INTRODUCTION to WOMEN’S HEALTH BLOCK MENSTRUAL PHYSIOLOGY

Paula J. Adams Hillard, M.D.
Professor
Department of Obstetrics and Gynecology
OBJECTIVES

• At the conclusion of the Introduction to Women’s Health Block, the student will be primed to:

• Ask questions that help to establish the generalizability of specific teaching in physiology, pathology, pharmacology, and other disciplines to both men and women.
Welcome to the Stanford WSDM Center ("wisdom"), the Stanford Center for Health Research on Women and Sex Differences in Medicine

WSDM aims to expand our knowledge of women’s health and sex differences in biology and medicine, from conception through the lifespan, in every medical discipline, from basic science to clinical research and population health science.
Objectives for each lecture

APGO Objectives (http://www.apgo.org)

HHD/POM/Clerkship

Process of Content Evaluation and Assessment:

Sequence, Gaps, Unintentional Redundancies

Ongoing assessment of curriculum with student input

Syllabus comprised of ppt
ESSENTIAL ELEMENT

Medical interview and physical exam
Collect and interpret cervical cytology
Modern Contraceptive technology
DDx Acute abdomen
Physiology of nI preg/labs
Embryonic and fetal development teratogenicity
Health and well-being of populations

EDUCATIONAL TOPIC

History--Women’s health
Gyn Exam
Dx and Management plan
Communication and interaction
Pap smear and cultures
Contraception and sterilization
Ectopic pregnancy
STDs and UTIs
Maternal-fetal physiology
Antepartum Care
Preconception care
Legal/ethical issues
preventive care and health maintenance
Spontaneous abortion
Contraception/Sterilization
Sexual assault
Domestic violence
Abortion
Amenorrhea
normal and abnormal uterine bleeding
Dysmenorrhea
menopause
Infertility
Endometriosis
Intrapartum care
Lactation
Disorders of the breast
Vulvar and vaginal diseases
Sexuality and modes of sexual expression
Med/Surg conditions in preg
Pre-eclampsia/eclampsia
3rd trimester bleeding
postterm pregnancy
vulvar neoplasia
Cervical disease and neoplasia
Uterine leiomyomas
endometrial carcinoma
ovarian neoplasms

Screening for reproductive cancers

http://www.apgo.org Student Resources
Educational Objectives with Videos and Cases
<table>
<thead>
<tr>
<th>Women’s Health in HHD</th>
<th>Physiology of Pregnancy</th>
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</thead>
<tbody>
<tr>
<td>• Menstrual Physiology 1&amp;2</td>
<td>• Medical Conditions in Pregnancy</td>
</tr>
<tr>
<td>• Abnormal Uterine Bleeding</td>
<td>• Female reproductive histology</td>
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<tr>
<td>• Pharmacology of gonadal hormones</td>
<td>• STIs---Viral, Bacterial</td>
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<td>• Principles of Contraception</td>
<td>• UTIs</td>
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<tr>
<td>• Abortion</td>
<td>• Pathology of vulva, cervix, endometrium (Path + Clinical-Abnormal Bleeding), myometrium, Fallopian tube, ovary (Path + Clinical-Abnormal Bleeding)</td>
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<td>• Gynecologic Diseases</td>
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## Women’s Health in HHD

### Quarter 4  
**HHD222**  
**Autumn 2015-16**  

**Week 12**

<table>
<thead>
<tr>
<th>Time</th>
<th>Monday 11/9</th>
<th>Tuesday 11/10</th>
<th>Wednesday 11/11</th>
<th>Thursday 11/12</th>
<th>Friday 11/13</th>
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<tr>
<td>9:30</td>
<td>Menstrual Physiology-1 (P. Hillard)</td>
<td>Menstrual Physiology-2 (P. Hillard)</td>
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<td>Myometrium – Fallopian Tube (T. Longacre)</td>
<td>Ovary {pathology and clinical} (T. Longacre)</td>
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<td>10:30</td>
<td>Testicular Physiology (N. Gesundheit)</td>
<td>Male Reproductive System Histology Lab (D. Salmi) [Fleischmann Labs]</td>
<td>Endometrium/Abnormal Uterine Bleeding {pathology and clinical} (P. Hillard/ T. Longacre)</td>
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<td>11:30</td>
<td>Testis Pathology (J. Higgins)</td>
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<td>5:30</td>
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<td></td>
<td>TA Review Session: (Menstrual Cycle_ [LK308]</td>
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## Women’s Health in HHD

### Quarter 4  |  HHD222  |  Autumn 2015-16
### Week 13

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<tr>
<th>Time</th>
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<th>Thursday 11/19</th>
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<tr>
<td>9:30</td>
<td>Sexual Function: Women and Men (Marcia Stefanick)</td>
<td>Ovarian Cancer Survivors (Patient Interview)</td>
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<td>Gonadal steroid pharmacology (office hours) (P. Hillard)</td>
<td>Sexually-transmitted Infections Module (S. Chen, M. Amieva) [LK120]</td>
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<td>10:30</td>
<td>Breast Pathology (K. Jensen)</td>
<td>Breast and Gyn Lab (P. Hillard, K. Jensen and staff) [Fleischmann Labs]</td>
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<td>Gyn Conditions Tutorial (P. Hillard and faculty)</td>
<td>HPV (J. Palefsky)</td>
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<td>Cervical path/ vulva/ pap smears (C. Kong)</td>
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<td>9:30</td>
<td>Contraception (P. Hillard)</td>
<td>Medical Conditions in Pregnancy (J. Faig)</td>
<td>[unscheduled]</td>
<td>Women's Health Block and Micro Final Exam (LK101/102, LK120)</td>
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<td>10:30</td>
<td>Abortion (P. Hillard)</td>
<td>GYN Lab (P. Hillard and faculty) [Fleischmann Labs]</td>
<td>Congenital Infections Module (S. Chen, M. Amieva) [LK101-102]</td>
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<td>OB Normal physiology (K. Harney)</td>
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<td>5:30</td>
<td>TA Review Session (Path ; Women's Health Exam) [LK304/305]</td>
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TUTORIAL

- Gynecologic Conditions  TUTORIAL 11/19/15
- Attendance STRONGLY ENCOURAGED—MAKE-UP REQUIRED
- View Videos
- In-class Interactive Session—small groups
- Lecture and Slides available from 2011
SPECIAL SESSION

• Pharmacology of Gonadal Steroids

• 11/19/15

• Mini-Videos x 4

OR


OR

• ALSO AVAILABLE: 2011 lecture and slides

• Office Hours 12/2/13 0930-1030 to discuss if needed
REVIEWS

TA Review Sessions +
Hillard OFFICE HOURS as needed, by arrangement

paula.hillard@stanford.edu

650-725-5986
OBJECTIVES

• At the conclusion of the segment on menstrual physiology, the student should be able to:
  • Describe the physiology of the normal menstrual cycle with regard to events taking place in the hypothalamus, pituitary, ovary, and uterus/endometrium
  • Draw a representation of pituitary and ovarian hormones throughout the normal menstrual cycle
TODAY’S JOURNEY:

REPRODUCTIVE FUNCTION, FROM OOCYTES TO OVARIES TO PITUITARY GONADOTROPINS TO STEROID HORMONES TO THE MYOMETRIUM ACROSS THE MENSTRUAL CYCLE AND ACROSS THE LIFESPAN
THE MENSTRUAL CYCLE: Oocytes & Primary Follicles

Ovarian germ cell number is maximal at mid-gestation, then decreases precipitously.


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Graafian follicle = Antral follicle

Primordial follicle = Primary oocyte

Corpus Luteum

Corpus Albicans

Primordial Follicle

Primordial Germ Cell

Primary Multilaminar Follicle

Primary Unilaminar Follicle

Graafian Follicle
STAGES OF FOLLICULAR GROWTH IN OVARY
A month in the life of the ovary.....
the Menstrual Cycle
Idealized 28-d Menstrual Cycle

Ovary

HPO

Endometrium
Synthesis of $E + P$
Ovarian function is driven by pulsatile secretion of FSH and LH which stimulate ovarian steroid hormone production.

The granulosa cells of the ovary are the only ovarian cells with FSH Receptors.

FSH stimulates growth of granulosa cells in primary follicles with 17 B estradiol produced from testosterone via Aromatase which is present in the granulosa cells.

A cohort of follicles (3-11/cycle) starts to respond to FSH at beginning of the cycle & grows over the span of several cycles--about 85 days. Selection of the dominant follicle is established during days 5-7, and consequently, peripheral levels of estradiol begin to rise significantly by cycle day 7.

Increasing estradiol and inhibin B from the dominant follicle, thru NEGATIVE feedback, suppress FSH secretion.
• Rise in estradiol has a NEGATIVE feedback effect on FSH, but a POSITIVE feedback effect on LH, with increased secretion.

• LH stimulates androgen production in the theca cells and optimize the final maturation and function of the dominant follicle.

• The dominant follicle is uniquely responsive to FSH, and it uses the androgen as substrate and further accelerate estrogen production.

• FSH induces the appearance of LH receptors on granulosa
Key Events in the Preovulatory Follicle

1. E2 secretion reaches a threshold to induce LH surge.
2. Acting through its receptors, LH initiates luteinization and progesterone production in the granulosa layer.
3. The preovulatory rise in progesterone facilitates the positive feedback action of estrogen and may be required to induce the midcycle FSH peak.

Rapidly rising estradiol then exerts a POSITIVE feedback effect, upregulating GnRH receptors in the pituitary, causing an OVULATORY SURGE of FSH and LH, triggering ovulation.
Luteal Phase

- The Corpus luteum develops and synthesizes estradiol and progesterone.
- Progesterone, (estradiol, and inhibin A) have a NEGATIVE FEEDBACK on the pituitary with inhibition of FSH and LH secretion, and suppression of new follicular growth.
- Regression of the corpus luteum occurs.
- In early pregnancy, hCG rescues the corpus luteum, maintaining luteal function until placental steroidogenesis is well established.
- If fertilization does not occur, the regression of the CL and declining levels of E&P lead to increasing FSH/LH secretion, moving toward the next cycle.
The diagram illustrates the menstrual cycle, highlighting the follicular phase (proliferative) and the luteal phase (secretory). Key hormonal changes are depicted:

- **Basal Body Temperature (BBT)**
- **Progesterone**
- **17β-Estradiol**
- **FSH**
- **LH**

The cycle phases are marked by changes in these hormones, with specific peaks and troughs correlating with the menstrual events. The follicular phase is characterized by rising FSH and LH, which peak around ovulation. Following ovulation, progesterone and estradiol levels increase in the luteal phase, culminating in a rise in basal body temperature.
Luteal-Follicular Transition (WHY THE CYCLE OCCURS)

- The demise of the corpus luteum results in a nadir in the circulating levels of estradiol, progesterone, and inhibin.
- The decrease in inhibin-A removes a suppressing influence on FSH secretion.
- The decrease in E2 and progesterone allows a progressive and rapid increase in the frequency of GnRH pulsatile secretion and removal of the pituitary from NEGATIVE FEEDBACK suppression.
- The removal of inhibin-A and E2, as well as increasing GnRH pulses allow increased FSH secretion cf with LH.
- The increase in FSH rescues a ~70 day-old group of follicles from atresia, allowing a dominant follicle to begin to emerge.
The Endometrium through the Menstrual Cycle
Proliferative Phase
(The first $\frac{1}{2}$):
- $17\beta$ Estradiol stimulates endometrial growth (proliferation), growth of glands and stroma, and elongation of the spiral arteries
- Estradiol effect on cervical mucous: copious, watery, elastic
4.3.2 HORMONAL CHANGES THROUGHOUT THE MENSTRUAL CYCLE

The female reproductive system undergoes a recurring, cyclical series of structural and functional changes termed the menstrual cycle. The hypothalamus-pituitary unit secretes low levels of FSH and LH, then a surge of LH, and to a lesser extent FSH, then low levels of both hormones. In primates, a single ovarian follicle becomes the dominant follicle, develops to maturity, ovulates, luteinizes and forms a corpus luteum. The uterine endometrium proliferates and vascularizes prior to ovulation (proliferative phase corresponding to the follicular...
Secretory Phase
(The second ½):
- Progesterone effects: proliferation slows, glands more tortuous, increased mucous secretion, spiral arteries coil

- Progesterone effect on cervical mucous: thick, non-elastic, “hostile”
Menstruation

- Abrupt decline of E2 and P lead to sloughing of endometrium.
- Enzymatic degradation of the functional layer of the endometrium with its subsurface capillary plexus initiates menstruation.
- Coagulation, local vasoconstriction, and reepithelialization contribute to hemostasis.
PHASES OF THE MENSTRUAL CYCLE (Ovary):
1. Follicular phase
2. Luteal phase

PHASES OF THE ENDOMETRIUM:
3. Proliferative phase
4. Secretory phase
5. Menstrual phase
Regulation of the hypothalamo-pituitary system is a complex process involving both negative and positive feedback mechanisms. In the female, GnRH is secreted in a pulsatile manner by neurons with cell bodies in the hypothalamus. GnRH stimulates synthesis and glycosylation of prohormones of FSH and LH. Inhibin acts on the pituitary gonadotropes to suppress the synthesis and release of FSH, but not of LH. This modulatory effect of inhibin is termed negative feedback. Estradiol and progesterone from the gonads also exert negative feedback effects on FSH and LH production by negatively modulating production of GnRH in the hypothalamus. Steroid hormones have a much
H-P-O Axis Animations and References

- [http://drc.libraries.uc.edu/](http://drc.libraries.uc.edu/) Reproductive Physiology Animations

- Guyton and Hall, Textbook of Medical Physiology 13\(^{\text{th}}\) ed. available from Lane.stanford.edu--good for basics--Chapter 82

- Costanzo, Physiology.5\(^{\text{th}}\) Ed. 2015. Student Consult. Chapter 10

- Speroff L, Fritz MA. Clinical Gynecologic Endocrinology and Fertility. 9th Ed. 8th Ed. 2011. Lane.Stanford.edu; EXCELLENT, but ADVANCED