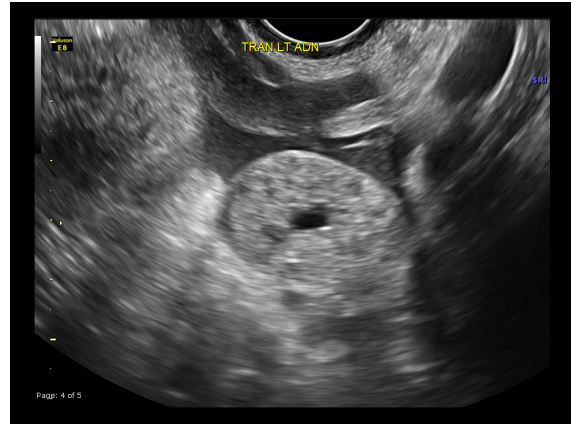
### Diagnosing Ectopic Pregnancy Six Strategies-Recommendations

- Ultrasound followed by hCG
- hCG followed by ultrasound
- Either progesterone protocol
  - More missed ectopic pregnancies
- Ultrasound followed by repeat ultrasound
  - May be applicable in poorly compliant patient
- Clinical exam only – NOT recommended

Garcia and Barnhart. Obstet Gynecol 2001; 97: 464-70

## Case Presentation

- 41 G2P0010 with LMP 3 weeks ago
- c/o vaginal bleeding and abdominal pain
- Unprotected intercourse x 10 years
- + UCG



## Ectopic Pregnancy

### hCG Dynamics with Spontaneous Resolution of Ectopic

Helsinki, Finland

118 patients

#### Entry criteria

- Decreasing or stable hCG
- No signs of rupture/intraperitoneal hemorrhage
- Adnexal mass < 4 cm
- No cardiac activity

Korhonen, Stenman, Ylostalo. Fertil Steril 1994; 61: 632-36 (Finland)

## Ectopic Pregnancy

### hCG Dynamics with Spontaneous Resolution of Ectopic

Helsinki, Finland

- TVS q 1-3 days
- Serial hCG until < 10 IU/L (3<sup>rd</sup> IS)
- Laparoscopy
  - Increasing hCG levels
  - Increasing abdominal pain
  - Intra-abdominal hemorrhage on TVS

Korhonen, Stenman, Ylostalo. Fertil Steril 1994; 61: 632-36

## Ectopic Pregnancy

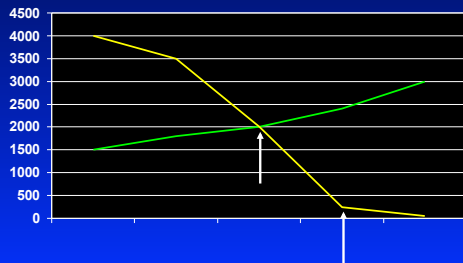
### hCG Dynamics with Spontaneous Resolution of Ectopic

#### Rate of Spontaneous Resolution

hCG < 200 IU/L	88%
hCG > 2000 IU/L	25%

Korhonen, Stenman, Ylostalo. Fertil Steril 1994; 61: 632-36

## Initial hCG

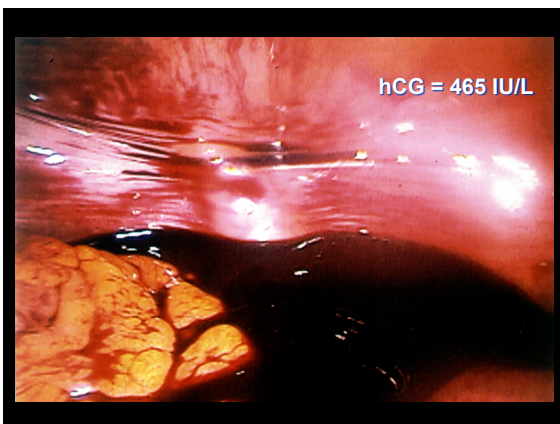
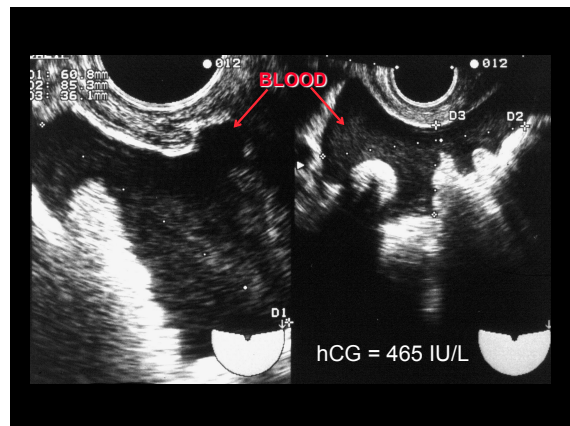


## Case Presentation

- 36 y.o. G3P0020 seen in ER with c/o slight spotting and mild abdominal discomfort
- Uterus: Mid-position, TNS
- Adnexa: No definite masses
- hCG = 357 IU/L
- Hct = 36.4
- D/C home with F/U 2 days in WCC

## Case Presentation

- WCC  
– c/o increasing pain and weakness



## Serum hCG and Tubal Rupture

<u><math>\beta</math>-hCG (IU/L)</u>	<u>Unruptured</u>	<u>Ruptured</u>
< 100	9.2%	11.4%
100 – 999	47.3%	38.6%
1000 - 9,999	38.2%	38.6%
> 10,000	5.3%	11.4%

Saxon et al. Obstet Gynecol 1997; 90: 46  
(McGill, Cleveland Clinic)

## Serum hCG and Tubal Rupture

hCG, mIU/mL	Unruptured	Ruptured	Rupture Rate %
< 1000	53	14 (41.2%)	20.9
1000-1999	14	6 (17.6%)	30.0
> 2000	38	14 (41.2%)	26.9

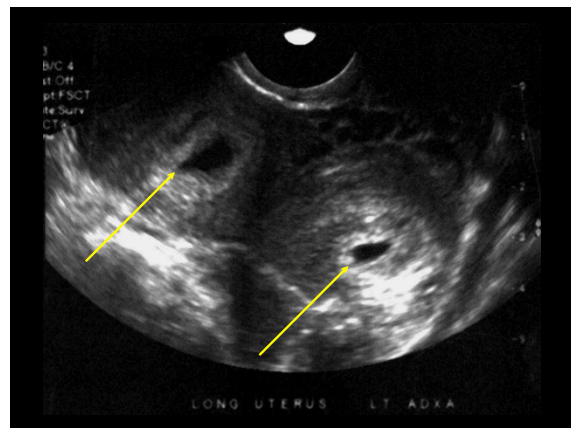
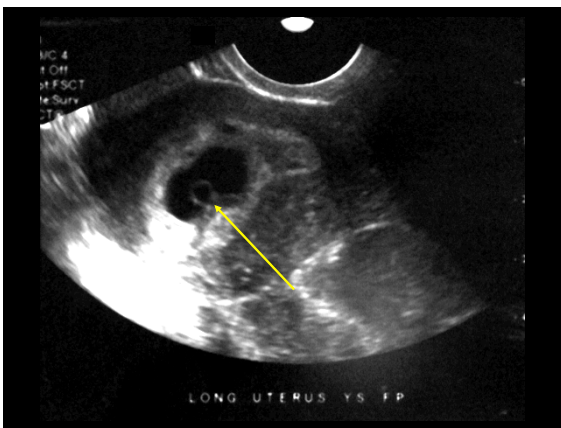
Frates et al. J Ultrasound Med 2014; 33:697-703.



## Case Presentation

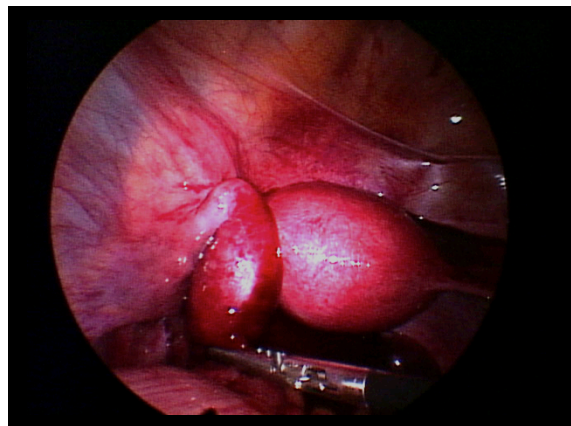
21 yo G1P0 at 6w3d by LMP

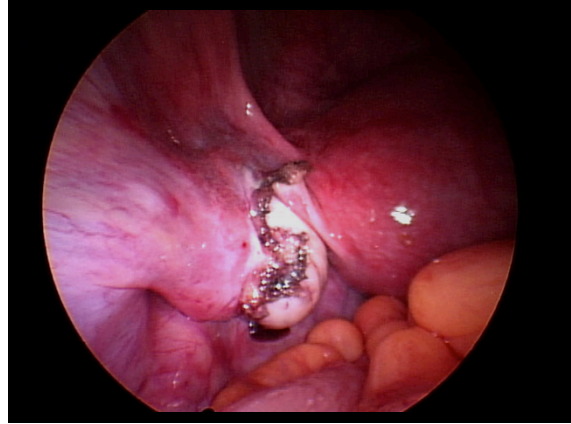
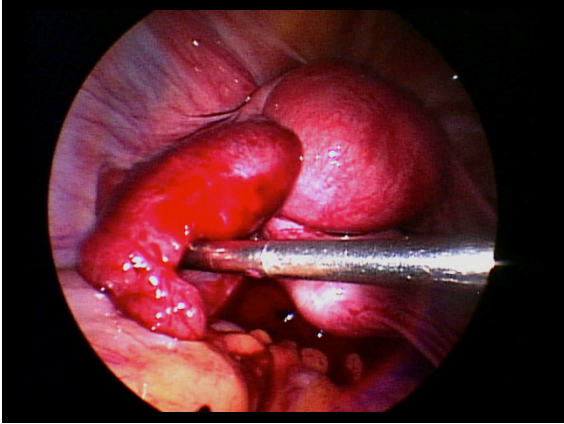
- c/o vaginal bleeding x 1 day
- LLQ pain x 1 day
- + home pregnancy test 3 days ago
- BC: progestin oral contraceptives
- Negative past gyn history
- **Quantitative hCG = 25,340**



## Case Presentation

- **Ultrasound**
- Uterus
  - IUP with + yolk sac, CRL c/w 5w6d
  - + cardiac activity
- Left adnexa
  - Mass = 4 x 3 x 4 cm, with gestational sac
- Diagnosis: **heterotopic pregnancy**





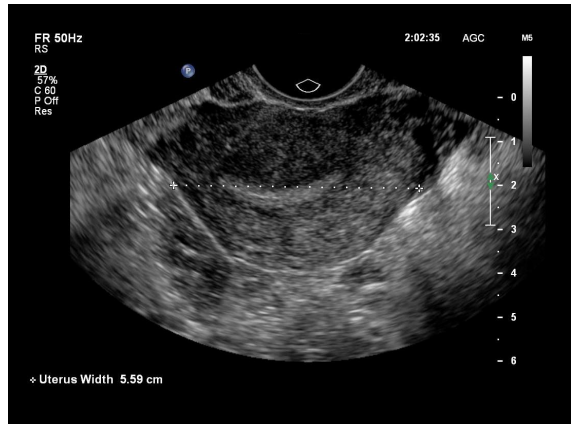
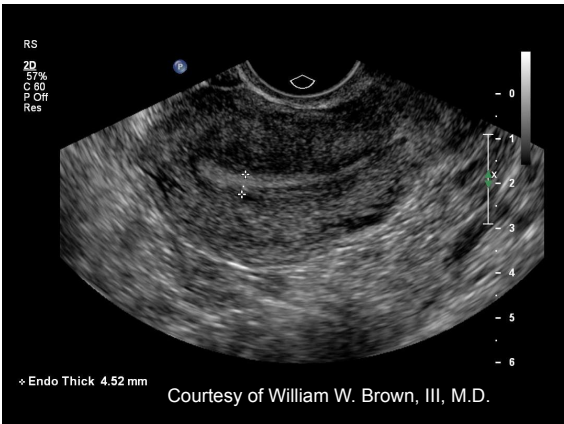
### Heterotopic Pregnancy

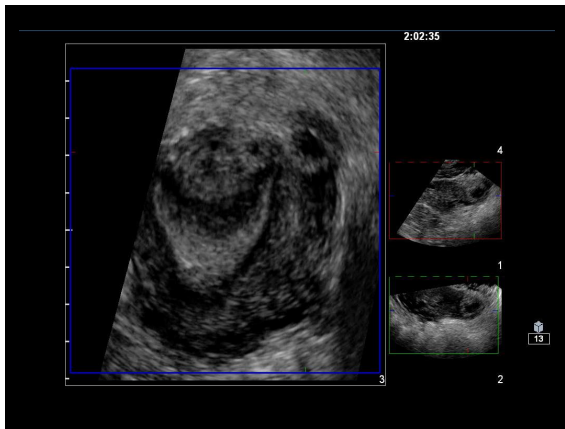
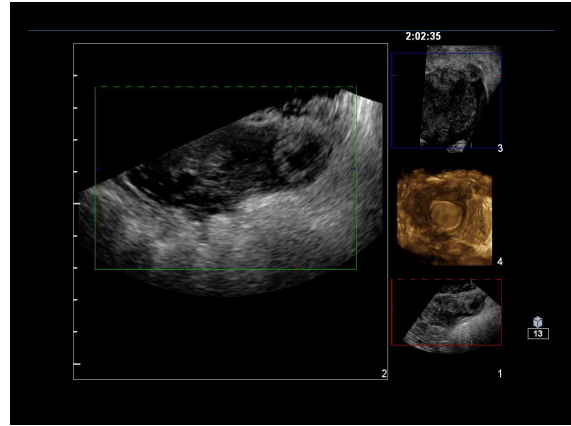
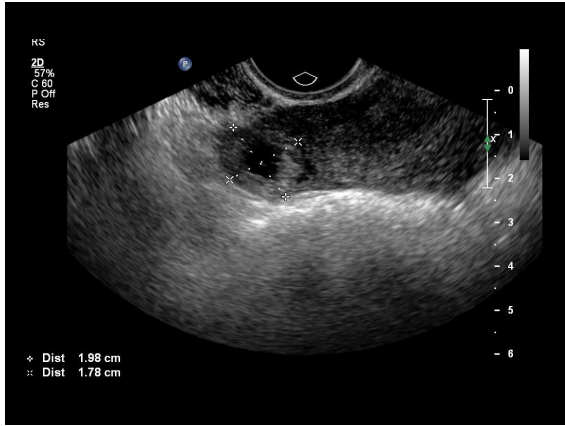
- More common with ART
- Incidence
  - Spontaneous 1:30,000
  - ART 1:110-1:667

Clayton et al. Obstet Gynecol 2006; 107:595-604.

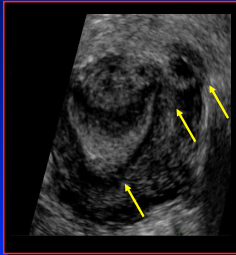
### Case presentation

- 28 y.o. G2P0010
- Presents with pelvic pain and vaginal spotting
- LMP = 7 weeks ago
- hCG: positive



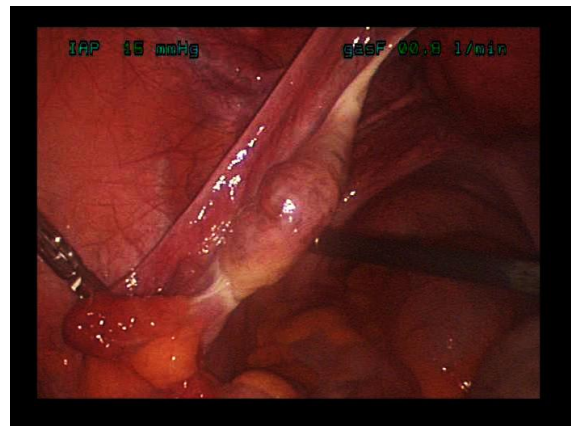
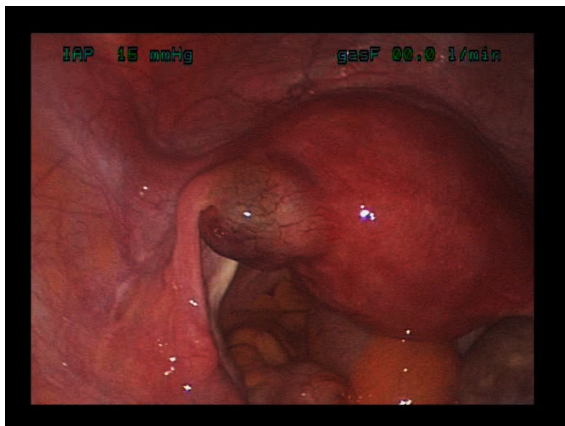


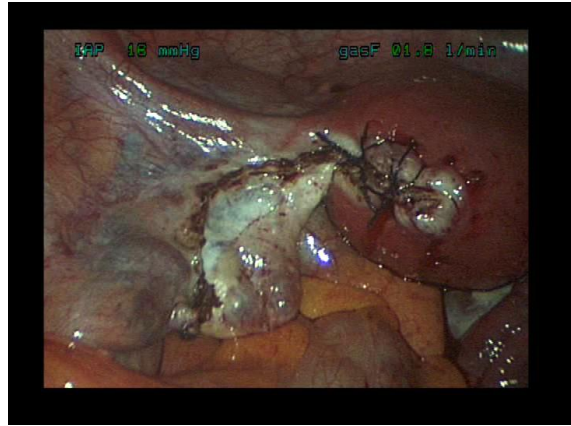
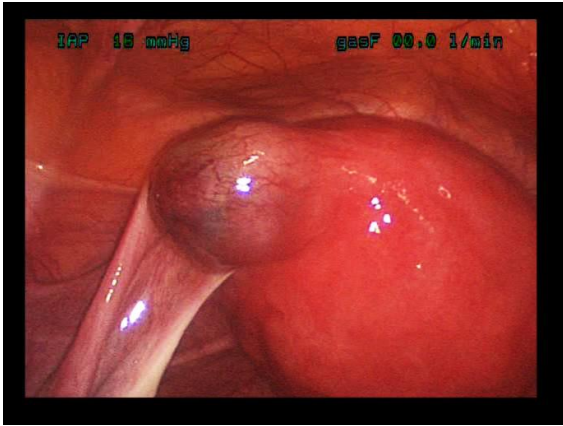
### Ultrasound Diagnosis of Interstitial Pregnancy



- Empty uterine cavity
- Chorionic sac > 1 cm from the lateral edge of the uterine cavity (endometrium)
- Thin (<5 mm) layer of myometrium surrounding the chorionic sac

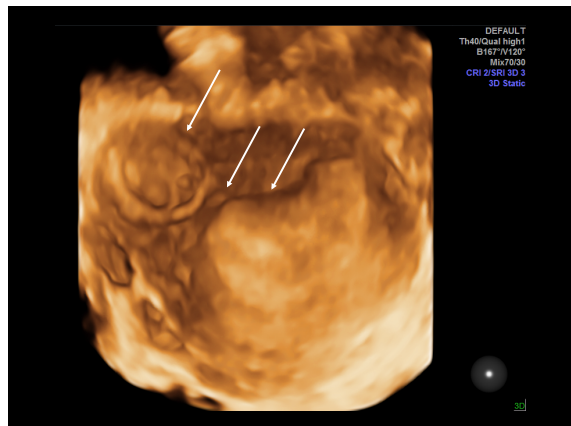
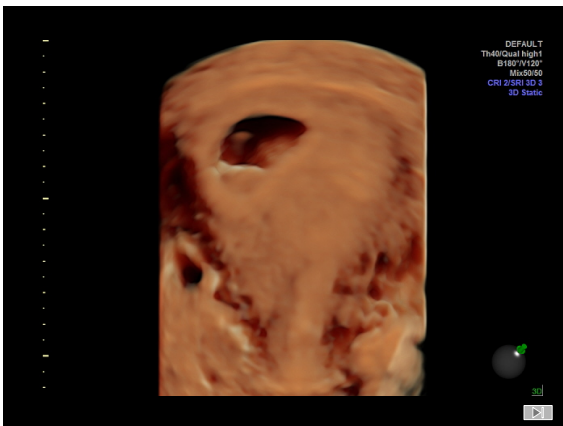
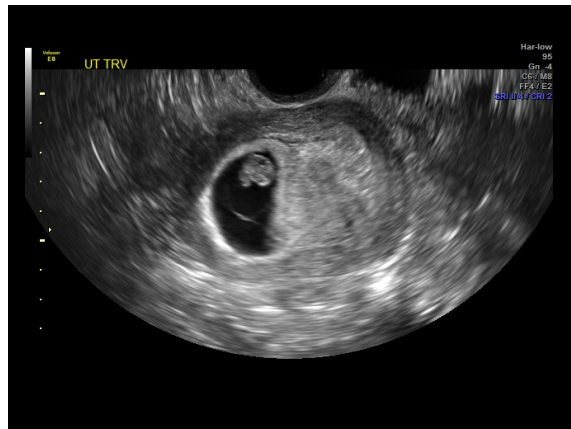
Timor et al. Obstet Gynecol 1992;79:1044





## Terminology

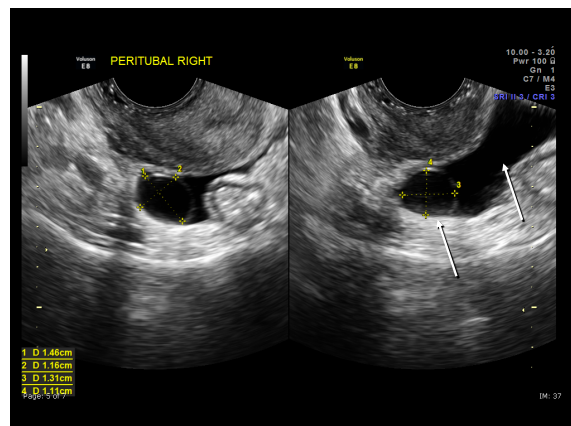
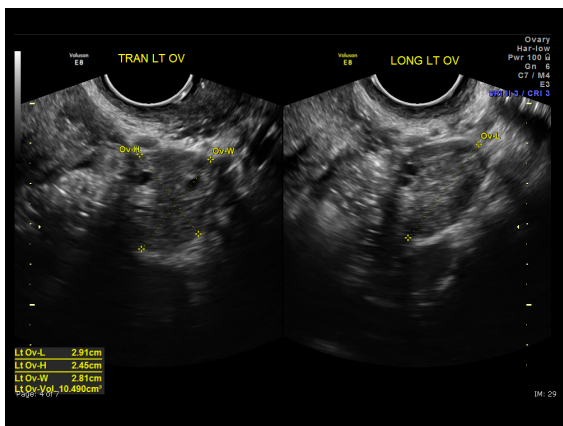
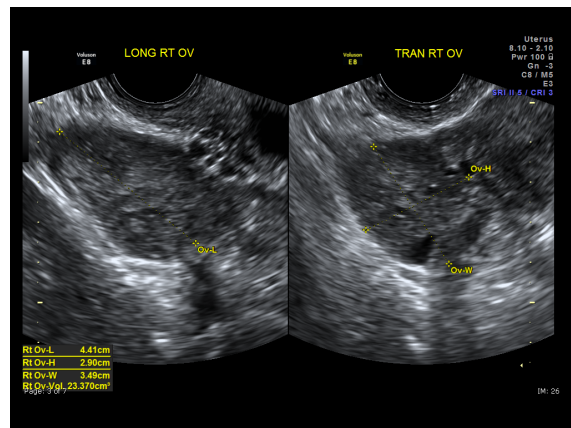
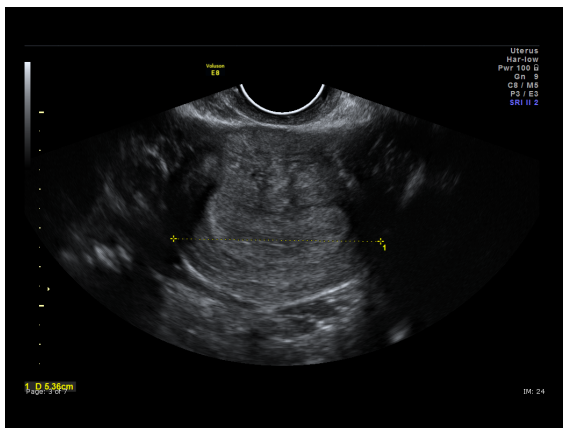
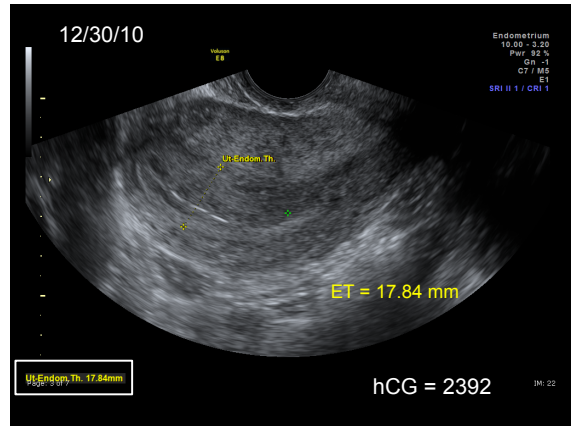
- **Interstitial pregnancy**
  - Embryo implants in the interstitial or intramural portion of the Fallopian tube
- **Cornual pregnancy**
  - Pregnancies that occur in a rudimentary horn, unicornuate uterus, cornual region of a septate uterus, a bicornuate uterus, or a uterus didelphys
- **Angular pregnancy**
  - Embryo implants in one of the lateral angles of the uterine cavity, medial to the utero-tubal junction

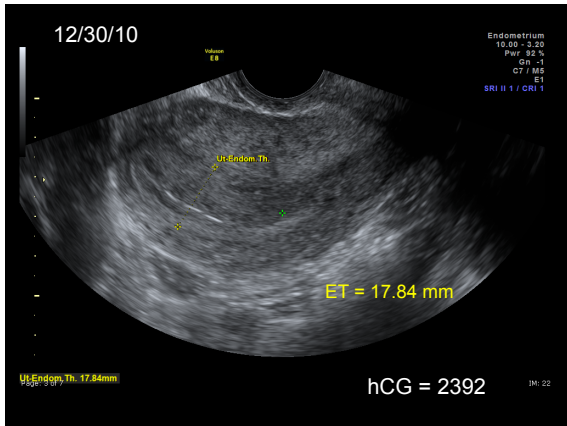




## Case Presentation

- 23 y.o. G2P1001
- Enters c/o slight spotting and cramping
- LMP = Unknown
- UCG = positive
- hCG = 2,392





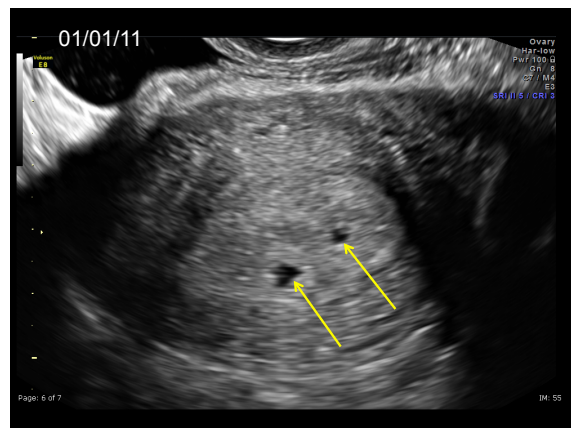
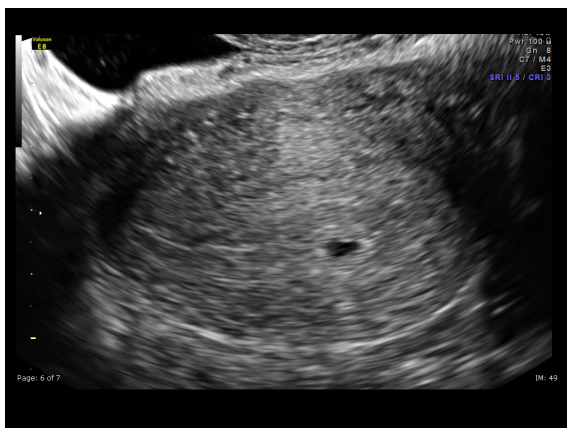
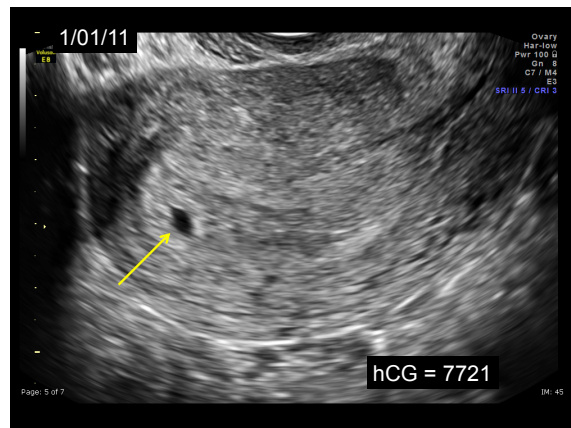
## Consensus Nomenclature

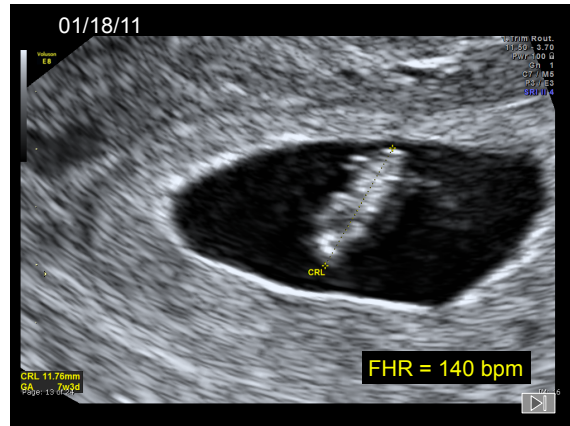
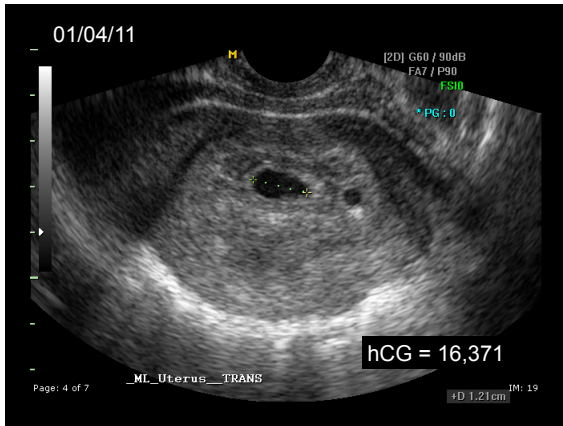
- Pregnancy of unknown location (PUL)
  - Possible IUP
    - Increased endometrial thickness

Barnhart et al. Fertil Steril 2011; 95: 857-866

## Quantitative hCG

12/30/10	2392
1/01/11	7721





## Ectopic Pregnancy-Summary

- Ultrasound can be justified prior to obtaining a quantitative hCG
  - ~ 50% of ruptured ectopics had hCG levels below the discriminatory zone (<1000 IU)
- Endometrial thickness when hCG < discriminatory level
  - An endometrial thickness  $\leq 8$  mm is associated with an abnormal pregnancy 97% of the time

## Ectopic Pregnancy-Summary

- The discriminatory level has changed
  - It may be as high as 2500-3500 IU/L
- A cystic structure within the endometrium, in the absence of an adnexal mass
  - Is associated with an IUP in > 99% of patients

## Ectopic Pregnancy-Summary

- Finding an IUP r/o ectopic pregnancy
  - Exception: heterotopic pregnancy
    - (1:667-1:30,000)
- Finding of embryo  $\pm$  heart beat or yolk sac in adnexa
  - Diagnostic of ectopic pregnancy
- No IUP. Complex/solid mass, sep from ovary
  - 92% likelihood of ectopic

