Fertility Medications

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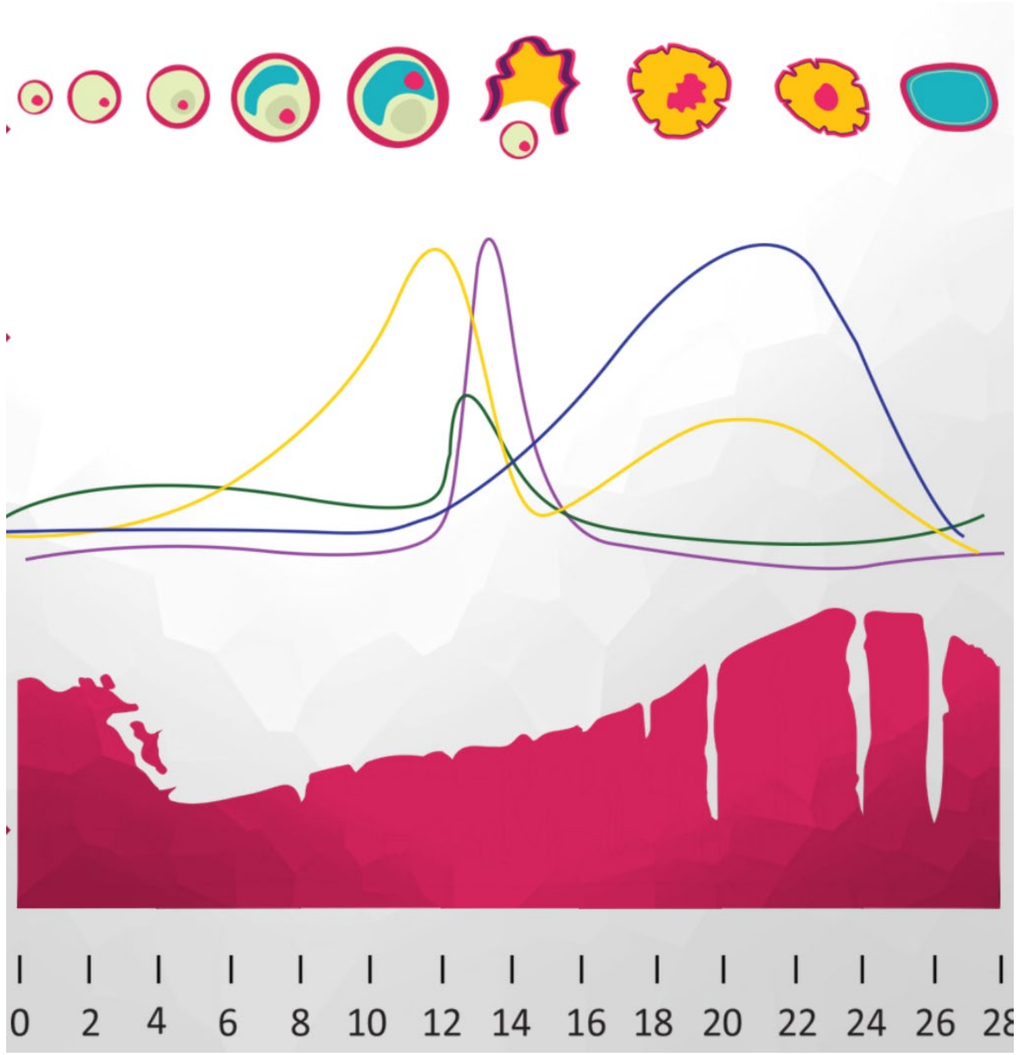
Fertile Health

Objectives

At the conclusion of this presentation, participants should be able to:

- Review the principles of superovulation
- Discuss the mechanism of action for oral meds
- Explain the two different methods of pituitary suppression
- Compare and contrast 2 different medications utilized to trigger ovulation in IVF cycles.

Part 1: Hormone Levels in a Natural Cycle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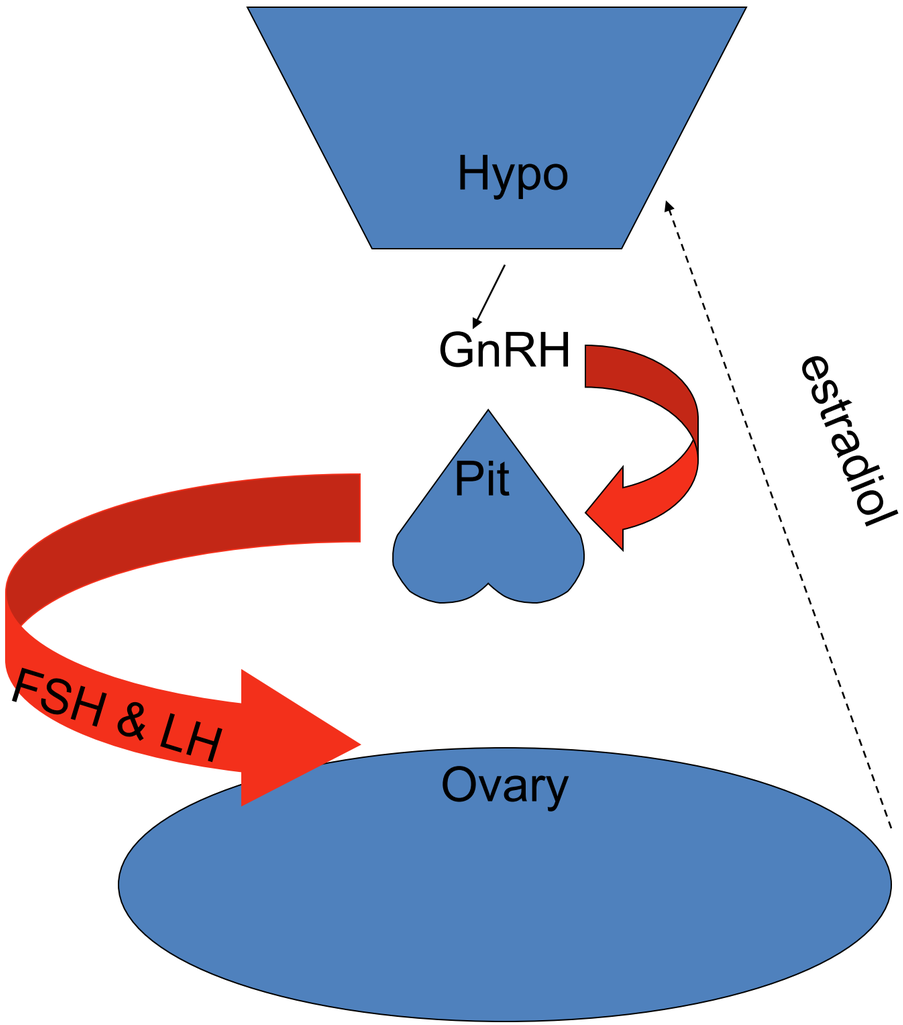
Ovulation Induction and Superovulation

- Ovulation Induction
  - Induce the development of at least one follicle (in anovulatory women) to provide an opportunity for pregnancy
- Superovulation (Controlled ovarian stimulation)
  - Increase the number of follicles recruited in order to increase the opportunity for pregnancy

Hypothalamic-Pituitary-Ovarian Axis (HPO Axis)



PART 1: ORAL OVULATION INDUCTION AGENTS

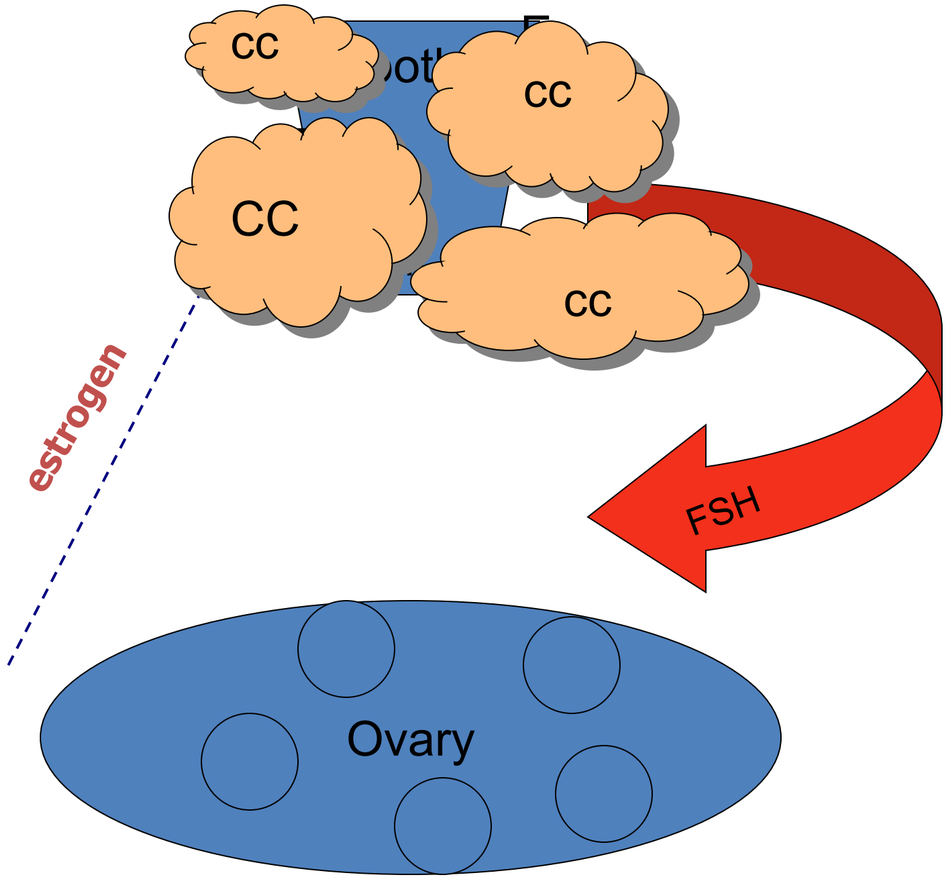
Oral Ovulation Induction Agents

- Clomiphene Citrate (Clomid)
  - Only oral medication FDA approved for ovulation induction
  - Approved for clinical use in US in 1967
- For anovulatory women, goal is to produce dominant follicle and ovulate
- In ovulatory women, goal is multifollicular response

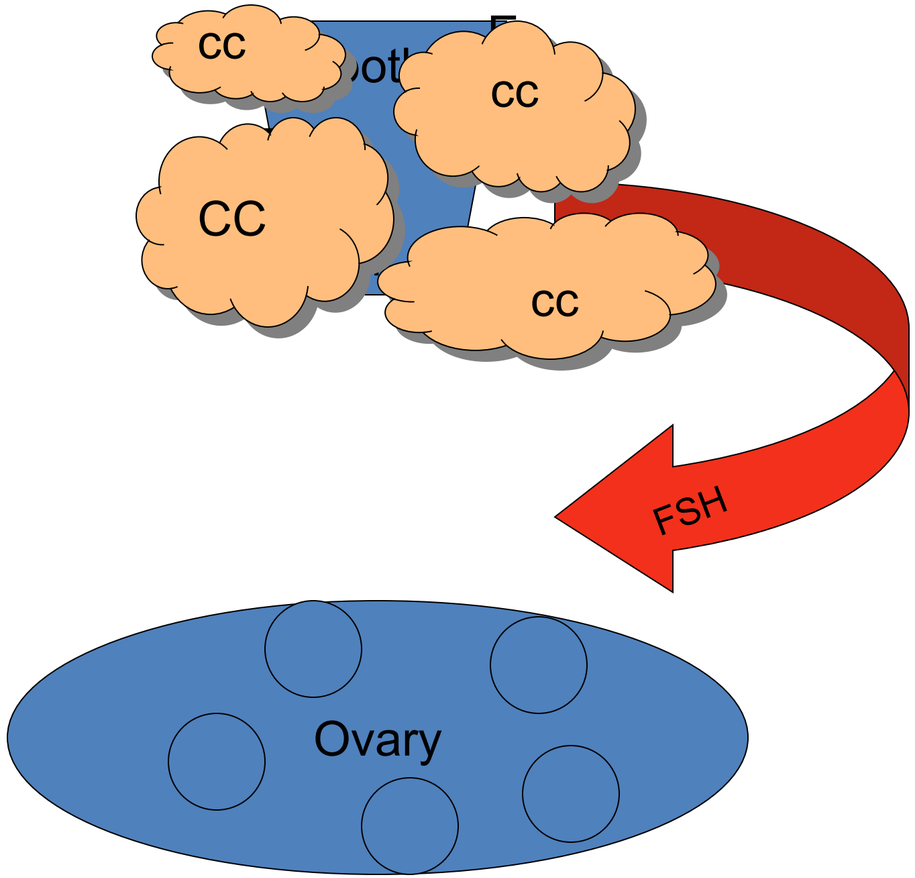
Clomiphene Citrate (CC)

- Originally Breast Cancer Drug
  - Chemically related to Tamoxifen
- Similar structure to estrogen
  - Binds to and depletes estrogen receptors
  - The hypothalamus prevents accurate interpretation of circulating estrogen levels; perceives low levels, and stimulates gonadotropin release from the pituitary

CC-Mechanism of Action



CC-Mechanism of Action



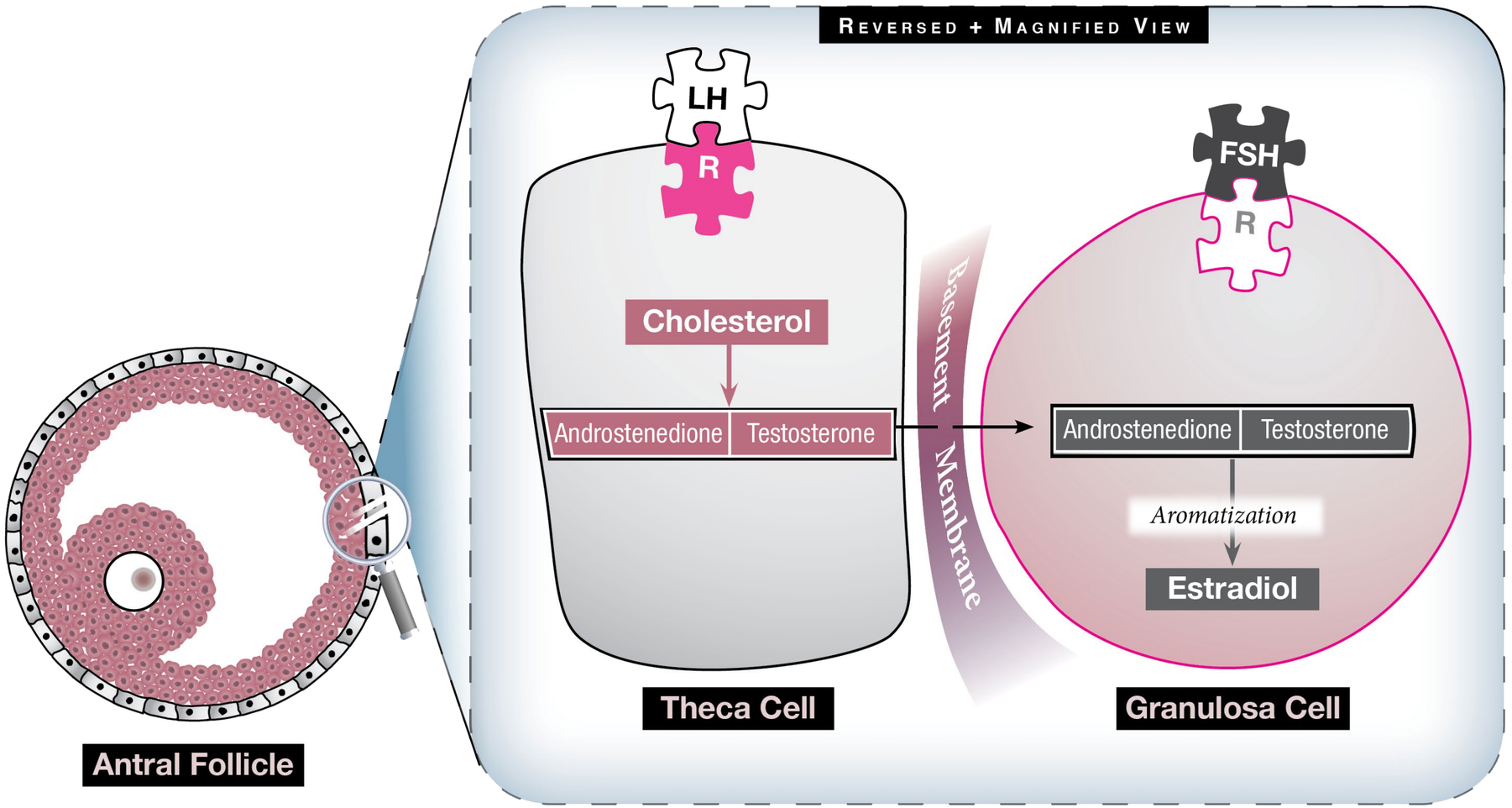
Clomiphene Citrate

- Disadvantages:
  - High ovulatory, but low pregnancy rates (Dickey 1996;Gysler,1982)
  - Anti-estrogen effects on cervix, vagina, and endometrium (Speroff, 1994)
    - Possibly responsible for low pregnancy and higher miscarriage rates (Franks, et al, 1985)
  - Long half-life (about 2 weeks)
  - Side effects related to anti-estrogenic effect and include vision changes, hot flashes, and irritability
    - More serious: ovarian torsion ;higher risk of twins; neoplasm?

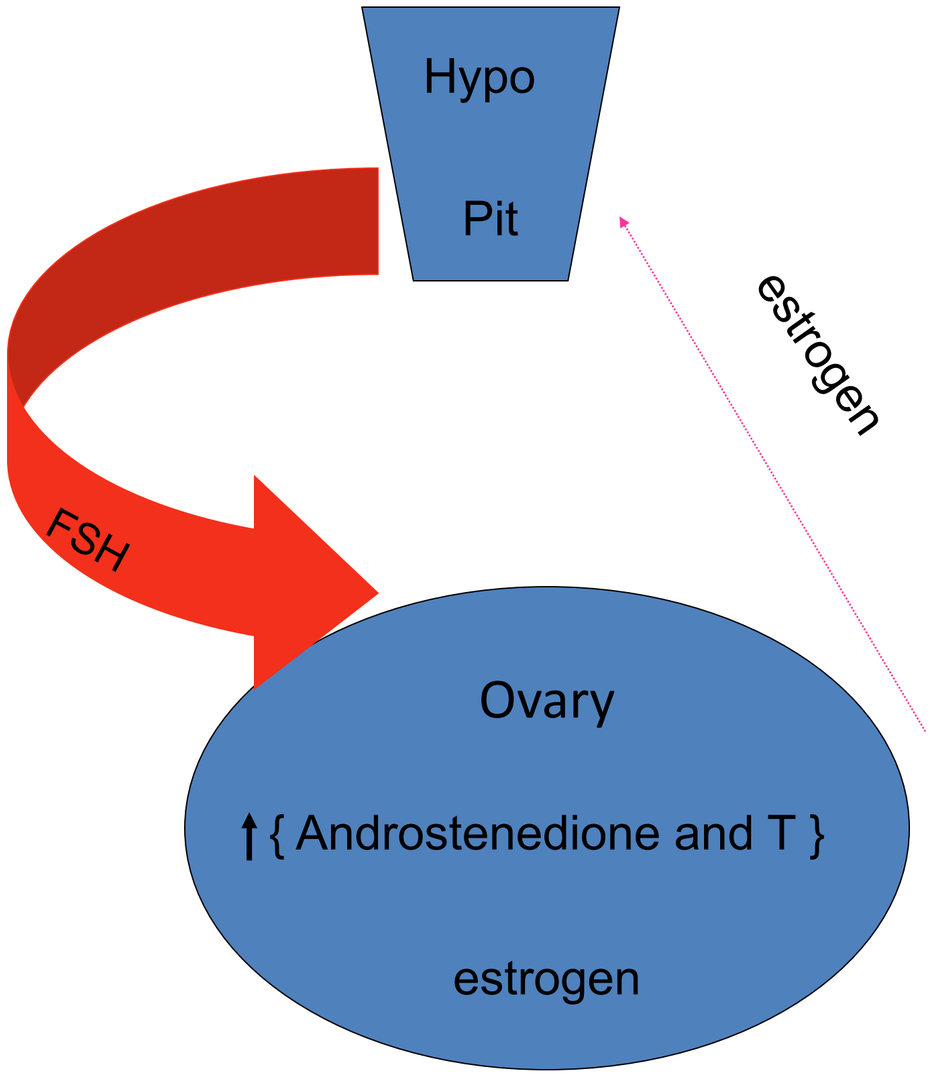
Aromatase Inhibitors (AIs)

- Inhibit aromatase enzyme, resulting in reduction of estrogen synthesis
- Originally used as a therapy for breast cancer patients
- Unlike CC, do not lead to estrogen receptor depletion

Estrogen Production



Aromatase Inhibitors



Letrozole

- Early studies mostly focused on CC resistant patients
- Letrozole seems as effective, if not superior to, clomiphene citrate in many studies
  - *10 patients with PCOS who were resistant to CC or had thin (<5 mm) lining were given letrozole
  - 7 ovulated, 1 conceived, one biochemical pregnancy
  - Endo thickness prior to ovulation was 7-9 mm

**Mitwally et al, 2000*

Letrozole

- Short half-life (about 48 hours)
  - Should not affect cervical mucous
- Avoids peripheral antiestrogenic effects of CC (migraines, headaches, PMS-like symptoms)
  - Hot flashes, irritability, mood swings in only about 2% of patients

When Oral OI Therapy Fails...

- Physicians might have proceeded with injectable gonadotropin (GND) therapy
  - Expensive
  - High risk of ovarian hyperstimulation syndrom(OHSS) and multiple gestation
  - Invasive
- Is there an intermediate step?

When Oral OI Therapy Fails

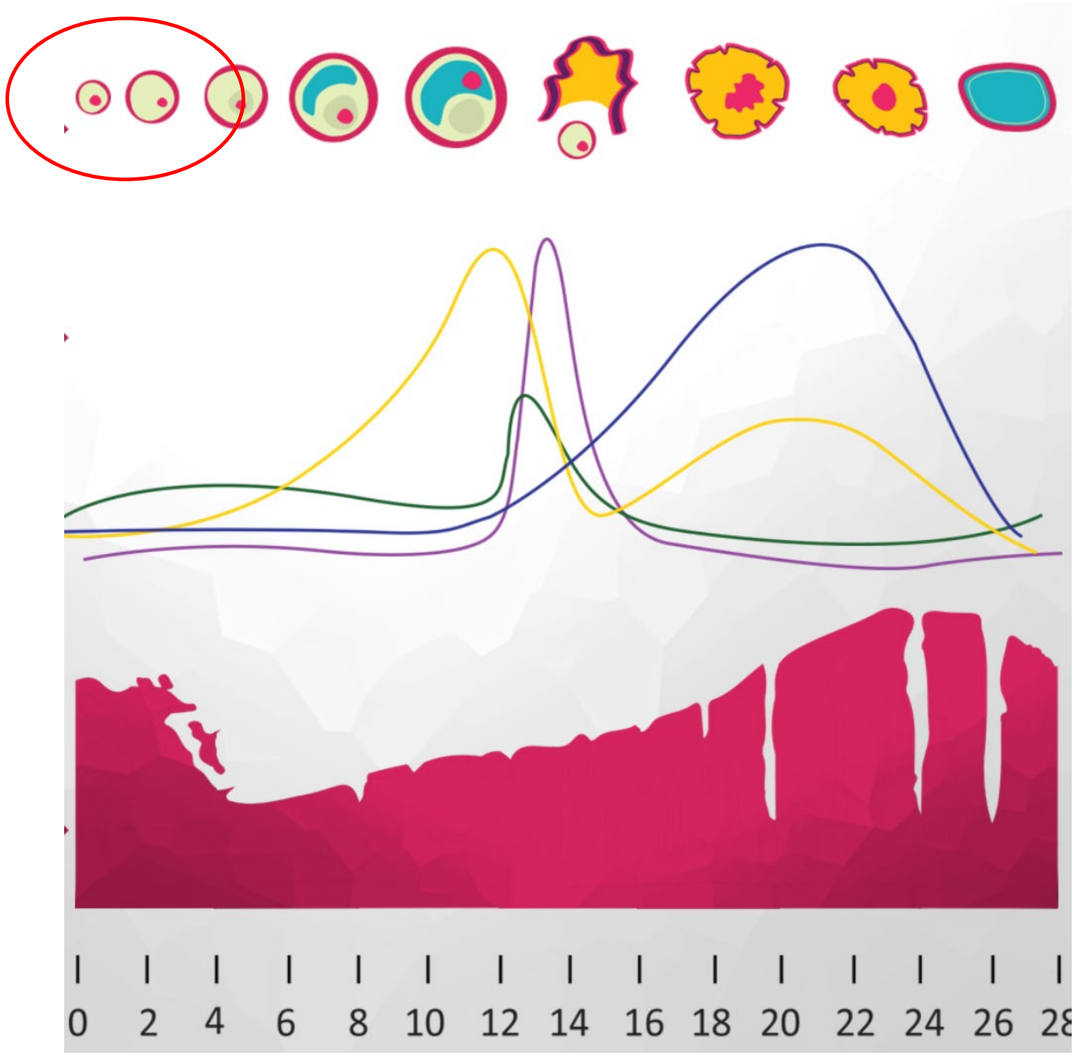
- Consider letrozole administration prior to GND therapy
- Letrozole may potentiate GND therapy by:
  - Resulting androgenic environment in ovaries may sensitize FSH receptors (Mitwally and Casper, 2002).

PART 2: PRINCIPLES OF SUPEROVULATION

Principles of Superovulation

In gonadotropin-treated cycles:

- Small (<10 mm) follicles need constant, exogenous FSH in order to grow and mature
  - FSH levels rise and stay elevated until trigger shot
- Once follicles reach 10-12 mm, theca cells become receptive to LH stimulation
  - Maturing follicle may become less dependent on FSH at this point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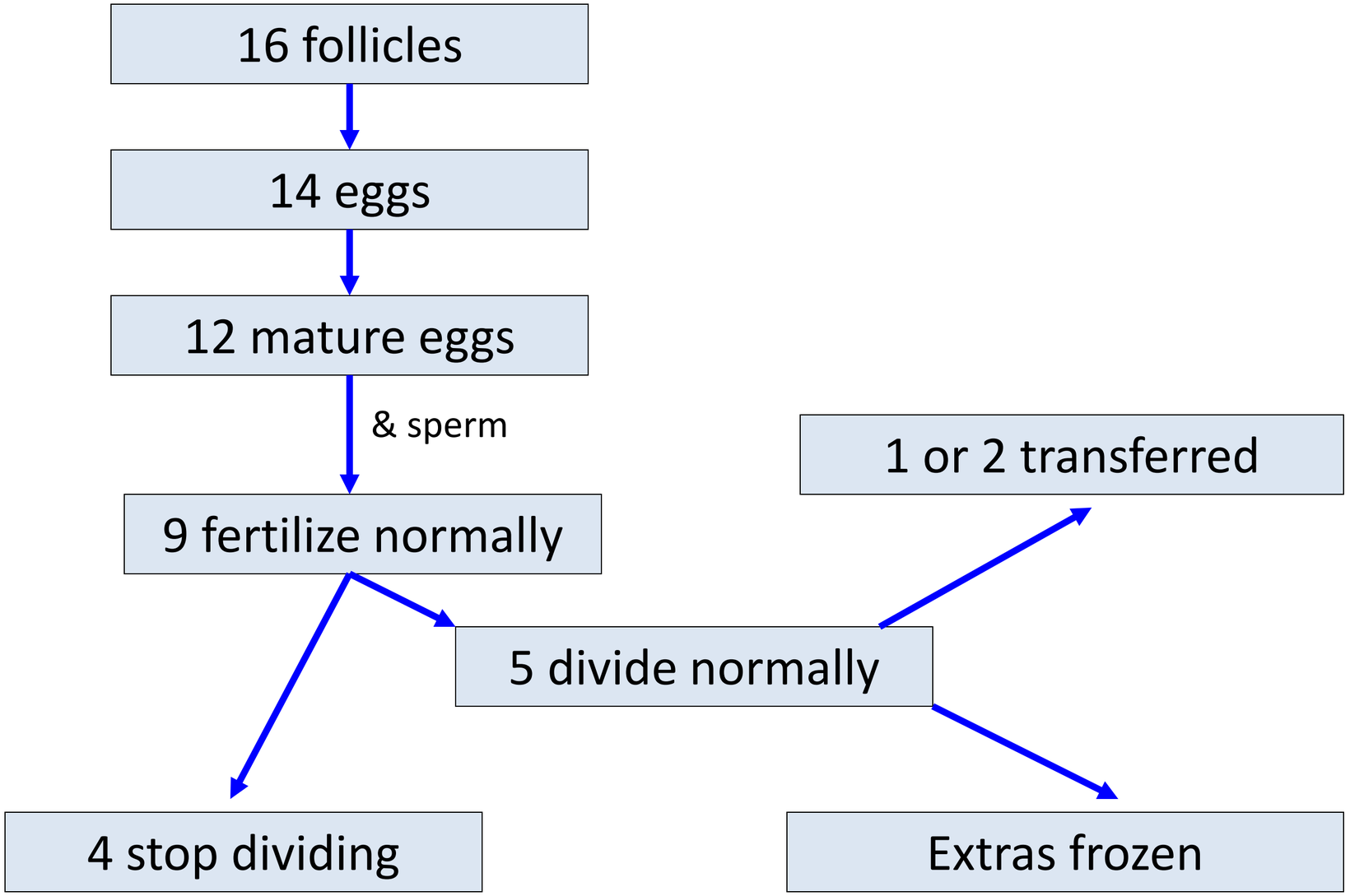
Standard IVF



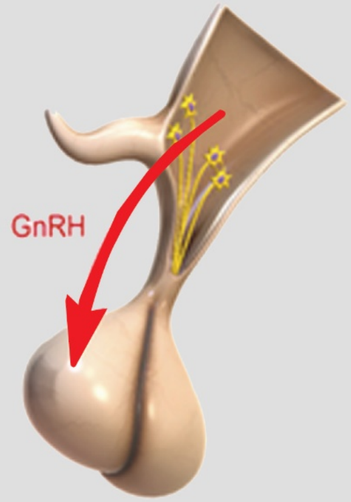
Superovulation Meds

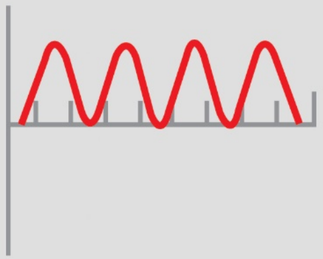
- Follistim, Gonal F and Bravelle are **FSH-only** products
- Menopur contains 75 IU of FSH and 75 IU of LH
- LdhCG is **LH-only** product

PART 3: PITUITARY SUPPRESSION

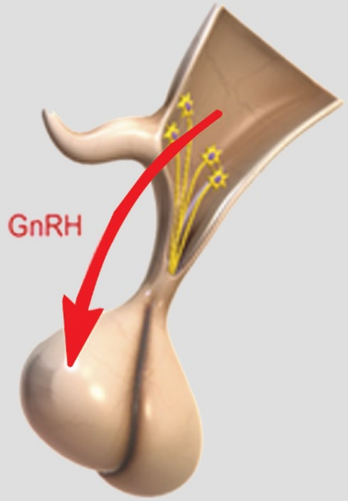
GnRH Analogs

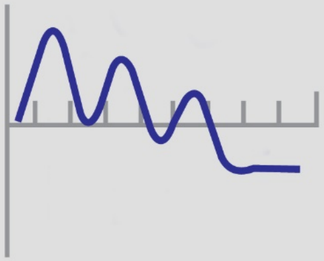
Physiologic



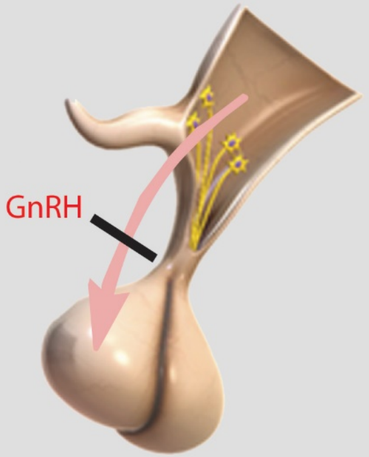


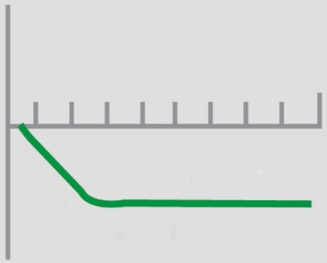
Agonist-
Leuprolide
/MF
leuprolide





Antagonist-
Ganirelix/Cetrotide





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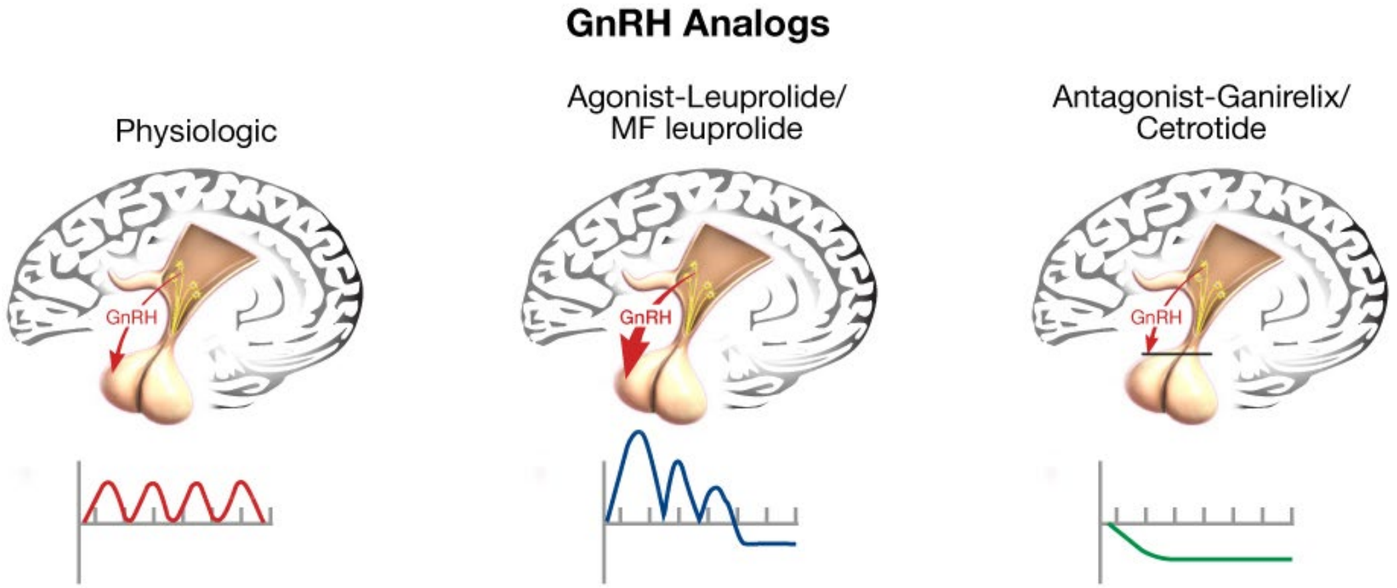
GnRH Analogs



Fertile Health

GnRH Analogs

Agonist

- Hypersecretion followed by desensitization
- LH suppression can be profound and mimic hypogonadotropic hypogonadism (HH)
- Can be used in “flare protocols”

Antagonist

- Competitive binding
- Immediate rapid *reversible* suppression of gonadotropin secretion (1-2 hours after drug administration)

PART 4: SUPEROVULATION MEDS

Common Medication Protocols

- Down regulation with GnRHa
- Suppression with GnRH antagonist
- Leuprolide acetate “flare” protocol
- Luteal estrace protocol (antag or flare)
- Clomid or aromatase inhibitors + agonist flare or antagonist + gonadotropins

IVF Stimulation Protocols Based on Expected Ovarian Response

Ovarian Reserve	Low	Average	High
BAFC	<8	8-15	15-30
AMH	< 1	1.0-3.5	>3.5
Special Concerns	Cycle Cancellation		OHSS
Typical Protocol	Let/MD Flare	Antagonist Down Reg (if need to tighten cohort)	Antagonist with agonist trigger
Meds	450^{+} IU FSH + LH (75-150)	300-450 IU FSH + 75 LH (add back if antagonist)	150-300 IU FSH + 75 LH (May decrease FSH as follicles grow)

PART 5: TRIGGERING OVULATION IN IVF CYCLES

hCG

- Used to be only option for trigger
- hCG has the same biological actions as LH
- Clinical uses
  - To augment follicular development (ldhCG)
  - To cause ovulation
  - To cause final maturation of oocyte
  - For luteal support (no longer used for this)

Triggering ovulation in IVF cycles

- hCG commonly used
  - *Long ½ life sustains LH activity during (critical) implantation period (about 10 days).
    - LH crucial for adequate corpus lutea
  - Contributes to the occurrence of OHSS
- Once antagonists approved for use, now have option of using GnRH agonist (GnRHa) for surge
  - Suppressive effect of antagonist can be reversed immediately by administration of agonist
  - Surge due to “flare effect”
  - Shorter half-life: *LH activity for 48 hours, then suppressive (more physiologic)

GnRH agonist (only) for surge: prospective, multicenter study*

- No significant differences in: # mature oocytes, # oocytes retrieved, fertilization rates, # of embryos transferred or embryo score(s)
- Lower ongoing pregnancy rate: **5.6% vs 41.7%** (P=0.012) in the agonist group prompted discontinuation of the study
- No cases of OHSS in either group

Kolibianakis, et al 2005

Why are ongoing pregnancy rates so poor in the Agonist arm?

Authors hypothesized that:

- Agonist may cause irreversible luteolysis*
  - –When given agonist, both endogenous and exogenous LH were low* **
  - –HRT given in luteal phase may not be enough to counteract this* **
  - –A luteal phase (in a *stimulated* IVF patient) entirely dependent on exogenous HRT may not be sufficient

*Kolibianakis et al, 2005; **Humaidan et al, 2005

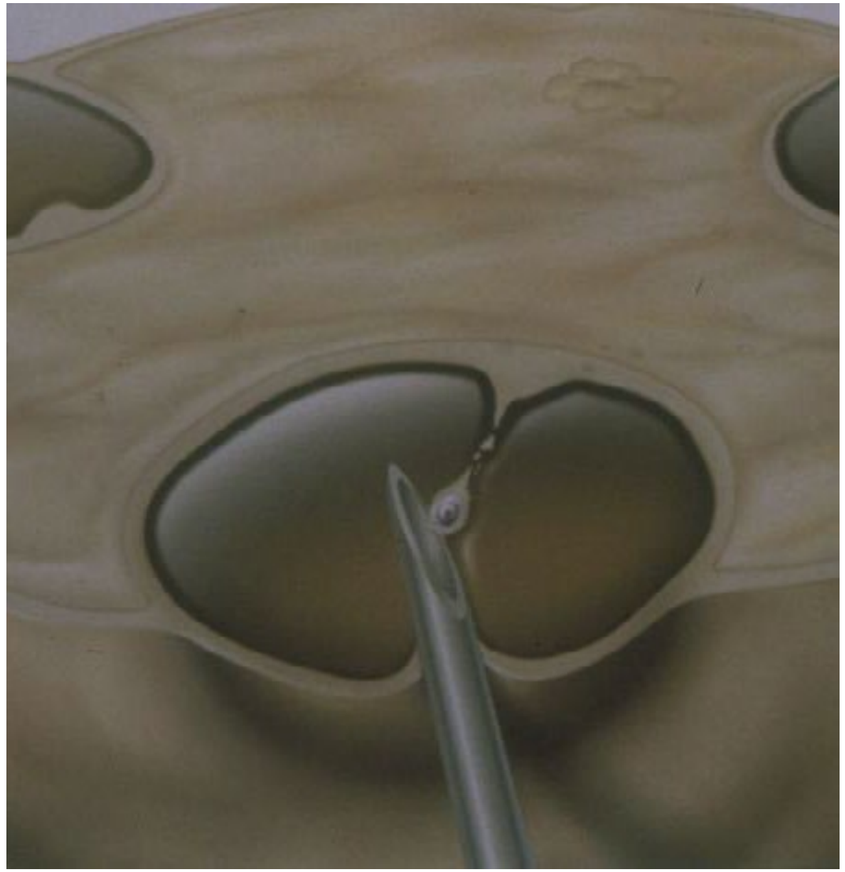
Agonist vs hCG for Surge: Conclusions

- GnRH agonist for surge prevents OHSS
  - Consider in high-risk groups (PCOS, Male factor, and/or donors)
  - If freezing embryos, subsequent FET cycle shouldn’t be affected
- Agonist sufficient to mature and ovulate follicles
- Low pregnancy and implantation rates probably related to an ineffective corpus luteum if no hCG given

PART 6: LUTEAL PHASE MEDS AND COQ10

Luteal Phase Meds

- Sometime necessary in non-IVF cycles
- Prog always necessary in stimulated and unstimulated (FET, Donor) cycles
  - Vaginal
  - IM
  - Oral not usually used due to first pass effect
- Estrogen often used in stimulated and always used in unstimulated cycles
  - In stimulated cycles might decrease chance of spotting



Window of Receptivity

- In a natural cycle, ovary and uterus in synchrony, so need to replicate this in stimulated cycle.
- It closes prematurely if:
  - P4 is elevated at trigger
  - P4 is administered too early

COQ10

Coenzyme-Q10

- Animal model
  - Injecting old, retired breeding mice with Co-Q10 (the equivalent of 600-800 mg) daily for a month:
    - More CoQ10 in ovary, ovarian vein, follicles
    - Less reactive oxygen species
    - Ovaries 30% heavier
    - More eggs
    - More genetically normal offspring

Conclusions

- Oral medications first line for most patients
    - Clomid-FDA approved (except for PCOS) but may have detrimental effects on lining
    - Using letrozole prior to GND or IVF cycles may enhance ovarian response
- There are 2 options for pituitary suppression
- Using GnRH agonist trigger with hCG can help prevent OHSS, and patients need full luteal support
- The timing of progesterone start critical and “starts the clock” re: window of implantation and embryo transfer.