Pregnancy of Unknown Location (PUL):

Evidence-based practices for patient-centered care

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Disclosures

- No relevant financial relationships with ACGME defined commercial interests.

- Will discuss off-label use of mifepristone.

- Presentation adapted from presentation given with Rachel Flink-Bochacki, Misha Pangasa and Ashley Brant at Society of Family Planning Annual Meeting in Seattle in October 2024.

Learning Objectives

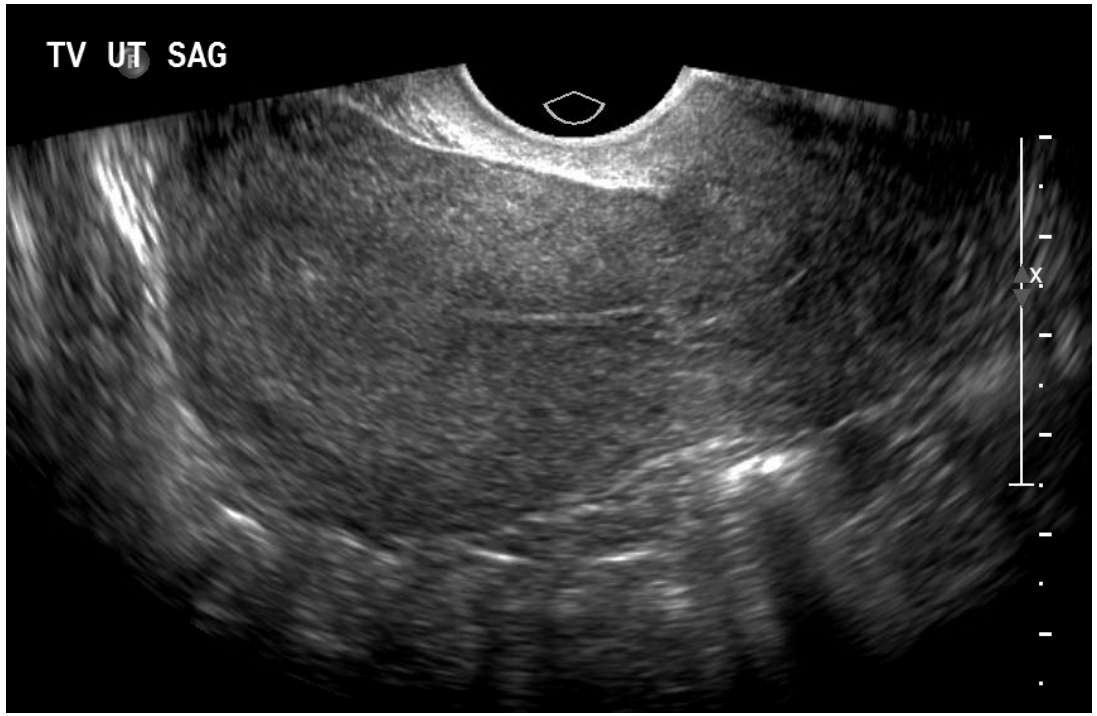
- Describe diagnosis of PUL outcomes using expectant management, incorporating laboratory, ultrasound, and clinical findings.
- Describe simultaneous diagnostic and treatment strategies utilizing medication and procedural care for PUL when expectant management is not desired.
- Understand the impact of abortion climates on patient-centered care for abnormal PUL.
- Apply knowledge to PUL clinical scenario

Background

Setting the stage

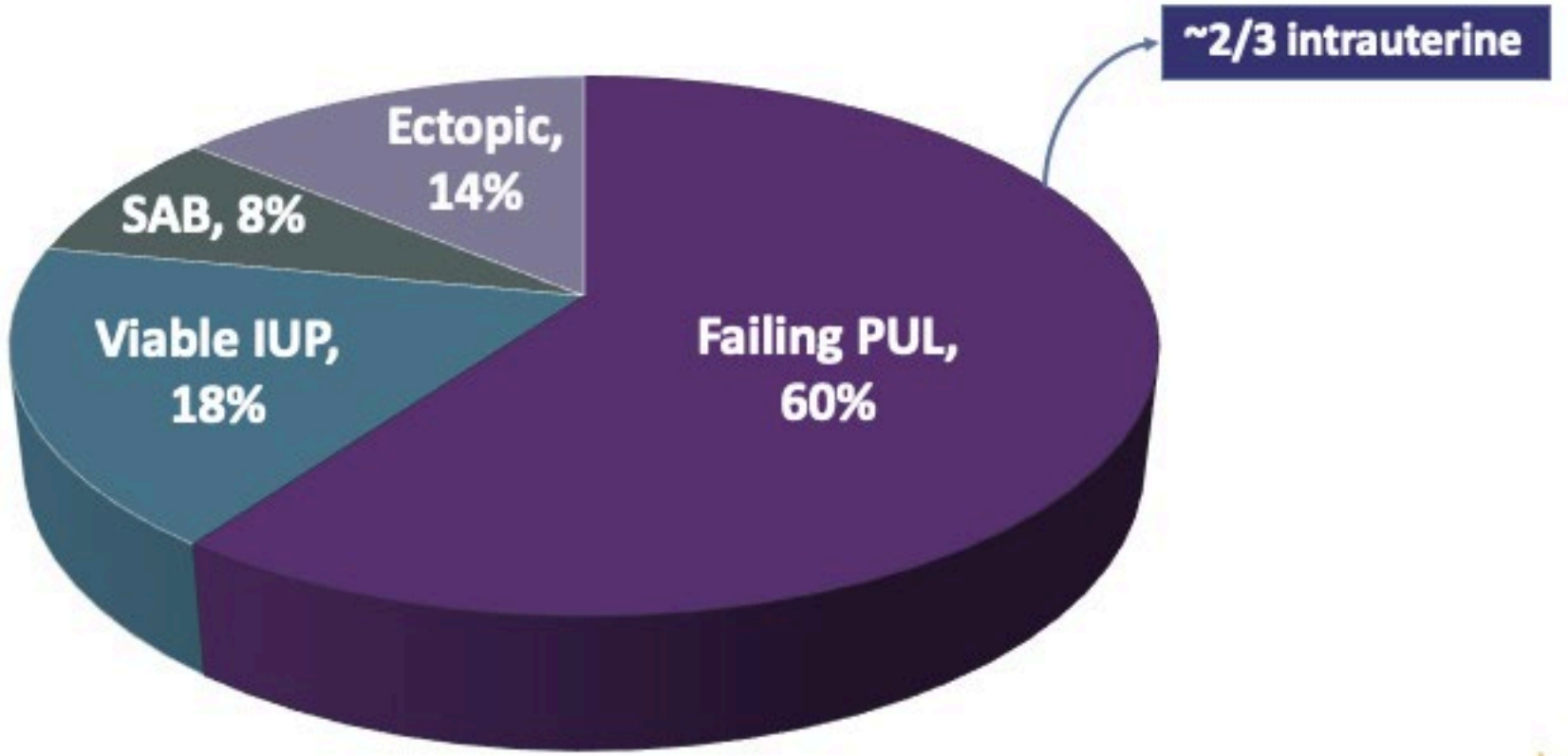
Pregnancy of Unknown Location (PUL)

- Definition: positive pregnancy test + non-diagnostic ultrasound
- Prevalence: 8.7%
  - Recent cohort: 4.5% overall (2.5-8.4% depending on setting)



Kirk at al, *Hum Reprod* (2007)
Javlekar et al, ACOG ACSM (2023)

Natural History of PUL



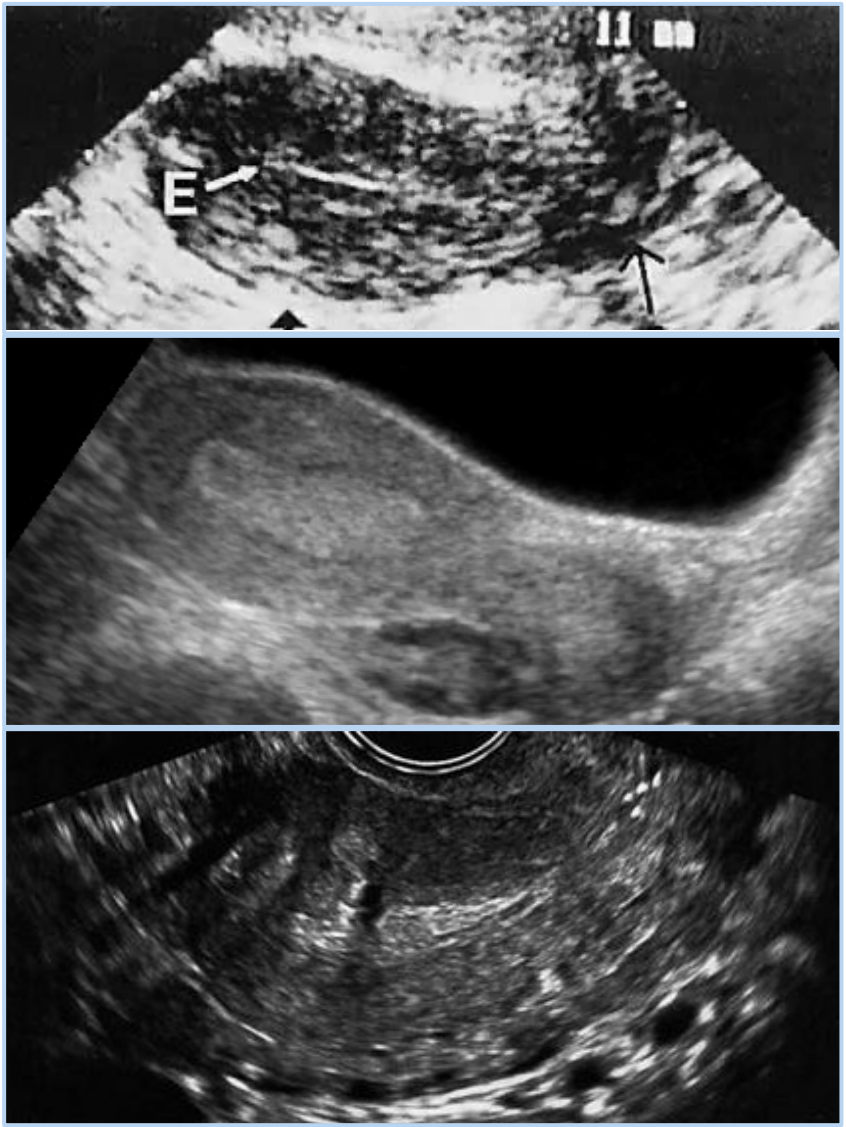
Barnhart et al, Obstet Gynecol (2008)
Shaunik et al, Am J Obstet Gynecol (2011)

PUL and ultrasound discriminatory zone

- Discriminatory zone: bHCG level where <u>normal</u> intrauterine pregnancy should be seen on ultrasound
  - If bHCG > DZ and no IUP is seen, assumption is that pregnancy is abnormal

PUL with DZ 2000-3000:
- 1.7% viable IUP
- 65.5% nonviable IUP
- 32.8% ectopic pregnancy

PUL with DZ > 3000:
- 0.5% viable IUP
- 66.3% nonviable IUP
- 33.2% ectopic pregnancy



Doubilet et al, N Engl J Med (2013)

ACOG recommended DZ

- Conservatively high: 3,500 mIU/mL
- Assumes patient's values

	β-hCG Level for Given Predicted Probability (95% CI) of Visualizing Structure*				
	50%	90%	95%	99%	Highest β-hCG Where Structure Not Seen
Gestational sac	879 (553–1,310)	1,918 (1,368–3,970)	2,363 (1,641–5,201)	3,510 (2,294–8,910)	2,317
Yolk sac	1,826 (1,211–2,516)	5,412 (3,843–9,037)	7,832 (5,293–15,007)	17,716 (10,264–48,132)	9,975
Fetal pole	10,091 (7,753–12,619)	24,599 (20,120–31,982)	30,982 (25,021–41,374)	47,685 (37,346–66,919)	35,486

β-hCG, β-human chorionic gonadotropin; CI, confidence interval.
* Logistic regression model using fractional polynomials to quantify the association between serum β-hCG level and probability of visualizing each structure through transvaginal ultrasonography. Gestational sac and fetal pole modeled using $\beta\text{-hCG}^{0.5}$.

Serum β-Human Chorionic Gonadotropin Levels and Predicted Probability of Detection in Viable Intrauterine Gestations (n=366)

Connolly et al, Obstet Gynecol (2013)
ACOG, Tubal Ectopic (2018)

Management options for PUL

- Expectant management
- Active management
  - Medical
  - Surgical

<u>Surgical management</u>

- Endometrial biopsy
- Uterine aspiration (MVA), dilation and curettage (D&C)
- Laparoscopy (with resection of ectopic)

<u>Medical Management</u>

- Mifepristone + misoprostol

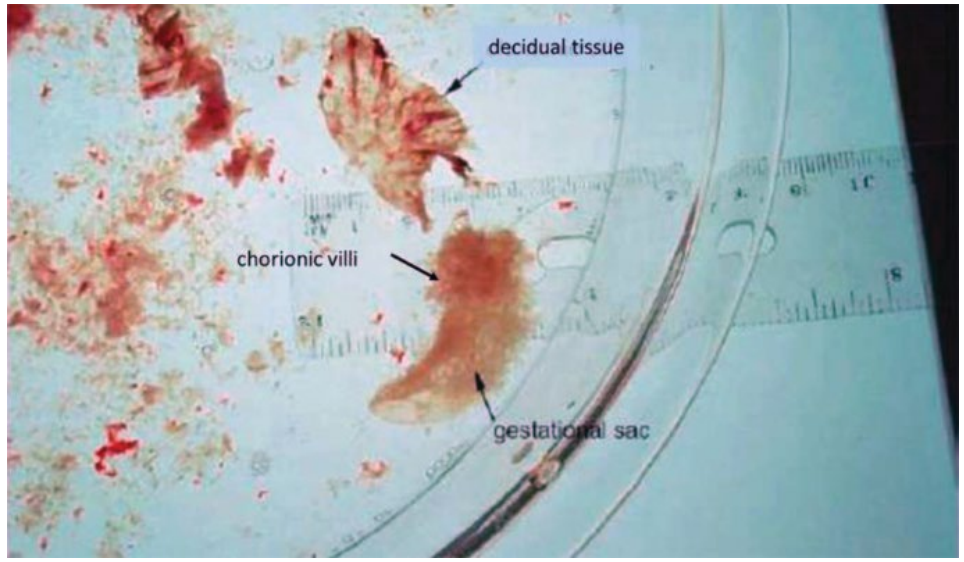
Effectiveness of different treatment options

	Mifepristone + misoprostol	Misoprostol alone	Methotrexate +misoprostol	Methotrexate alone	Uterine aspiration
Undesired intrauterine pregnancy	95-99%	78-87%	89-95%	69-84%	>99% 98% if <6w
Intrauterine early pregnancy loss	80-89%	65-81%			>99%
Ectopic pregnancy				70-95%	
Pregnancy of unknown location	85%		72%	53%	

Raymond et al, Contraception (2023); Wiebe et al, Obstet Gynecol (2002); Wiebe, Contraception (1999); Barnhart et al, Fertil Steril (2004); Wiebe, Int J Gynecol Obstet (2009); Paul et al, Am J Obstet Gynecol (2002); Goldberg et al, Obstet Gynecol (2022); Ozeren et al, Contraception (1999)

Determining success of management

- Medication management of intrauterine pregnancy
  - Mife/miso → 80% bHCG decline in 1 week
  - MTX+ miso → 50% decline in 48 hours post-miso
- Medication management of ectopic pregnancy
  - MTX alone → 15% bHCG decline between day 4-7
    - Follow bHCG to negative
- Uterine aspiration
  - POC exam → chorionic villi indicate IUP
  - bHCG → >50% decrease in 12-24 hours after aspiration



Lichtenburg et al (2009); Rivera et al, Am J Obstet Gynecol (2009); Creinin, Am J Obstet Gynecol (1996)

Diagnosis

Goal should be to replace the diagnosis of PUL with alternative diagnosis

Expected hCG trend in normal pregnancies

- Rate of 48H rise depends on starting value.
  - Minimum expectations (1st percentile):

Initial bHCG	Minimal rate of rise in 48h
< 1,500	49%
1,500 – 3,000	40%
> 3,000	33%

- 99% of normal intrauterine pregnancies have a rate of increase faster than these minimums
- hCG trend of ectopic pregnancies can mimic trend of IUP & SAB
  - Additional hCG value → improves prediction of ultimate outcome

Barnhart et al, Obstet Gynecol (2016), Dillon et al, Fertil Steril (2012); Zee et al, Hum Reprod (2013)

Predictive tools &models

- hCG ratio
  - (48-h bHCG)/ (0-h bHCG)= bHCG ratio
    - <0.87→ Likely failed PUL
    - ≥0.87 and ≤1.66→ Likely ectopic/PPUL
    - >1.66→ Likely ongoing IUP
- Mathematical prediction models
  - M4: bHCG ratio
  - M6: bHCG ratio + progesterone level
    - Risk stratification:
      - Risk of ectopic pregnancy
      - Risk of failed PUL
      - Chance of intrauterine pregnancy
    - External validation in US population needed

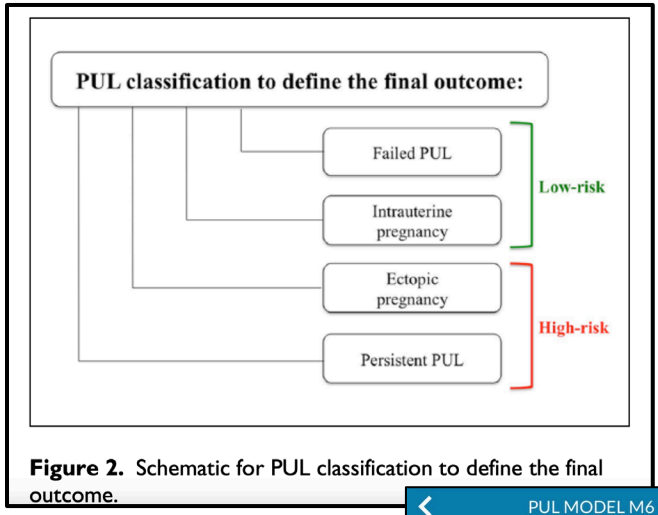
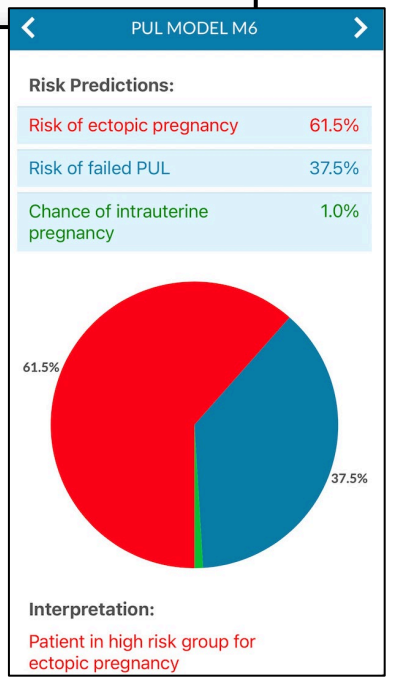


Figure 2. Schematic for PUL classification to define the final outcome.



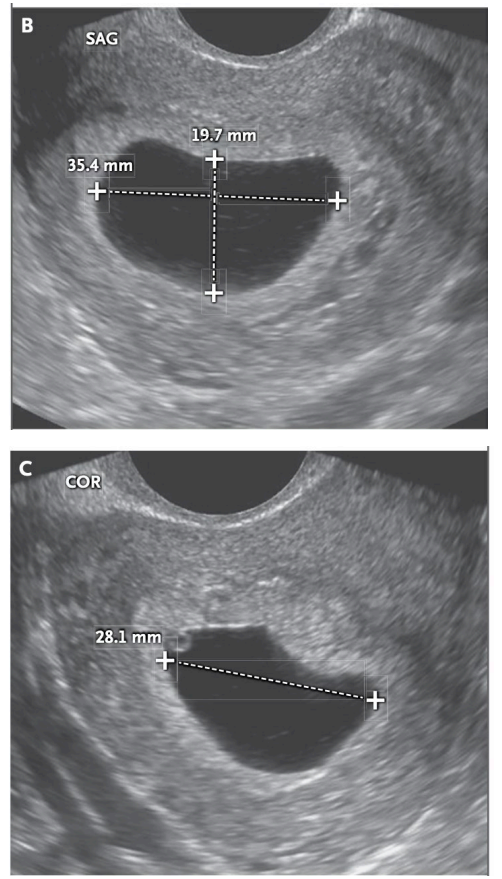
Condous et al, BJOG (2006); Barnhart et al, Hum Reprod (2010); Bobdiwala et et, Women's Health (2017); Fistouris et al, BMJ Open (2022)

Ultrasound diagnosis

Table 2. Guidelines for Transvaginal Ultrasonographic Diagnosis of Pregnancy Failure in a Woman with an Intrauterine Pregnancy of Uncertain Viability.*

Findings Diagnostic of Pregnancy Failure	Findings Suspicious for, but Not Diagnostic of, Pregnancy Failure†
Crown–rump length of ≥7 mm and no heartbeat	Crown–rump length of <7 mm and no heartbeat
Mean sac diameter of ≥25 mm and no embryo	Mean sac diameter of 16–24 mm and no embryo
Absence of embryo with heartbeat ≥2 wk after a scan that showed a gestational sac without a yolk sac	Absence of embryo with heartbeat 7–13 days after a scan that showed a gestational sac without a yolk sac
Absence of embryo with heartbeat ≥11 days after a scan that showed a gestational sac with a yolk sac	Absence of embryo with heartbeat 7–10 days after a scan that showed a gestational sac with a yolk sac
	Absence of embryo ≥6 wk after last menstrual period
	Empty amnion (amnion seen adjacent to yolk sac, with no visible embryo)
	Enlarged yolk sac (>7 mm)
	Small gestational sac in relation to the size of the embryo (<5 mm difference between mean sac diameter and crown–rump length)

* Criteria are from the Society of Radiologists in Ultrasound Multispecialty Consensus Conference on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy, October 2012.
† When there are findings suspicious for pregnancy failure, follow-up ultrasonography at 7 to 10 days to assess the pregnancy for viability is generally appropriate.

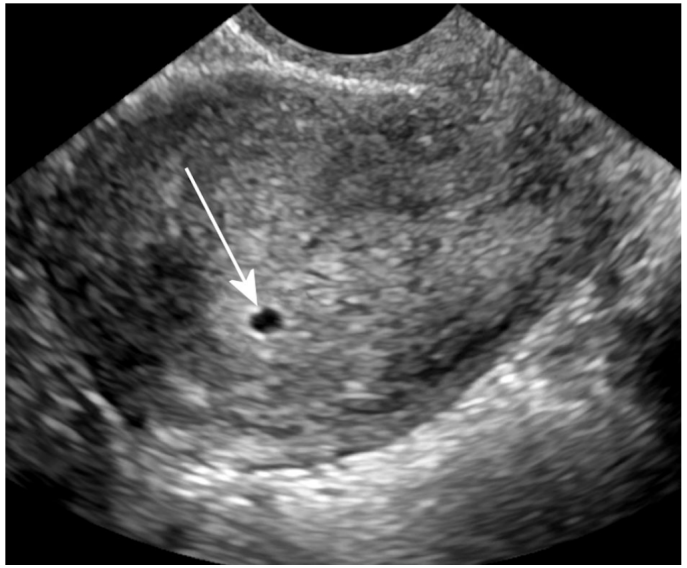


Doubilet et al, N Engl J Med (2013)

Prediction model incorporating US

- Sac-like structure + bHCG + absence of extraovarian adnexal mass → "virtually diagnostic of an intrauterine pregnancy"

- Pregnancy Prognosis Calculator
  - Age, MSD, bHCG and vaginal bleeding
  - Regression model AUC 0.823
  - https://tinyurl.com/Prognosis-PD



Doubilet et al, J Ultrasound Med (2021); Phillips et al, J ultrasound Med (2020).

Pregnancy prognosis calculator

Pregnancy Prognosis

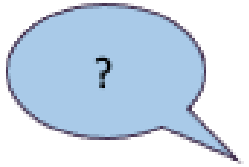
First Trimester Prognosis Calculator For Singleton Very Early Intrauterine Pregnancy Seen on Ultrasound[1]	
Doubilet et al*	
Double click yellow cells to enter information, then click here	
Maternal age (17-45 years)	20
Mean sac diameter (2-20 mm)	3
Vaginal Bleeding? (Y or N)	n
hCG rise prior to sonogram[2,3] A if appropriate S if suboptimal N if not measured	S
Probability live at end of first trimester	**43.9%**

[1] Ultrasound demonstrates a saclike structure in the mid-uterus, without yolk sac or embryo

[2] This calculator does not apply if serial hCG values are unchanged or decreasing

[3] Appropriate: initial hCG <5000 that at least doubles in 2 days
Suboptimal: initial hCG <5000 that fails to double in 2 days
Not measured if initial hCG >5000 or serial hCG's not obtained

Based on: median change in hCG in normal pregancies is 2.24-fold rise in 2 days [Barnhart et al, Obstet Gynecol 2004;104:50-55]



What us the prognosis of a 20 y.o. with a 3 mm MSD, no vaginal bleeding and a sub-optimal rise in bHCG prior to US?

Based on anticipated MEDIAN change in bHCG → If below minimal rise expected, high likelihood for abnormal pregnancy.

Doubilet et al, J Ultrasound Med (2021); Barnhart et al, Obstet Gyncol (2004)

Patient Goals

The context to clinical decision making

The implications of diagnostic certainty

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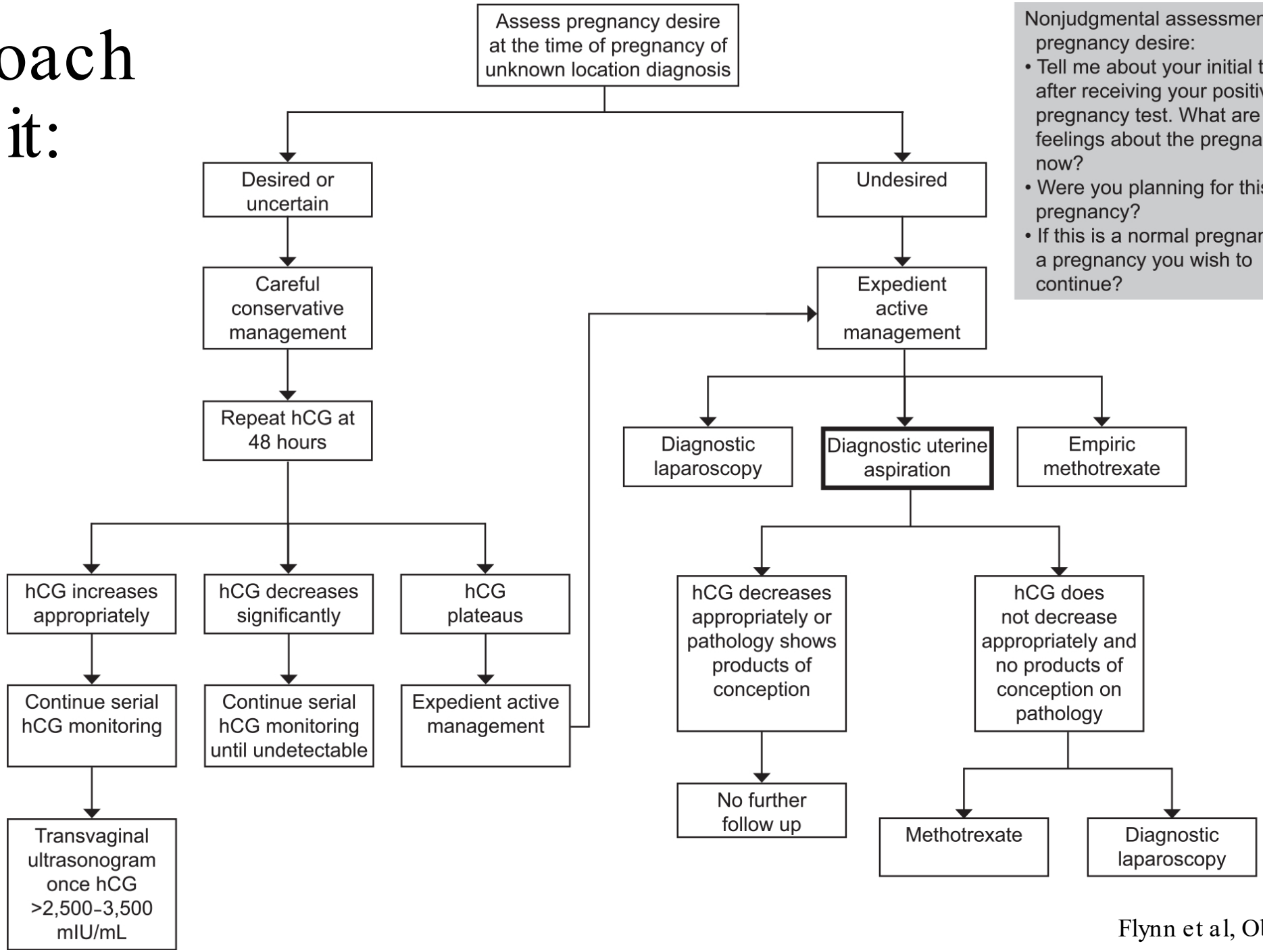
Doubilet et al, N Engl J Med (2013), Judge-Golden &Flink-Bochacki, Obstet Gynecol (2021), Richardson et al, Ultrasound Obstet Gynecol (2017)

Approach to visit:



Nonjudgmental assessment of pregnancy desire:

- Tell me about your initial thoughts after receiving your positive pregnancy test. What are your feelings about the pregnancy now?
- Were you planning for this pregnancy?
- If this is a normal pregnancy, is it a pregnancy you wish to continue?

Flynn et al, Obstet Gynecol (2020)

Patient Attitudes and Preferences for Management of PUL

- Health of the pregnancy
- Health of self
- Future family planning
- Diagnostic certainty and prediction

Patients were constantly recalibrating their preferences in response to evolving clinical management

Wu et al, F S Rep (2022)

ACOG

Consider other clinical factors when interpreting the Society of Radiologists in Ultrasound guidelines, including

- **the person's desire to continue the pregnancy**
- **willingness to postpone intervention to achieve 100% certainty of pregnancy loss**
- the potential consequences of waiting for intervention
  - the need for an unscheduled visit or procedure
- patient anxiety

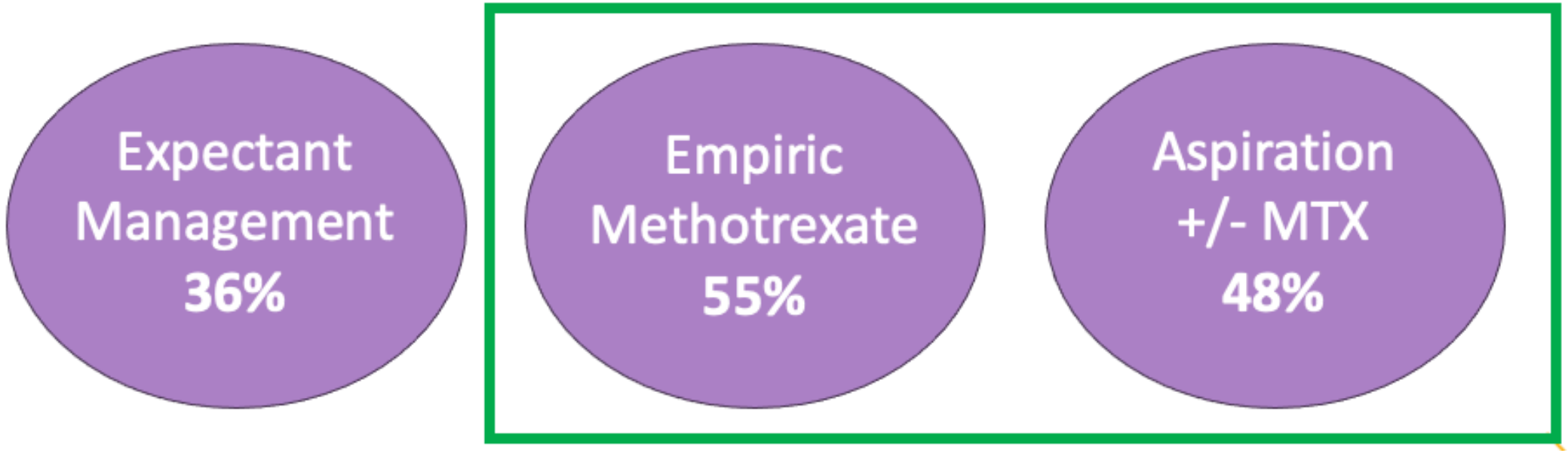
<u>It is important to include the patient in the diagnostic process and to individualize these guidelines to patient circumstances.</u>

ACOG Practice Bulletin #200, Obstet Gynecol (2018)

Treatment Protocols

Management of abnormal PUL

- Population: persistent PUL
- Outcome: successful resolution of pregnancy without change in management approach



Barnhart et al, N Eng J Med (2021)

Medication abortion for PUL

- Primary outcome: time to diagnosis of pregnancy location

	Same-Day Start n=55	Delay for Diagnosis n=394	p-value
Time to diagnosis (median, days)	5	9	0.005
Ongoing Pregnancy Rate	10.4%	2.5%	0.041
Successful Medication Abortion	85.4%	96.7%	0.013
Serious Adverse Event	0	2.4%	0.611

Delay group: 18% EPL + 8% Ectopic pregnancy = 26% did not need an abortion
No ectopic pregnancy in same-day MAB group

Goldberg et al, Obstet Gynecol (2022)

Expected trends after treatment

- Methotrexate +/- misoprostol:
  - Expect at least 15% decline between day 4 & 7
- Uterine aspiration (12-24h post aspiration hCG)
  - <15% decline or increase = consider EP
  - >50% decline = suggest IUP
  - 49-15% decline = individualize Next page
- Mifepristone + misoprostol
  - >50% decline by 4-7 days after mifepristone (48-72h after misoprostol)
  - >80% drop in hCG by day 7 (99.5% positive predictive values for successful medication abortion)

Bharadwa et al, Contraception (2024).
ACOG, Tubal Ectopic Pregnancy (2018)

Following hCG after management

- Goal: Assessing need for further intervention
- Declining hCG does not negate risk of EP
  - Uterine aspiration
    - 15-49% decline @ 12-24 hours
      - 3 of 46 had persistent plateau or rising hCG necessitating treatment for EP
- ACOG: Can consider expectant management of EP only if hCG <200
- Awomen with decreasing hCG values and a possible EP should be monitored until non-pregnant values are reached.

Rivera et al, Am J Obstet Gynecol (2009).
Insogna et al, A, J Obstet Gynecol, (2017)
ACOG, Tubal Ectopic Pregnancy (2018)

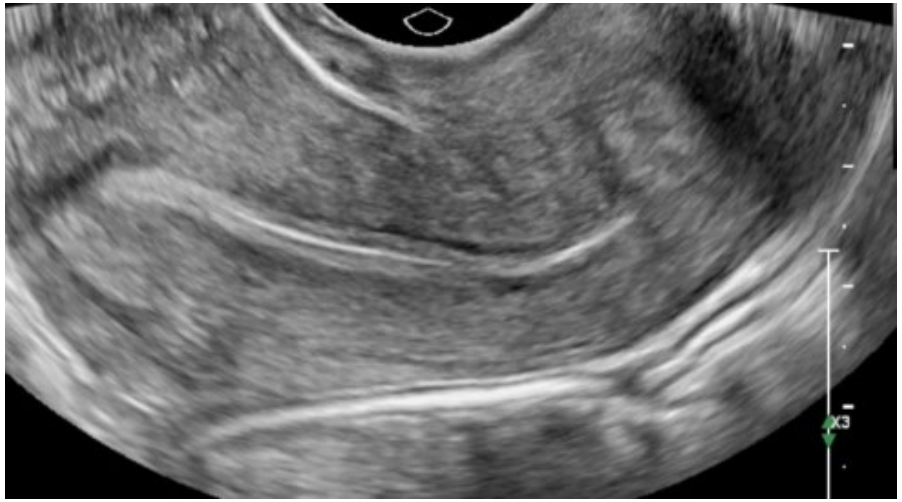
Post-abortion care

- Offer supportive care &use unbiased language
- Aim to understand clinical circumstances of abortion
  - No-touch vs Ultrasound?
  - Medication or procedure?
  - Were labs done?
  - Are labs needed?
- We may play a critical role in their follow-up
- Contraception

Case

Case

- 27 yo G3P1011 presents for OB care at 5w3d by LMP.
- Prior SVD x 1, ectopic x 1 treated with methotrexate.
- Vitals and exam WNL



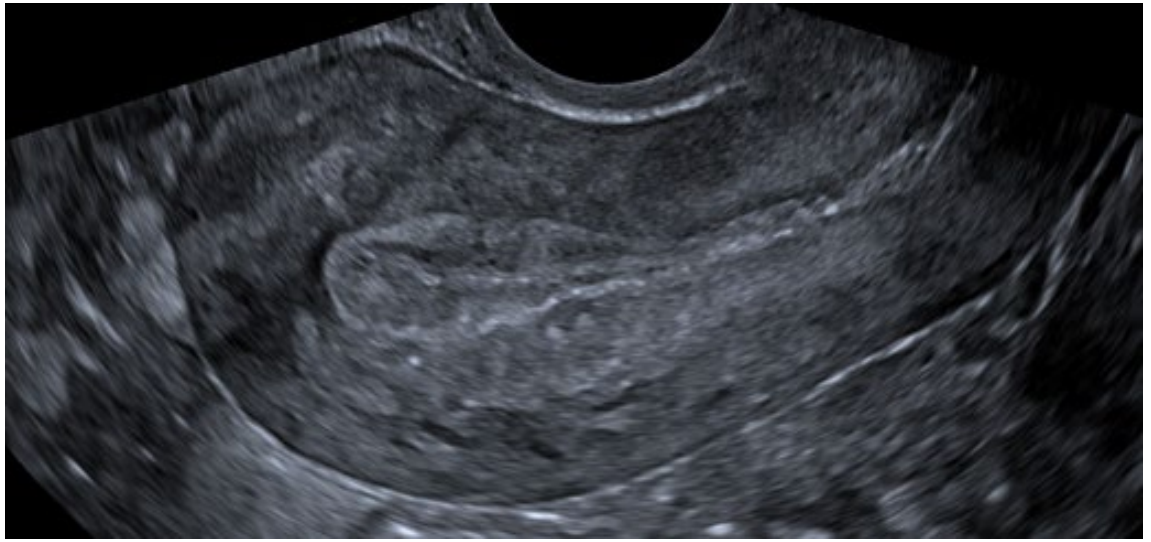
- TVUS shows PUL and normal adnexa.
- bHCG: 1860 mIU/mL

Ectopic precautions
Repeat hCG 48 hours

Case

- Recommended repeat hCG @ 48h
  - 1860 mIU/mL→ 2034 mIU/mL
  - 9.4% increase
- Repeat US shows only thickened EMS
- Vitals and Exam remain WNL

Initial bHCG	Minimal rate of rise in 48h
<1,500	49%
1,500 – 3,000	40%
>3,000	33%



Case

- Patient discloses this is an undesired pregnancy. Her priority is preserving health and future fertility potential.
- How do you counsel this patient?

- Offered Expectant vs Medical vs Procedural management given clinician's reasonable medical judgement this this pregnancy is abnormal.
  - Methotrexate + misoprostol
  - Office MVA and serial hCG
  - Mifepristone + miso

Case

- Patient undergoes office MVA
  - No Villi seen
  - hCG trend
    - hCG @ MVA: 2034 mIU/mL
    - hCG @ 24 hours: 1642 mIU/mL
    - 23% decline in 24 hours = individualize
  - Patient offered continued hCG surveillance vs ectopic treatment
    - Offered surgical vs medical management, she elected for treatment with methotrexate.
    - During surveillance, she had 25% decline in hCG between D4 and D7
    - hCG trended until at non pregnant level

- **Uterine aspiration** (12-24h post aspiration hCG)
  - <15% decline or increase = consider EP
  - >50% decline = suggest IUP
  - 49-15% decline = individualize

Take away

- We understood patient goals
- Used a variety of modalities (hCG, US and expected clinical thresholds) to formulate plan that in our reasonable medical judgment prioritized her goals and safety.
- Expediated management = early EP diagnosis

Questions

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