Abnormal Uterine Bleeding

Evaluation and Management of Ovulatory Dysfunction

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Disclosure

- *Consultant*
  - *Boston Scientific Corporation*
  - *CooperSurgical*
  - *Gynesonics*
  - *HOLOGIC, Inc.*
  - *KARL STORZ Endoscopy*
  - *Minerva Surgical*
- *Speaker's Bureau*
  - *Ethicon, Inc.*
  - *Boston Scientific Corporation*

Objectives

- Review the normal ovulatory menstrual cycle
- Apply pathophysiologic mechanisms to the diagnosis and management of ovulatory dysfunction
- Employ appropriate diagnostic criteria including history, exam, labs and imaging to the diagnosis of ovulatory dysfunction
- Utilize medical management to treat ovulatory dysfunction

FIGO revamps nomenclature for abnormal uterine bleeding

Munro MG, Critchley HOD, Fraser IS. The FIGO systems for nomenclature and classification of causes of abnormal uterine bleeding in the reproductive years: who needs them? Am J Obstet Gynecol. 2012;207(4):259–265.

American College of Obstetrics and Gynecology (ACOG) 2012

- **Refined definition of chronic AUB**
- **New category acute AUB**
- **Clinical dimensions of menstruation**
  - **Regularity of onset**
  - **Frequency of onset**
  - **Duration of menstrual flow**
  - **Heaviness, or volume of menstrual flow**

Normal Parameters
medians and 5th and 95th percentiles

Abnormal Uterine Bleeding

FIGO

International Federation of Gynecology and Obstetrics

Nomenclature System

- **Eliminated Misleading Terms**
  - Dysfunctional Uterine Bleeding (DUB)
  - Menorrhagia

Abnormal Uterine Bleeding (AUB)

  - Polymenorrhagia
  - Polymenorrhea
  - Metrorrhagia
  - Oligomenorrhea

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AUB Classification System

PALM-COEIN

- **P**olyp
- **A**denomyosis
- **L**eiomyoma
- **M**alignancy and hyperplasia
- **C**oagulopathy
- **O**vulatory disorders
- **E**ndometrial dysfunction
- **I**atrogenic
- **N**ot otherwise classified

Structural imaging, histology or both

Unrelated to structural abnormalities

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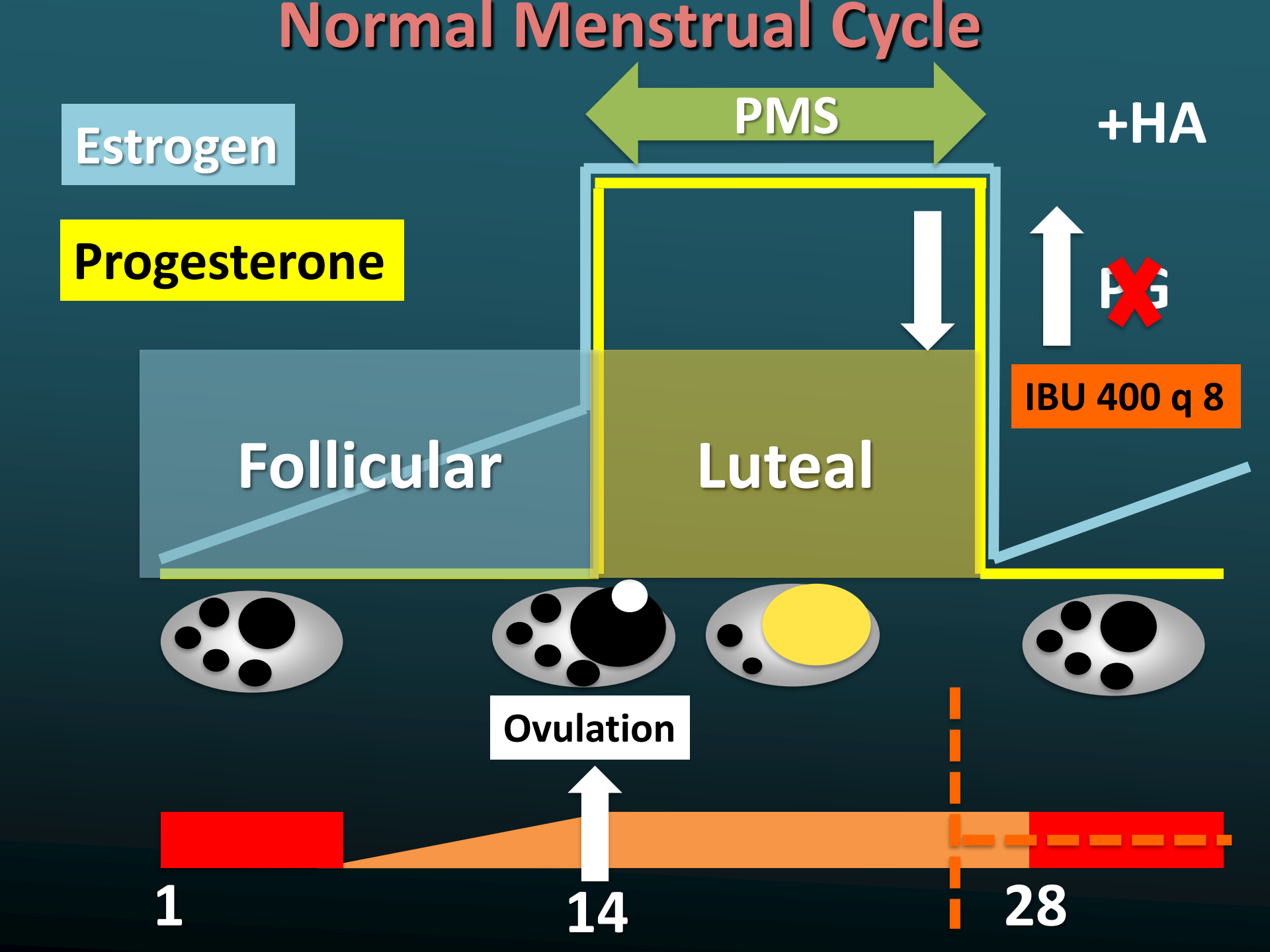
AUB Classification System

PALM-COEIN

- **AUB-P** Polyp
- **AUB-A** Adenomyosis
- **AUB-L** Leiomyoma
- **AUB-M** Malignancy and hyperplasia
- **AUB-C** Coagulopathy
- **AUB-O** Ovulatory disorders
- **AUB-E** Endometrial dysfunction
- **AUB-I** Iatrogenic
- **AUB-N** Not otherwise classified


Normal Menstrual Cycle
Estrogen
Progesterone
PMS
+HA
PG
IBU 400 q 8
Follicular
Luteal
Ovulation
1
14
28

Department of Health and Human Services Questionnaire

Acne

Anxiety

Breast swelling and tenderness

Upset stomach

Mood swings

Trouble remembering

Headache

Uterine cramps

noun **mo·li·men** \mə-ˈlī-mən\
plural **mo·lim·i·na** \mə-ˈlim-ə-nə\

Food cravings

Joint or muscle pain

Depression

Irritability

Fatigue

Difficulty sleeping

Backache

Constipation

Bloating

Diarrhea

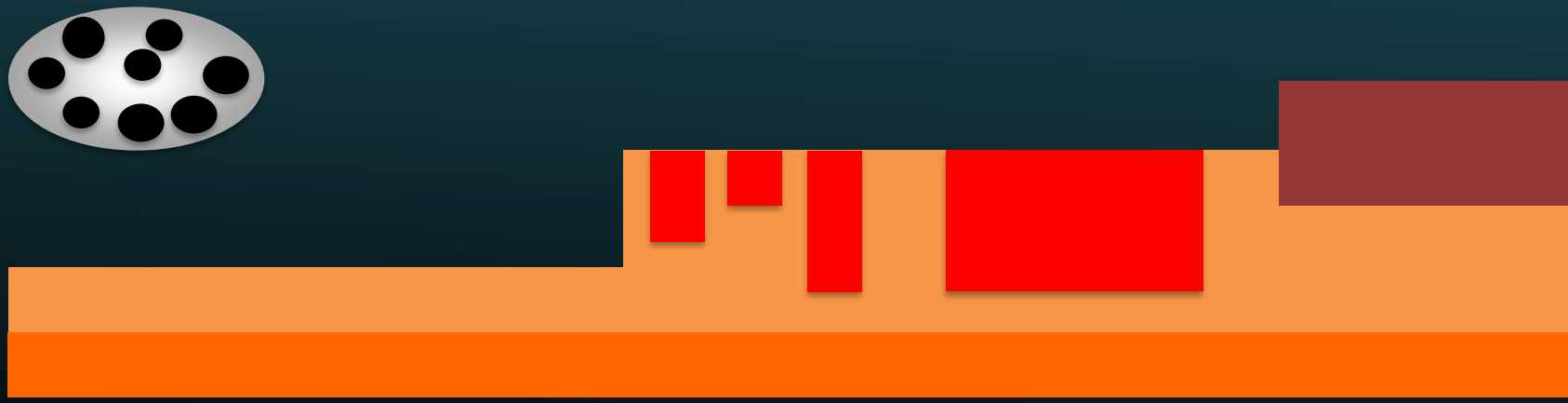
Trouble concentrating

Anovulatory Menstrual Cycle

Estrogen

Progesterone

Adenocarcinoma



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Anovulation

Hypothalamic Dysfunction
- Primary hypothalamic
- Anorexia Nervosa
- Extreme exercise

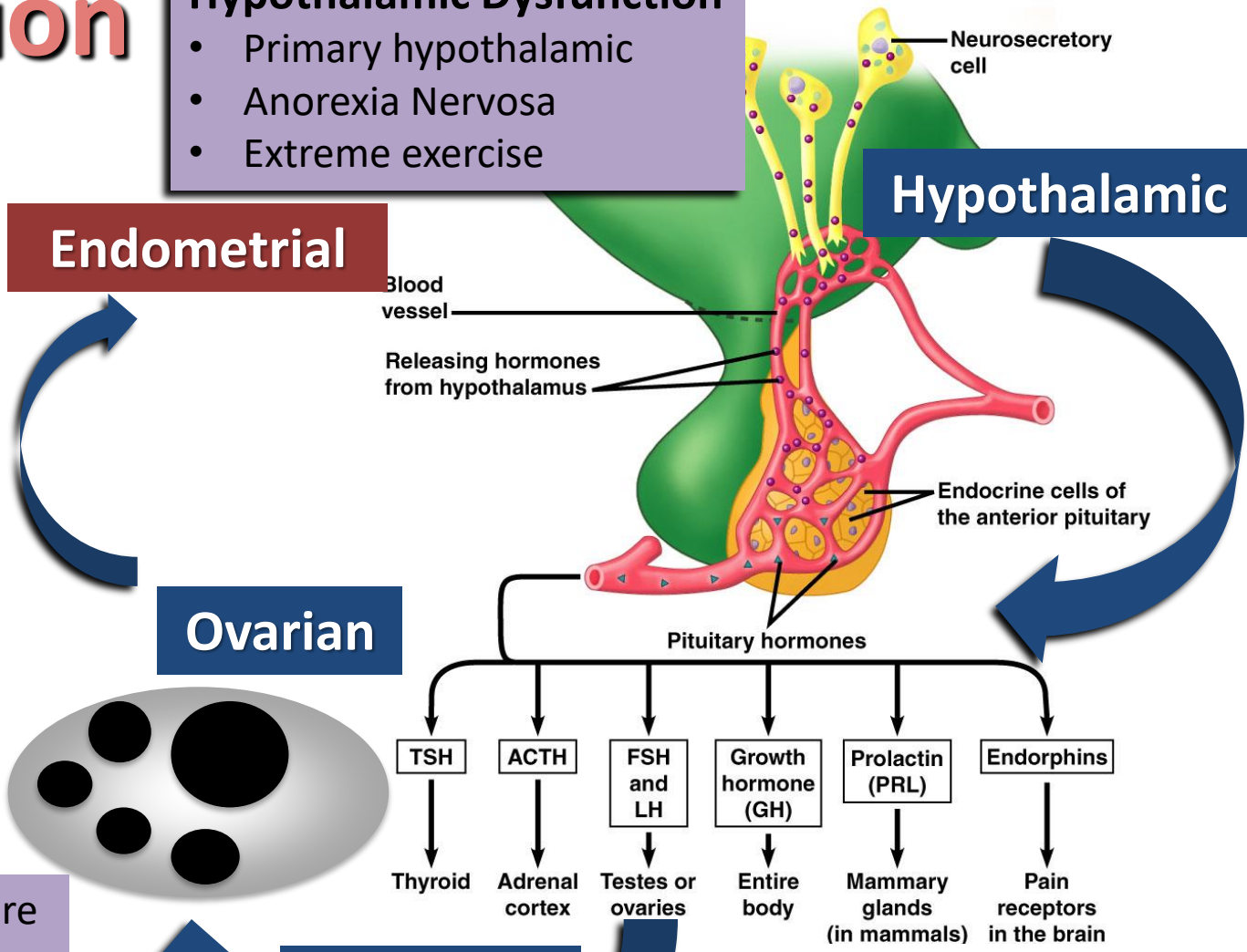
Physiologic
- Adolescence
- Perimenopause
- Lactation
- Pregnancy

Hyperinsulinemic
- PCOS
- DM/Pre-diabetes
- Metabolic syndrome
- Obesity

- Premature ovarian failure
- Iatrogenic (chemo/rad)

Hyperandrogenic
- PCOS
- CAH
- Androgen tumors

- Hyperprolactinemia
- Thyroid disease
- Primary pituitary disease
- Medications



AUB-O

Chronic Unopposed Effects of Estrogen on the Endometrium

- Disorder of ovulation
- Must exclude other etiologies of AUB
  - Polyps, adenomyosis, leiomyomas, coagulopathy
- Irregular menstrual bleeding
- Medical management preferred to surgical

History

- Age
- Menstrual
  - Irregular menstrual bleeding
- Medical history – ovulatory dysfunction
  - Diabetes or pre-diabetes, PCOS, metabolic syndrome, thyroid disorders, obesity
- Medications
- Family history
  - Colon or endometrial carcinoma

Suggested "normal" limits for menstrual parameters in the mid-reproductive years

Clinical dimensions of menstruation and menstrual cycle	Descriptive term	Normal limits (5th-95th percentiles)
Frequency of menses, d	Frequent	<24
	Normal	24-38
	Infrequent	>38
Regularity of menses: cycle-to-cycle variation over 12 months, d	Absent	No bleeding
	Regular	Variation ± 2-20
	Irregular	Variation >20
Duration of flow, d	Prolonged	>8.0
	Normal	4.5-8.0
	Shortened	<4.5
Volume of monthly blood loss, mL	Heavy	>80
	Normal	5-80
	Light	<5

Munro. FIGO system for abnormal uterine bleeding. Am J Obstet Gynecol 2012.

Menstrual History

Women with normal volume of menstrual blood loss

- How often do you change your pad/tampon on peak flow days?
  - Change pads/tampons at >/ 3 hour intervals
- How many pads/tampons do you use over a single cycle?
  - Use fewer than 21 pads/tampons per cycle
- Do you need to change the pad/tampon during the night?
  - Seldom need to change the pad/tampon during the night
- How large are any clots that are passed?
  - Have clots less than 1 inch in diameter
- Has a medical provider told you that you are anemic?
  - Are not anemic

Menstrual History

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Heavy Menstrual Bleeding (HMB)

"HMB should be defined as excessive menstrual blood loss which interferes with the woman's physical, emotional, social and material quality of life, and which can occur alone or in combination with other symptoms."

- Regularity of onset
- Frequency of onset
- Duration of menstrual flow
- Heaviness, or volume of menstrual flow

Medications Causing Hyperprolactinemia

Medication Class	Frequency of Prolactin Elevation	Mechanism
Antipsychotics		**Dopamine (D2) Receptor Blockade**
Chlorpromazine	Moderate	
Haloperidol	High	
Loxapine	Moderate	
Risperidone	High	
Paliperidone	High	
Cyclic Antidepressants		**Indirect PRL affect via serotonin**
Amitriptyline	Low	
Desipramine	Low	
Clomipramine	High	
Nortriptyline	None	
Antiemetics		**Dopamine (D2) Receptor Blockade**
Metoclopramide	High	
Prochlorperazine	Low	
Antihypertinsives		
Verapamil	Low	Not understood
Methyldopa	Moderate	Decreased DA synthesis

Exam

- Signs of hyperandrogenism
  - Hirsuitism, acne, male-pattern hair loss
- Signs of insulin insensitivity (hyperinsulinemia)
  - Acanthosis, skin tags
- Body weight
  - Obesity, underweight

Lab Evaluation

- **Ovulatory Dysfunction**
  - Pregnancy test (βhCG)
  - Thyroid stimulating hormone (TSH)
  - Prolactin (PRL)
  - Complete blood count w/differential (CBC)
    - Anemia
    - Iron studies if anemic (TIBC, iron, ferritin)
  - Follicle stimulating hormone (FSH)

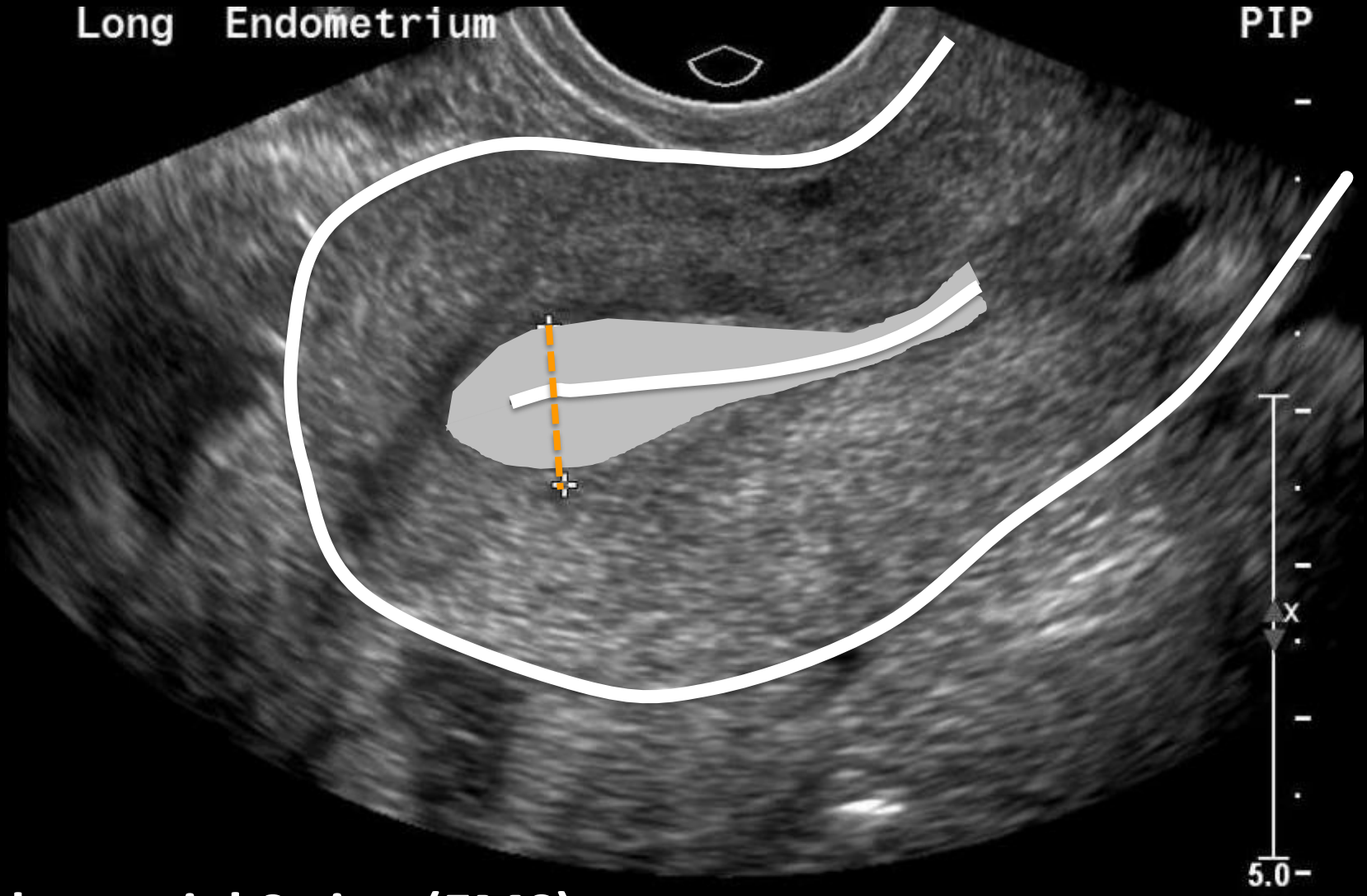
  - HgA1C
  - Androgens (if viralization present)

Imaging

Pelvic Ultrasound

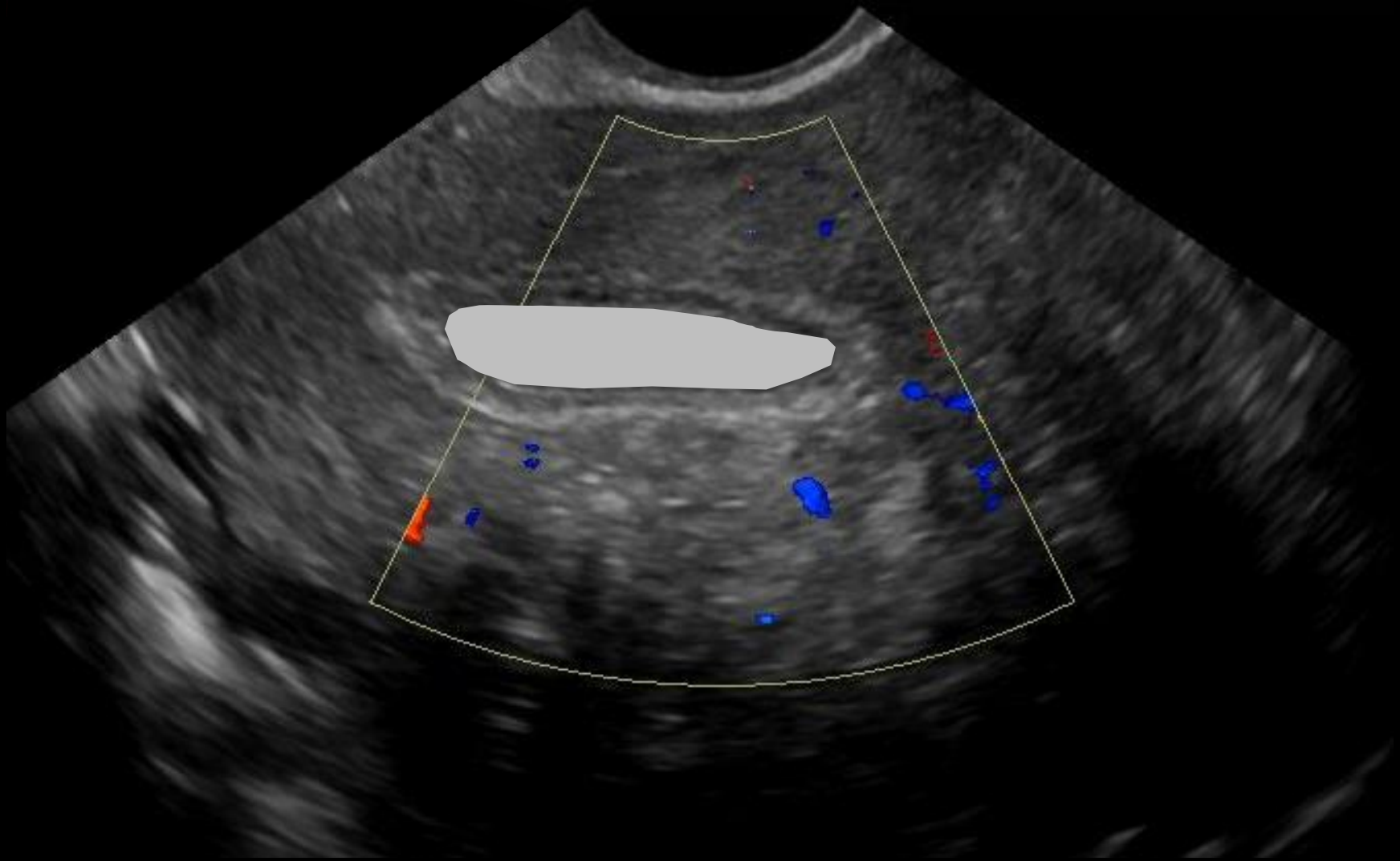
- Cycle Timing
  - Cycle day 4-8 minimizes endometrial thickness
- Transabdominal
  - Masses extending above the pelvic brim, bladder
- Transvaginal
  - Uterus
    - Endometrium, myometrium, cervix
  - Adnexa
    - Fallopian tubes, ovaries
  - Culdesac

Normal Tri-laminar Endometrium
Transvaginal Ultrasound

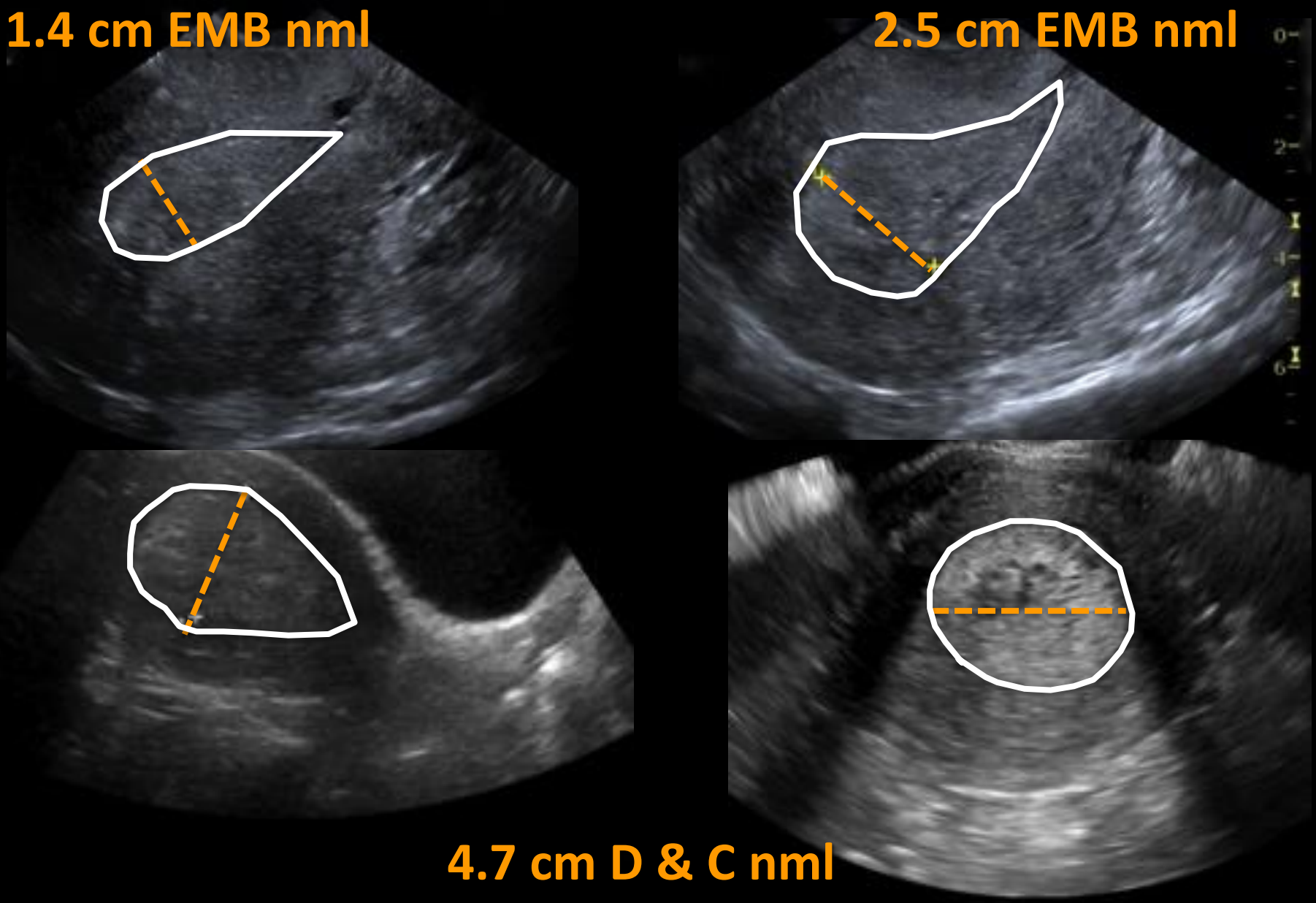


Endometrial Stripe (EMS)

TVUS with Endometrial Polyp

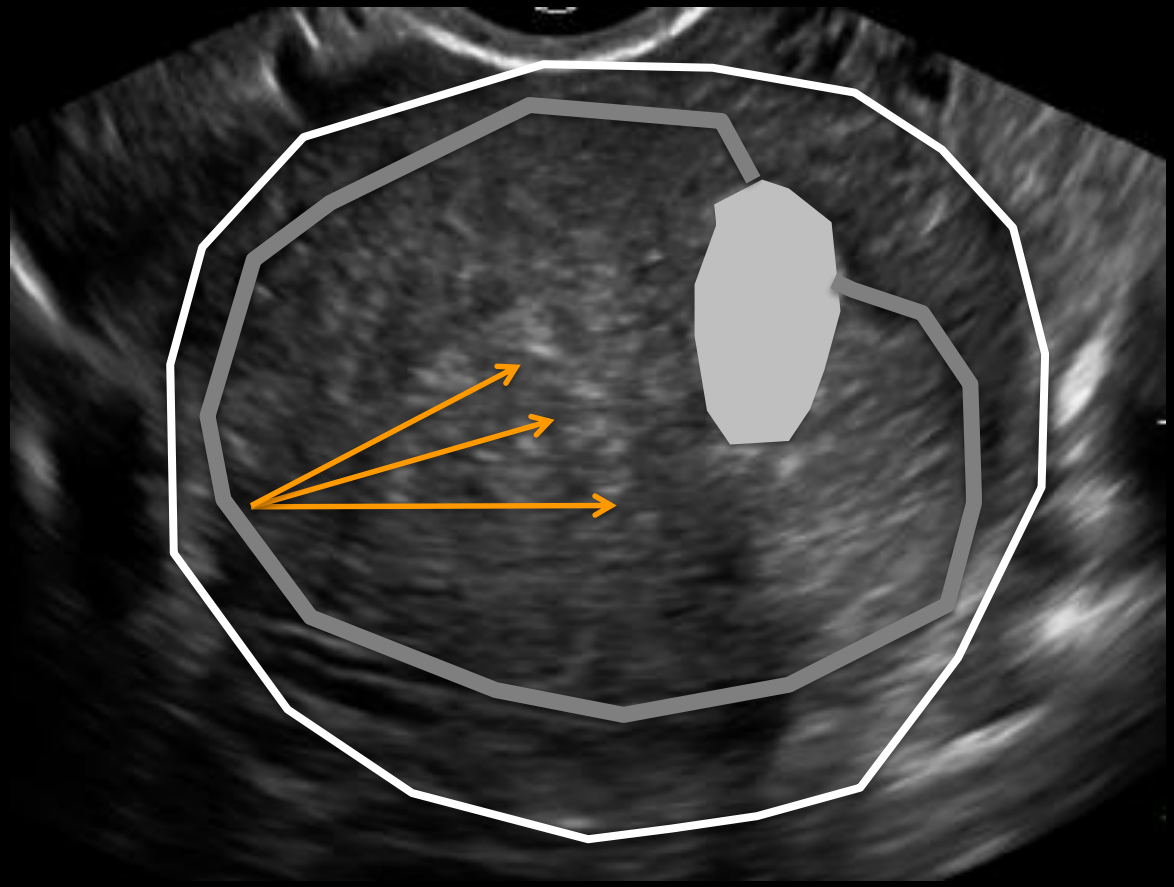


Progressively Enlarging Endometrium
Transvaginal Ultrasound

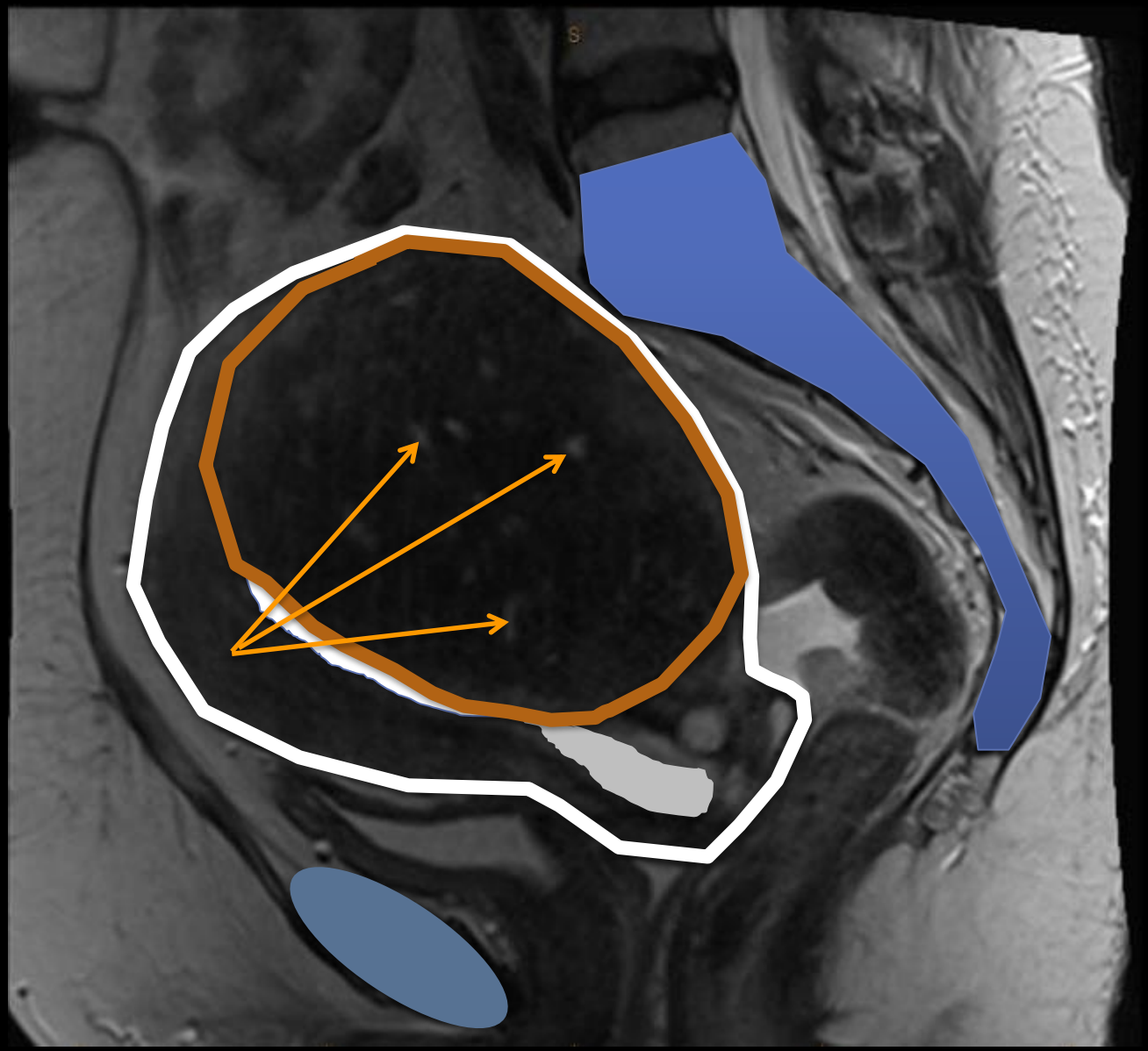


TVUS with Adenomyosis

gland-in-the-muscle



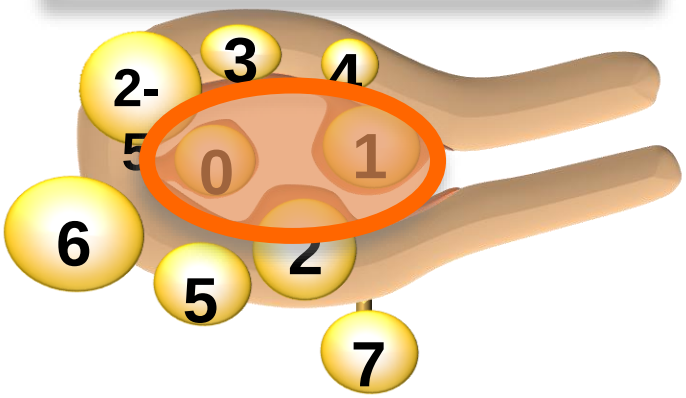
MRI with Adenomyosis



Polyp		**C**oagulopathy
Adenomyosis		**O**vulatory Dysfunction
Leiomyoma	**S**ubmucous	**E**ndometrial
	Other	**I**atrogenic
Malignancy & Hyperplasia		**N**ot Classified

Leiomyoma Subclassification System

S - Submucous	0	Pedunculated Intracavitary
	1	<50% Intramural
	2	≥ 50% Intramural
O - Other	3	Contacts endometrium; 100% Intramural
	4	Intramural
	5	Subserosal ≥50% Intramural
	6	Subserosal < 50% Intramural
	7	Subserosal Pedunculated
	8	Other (specify eg. cervical, parasitic)

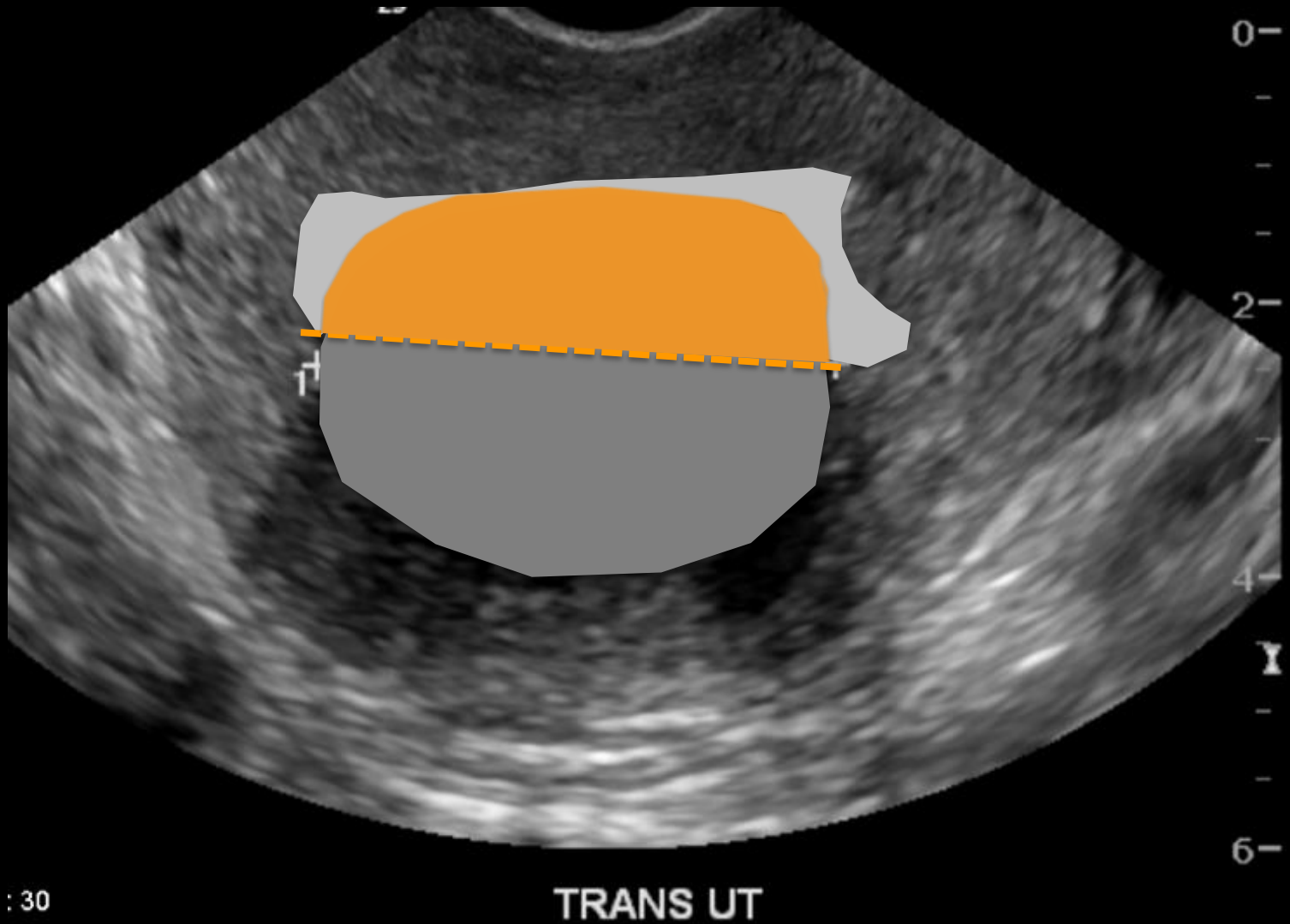


Hybrid Leiomyomas (impact both endometrium and serosa)	Two numbers are listed separated by a dash. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below	
	2-5	Submucous and subserus, each with less than half the diameter in the endometrial and peritoneal cavities respectively.

FIGO AUB Classification System

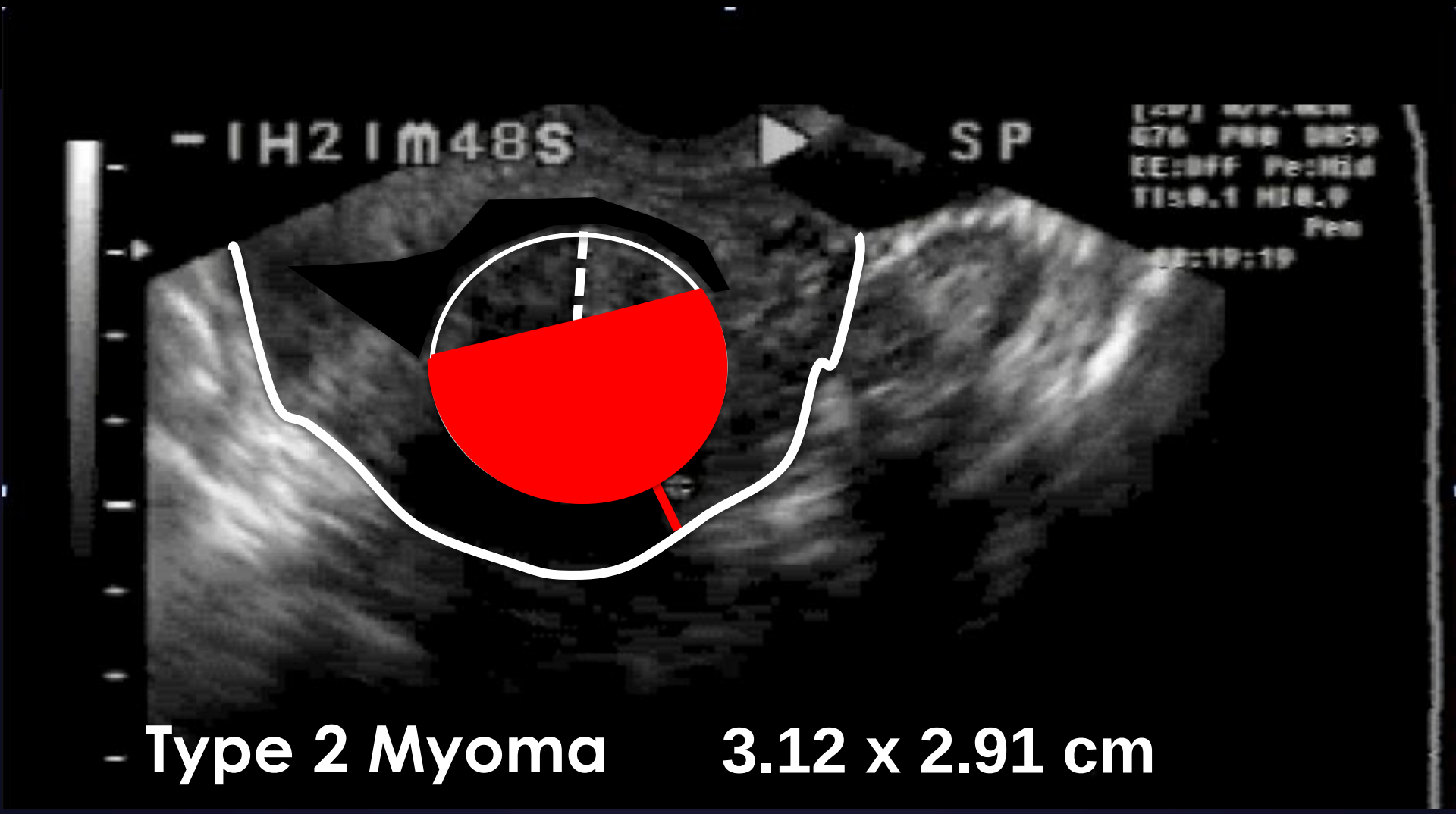
Courtesy of Malcolm Munro, MD

TVUS with Submucous Myoma



Preoperative Decision Making

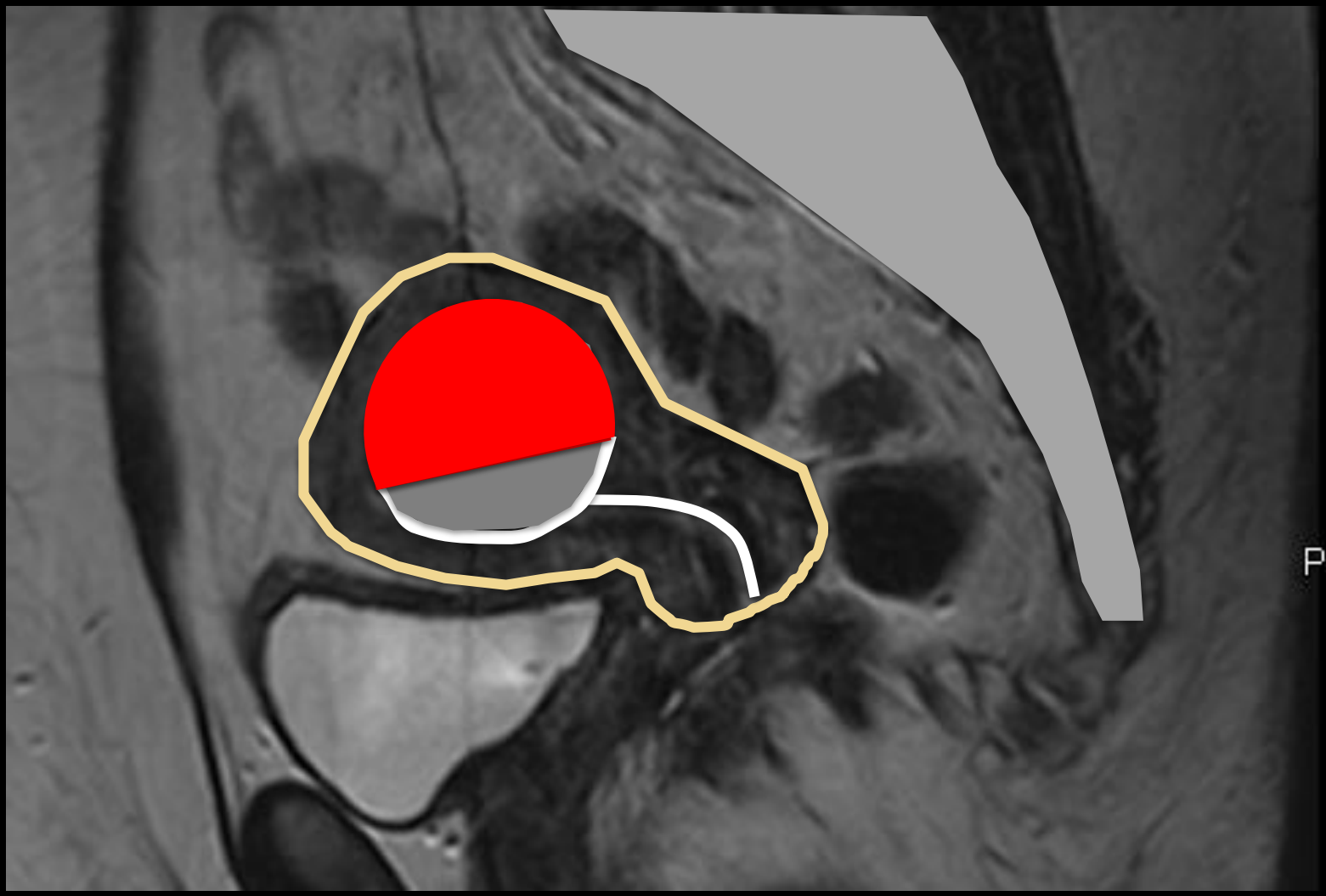
Sonohysterogram/Saline Infusion Study (SIS)



Type 2 Myoma 3.12 x 2.91 cm

Preoperative Decision Making

T2 MRI Sagittal



Type 2 Myoma 5.92 x 5.78 x 6.1 cm

Endometrial Adenocarcinoma

- Incidence endometrial adenocarcinoma
  - Most common gyn CA of women in U.S.
  - Increases with age: median age 61
- Risk factors
  - Family history
    - 1st degree relative
    - Lynch (colorectal ca/endom ca)
  - Exogenous estrogen
    - Unopposed estrogen
    - Tamoxifen (menopausal women)
  - Annovulation
    - Diabetes, obesity, metabolic syndrome, PCOS hyperestrogenism
  - Hypertension

Adenocarcinoma Age Related Risk

20 to 34 -- 1.5%
35 to 44 – 6.0%
45 to 54 – 19%
55 to 64 – 32.6%
65 to 74 – 22.6%
75 to 84 -- 13.5%
85 or older – 4.8%

Histologic Evaluation

Endometrial Biopsy

- **Who should have an endometrial biopsy?**
  - Risk for endometrial carcinoma
    - Age related risk > 45 with AUB
    - Risk factor assessment
  - Anovulatory bleeding
  - Risk for endometrial hyperplasia

Adenocarcinoma
Age Related Risk

20 to 34 -- 1.5%
35 to 44 – 6.0%
45 to 54 – 19%
55 to 64 – 32.6%
65 to 74 – 22.6%
75 to 84 -- 13.5%
85 or older – 4.8%

GYNECOLOGICAL ENDOCRINOLOGY

http://informahealthcare.com/gye
ISSN: 0951-3590 (print), 1473-0766 (electronic)

Gynecol Endocrinol, 2013; 29(4): 315–318
 DOI: 10.3109/09513590.2012.752458

informa
healthcare

- 120 women
- Endometrial thickness and chronic anovulation
- Anovulatory period 145 +/- 186 days
- Endometrial thickness 7.1 +/- 3.2 mm
- Positive correlation with BMI
- No correlation with
  - Age, serum androgens, estradiol, FSH, LH
- Women with metabolic syndrome > BMI

for metabolic syndrome. We concluded that endometrial thickness in women with ovulatory dysfunction is positively correlated with body weight status but is not correlated with serum androgens or E_2 levels.

Histologic Evaluation

Endometrial Biopsy

Pipelle endometrial sampling. Sensitivity in the detection of endometrial cancer

Guido et al. J Reprod Med 1995 Aug;40(8):553-558

- Patients with known endometrial CA
- Undergoing hysterectomy
- Pipelle biopsy adequate for analysis 97%
- CA in 54 of 65 patients
- Sensitivity 83 +/- 5% (mean +/- SD)
- Of 11 false negatives
  - 5 with CA in polyps only
  - 3 with disease localized to < 5% of endometrium

Histologic Evaluation

Endometrial Biopsy Results for AUB-O

Pipelle endometrial sampling 4.2% of endometrial surface area.

Rodriquez et al. Am J Obstet Gynecol. 1993 Jan;168:55-9

- Disordered, proliferative endometrium with stromal breakdown. Negative for hyperplasia or atypia……
- Simple or complex hyperplasia…
- Hyperplasia with atypia…
- FIGO Grade (1-3) adenocarcinoma…

Endometrial Adenocarcinoma

Risk Factors

- Stage IVB adenocarcinoma of the endometrium with metastases to ovaries and colic peritoneum with greater than 50% invasion into the myometrium.

Endometrial Adenocarcinoma

Risk Factors

- 39 y.o. woman with PE, admitted to hospitalist service for anticoagulation. Heavy, AUB with severe anemia requiring blood transfusion. Discharged to follow-up with “on-call Gyn”. Patient weights 243 lbs. and is 67 inches tall with BMI 38. History of irregular menses since her 20’s.

AUB-O Management

- Sustained weight loss
- Estrogen and Progesterone therapy
  - Vaginal ring
  - Transdermal
  - Oral contraceptive pill (OCP)
- Progestin

AUB-O Management

Combined Oral Contraceptive

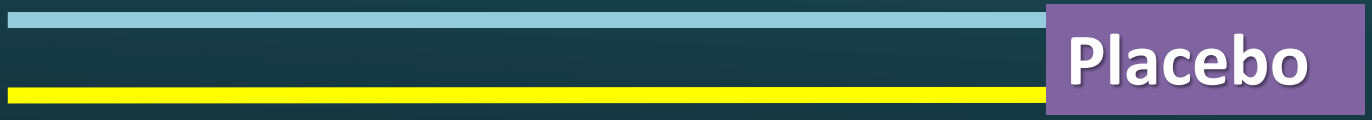
- Cyclic
  - Oral daily
  - Withdraw bleeding occurs with stopping
  - Regular shedding of endometrium
- Continuous
  - Monophasic pill only
  - Oral daily use without placebo
  - Breakthrough bleeding common
- OCP side-effects
  - Stops ovulation, decreases acne, nausea, bloating, decreases ovarian cancer risk

Menstrual Cycle Cyclic OCP's

Estrogen

Progesterone

OCPs

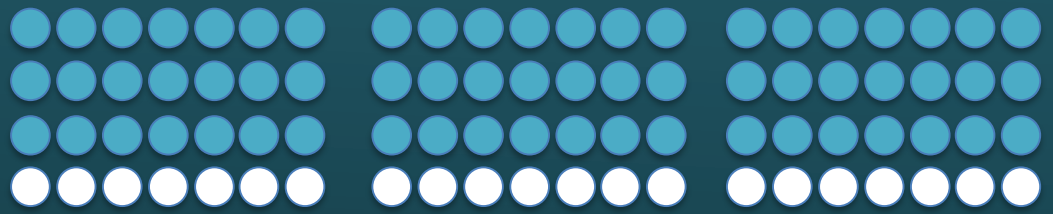


Menstrual Cycle Continuous OCP's

Estrogen

Progesterone

OCPs



AUB-O Management

Progestin

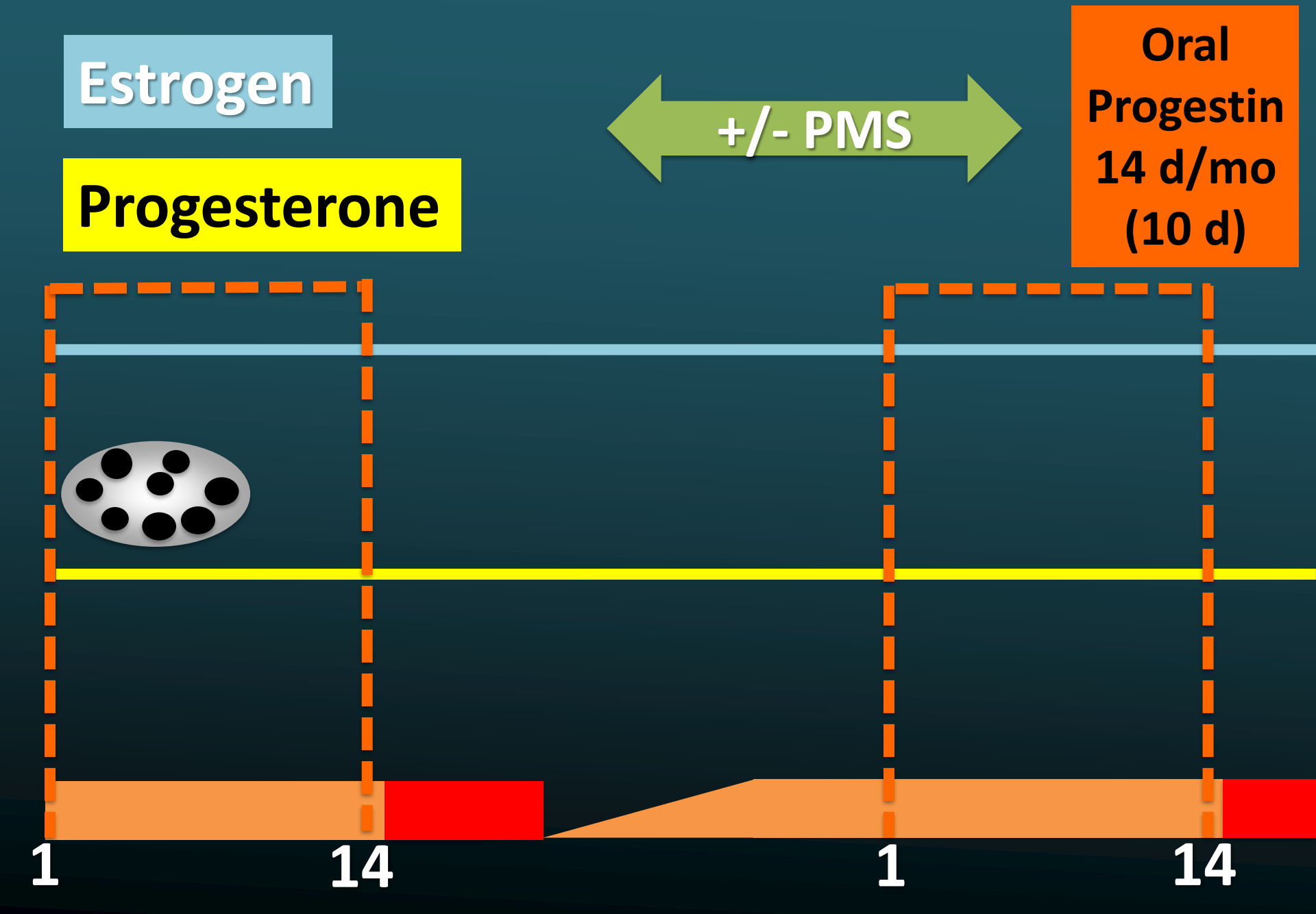
- Cyclic
  - Oral 10 to 14 days per 30 days
  - Withdraw bleeding occurs with stopping
  - Regular shedding of endometrium
- Continuous
  - Oral daily use
  - Implant (Nexplanon)
  - Injectable (Depo-Provera)
  - Levonorgestrel intrauterine system (LNG IUS –Mirena)
- Progestin side-effects
  - Bloating, headache, constipation, fatigue, acne, food cravings, AUB

AUB-O Management

Progestin

- Cyclic
  - Aygestin (norethindrone)
    - 5 mg PO daily HS to BID for 10 – 14 days per 30 days
  - Provera (medroxyprogesterone acetate)
    - 10 mg PO daily HS for 10 – 14 days per 30 days
  - Prometrium (micronized progestin)
    - 100 mg to 200 mg daily HS (up to 400 mg)
    - 10 – 14 days per 30 days
- Continuous
  - Oral daily use

Anovulatory Menstrual Cycle Cyclic Progestin



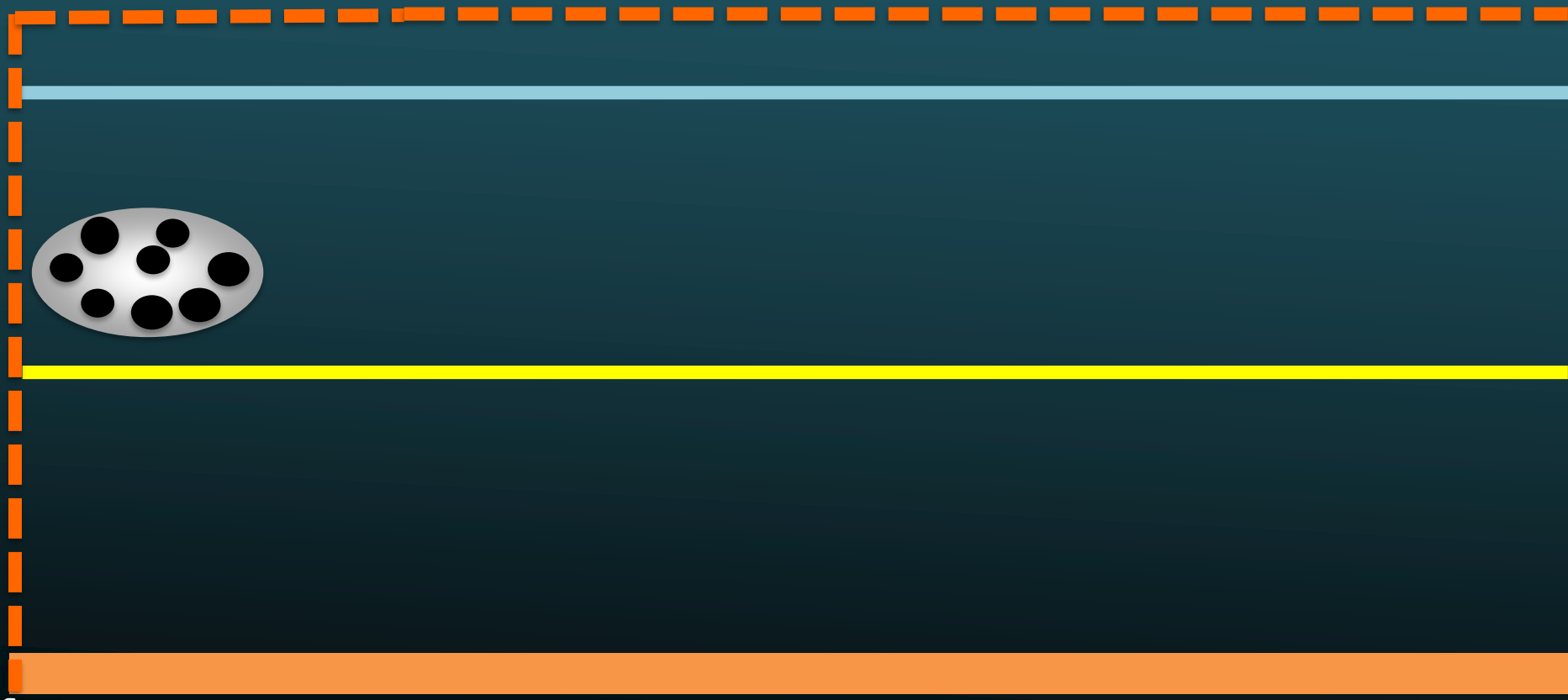
Anovulatory Menstrual Cycle
Continuous Progestin

Estrogen

Progesterone

+/- PMS

Oral Progestin Daily



AUB-O Management

Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding (Review)

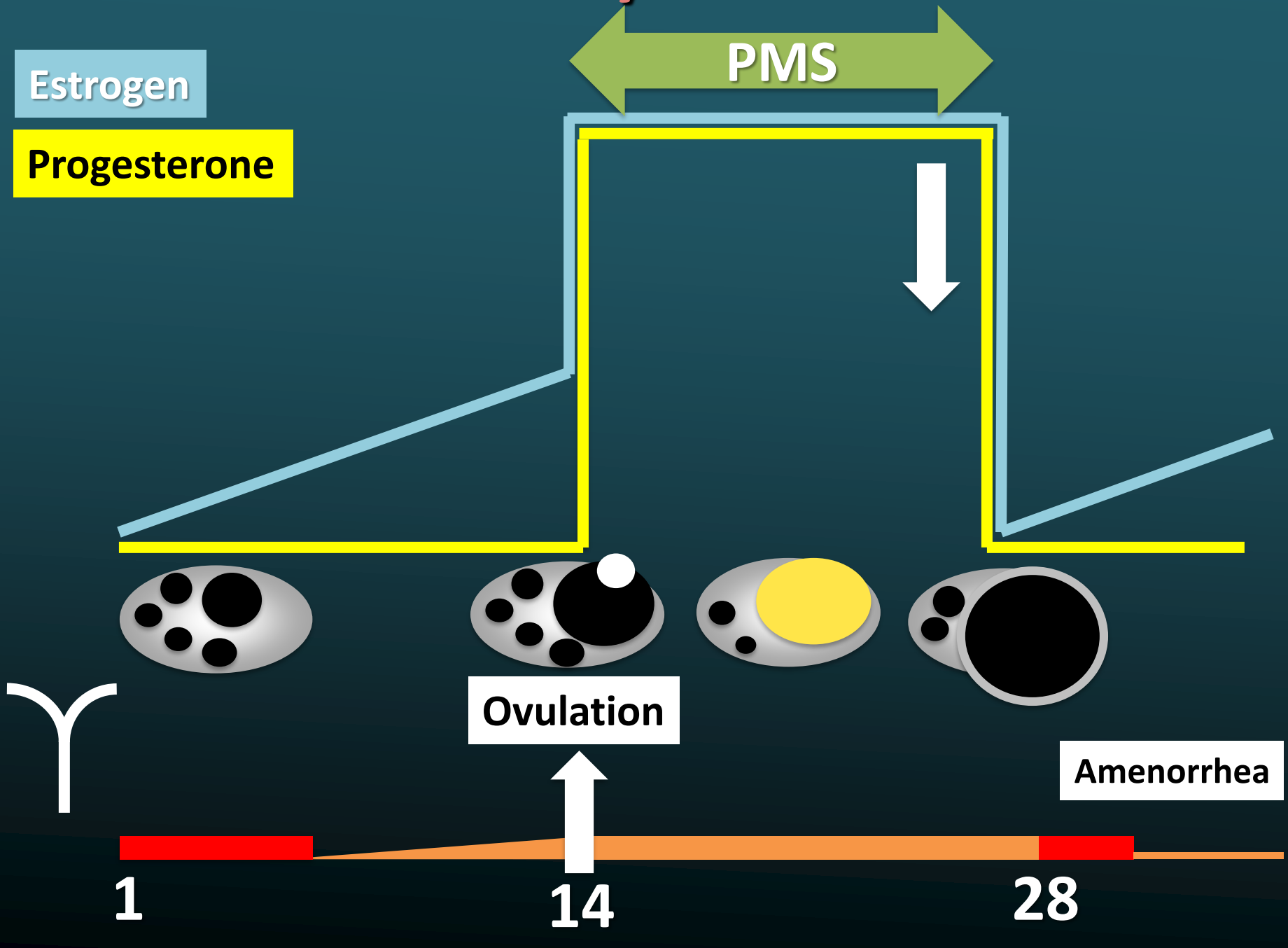
April 2015

Lethaby A, Hussain M, Rishworth JR, Rees MC

THE COCHRANE COLLABORATION®

- More effective than oral medication for HMB
  - Greater reduction in HMB approximately 80%
  - Improved quality of life
  - More acceptable long term
  - Associated with pelvic pain, breast tenderness and ovarian cysts
  - Associated with abnormal bleeding
  - Associated with amenorrhea
  - Less affective than a hysterectomy for Tx HMB

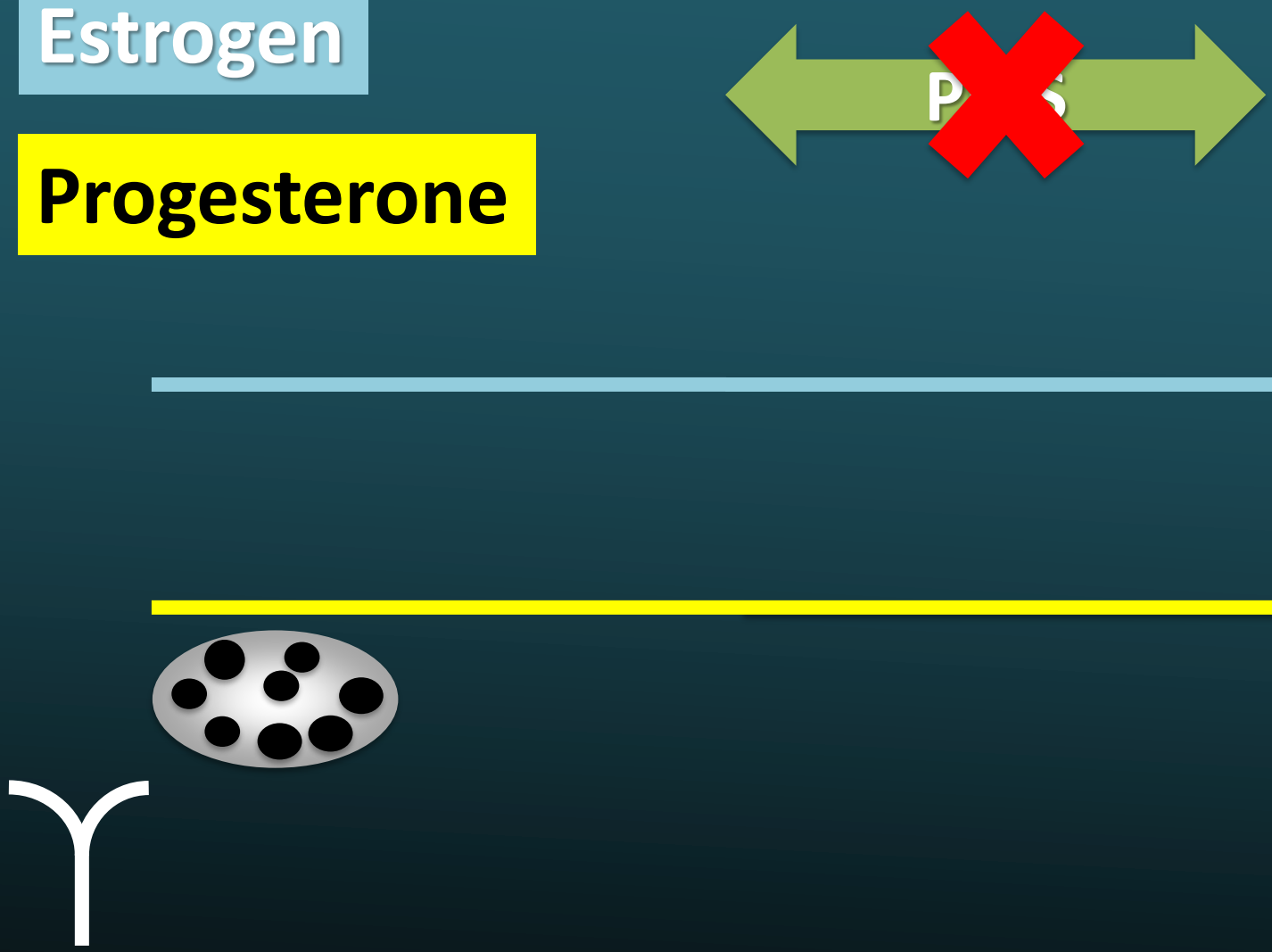
Menstrual Cycle LNG IUS



Anovulatory Menstrual Cycle LNG IUS

Estrogen

Progesterone



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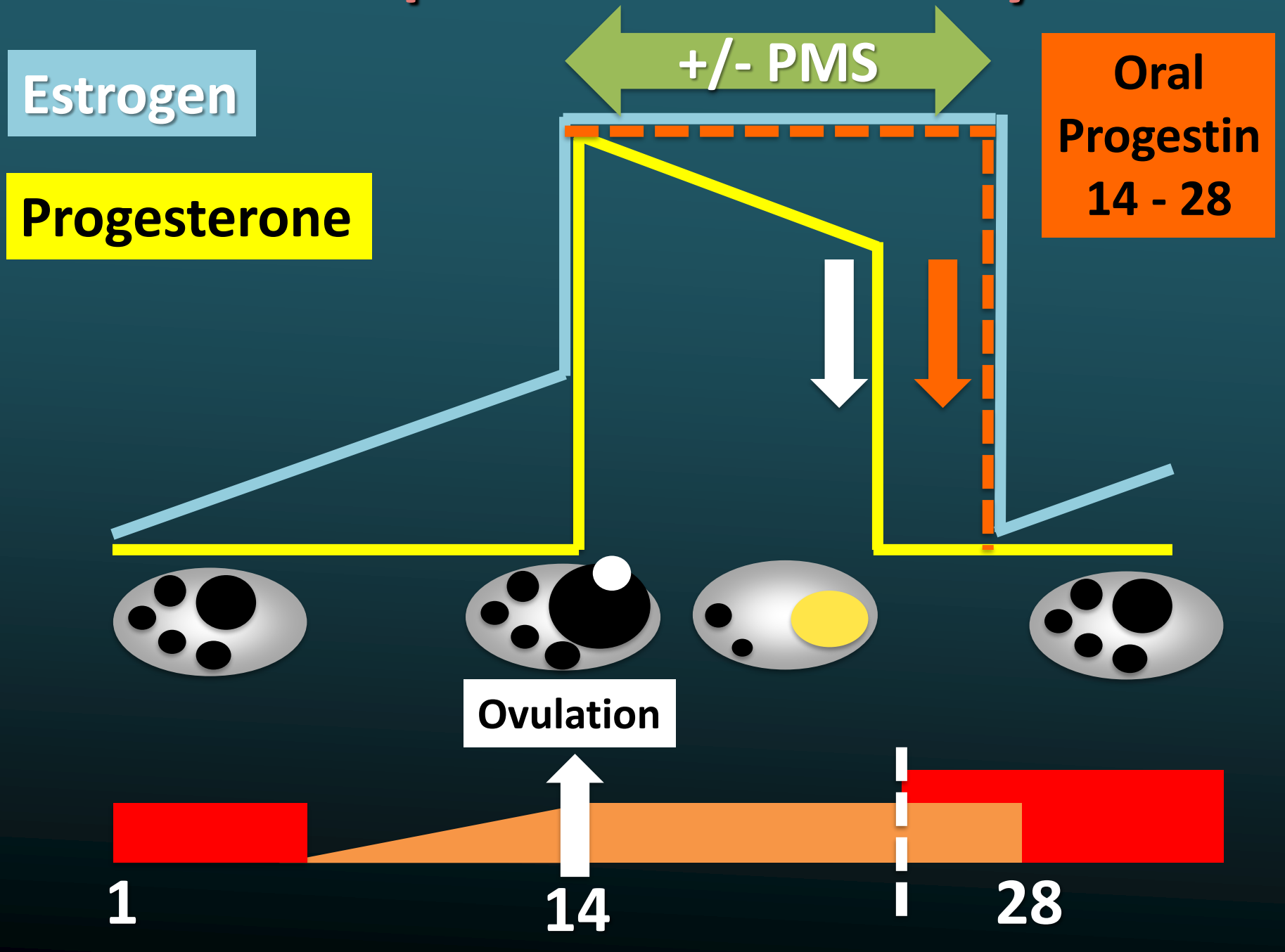
Efficacy of the levonorgestrel intrauterine system (LNG-IUS) in the prevention of the atypical endometrial hyperplasia and endometrial cancer: retrospective data from selected obese menopausal symptomatic women

Gynecological Endocrinology, 2013; 29(2): 156–159

Michele Morelli, Annalisa Di Cello, Roberta Venturella, Rita Mocciaro, Pietro D'Alessandro & Fulvio Zullo

- Retrospective n = 34
- Obese, menopausal women with AUB
  - Simple hyperplasia 58.8%
  - Complex hyperplasia 41.2%
- 91% at 36 months w/o AUB
- EMS 8.2 +/- 2.2 to 3.2 +/- 1.5 mm, $p < .05$
- Histologic regression of hyperplasia
  - 79.4% at 12 months
  - 97.5 % at 36 months
  - EH persisted 2.5% no progression to atypia or CA

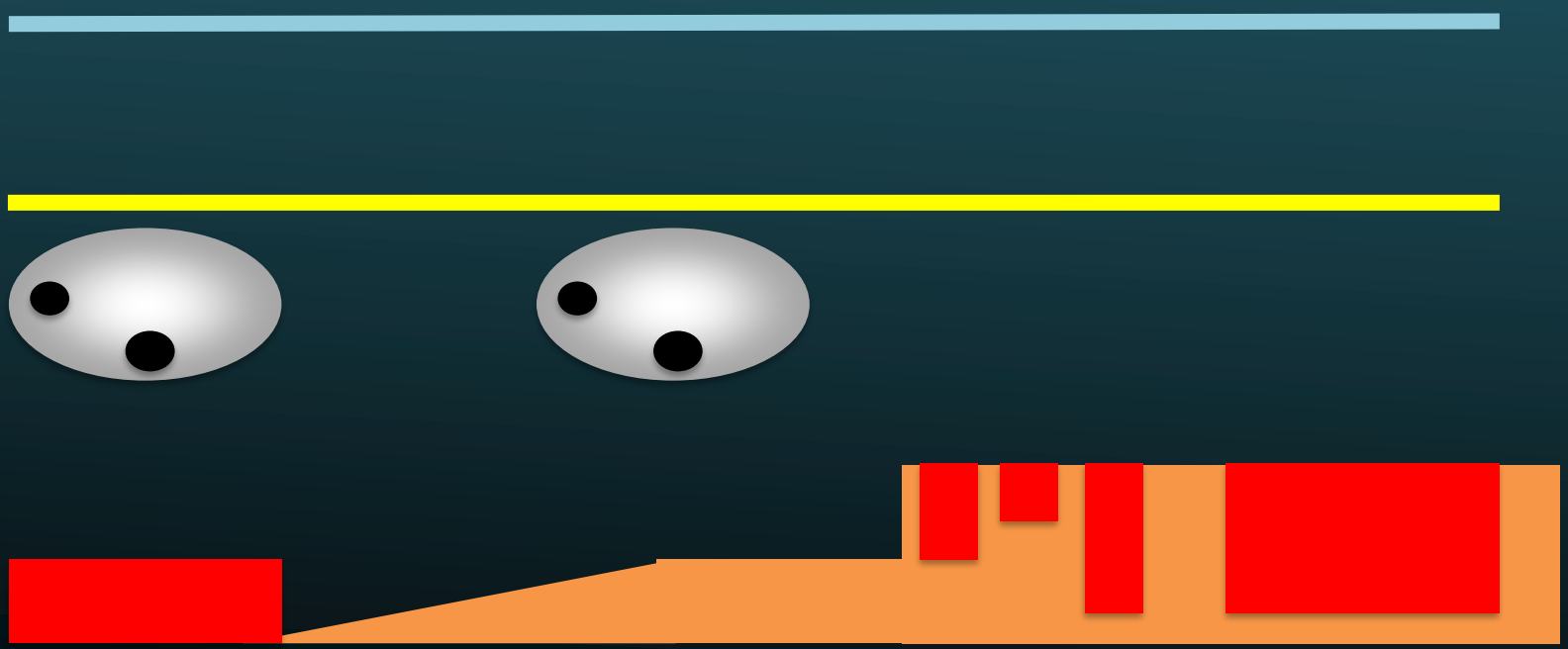
Perimenopausal Menstrual Cycle



Perimenopausal Anovulation

Estrogen

Progesterone



Reimbursement

2015

No Global

In-Patient (21), Out-Patient (22), ASC (24)		
IUD Placement 58300		
2014 RVU	2015 Medicare CF 35.7547	125% CF 44.6934
Non-Facility/Office (11)		
2.13	$ 76.16	$ 95.2

Reimbursement

2015

No Global

In-Patient (21), Out-Patient (22), ASC (24)		
IUD Removal, Replacement 58301		
2014 RVU	2015 Medicare CF 35.7547	125% CF 44.6934
Non-Facility/Office (11)		
2.84	$ 101.54	$ 126.93