

A 46 year-old woman reports her periods have become increasingly irregular and heavy over the last 6-8 months. Sometimes they come 2 times per month and sometimes there are 2 months between. LMP 2 months ago. She bleeds 10 days with clots and frequently bleeds through pads to her clothes. She also has diabetes and is obese.

Q1: Which is the first test should you order in this patient?

- 1. FSH
- 2. Testosterone & DHEAS
- 3. Urine hcg
- 4 TSH
- 5. Transvaginal Ultrasound (TVUS)
- 6. Endometrial Biopsy (EMB)

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Step 1: Pregnant?

Pregnant

- Ectopic
- S bortion
- Thre Abortion
- M
- Tra ma
- Other causes

Not Pregnant

- Anovulation ***
- Anatomic/structural **
- Neoplastic *
- Infectious
- Iatrogenic
- Non-gynecologic

* = Most likely for this patient

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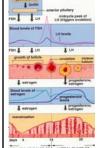
Terminology: What is abnormal?

- Normal: Cycle= 28 days (21-35); Length=2-7 days; heaviness=self-defined
- Too little bleeding: amenorrhea or oligomenorrhea
- Too much bleeding: Menorrhagia (regular timing but heavy (according to patient or >80cc) OR long flow (>7 days)
- <u>Irregular bleeding</u>: Metrorrhagia, intermenstrual or postcoital bleeding
- Irregular and Excessive: Menometrorrhagia
- Preferred term for non-pregnant heavy and/or irregular bleeding = Abnormal Uterine Bleeding (AUB)





Pathophysiology: Anovulatory Bleeding



Bricks & Mortar

<u>Estrogen</u>=Bricks, build endometrium <u>Progesterone (P)</u>=Mortar, stabilizes, only have P if ovulate

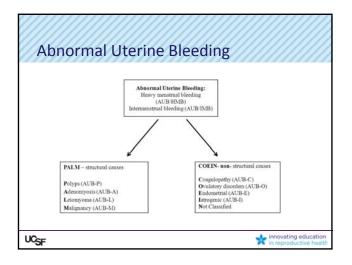
Normal menses: Withdrawal of P causes wall to fall down, all at once (orderly bleed)

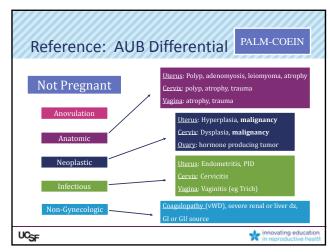
Anovulation: No P so when wall grows too tall, it falls. It is heavy when wall is tall. Bricks can also fall intermittently & incompletely – irregularly, irregular











History and Physical Examination

- Hx: bleeding pattern, symptoms of anemia, sexual & reproductive history, chronic medical illness, medication
- Acute v. chronic
- PE: signs of hypovolemia and anemia, thyroid examination, gynecologic exam, abdominal examination, (screening for cervical dysplasia and STI)
 - Obesity: up to 60% of women who do not ovulate are obese increased estradiol & testosterone; elevated insulin → disordered follicular development



Initial Work-up: Menometrorrhagia

• Always: Urine pregnancy

• Usually: TSH

• Maybe: Hct, r/o coagulopathy

• Maybe: EMB (Endometrial Biopsy)

• Maybe but later: Transvaginal Ultrasound

• <u>Usually not necessary</u>: FSH, LH, Testosterone, Estradiol





A Rational Approach to EMB

 $\underline{Post-Menopause} \colon ALL \text{ women WITH } \underline{ANY} \text{ BLEEDING (except 4-6 months after HT)}$

Recent onset irregular bleeding: Consider treating first and if bleeding normalizes, no need for EMB

 \geq 50: All women with recurrent, <u>irregular</u> bleeding (consider not doing if periods light and spacing out)

 $\underline{45\text{-}50:} \ Recurrent irregular \ bleeding \ plus \ge 1 \ risk \ factor \ OR > 6 \ mos \\ menometrorrhagia \ (consider \ not \ doing \ if \ periods \ light \ and \ spacing \ out)$

<45: Long hx (>2 yr?) of untreated anovulatory bleeding or failed medical management

 $\underline{\mathsf{EMB}}\ \mathsf{is}\ \mathsf{not}\ \mathsf{perfectly}\ \mathsf{sensitive}\ \mathsf{so}\ \mathsf{further}\ \mathsf{evaluation}\ \mathsf{mandatory}\ \mathsf{if} \mathsf{:}$

- 1. Persistent AUB after negative EMB
- 2. Persistent AUB after 3-6 months of medical therapy

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Do all women with AUB need an ultrasound?

Although TVUS is the best imaging choice for pelvic pathology (ie better than MRI, CT)....

- 80% with heavy menstrual bleeding have no anatomic pathology
- Incidental findings such as functional ovarian cysts and small fibroids (~50%) are often found leading to anxiety and unnecessary treatments
- SO....treat first, TVUS if treatment fails

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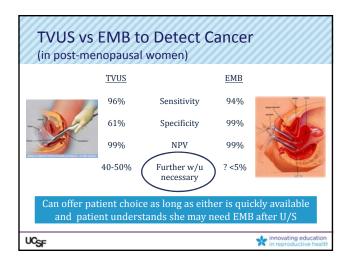
What about U/S instead of EMB for post-menopausal bleeding?

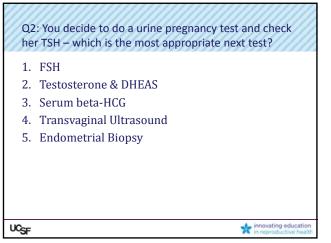
Transvaginal Ultrasound

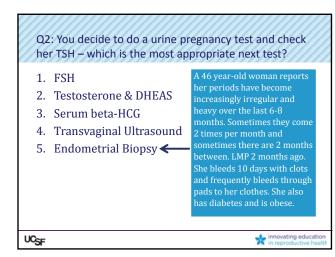
- Measure endometrial stripe
- Abnormal= >4 mm (or 5)
- Non-specific: myomas, polyps also cause thick EM
- · Operator skill mandatory
- NOT USEFUL PRE-MENOPAUSE

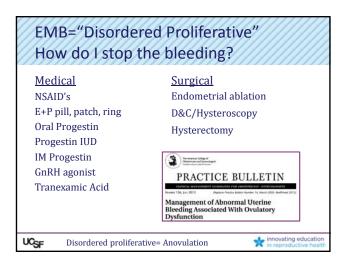


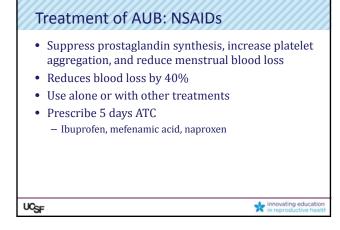












Treatment of AUB: CHC

- CHC pill, patch, ring improve cycle control, decrease menstrual blood loss by 40% when used traditionally or continuously
 - One COC (with estradiol) approved by FDA for heavy menstrual bleeding
 - COCs often used to treat acute and chronic AUB
 - Few studies support up to 70% decreased EBL with COC and one study with vaginal ring

Bradley, AJOG, 2016

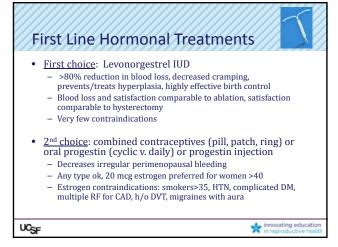


Treatment of AUB: Progestins

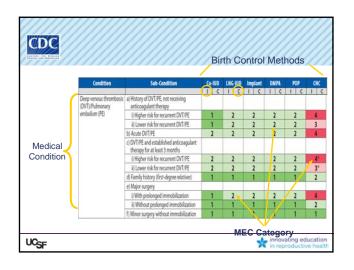
- Oral progestin
 - If ovulatory AUB = HMB: <u>daily</u> or days 5-26 "extended use" progestin decreases blood loss
 (MPA 2.5-10mg qd, norethindrone 2.5-5mg qd, NETA 5 TID)
 - Low satisfaction with extended use
 - If anovulatory: <u>cyclic</u> progestin -12-14 d/month improves menses in half of women
- Injectable progestin
 - 50% amenorrhea after 1 year, irreg. bleeding in first few months and 50% at one year $\,$
- · Intrauterine progestin
 - Significant decrease in blood loss, superior to other progestins and CHCs

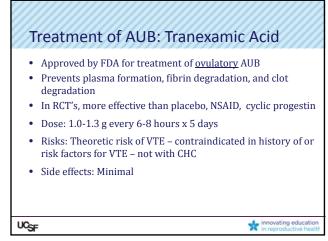
Bradley, AJOG, 2016; Heikinheimo, Best Practice & Research Clin Ob Gyn, 2017.

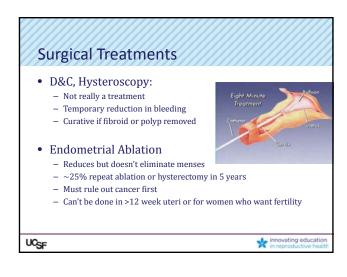


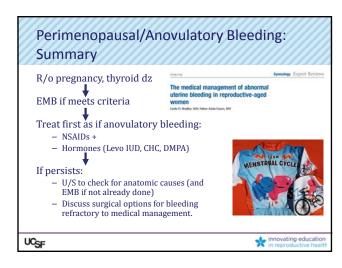










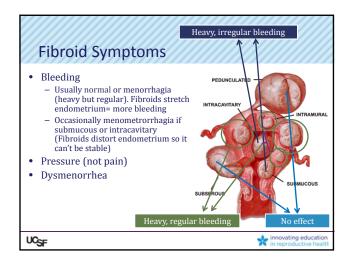


Case 2: Is it the fibroids?

Same history as Case 1 except she has fibroids....On examination her uterus is 16 weeks' size

- Very common → 80% of hysterectomy specimens (done for any reason) and ~75% have on U/S at age 50
- About 50% are asymptomatic
- Grow slowly until menopause and then decrease by ~50% (can still cause bleeding post-menopause)

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Is the bleeding due to the fibroids?

- Fibroids are common in later 40s
- Anovulation is common in later 40s
- The increased bleeding seen typically due to increased volume or distortion of the endometrium
- <u>Therefore</u>: Thin the endometrium by treating as anovulatory bleeding.

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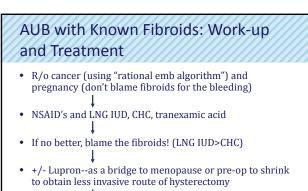


Treatment of AUB and Fibroids

- LNG-IUD: approved by FDA for women with fibroids unless distorted uterine cavity
- Combined hormonal contraception
- NSAIDS
- · Tranexamic acid
- GnRH agonist to shrink fibroids before surgery, or bridge to menopause
- (SPRMS investigational)

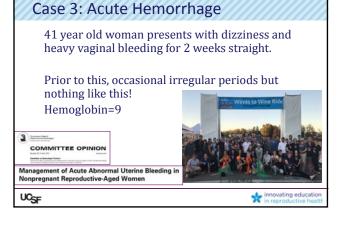
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• Other tx (hysteroscopic resection if <3 cm, myomectomy,

MR-guided focused u/s, RFA, UAE, hysterectomy)



Acute AUB Treatment

ABC's and Stop the bleeding!

- Consider ED for transfusion
- Medical management
 - Estrogen Rapid endometrial growth, vasospasm of arteries, platelet aggregation, increasing clotting supportive factors
 - CEE 25 mg IV q 4-6 hours for 24 hours, followed by progestin or COC for 10-14 days
 - COC: 1 tab TID x 7 days then taper
 - Progestin: medroxyprogesterone acetate 20mg TID x 7 days
 - Tranexamic acid 1.3 g TID x 5 days
- Other options: D&C, foley bulb tamponade, emergency hysterectomy



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COC Taper

- Don't want to give 2-4 COC's per day and then stop suddenly b/c will have large withdrawal bleed
- Taper: 3 x 4 days, 2 x 4 days then 1 per day for 1-2 months (60+ pills required).
- Instruct not to take placebos and give at least 3 packs of pills at once.
- Give with anti-emetic, split bid (i.e. 2 bid rather than 4 all at once)





Case 4: Because of her contraceptive...

- A 32 year-old woman has recently initiated the birth control pill.
- She has had spotting for 30 straight days! She is annoyed.



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Case 4: Because of the injection...

- A 32 year-old woman has recently initiated the contraceptive injection.
- She has had spotting for 30 straight days! She is annoyed.



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Case 4: Because of the implant...

- A 32 year-old woman has recently initiated the contraceptive implant.
- She has had spotting for 30 straight days! She is annoyed.



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Case 4: Because of the IUD...

- A 32 year-old woman has recently initiated the levonorgestrel IUD.
- She has had spotting for 30 straight days! She is annoyed.

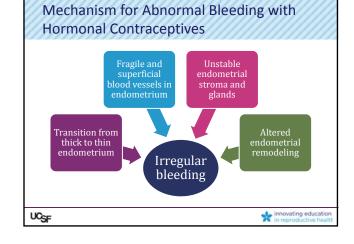


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Reasons for dissatisfaction leading to contraceptive discontinuation | Condom | Pill | Injection | n=1637 | n=579 |

	Condom	Pill	Injection	LNG implant
	n=705	n=1637	n=579	n=66
	% Reporting the following reasons			
Too expensive	2.2	3.2	2.1	1
Too difficult or messy to use	15.2	5.7	1.2	10.4
Partner unsatisfied	38.6	2.8	2.6	1.2
Experienced side effects	17.9	64.6	72.3	70.6
Worried about side effects	2	13.1	4.2	4.2
Did not like the changes in menstrual periods	1.5	12.7	33.7	19.3
Experienced contraceptive failure	7.5	10.4	5.7	8.3
Worried about effectiveness	13.2	3	2.2	0
No protection against STIs	1.1	2.1	1.3	0
Other health problems/doctor's advice	2.5	8.5	5.7	9.2
Method decreased sexual pleasure	37.9	4.1	8.2	1.1
Too difficult to obtain	1.5	1.8	2	0
Other reason	15.4	10.6	8.1	10.2



COCs: Setting Expectations



- · Unscheduled bleeding
 - -10-30% in the first month
 - Less than 10% by the third month
- Amenorrhea
 - Less than 2% in the first year
 - Up to 5% after 1 year

UCF Speroff L & Darney PD, Clinical Guide for Contraception 4th Ed, 2011



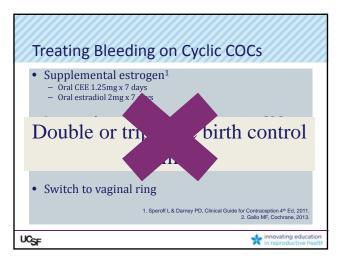
COCs: General Counseling

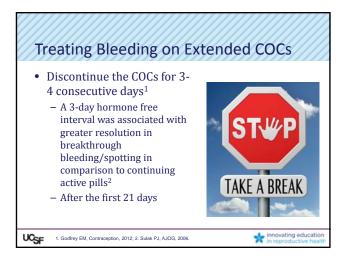
- $\bullet\;$ Take pill at the same time each day
 - Inconsistent pill use associated with increased risk of unscheduled bleeding¹
- Stop smoking!
 - Smokers more likely to experience unscheduled bleeding/spotting 1
 - Among smokers, bleeding more likely to persist

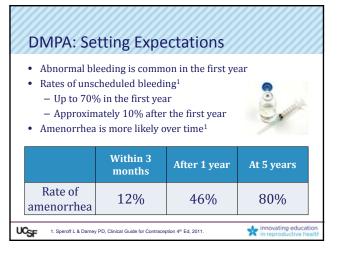
Rosenberg, Contraception, 1996.













Etonogestrel Implant: Setting Expectations

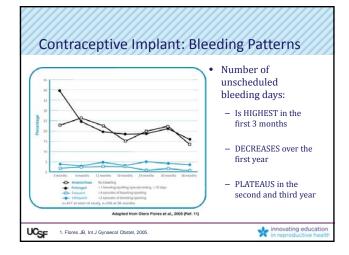
- Most women experience a reduction of menstrual bleeding¹
- Bothersome bleeding reported in 25% of patients²
 - 6.7% reported frequent bleeding
 - 17.7% prolonged bleeding
- Rates of amenorrhea³
 - Approximately 20% in first year
 - 30-40% after 1 year



1. Mansour D, Cor Care, 2008 3. Spe

 Mansour D, Contraception, 2011.
 Mansour D, Eur J Contracept Reprod Health Care, 2008
 Speroff L & Darney PD, Clinical Guide for Contraception 4th Ed, 2011.





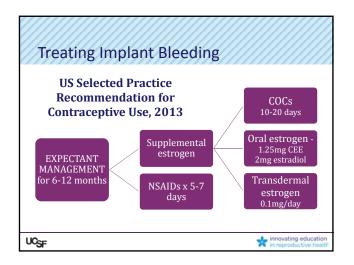
Contraceptive Implant: Bleeding Patterns

- More unpredictable bleeding pattern¹
 - Amenorrhea may not be sustained if achieved
 - "Favorable" pattern in the first 3 months predicts a continued favorable pattern
 - For those with an "unfavorable" bleeding pattern, 50% report improvement over time

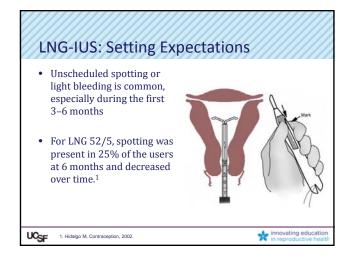
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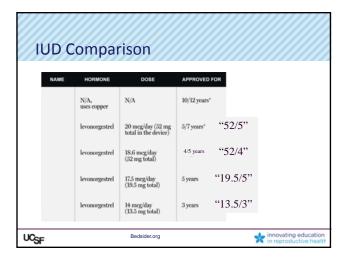
1. Mansour D, Eur J Contracept Reprod Health Care, 2008.

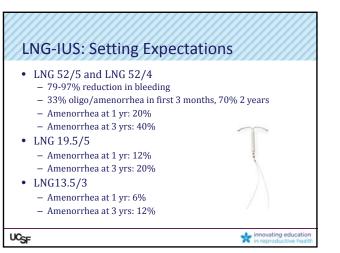


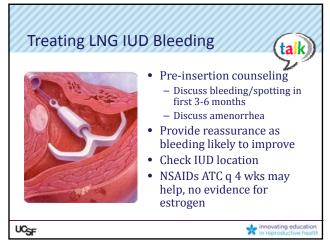


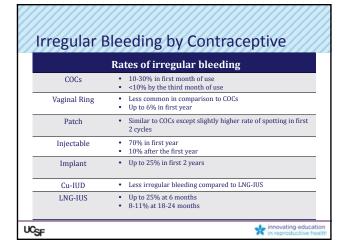


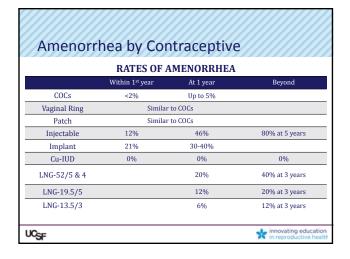


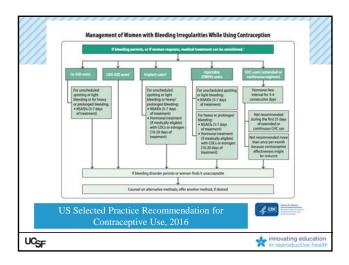


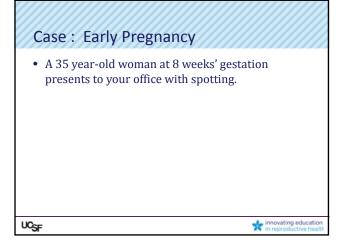


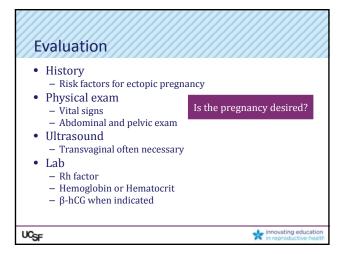












Case 5: Bleeding in Early Pregnancy • Keep the patient informed. - Provide reassurance that not all vaginal bleeding & cramping = an abnormality, but avoid guarantees that "everything will be all right" - Assure that you are available • What does the bleeding mean? - Up to 20% chance of ectopic pregnancy - 50% ongoing pregnancy with closed cervical os - 85% ongoing pregnancy with viable IUP on sono - 30% of normal pregnancies have vaginal bleeding

Ectopic Pregnancy

- 1-2% of all pregnancies
- Up to 20% of symptomatic pregnancies
- ½ of ectopic patients have no risk factors
- Mortality has declined: 0.5/100,000
 6% of pregnancy-related deaths
- Early diagnosis important
- Concern about management errors

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Early Pregnancy Loss (EPL)

- 15-20% of clinically recognized pregnancies
- 1 in 4 women will experience EPL
- Includes all non-viable pregnancies in first trimester = miscarriage





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Pregnancy of Unknown Location

- When the pregnancy test is positive and no signs of intrauterine or extrauterine pregnancy on u/s
 - $\boldsymbol{-}$ We try to follow these women until a diagnosis is made
 - We have to weigh risk of ectopic pregnancy (EP)
 - Sometimes no final diagnosis both EPL and EP may resolve spontaneously
- More commonly encountered in symptomatic early pregnancy, but can also be encountered in asymptomatic women, especially when u/s early

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Simplified Workup of Bleeding &/or Pain

- 1. Where is the pregnancy? \rightarrow U/S (same day)
- 2. If the pregnancy undesired? \rightarrow uterine aspiration
- 3. If desired and we can't tell where it is: Is it normal or abnormal? → quantitative (serial) Beta-HCG
 - If Bhcg above threshold (>3,000) and no IUP = **Abnormal**
 - Most likely an abnormal IUP

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IUP=Intrauterine pregnancy



Simplified Workup of Bleeding &/or Pain

- Where is the pregnancy? \rightarrow U/S (same day)
- 2. If the pregnancy undesired? \rightarrow uterine aspiration
- 3. If desired and we can't tell where it is: Is it normal or abnormal? → quantitative (serial) Beta-HCG
 - If Bhcg above threshold (>3,000) and no IUP = Abnormal - Serial beta HCGs:
 - If Bhcg drops > 50% in 48 hours = Abnormal
 - If Bhcg rises > 50% in 48 hours = Most likely normal (can be EP) - Continue to follow and repeat u/s
 - If between = Most likely abnormal (still can be normal) Continue to follow and repeat u/s
- 4. If pregnancy clearly abnormal, if undesired or desires definitive dx → uterine aspiration

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IUP=Intrauterine pregnancy



Conclusions



- <u>Diagnosis:</u> think of pregnancy, then anovulation
- Work-up: Always rule out pregnancy. If irregular: TSH, PLN. ?HCT, ?EMB, TVUS if initial tx fails.
- <u>Treatment</u>: all bleeding treated similarly
 - · NSAID's plus hormones. Persistent abnormal bleeding requires continued work-up even if EMB and/or ultrasound are negative.
- Hormonal or copper birth control: set expectations

Thanks to Rebecca Jackson and Sara Whetstone for sharing slide



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Society of Radiologists in Ultrasound: No Gestational Sac

- HCG 2000 3000
 - Non-viable pregnancy most likely, 2X ectopic
 - Ectopic is 19 x more likely than viable pregnancy
 - For each viable pregnancy:
 - 19 ectopic pregnancies
 - 38 nonviable pregnancies
 - 2% chance of viable pregnancy
- HCG > 3000
 - Ectopic 70 x more likely than viable pregnancy

0.5% chance viable IUP



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