



## Abnormal uterine bleeding: Wading through the evidence on treatment effectiveness

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NEOGS  
October 24, 2012



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## Disclosures

- I have no financial relationship with a commercial entity producing health-care related products and/or services



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## Objectives

- To be able to describe the definitions of abnormal uterine bleeding (AUB) and dysfunctional uterine bleeding (DUB) and where they are heading
- To be able to compare and contrast medical and surgical therapies for AUB not caused by structural abnormalities or systemic diseases
- To be able to develop strategies for choosing the best treatment for your patient in your practice



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## Prevalence

- Abnormal Uterine Bleeding
  - Any alteration in the volume or pattern of menstrual blood flow
- Estimated that AUB affects 10-30% of women
- The most common group of gynecologic disorders for which women seek care
- 5-10% of women of reproductive age seek medical care for heavy menstrual bleeding



**Oceans Womb by Ciska**  
 Mori et al 1990, Prentice et al 1999, Lui et al 2007,  
 Kjerulff et al 1996, Oehler et al 2003

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## Why is AUB important?

- Women w/ AUB less likely to rate their health as excellent or good
- Women with AUB work an average of 3.6 weeks less per year than women without AUB
  - Work loss from heavy bleeding is estimated to be \$1692 per woman
- Estimated total direct cost AUB \$1- \$1.55 billion annually



**"Menorrhagia Healing" by Barbara Bruch**  
 Cote et al 2002, Cote et al 2003, Liu et al 2007

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## Problematic definitions

- The Menstrual Disorders Working Group FIGO developed a nomenclature and classification system to describe the symptom and etiologies of AUB
  - Approved by the FIGO executive board and supported by ACOG
  - Simple symptom description
  - Classification system for etiologies



Fraser and Sungurtekin 2000; Fraser et al 2007, Munro et al 2011

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## Problematic definitions Time for clarification....

- Heavy Menstrual Bleeding (regular)
  - Heavy Menstrual Bleeding (irregular)
  - AUB-E (presumed endometrial dysfunction)  
AUB-O (Ovulatory dysfunction)
- More detail later.....




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## Definition clarification Simple symptom description

Frequency	Frequent Normal Infrequent Absent
Regularity	Regular Irregular
Duration	Prolonged Normal Shortened
"Volume"	Heavy Normal Light




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## "Volume" revisited

- Traditionally in research, bleeding measured by volume of menstrual blood lost per cycle (>80 ml cut-off)
  - Actual volume of MBL/ cycle is not the main reason women seek care for heavy menstrual bleeding

Heavy menstrual bleeding (HMB) is defined as excessive menstrual blood loss which interferes with a woman's physical, social, emotional and/or material quality of life. It can occur alone or in combination with other symptoms.

UK – NICE Guidelines 2007



Hallberg et al 1966; Higham et al 1990; Janssen et al 1995; OFlynn et al 2000; Warner et al 2004

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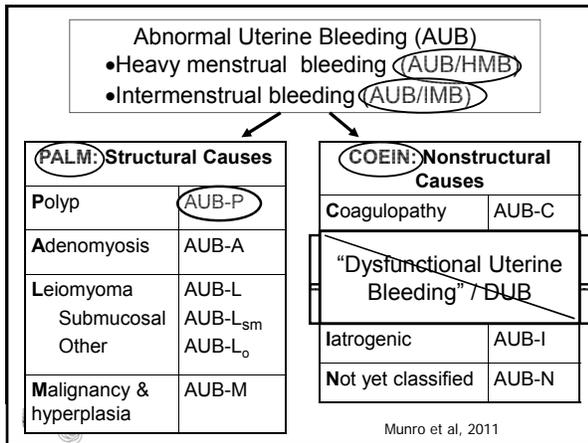
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Coagulopathy	<h2 style="margin: 0;">AUB-O: Ovulatory dysfunction</h2> <p style="margin: 0;">(formerly “Anovulatory DUB”)</p>
Ovulatory Dysfunction	
Endometrial	
Iatrogenic	
Not Otherwise Classified	

**HEAVY AND IRREGULAR**

**Possible CAUSES**

- Obesity
- Low Body Weight
- Weight Change
- Psychological Stress
- Endocrinopathy

- **Unopposed estrogen**
- **Endometrium sloughs off in an uncoordinated fashion with uneven break down**
- **Excessive proliferation and increased dilated draining veins and decreased spiral arterioles**
- **Higher PGE than PGF**

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Coagulopathy	<h2 style="margin: 0;">AUB-E: Endometrial dysfunction</h2> <p style="margin: 0;">(formerly “Ovulatory DUB”)</p>
Ovulatory Dysfunction	
Endometrial	
Iatrogenic	
Not Otherwise Classified	

**HEAVY AND REGULAR**

Caused by local disturbances in endometrial function—deficiencies or excesses of proteins that have an impact on coagulation

**REDUCED LEVELS**

- **Vasoconstrictors**
  - PG F2 $\alpha$ , Endothelin-1
- **Clotting Mechanisms**
  - Tissue factor pathway

**INCREASED LEVELS**

- **Vasodilator**
  - PG E2, PG I2
- **Fibrinolytic Activity**

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## Treatment of AUB Focus on AUB-O and AUB-E



"Ode to U"  
Stephanie Wirth



- Treat underlying systemic disorders or structural issues which you think *cause* the bleeding
- Management of AUB caused by
  - AUB-O: Ovulatory dysfunction (formerly "anovulation/DUB")
  - AUB-E: Endometrial dysfunction (formerly "ovulatory DUB")

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## Treatment of AUB-E and AUB-O



- Effectiveness of treatments differ for women with acute, women with ovulatory, and women with anovulatory heavy menstrual bleeding
- Studies can be difficult to compare and interpret, population not always clear
  - Most studies excluded women with irregular menses
  - Most studies included only women with >80 ml MBL



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## Acute AUB

is an episode of bleeding that is of sufficient quantity to require immediate intervention to prevent further blood loss

## Treatment OPTIONS



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Think about treatment...

A 37 year old non-pregnant woman presents to the emergency room with heavy uterine bleeding for the past 12 days.

On examination, her vital signs are stable and you observe she has a moderate amount of bleeding. Her HgB is 9 g/dl. She is a non-smoker and has a negative medical history.



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Which of the following would **NOT** be the best first line treatment for this patient?

- A. Dilation and curettage
- B. Conjugated equine estrogen 25mg IV q6
- C. Oral contraceptive TID x 1 wk
- D. Medroxyprogesterone acetate 20mg TID x 1 wk



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Acute uterine bleeding

## Estrogen

- "Use of IV Premarin in the treatment of DUB" – Double blind RCT of 34 women
- Compared proportion of patients in whom bleeding stopped in response to either 25 mg IV conjugated equine estrogen or IV placebo
- *In 5 hours*, Bleeding stopped in 72% of patients who received IV estrogen and in 38% who received placebo
- **IV conjugated equine estrogen: 25 mg IV q6 hrs until bleeding stops or up to 24 hours**



Devore et al 1982

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## COC Tapers/Cascades

- Initially based on expert opinion until RCT by Munro et al October 2006
  - Compared COC taper & oral progestin
  - 16 women in COC group
  - 95% avoided surgery in the next 28 days
  - Average 3 days to bleeding cessation

- **COC w/ 35 µg E2/1mg norethindrone TID x1 week then qd x 3 weeks**



Munro et al 2006

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## Oral progestin

- Oral progestin arm of the Munro et al study
  - All 17 women in MPA group avoided unplanned surgical intervention
  - 65% stopped bleeding at 1 month follow up, mean time 3 days

- **Medroxyprogesterone acetate 20 mg PO TID x 1 week then daily x 3 weeks**



Munro et al 2006

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## Tranexamic acid

- Given its mechanism of action (decreasing fibrinolysis) likely effective for Acute AUB
  - Supported as a rx by experts (PO or IV)
  - No studies for acute AUB
  - Shown to reduce intra-operative bleeding for orthopedic procedures

- **1.3 grams PO TID x 5 days or 10 mg/kg IV q8 hr up to 5 days**



James et al 2011; Alshryda et al 2011; Lethaby et al 2000; Lukes et al 2010

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### Chronic AUB

- Present for the majority of the last six months
- For this talk – presumed secondary to AUB-O or AUB-E

<p><u>Evidence for RX</u></p> <p>LNG IUS          Oral progestin          Cyclic OCs          Tranexamic Acid          NSAIDS          Endometrial ablation</p>		<p><u>AUB-O only</u>          ovulatory dysfunction</p> <p><u>AUB-E only</u>          endometrial dysfunction</p> <p>Unclear or mixed populations</p>
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### Think about treatment...

A 28 year old non-pregnant woman seeks treatment for heavy and irregular menstrual bleeding. Her periods are unpredictable and last for 7-10 days. Her period starts 1-2 weeks before or after the expected time.

**Heavy and irregular:  
Likely diagnosis AUB-O**

Physical examination and ultrasound are normal. She has no medical problems.

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Which option is the best for this patient's bleeding?

- A. COCs
- B. Luteal phase progestin (10-14 d/cycle)
- C. LNG-IUS
- ~~D. Tranexamic Acid~~
- ~~E. NSAIDs~~

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AUB-O



## Combined oral contraceptives

- Physiologically it makes sense that COCs should work for ovulatory dysfunction by exogenously cycling hormones
  - Inadequate/Limited evidence
- One RCT compared the efficacy of a triphasic combination COCs in the treatment women with irregular bleeding (some heavy, some not)
  - 73.2% of COC group reported bleeding was improved (vs. 39.6% of placebo group)

 Davis et al 2000; Cochrane Review by Hickey et al, updated 2009

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AUB-O



## Oral progestin

- Luteal phase oral progestin may be effective in regulating bleeding in women with *irregular* uterine bleeding associated with anovulation
  - Inadequate/limited evidence
- Norethindrone acetate 5mg TID, days 12-25
- Medroxyprogesterone acetate 10mg TID, d 12-25
  - 48% reduction in MBL

 Cochrane Review by Hickey et al, updated 2010; Fraser et al 1990

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## Think about treatment...

A 37 year old non-pregnant woman has cyclic heavy bleeding over the past 6 months. She changes her pads every 2-3 hours based on her period. She has no other symptoms. She has no other medical problems. Her EMB and ultrasound are normal.

**Heavy and regular:  
Likely diagnosis AUB-E**



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Which treatment is the best to ↓ this specific pt's bleeding?

- A. COCs
- B. Depo-MPA IM
- C. Luteal oral progestin (10-14 d/cycle)
- D. Extended oral progestin (21 d/cycle)
- E. Levonorgestrel IUS



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Let's say she is not a smoker...Which option is best to ↓ this pt's bleeding?

- A. COCs
- B. Depo-MPA
- C. Luteal oral progestin (10-14 d/cycle)
- D. Extended oral progestin (21 d/cycle)
- E. Levonorgestrel IUS



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Patient is a smoker but refuses IUD.  
Which option is best to ↓ her bleeding?

- ~~A. COCs~~
- B. Depo-MPA ???
- ~~C. Luteal oral progestin (10-14 d/cycle)~~
- D. Extended oral progestin (21 d/cycle)



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AUB-E



## Levonorgestrel IUS

- LNG-IUS reduces MBL by 71-96%
- Most effective, best tolerated non-surgical option for *heavy and regular* menstrual bleeding
  - Reduction MBL same for LNG-IUS and extended cycle oral progestin
    - Patient satisfaction much less for oral progestin
  - More effective than luteal phase oral progestin, Depo MPA, NSAIDs

Cochrane Review by Lethaby et al, updated 2009 (1)  
Endrikat et al 2009; Shabaan et al 2011

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AUB-E



## LNG-IUS

- Two recent RCTs showed greater reductions in bleeding (83-87%) with LNG-IUS than with COCs (35-68%)
- Greater reduction in bleeding (73%) than 5 mg daily oral MPA (49%) or IM Depo-MPA (33%)
- RCT: LNG IUS vs. hyst with 5 years f/u
  - 42% of women randomized to LNG IUS had hysterectomy within 5 year f/u
  - LNG IUS group less cost overall
  - No difference in quality of life scores

Endrikat et al 2009; Shabaan et al 2011;  
Kucuk et al 2008; Hurskainen et al 2004

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AUB-E  
AUB-C



## Depo Medroxyprogesterone acetate

- Most data for its use based on amenorrhea rates in contraception studies (25% at 3-6 months and 46% at 9-12 months)
- RCT: Depo-MPA vs. daily oral MPA (5 mg) vs. LNG-IUS
  - “No difference” found between low dose oral MPA and Depo (49% reduction in bleeding vs. 33%)
  - Inferior to LNG-IUS

Hubacher et al 2009; Kucuk et al 2008

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**Think about treatment...**

A 35 year old non-pregnant woman seeks treatment for heavy and regular menstrual bleeding. She cannot contain her clots with tampons and ultrasound are normal. Her HgB is 10 g/dl. She is a nonsmoker with no medical problems.

**Heavy and regular:  
Likely diagnosis AUB-E**



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You counsel the patient that for heavy & regular menstrual bleeding...

- A. Comparisons of COCs found monophasic pills to be more effective than triphasic pills
- B. All COC formulations are FDA approved to treat heavy bleeding
- C. COCs may ↓ blood loss by around 50%**
- D. All of the above



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AUB-E

**Combined oral contraceptives**

- Physiologically makes sense - Medical opinion supports use for *heavy and regular* bleeding
- Most popular first line treatment among U.S. gynecologists
- However, a systematic review conducted in 2009 found inadequate studies to conclude on their effectiveness
  - At that time: Fraser et al in 1991 the only study - May reduce MBL 43% @ 3 months



Cochrane Review by Farquhar et al, updated 2009; Matteson et al 2011; Fraser et al 1991

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AUB-E



## Combined oral contraceptives

- 2 RCTs: "Novel" COC vs. placebo
  - COC reduced menstrual bleeding up to 69%
  - 29-44% in the COC group had normalization of menses (with the decrease seen from 2<sup>nd</sup> cycle onward)
- 2 RCTs: COC vs. LNG-IUS
  - Though less effective than LNG-IUS, COCs effective in decreasing MBL (35-68%) and improving QOL

 Jensen et al 2011; Fraser et al 2011; Endrikat et al 2009; Shabaan et al 2011

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AUB-E



## Oral progestin

- Extended oral progestin may be effective for rx *heavy and REGULAR* bleeding
  - Use may be limited by tolerability
  - Luteal phase progestin (for 10-14 d of cycle) NOT EFFECTIVE
- Norethindrone acetate 5mg TID, days 5-26
  - 37-87% reduction in MBL

 Cochrane Review by Lethaby et al, updated 2009 (2); Fraser et al 1990; Irvine et al 1998

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AUB-E



## Tranexamic acid

- Antifibrinolytic: Decreases fibrinolysis in the endometrium
- Reduces MBL by 30-60% (Recent RCT – 40% reduction)
  - Better than luteal phase progestin, NSAIDS
  - Has not been compared to COCs, extended cycle progestin, LNG-IUS
- **Two 650 mg tablets TID for up to a maximum of 5 d/ month**

 Lukes et al 2010; Cochrane Review by Lethaby et al, updated 2009 (3)

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AUB-E



## NSAIDs

- Limited studies have shown NSAIDs effective in treating heavy and regular bleeding
  - 20-40% reduction in MBL
- No difference between NSAIDs in effectiveness (Naproxen, Mefenamic acid)
- Less effective than tranexamic acid and danazol
- Data limited comparing to luteal phase progestin, LNG IUS, COCs

Cochrane Review by Lethaby et al, updated 2009 (4)

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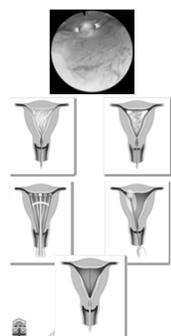
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## Endometrial ablation



- 1<sup>st</sup> generation: Resectoscopic
  - Rollerball
  - Transcervical endometrial resection
- 2<sup>nd</sup> generation: Non-resectoscopic
  - Heated free fluid (hydrothermablation)
  - Thermal balloon
  - Microwave
  - Cryotherapy
  - Radiofrequency bipolar

<http://healthwoman.org/2009/01/16/global-ablation-for-abnormal-bleeding-a-new-solution-to-an-old-problem/>

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Which is true about resectoscopic vs. non-resectoscopic (global) ablation techniques?

A. Resectoscopic techniques greater ↓ in blood loss

B. Global techniques greater ↓ in blood loss

**C. Both are largely equivalent in blood loss reduction**

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Which of the following is the most effective ablation technique?

- A. Heated fluid
- B. Radiofrequency**
- C. Thermal Balloon
- D. All equally effective




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### Global endometrial ablation

- Most studies: only heavy and *regular* bleeding
  - Satisfaction: 50-95%
  - Amenorrhea: 13%-64%
  - Failure rates: 8 - 42%
  - Hysterectomy rates: 5-29%
- No difference between resectoscopic and global methods in bleeding reduction and QOL
- Differences have been shown between global methods



Matteson et al 2012; Dickersin et al 2007; ACOG PB 2007; Penninx et al 2011; Cochrane review by Lethaby et al, 2009 (5)

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### Comparisons of global ablation techniques

- Radiofrequency ablation better than balloon and heated fluid in RCTs
- Radiofrequency versus heated fluid

Outcome	Time	RFA	HTA	RR (CI)
Amenorrhea	1 y	47%	24%	2.0 (1.2-3.1)
	5 y	55%	37%	1.5 (1.05-2.3)
"failure"	1 y	8%	28%	---
	5 y	19%	44%	0.43 (0.25-0.74)
Hyst	1 y	5%	11%	---
	5 y	12%	20%	---



Cochrane review by Lethaby et al, 2009 (5); El-Nashar et al 2009; Penninx et al 2010; Penninx et al 2011; Daniels et al 2012

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**Key predictors of “success” and failure?**

- Predictors of amenorrhea
  - Age > 45 years OR 2.6 (1.6-4.3)
  - Uterine length <9cm OR 1.8 (1.1-3.1)
  - Endo stripe <4mm OR 2.7 (1.2-6.3)
- Predictors of failure
  - Age < 45 years HR 2.6 (1.3-5.1)
  - parity ≥ 5 HR 6.0 (2.5-14.8)
  - Prior tubal HR 2.2 (1.2-4.0)
  - Hx dysmenorrhea HR 3.7 (1.6-8.5)

El-Nashar et al 2009

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**LNG-IUS vs. ablation**

- Satisfaction, quality of life, risk of treatment failure similar with LNG-IUS and endometrial ablation (TCER, balloon)
- Conflicting results about bleeding reduction
- Decision analyses have shown LNG-IUS preferable balancing effect vs. cost

Cochrane review by Marjoribanks et al, updated 2010;  
NICE guidelines 2007; Kaunitz et al 2009

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Mixed populations w/heavy bleeding



**Hysterectomy vs. Ablation**

- Hysterectomy better
  - Bleeding reduction at 1 yr
  - Satisfaction at 2 yrs post-op
  - Some evidence improved health status
    - social functioning, energy, pain and general health
- Ablation better
  - Surgery duration, hospital stay and recovery time
  - Most adverse events (both major and minor)
  - Overall “costs” but not cost-effectiveness

Dickersin et al 2007; Cochrane review by Lethaby et al, updated 2009 (6)

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### Choosing the right treatment for the right patient....

- Must consider the etiology behind the patient's heavy bleeding. Some treatments:
  - Effective for irregular bleeding, not regular bleeding
  - Only studied for regular bleeding – but does that mean they WON'T work for irregular bleeding?
  - Many studies only include patients with confirmed MBL > 80 ml
- Research in this area plagued by small sample size, variety of comparison groups, limited number of studies




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### Conclusions

- Acute AUB
  - IV estrogen, multiple pill regimens of progestin and COCs appear to be effective, TXA likely also effective
- AUB-E: heavy and regular
  - LNG IUS and ablation - the most effective treatments
  - Shown effective – COCs, TXA, 21 days PO progestin, NSAIDs
- AUB-O: heavy and irregular
  - Cyclic COCs, luteal phase progestin may be effective
  - Limited data on other treatments (most studies excluded irregular bleeders) - may be considered




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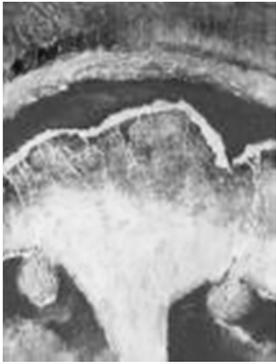
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**Thank you!**

**Any Questions?**

"Uterus" Artwork by Veronica Jackson




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