# OVULATION

FLAME LECTURE: 213B

STELLER 9.17.15

# Learning Objectives

- To define the normal menstrual cycle and describe its endocrinology and physiology
- Prerequisites:
  - FLAME LECTURE 213A: The Normal Menstrual Cycle
- See also – for closely related topics
  - FLAME LECTURE 214: Evaluation of AUB

# THE MENSTRUAL CYCLE - OVERVIEW

- The hormonally-regulated cycle that governs the anatomical changes in the ovary and uterus that are required for ovulation and support of an early pregnancy
- The menstrual cycle is directed by a complex interplay of positive and negative feedback loops between the hypothalmus, anterior pituitary, and ovaries termed the HPO AXIS

# HPO AXIS (SIMPLISTIC)

HYPOTHALMUS – PULSITILE RELEASE OF GNRH

↓

ANTERIOR PITUITARY – SECRETES LH & FSH

↓

OVARY – SECRETES ESTROGEN, PROGESTERONE, & INHIBIN

FEEDBACK

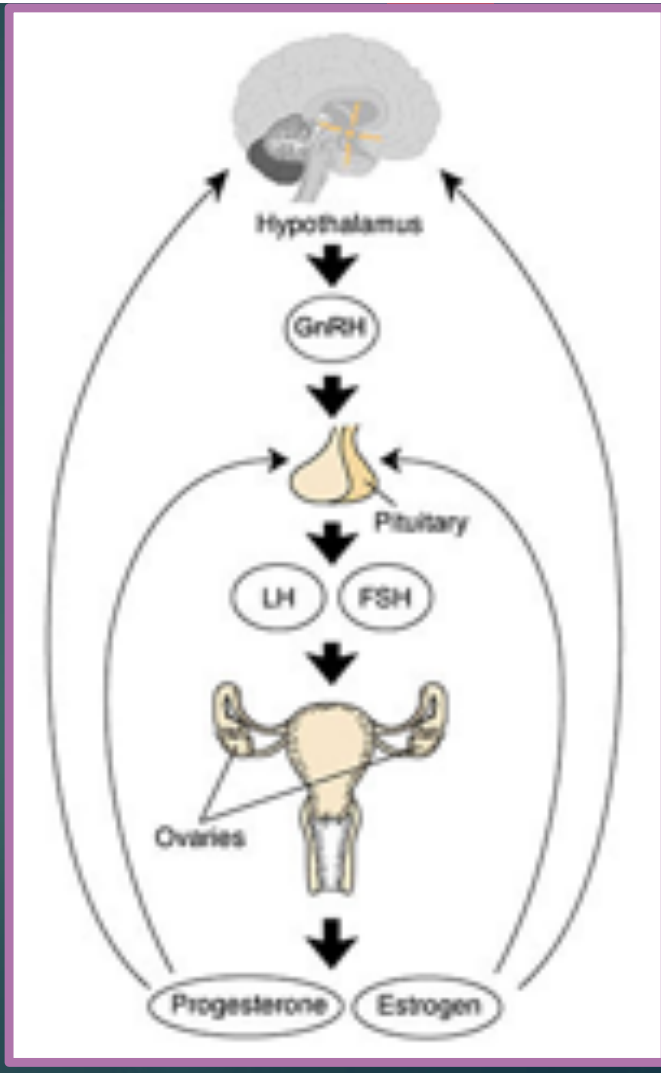
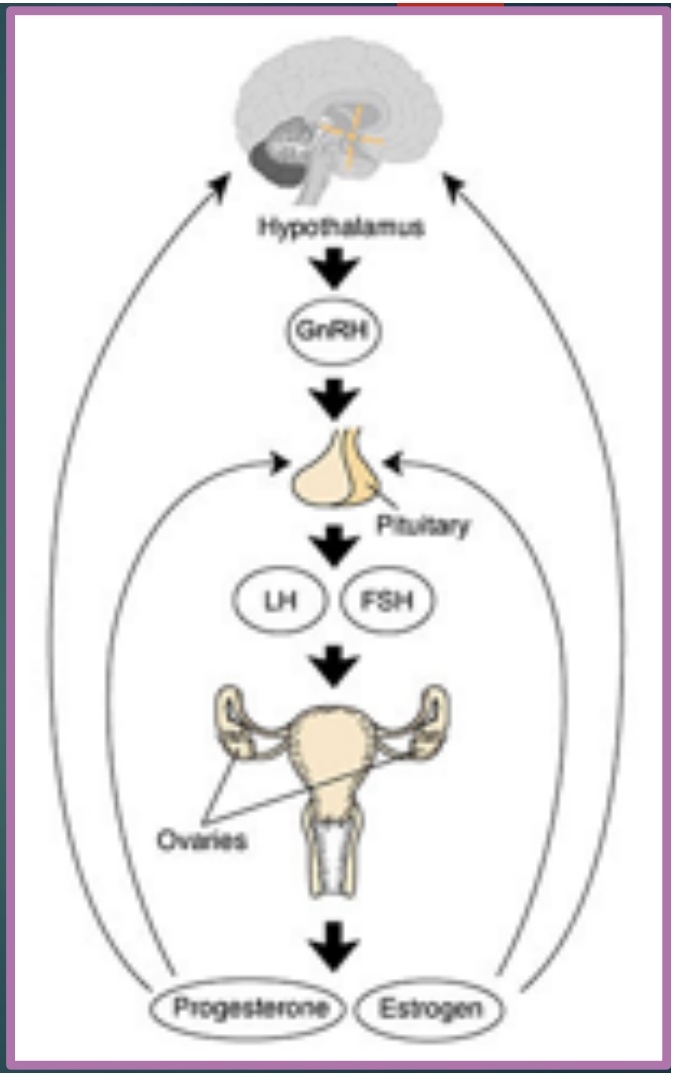



Image from embryology.med.unsw.edu.au

# HPO ('Less' simplistic)

1. FSH is the fuel that drives the race of follicle maturation
2. As the follicles (with eggs inside) grow, they create *egg-xhaust* = estradiol (E2)
3. This increase in E2 drives endometrial growth and starts to suppress FSH
4. The follicle which is MOST sensitive to FSH, will grow the best and win the race; the rest die
5. Having a super high E2 for > 50 hours causes the LH surge which triggers ovulation and expulsion of the egg from the follicle
6. The follicle that secreted the egg then turns into corpus luteum and secretes progesterone
7. If no pregnancy, E2/progesterone fall, the endometrium sheds, and FSH (no longer suppressed) will then start the next race

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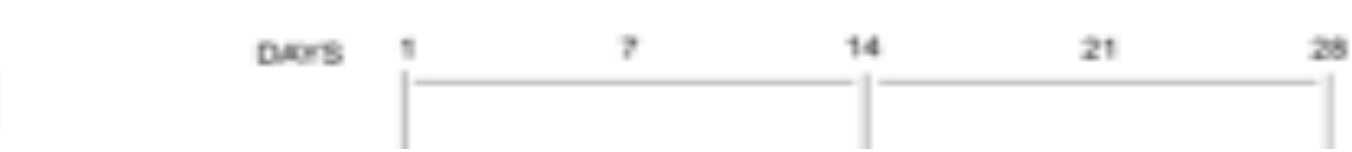



**Below you can see graphically, the timing of secretion of each of these hormones in relation to the phase occurring in the uterus and ovary!**

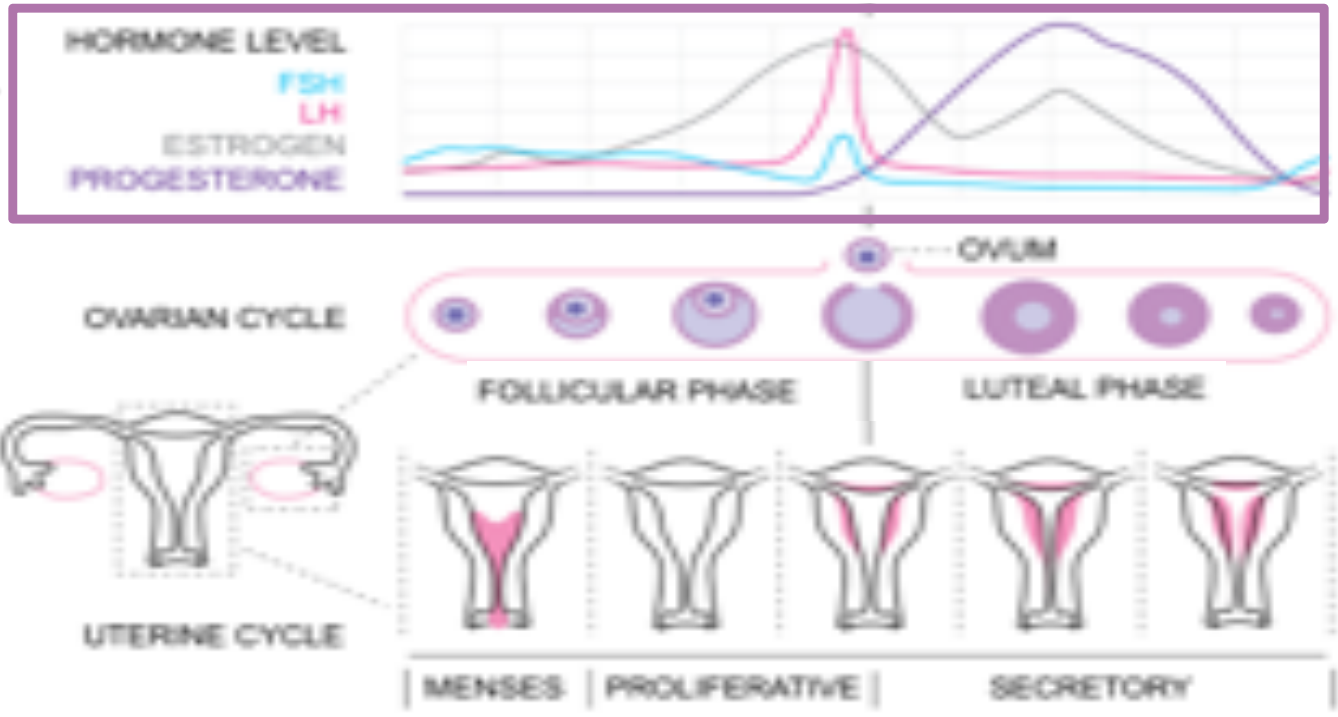
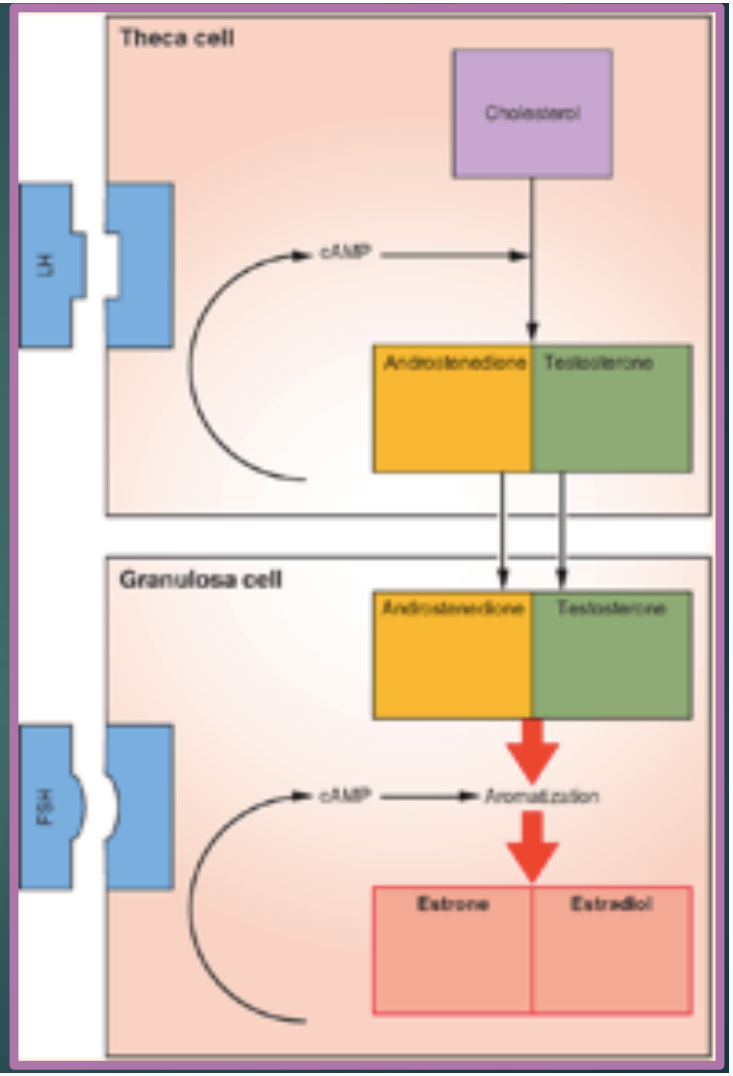



Image from Wikipedia

Image from Magann 2000

# More details at the level of the ovary…

- How the pituitary stimulates creation of E2 by ovarian cells is termed the "2-cell, 2-gonadotropin Hypothesis"
- Thecal Cells:
  - Bind LH → triggers conversion of cholesterol to androstenedione and testosterone
  - Testosterone converted to DHEA via 17a hydroxylase
  - Testosterone & DHEA are transported across the basement membrane to granulosa cells
- Granulosa Cells:
  - Bind FSH → Testosterone & DHEA are converted to E2 & Estrone via Aromatase → rest is history



# THE RACE IS ABOUT TO START. LOTS OF TEXT. NOT ENOUGH PICTURES.

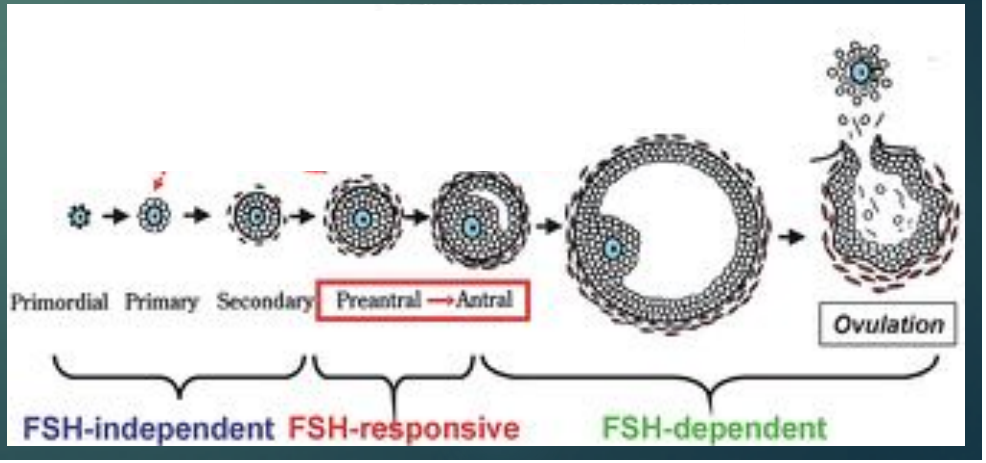
STAY WITH ME.

Image from: Ovarianresearch.biomedcentral.com

# THE RACE = THE FOLLICULAR PHASE

- Made up of 4 sub-phases: Primordial, Atretic, Preantral, Antral
- Primordial: while a female fetus is developing, 6-7 million oocytes are first created, however they start dying off, and by puberty only 3-500,000 remain
  - All of these oocytes are arrested in prophase of Meiosis I until triggered

- Independent of pregnancy OR the menstrual cycle, batches of primordial follicles are triggered to start growing
- Usually they just die, but if they happen to be growing at the right time, they can be rescued from atresia by FSH (next slide)



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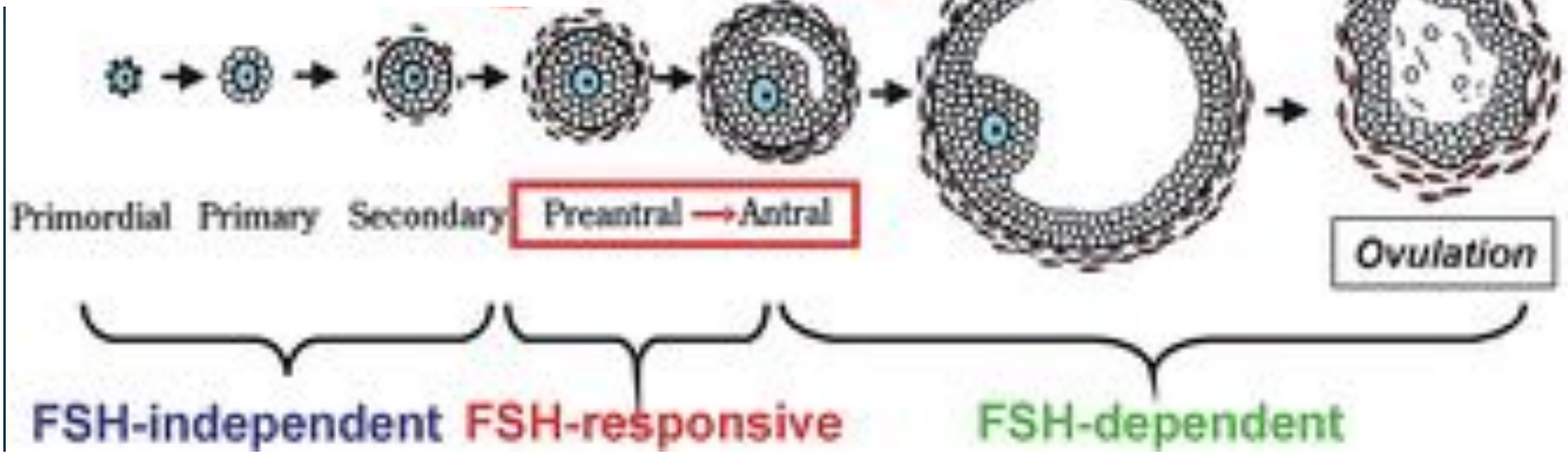
# THE RACE = THE FOLLICULAR PHASE

**FSH HARVESTS PREANTRAL FOLLICLES FOR THE RACE!**



# SOME PREANTRAL FOLLICLES ARE RESCUED!

1. As mentioned, initial follicular development from primordial follicles occurs independently of hormone influence
2. Once FSH has harvested the pre-antral follicles, FSH-induced aromatization of androgens in the granulosa cells results in the production of estrogen ("2-cell, 2-gonadotropin theory")
3. Together, FSH and estrogen increase the FSH receptor content of each follicle, and the race is on for each follicle to try and become the most sensitive to FSH to thus harvest the most fuel to become the dominant antral follicle

# WHICH ANTRAL FOLLICLE CAN BECOME DOMINANT?

1. Selection of the dominant follicle is established during cycle days 5–7, and consequently, serum E2 begins to rise significantly by day 7
2. E2 levels, produced by the dominant follicle, increase steadily and, through negative feedback, exert a progressively greater suppressive influence on FSH release
3. Defying all rules, the mid-follicular rise in E2 not only causes a decline in FSH levels, but has a positive feedback influence on LH secretion
4. Thus, LH levels rise steadily during the late follicular phase, stimulating androgen production in the thecal cells *(again 2-cell, 2-gonad. theory)*
5. A unique responsiveness to FSH allows the dominant follicle to utilize the androgen as substrate and further accelerate estrogen production
6. FSH starts to induce the appearance of LH receptors on granulosa cells…

- BONUS:
  - Inhibin-B, secreted by the granulosa cells in response to FSH, also directly suppresses pituitary FSH secretion

# ONE FOLLICLE HAS NOW BECOME A PRE-OVULATORY FOLLICLE

1. Estrogen production becomes sufficient to achieve and maintain peripheral threshold concentrations of E2 for > 50 hours that are required in order to induce the LH surge
2. LH binds to the LH-receptors on the pre-ovulatory follicle and initiates luteinization (defined later) and progesterone production in the granulosa layer
3. This preovulatory rise in progesterone facilitates the positive feedback action of estrogen and may be required to induce the midcycle FSH peak…

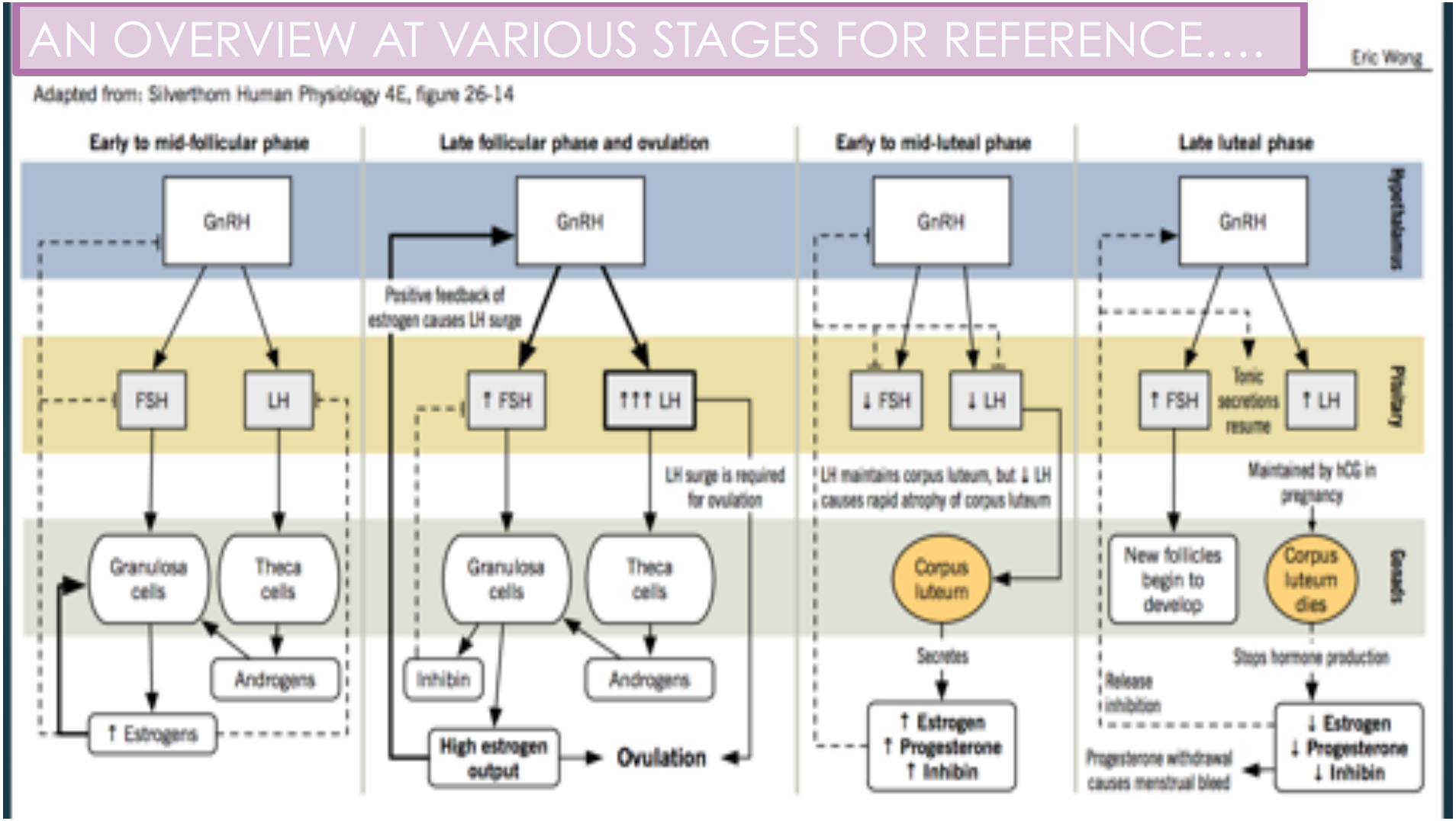
# THE LH SURGE TRIGGERS OVULATION

1. The LH surge initiates: a) the continuation of meiosis in the oocyte from Prophase I, b) complete luteinization of the granulosa, and c) the synthesis of progesterone and prostaglandins within the follicle
2. Progesterone and these prostaglandins then enhance the activity of proteolytic enzymes responsible for digestion and rupture of the follicular wall
3. The progesterone-influenced midcycle rise in FSH also serves to free the oocyte from its follicular attachments, and to ensure that sufficient LH receptors are present to allow an adequate normal luteal phase…

# WITH THE EGG RELEASED, THE LUTEAL PHASE BEGINS

- Progesterone, estradiol, and inhibin-A produced by the newly-vacant ovulatory follicle (now called the corpus luteum) will initially act centrally to suppress gonadotropins from rescuing a new set of primordial follicles to start the race over
  - If there is no pregnancy, the corpus luteum will involute and result in a nadir of these circulating hormones, and inhibin-A will no longer suppress FSH secretion. Further, the decrease in estradiol and progesterone will allow a progressive and rapid increase in the frequency of GnRH pulsatile secretion and a removal of the pituitary from negative feedback suppression
  - However in early pregnancy, hCG produced by the pregnancy, supports the corpus luteum, maintaining luteal function until placental steroidogenesis is well established

# AN OVERVIEW AT VARIOUS STAGES FOR REFERENCE….



# IMPORTANT LINKS / REFERENCES


- Fritz MA, Speroff L. Gynecologic Endocrinology and Infertility. 8th Edition. ISBN-13: 978-0781779685