The Menstrual Cycle

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Disclosure
Alison McAllister, ND, is employed by ZRT Laboratory. Conflict of interest was resolved through peer review of slide content.

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Learning Objectives

• At the conclusion of this activity, the participant will be able to:
  – Explain the two phases of Folliculogenesis.
  – Discuss the stages of a normal menstruation cycle.
  – Discuss menstrual irregularities as well as the common causes and treatments.

The Menstrual Cycle

Remembering Normal
• Takes approximately 12 menstrual cycles

2 Phases of Folliculogenesis

• PreAntral/ Gonadotrophin independent
  – Growth and differentiation
• Locally produced growth factors
• About 10 cycles

• Antral/Graafian/ Gonadotrophin dependant
  – Growth of the follicle up to 25mm
• FSH/LH control
• Growth factors
• About 2 cycles
• Then one is chosen and develops in about 14 days
1. Primordial follicle recruitment
2. Preantral follicle development
3. Selection and growth of the Graafian follicle
4. Follicle atresia

Folliculogenesis
- Starts around day 26 until day 14 of the cycle
- Corpus luteum fails → ↓Inhibin A and B
  → ↑FSH → follicle recruitment
- Dominant follicle chosen by day 5-7
- Follicles produce estradiol which increase estradiol receptors
- Higher estradiol increases LH receptor levels & LH

Folliculogenesis
- Follicle reaches >15mm and produces peak of LH
- LH peaks 34-36 hours prior to ovulation
- LH stimulates granulosa cells to dissolve, progesterone to be produced which causes FSH peak
- Prostaglandins and proteolytic enzymes are released in response to LH peak allowing for ovulation
The Menstrual Cycle

FSH and the Ovary

- Follicle stimulating hormone
  - Selection & growth of the dominant follicle
  - Stimulates aromatase in the granulosa cells which allows for estrogen production
  - Inhibited by inhibin and estradiol. So only the follicle with the most receptors wins. All others undergo atresia.

LH and the ovary

- Stimulates Androstenedine production
  - High in graafian follicles
- Differentiates thecal interstitial cells
- Acts with insulin and lipoproteins
Day 1-5

- Menses – shedding of the endometrium
- Follicles developing and starting to produce estrogen

Day 5-7

- FSH stimulates follicles
- One follicle becomes dominant (the one with the most FSH receptors)
- Follicle produces estradiol, androgens and inhibin
- FSH drops
- Estrogen stops menstruation
Day 7-13
- High Estradiol stimulates more and more LH production
- Dominant follicle fully matures
- LH level peaks – ovulation will occur 34-36 hours later

Ovulation – day 14
- Prostaglandins and proteolytic enzymes are released in response to LH peak allowing for ovulation
- Egg is released
- Corpus luteum produced under direction of LH
- Fertilization occurs within 24 hours

Ovulation til day 19-21
- Corpus luteum produces
  - Estradiol
  - Progesterone
  - Androgens
  - Inhibin
  - All keep FSH low

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Day 21-28

- Implantation occurs 8 days later OR
- Corpus luteum degrades allowing FSH to rise
- Next cycles follicles (5-6) are recruited
Corpus Luteum

- Produces estradiol and progesterone
- Gains color from large amount of cholesterol esters
- Expresses large amount of: StAR, P450scc, 3β-HSD, and P450arom
- Degrades by day 28 ending hormone production and starting the next cycle

OR

* Novai.vf.com
What is happening and what to do when it’s not going right?
Evaluation of Menstrual Irregularities

- History
  - Timing
  - Duration
  - Onset
  - Better with???
  - Worse with???
  - Change in cycle
  - Other medical conditions
  - Pregnancy/Infertility
  - Tampons/pads
  - Therapies tried
  - Family history

Evaluation of Menstrual Irregularities

- Labs & Imagining
  - CBC
  - Ferritin
  - Iron studies
  - TSH
  - Vitamin D
  - Estradiol & Progesterone
  - Ultrasound, vaginal
  - MRI

Ovulatory Cycle

- 24-36 days long
- Day 1 = 1st day of bleeding
- Ovulation on day 8 – 22
- Follicular phase variable length
- Luteal phase 12- 16 days. Consistent
- 25% pregnancy chance every cycle
Anovulatory Cycles

- Lack of ovulation despite menstrual cycles
- Cycle Length irregular
- Common causes
  - Stress – physical, mental/emotional
  - Low BMI (<20) or low body fat
  - Excessive exercise (dec. GnRH)
  - Brain tumors, infarcts, or irradiation
  - PCOS (70%)
  - Premature ovarian failure
  - Hyperprolactinemia
  - Hypothyroidism
  - Use donor eggs

Luteal Phase Deficiency

- Endometrium not implantation ready
- Insufficient progesterone level in the luteal phase
- Suggest...
  - Issues with folliculogenesis
  - Impaired FSH/LH levels

Ultrasound Evaluations
Frequent Bleeding

- Cycles less than 20 days apart
- Cycles that never end
- Causes...
  - Iron deficiency
  - Structural changes
  - Anovulatory cycles
  - Low or high estrogen
  - BMI too high or too low
Frequent Bleeding Treatments

- Depends on the severity of bleeding
  - Estradiol
  - Estradiol & progesterone
  - Iron
  - Vitamin K
  - Oral contraceptives
  - IUD
  - Surgery

The Menstrual Cycle

Metrorrhagia – SPOTTING!

- Defined as any bleeding between the end of the cycle and day 1 of the next cycle.
- Determine the amount of bleeding and timing of bleeding.
Metrorrhagia – Spotting

• Causes:
  – Structural
  – Mittelschmerz
  – Vaginal vs. uterine bleeding
  – Cervicitis
  – Ovulatory bleeding
  – Hormonal fluctuations

Metrorrhagia Treatments

• Oral contraceptives
• Estrogen
• Progesterone
• Vitex agnes-castus (Chaste tree berry)
• Maca & Other phytoestrogens

The Menstrual Cycle
Menorrhagia – Heavy Bleeding

• Determine the bleeding volume and number of days
  – 1 super tampon/pad per hour is a hemorrhage
  – Determine if changing because of saturation or because of hygiene
  – Having to get up at night suggests menorrhagia.
  – Clotting

Menorrhagia – Heavy Bleeding

• Causes
  – Structural
  – Iron deficiency
  – Thyroid deficiency
  – Estrogen excess
  – Progesterone deficiency

Menorrhagia – Heavy Bleeding

• Treatments:
  – Iron – 325mg; 4 times a day
  – Thyroid
  – Progesterone – luteal phase
  – NSAIDS
  – Estrogen – oral
  – Oral contraceptives
  – IUD
  – Uterine ablation
  – Hysterectomy
  – GnRH
The Menstrual Cycle

Oligomenorrhea – No menstrual cycles

- Determine the onset and LMP. Determine any cycle frequency.
- Causes
  - Structural – if teenager without ever having cycles
  - PCOS
  - Medications
  - Pituitary disorders - Prolactinoma
- Premature ovarian failure/Menopause
- Thyroid disorders
- Pregnancy
- Eating disorders/Weight
- Amenorrhea

Oligomenorrhea – No menstrual cycles

- Testing/Treatments
  - LH/FSH
  - TSH
  - Prolactin
  - BMI – height/weight
  - Estradiol, Progesterone & Testosterone
  - Progesterone challenge test
  - Ultrasound/MRI
Progesterone Challenge Test

Official Way
– 200mg po Progesterone for 10 days then discontinue.
– Wait 2 weeks
– If bleeding – you pass, but...
– If no bleeding – you fail – not enough estrogen
– If bleeding but it’s been a really really long time since the last cycle – repeat again days 14-28 again and see if it works again.

Vitex

• Vitex Agnes-Castus
  – Dopaminergic → reduce prolactin
  – Acts in the hypothalamus/pituitary – dec LH, inc FSH
  – Normalizes cycle esp oligomenorrhea
  – Increases corpus luteum health
    • Increases luteal estradiol and progesterone levels
  – Caution with other ovulatory stimulants

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Tribulus
- Increase FSH
- Increase E2
- 250mg TID days 5-14

Estradiol
- Be aware of increased coagulatory effects
- Use that to your advantage – oral may be preferred for heavy cycles
- Dosages may be low or actually higher than for HRT.

Progesterone
- Do not stop if pregnant
- 20mg from ovulation to day 26-28
- Orally 100-200mg days 14-28 or all month
- Vaginal suppositories – 50-200mg
Female Nutrients

- **Folic acid** – 800mcg minimum
  - Consider MTHF
  - Ovulation and endometrial health
- **B complex** – B6 & B12
- **Vitamin D**
- **Anti-oxidant**
- **Vitamin A** – 150,000 IU

Female Nutrients

- **Vitamin E**
- **Vitamin C**
- **Selenium** – 200-600mcg; thyroid dz
- **Iron** – 325mg/tablet with 25mg of elemental iron. Citrate/gluconate more absorbable.

Myo-Inositol

- Myo-inositol levels in follicular fluid is associated with good oocyte quality.
- 2000mg (2g) myoinositol + 400ug BID x 3 months vs 400 ug BID control
- Follicles > 15mm; visible, retrieved were significantly higher, average number of embryos and transfer quality. Reduced immature oocytes as well.
Myo-inositol vs. Metformin

- Women with PCOS – alone and in combo with r-FSH
- 120 women – metformin 1500mg/day or 4gms myo-inositol
- Metformin – 50% spontaneous ovulation; 18% of these became pregnant. An additional 11 women received pregnancy with rFSH. Total pregnancy rate 36.6%
- Myo-inositol – 65% spontaneous ovulation; 30% pregnancy. 38 women also given rFSH – additional 11 women became pregnant. Total pregnancy rate 48.4%

Maitake Mushroom

- Induces insulin sensitivity
- 79% ovulation with Maitake vs. 93% Clomiphene (80 women)
- Only 1 woman who failed either treatment did not ovulate with a combination treatment
  * Chen et al. 2010

Calcium and Vitamin D

- Needed for healthy follicular development
- Vitamin D – improve insulin resistance and secretion
- Dosage – as appropriate to correct deficiency
  - Minimum 1200 IU (1 TBSP Cod liver oil)
  * Thys-Jacobs et al. 1999 found 2/13 women became pregnant; 7/13 regular periods were established; 2/13 had normalization of DUB within 2 months.
Thank you
The End

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