



Infertility Evaluation and Treatment for the Female and Male Patient

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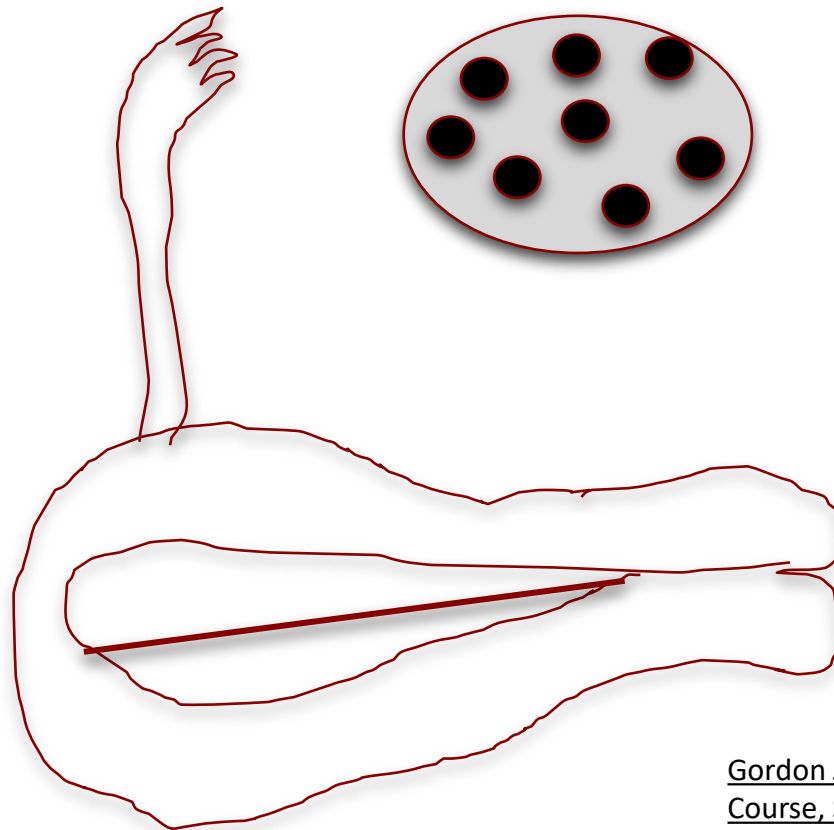
Reproductive Endocrinology and Infertility

University of Oklahoma Health Sciences Center





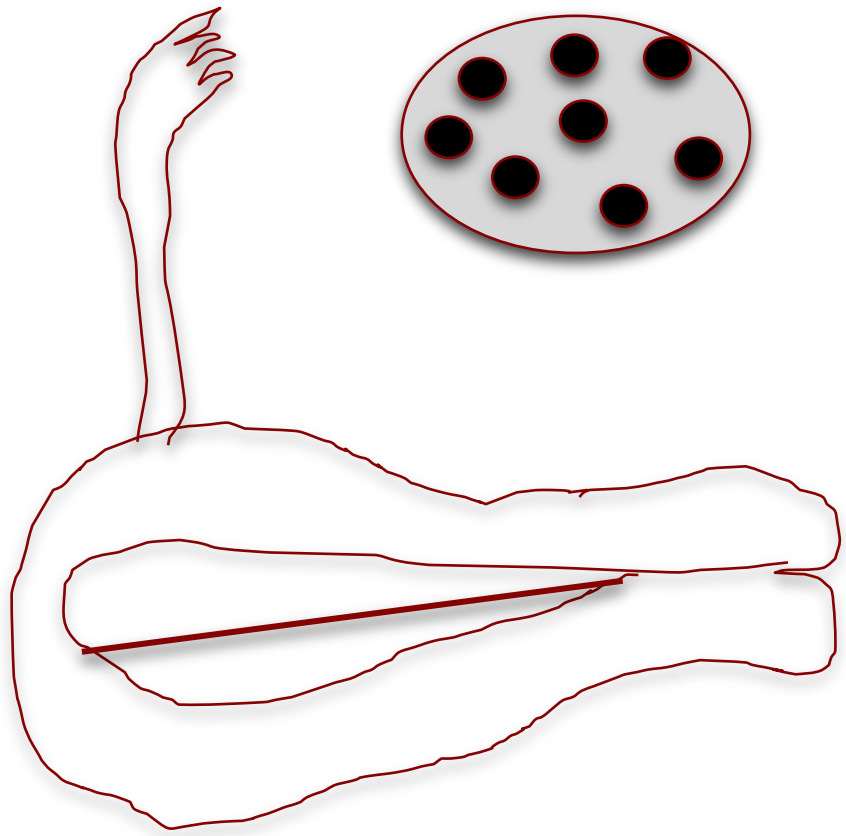




Gordon J. America's OB/GYN Board Review Course, September 2016. "Abnormal Uterine Bleeding."



GnRH

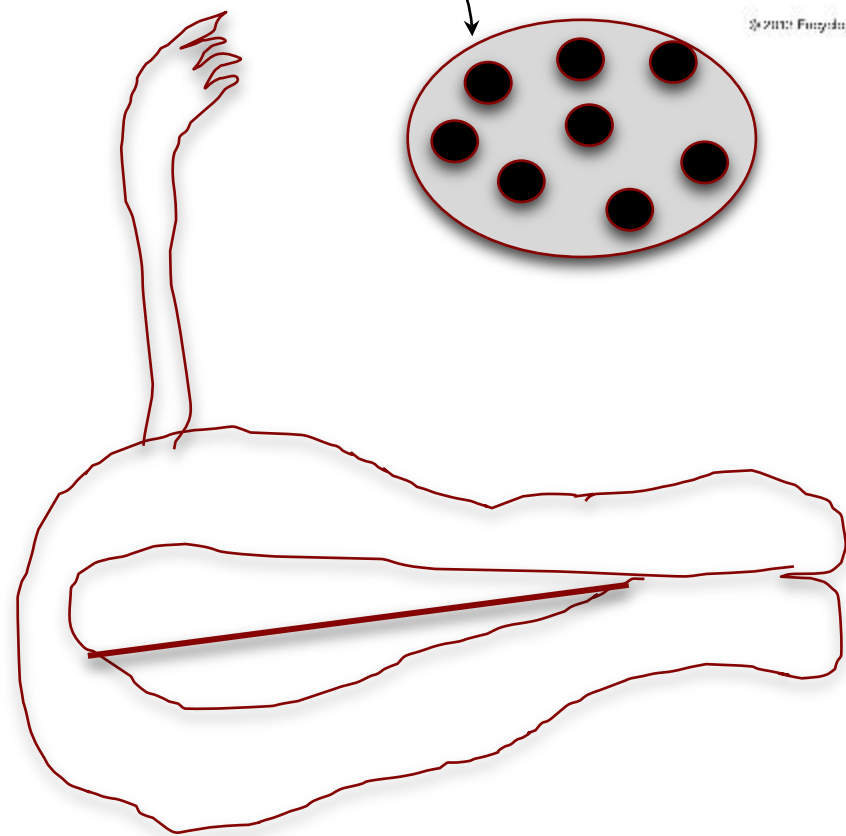
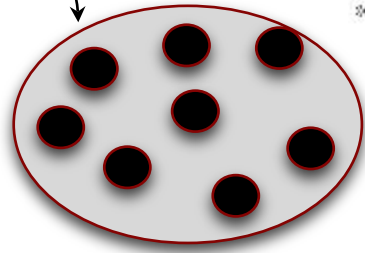




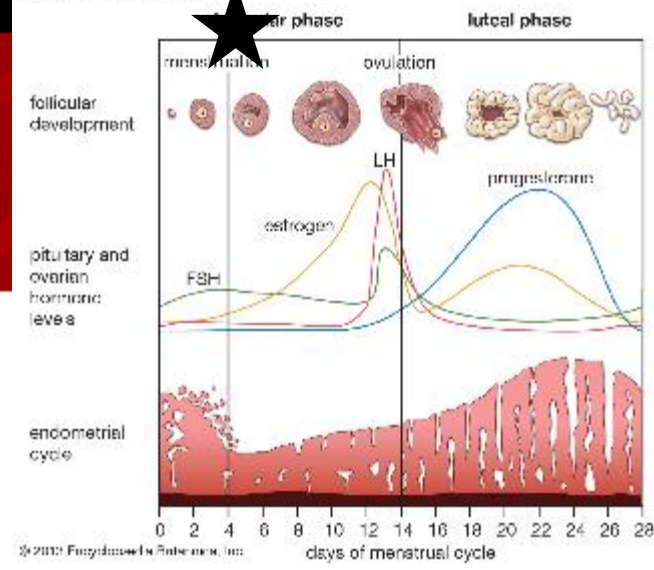
GnRH



FSH



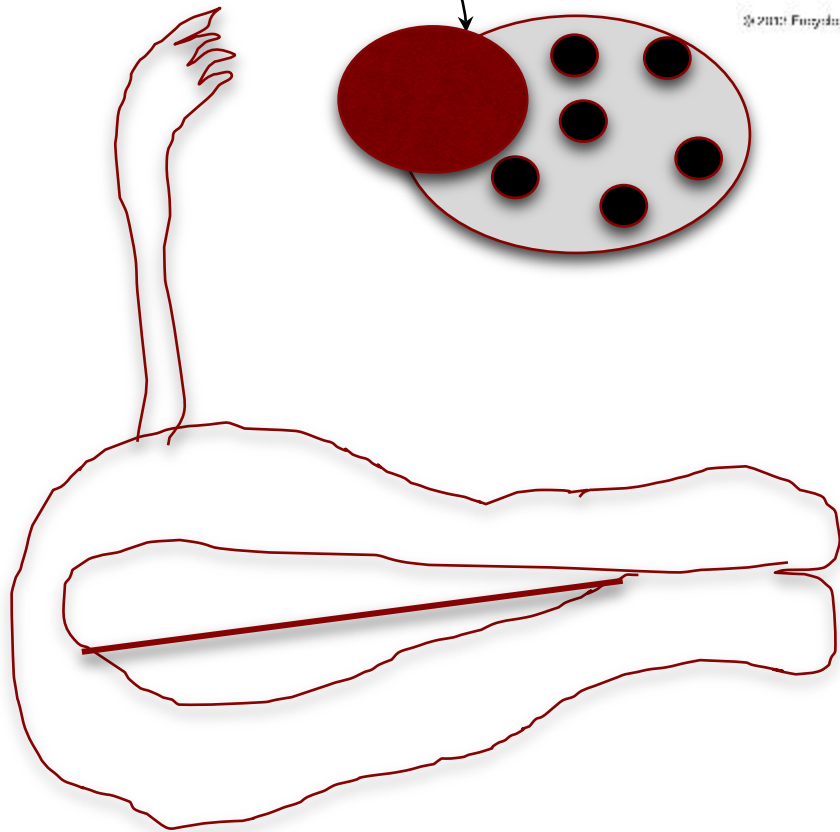
The menstrual cycle



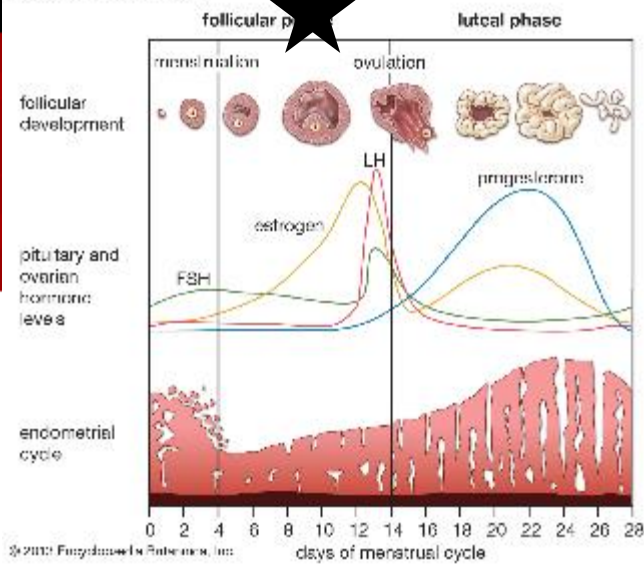


GnRH

FSH



The menstrual cycle

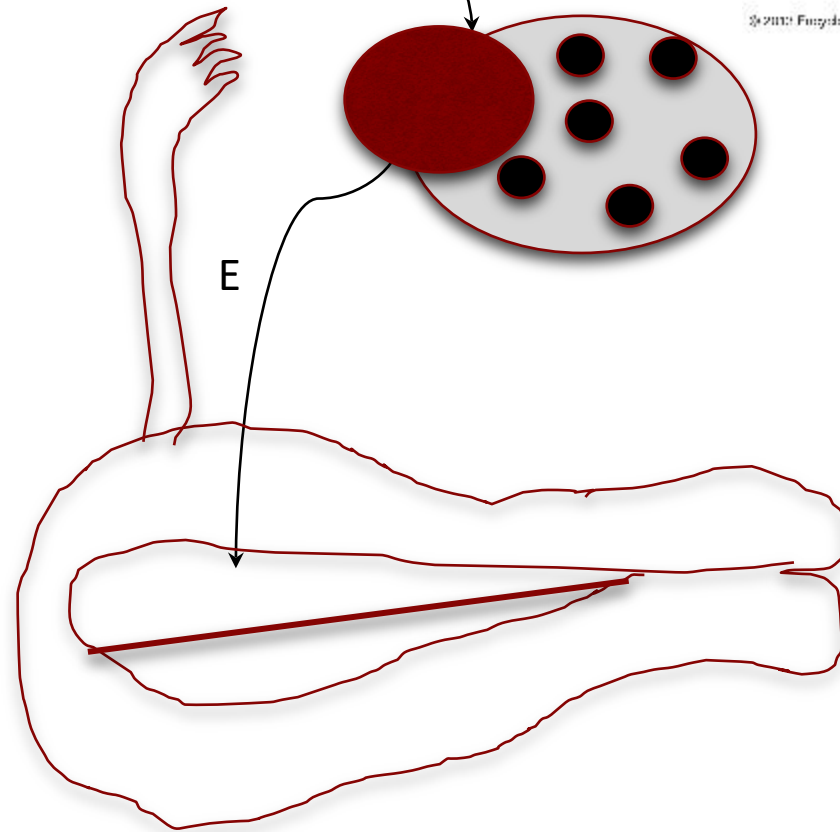




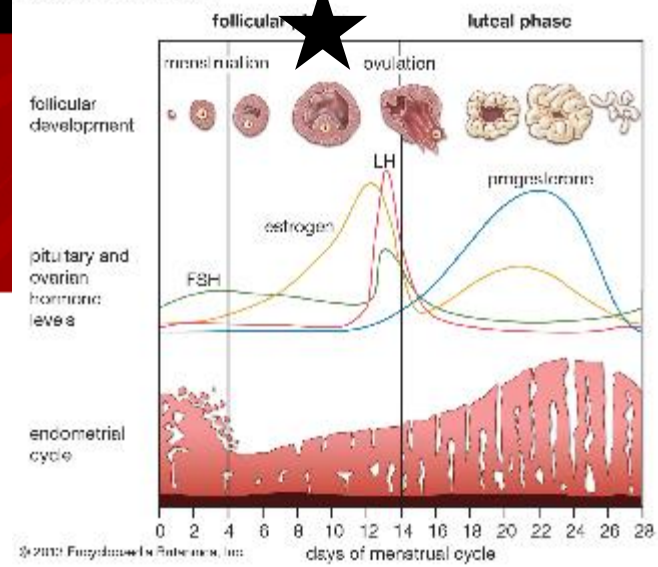
GnRH

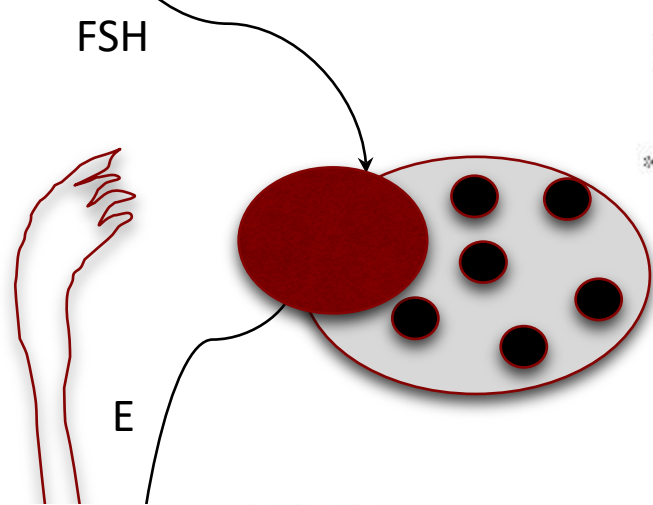
FSH

E



The menstrual cycle





The menstrual cycle

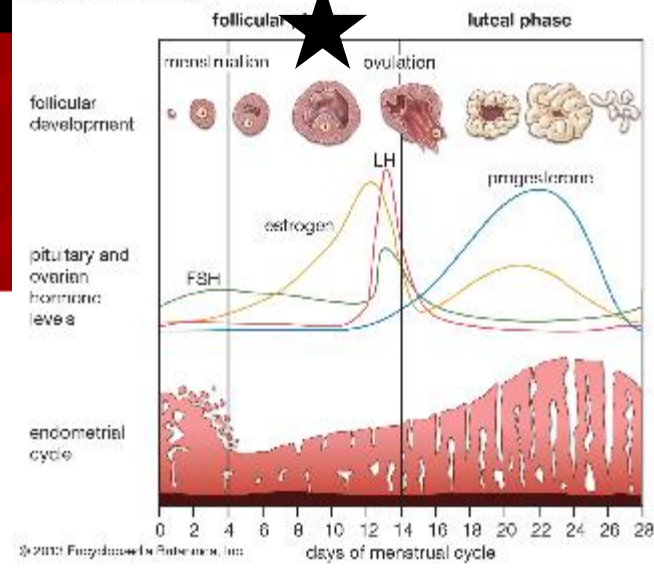
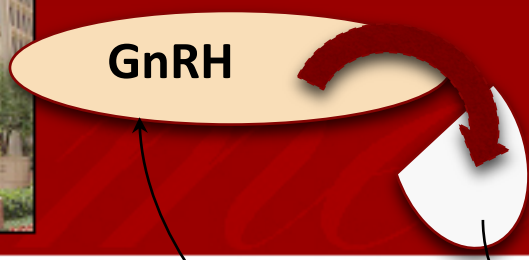
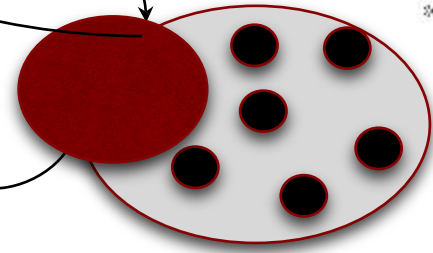


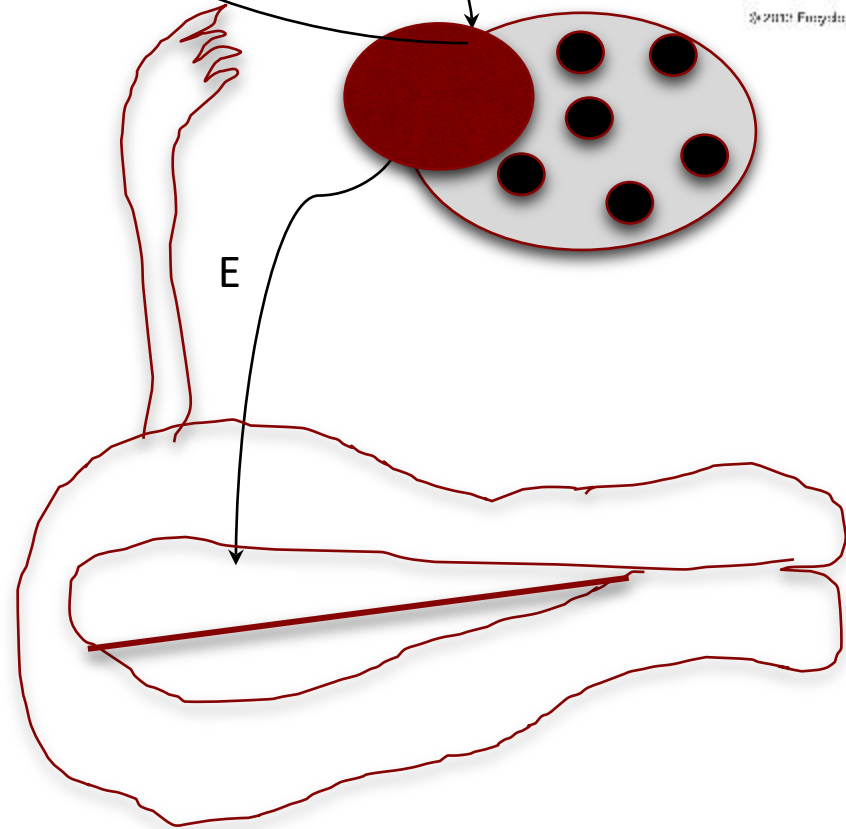
Figure 11. Trilaminar appearance of endometrium consistent with late follicular phase.



FSH

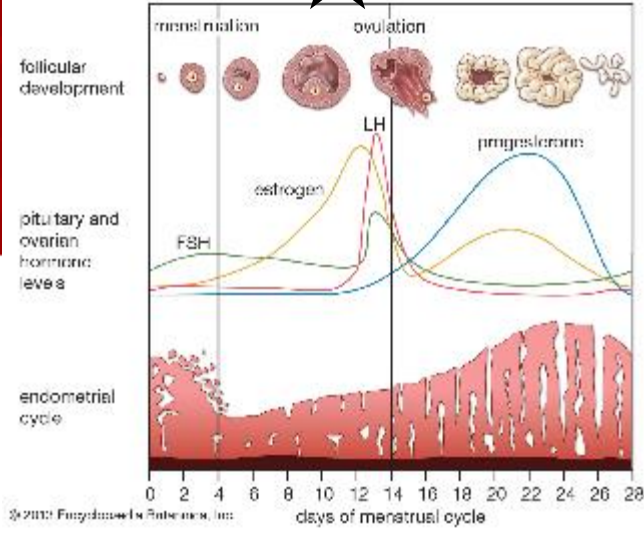


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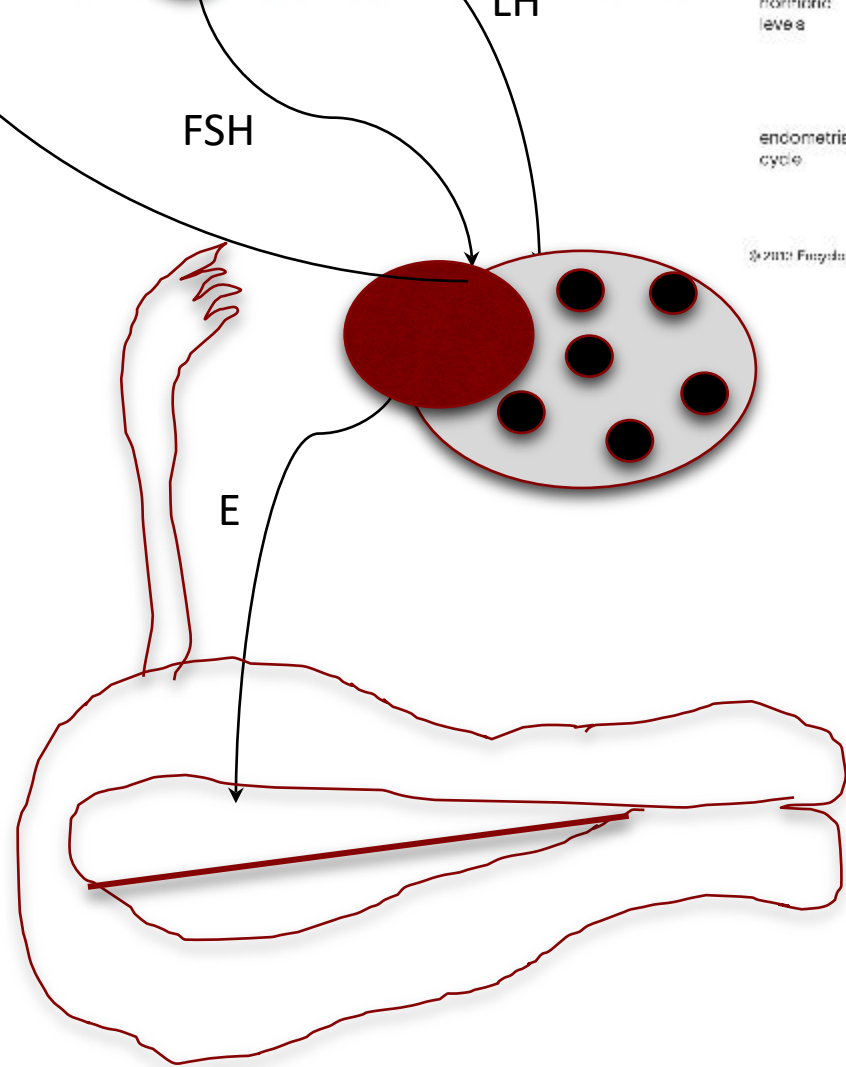
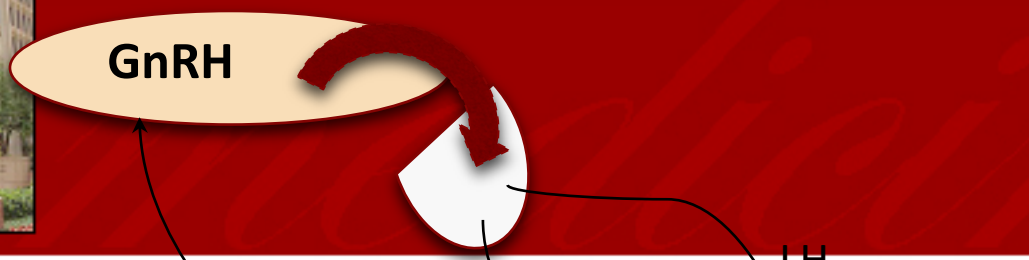


The menstrual cycle

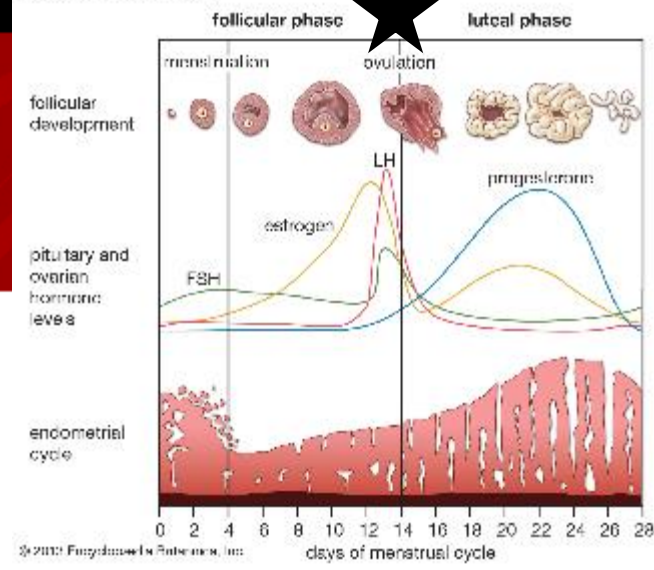
follicular phase  luteal phase



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The menstrual cycle



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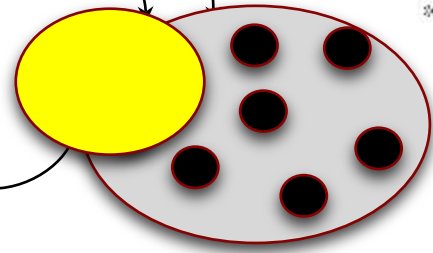


GnRH

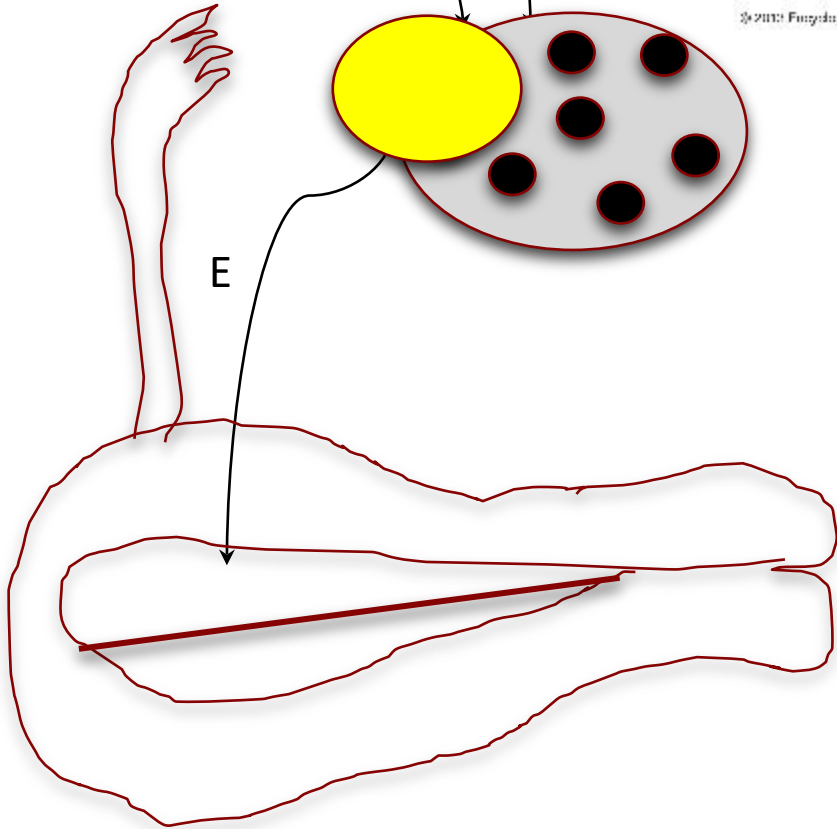


LH

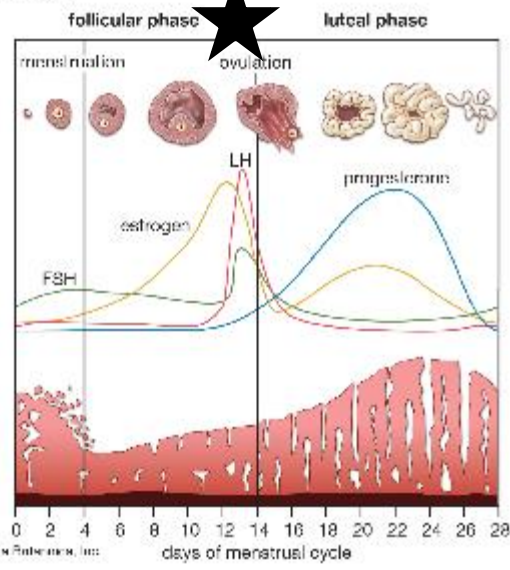
FSH



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The menstrual cycle



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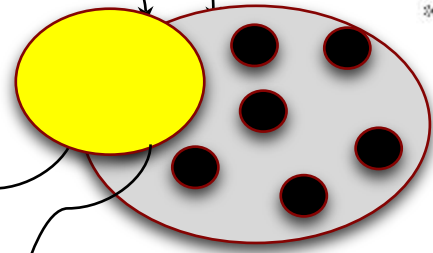


GnRH



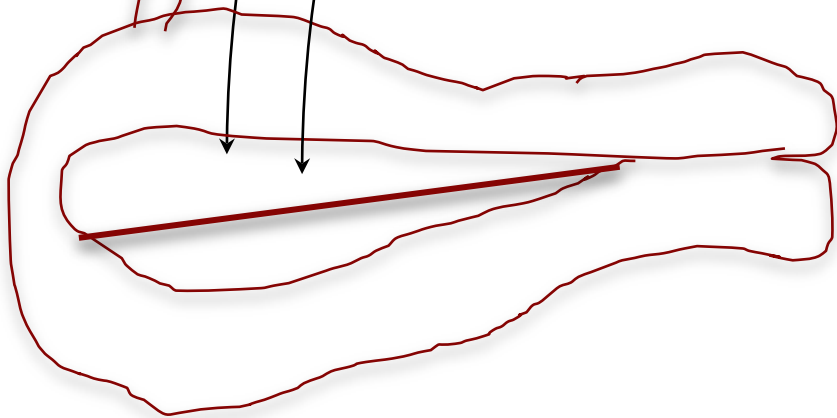
LH

FSH

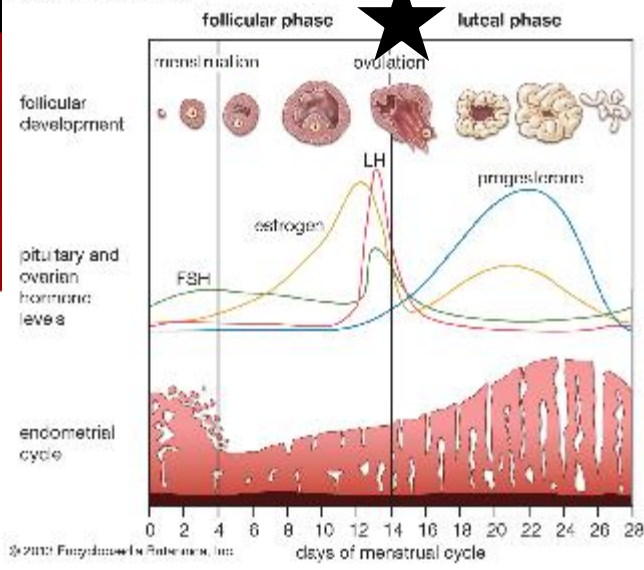


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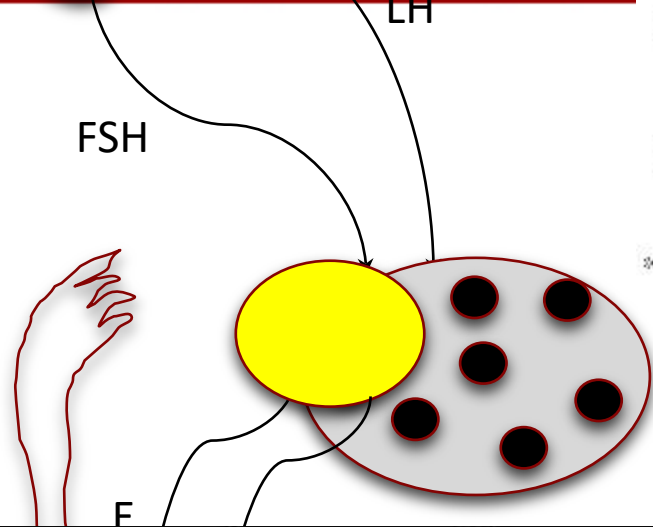
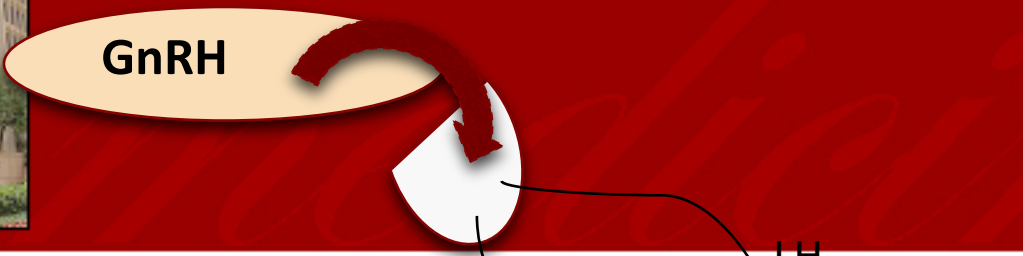
P



The menstrual cycle



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The menstrual cycle

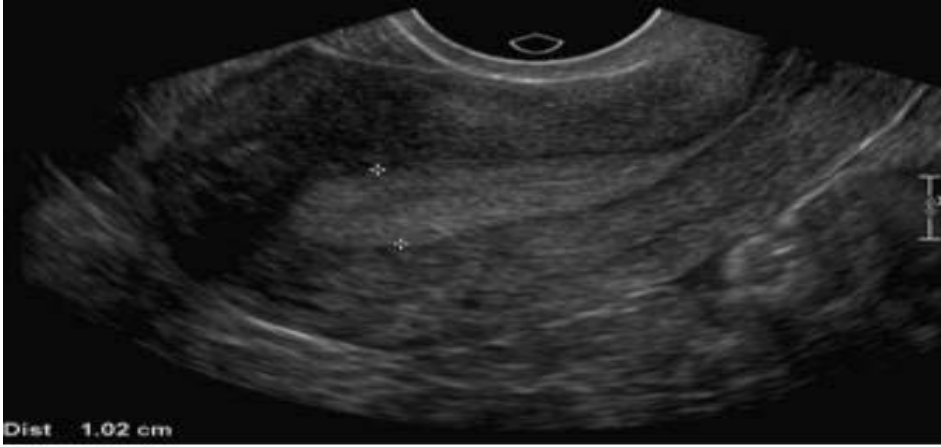
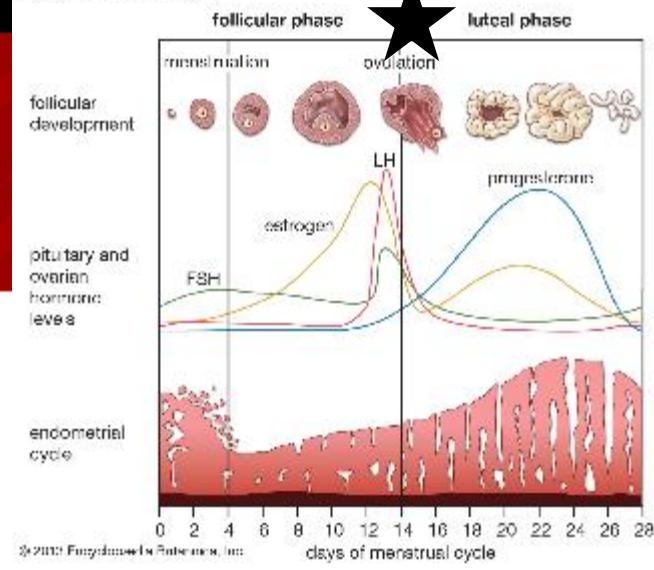


FIG 26-33 Secretory endometrium. Transvaginal sonogram in the sagittal plane on day 19 of the menstrual cycle shows a uniformly echogenic endometrium (*calipers*) measuring 10.2 mm. The functional layer of the endometrium has become isoechoic with the basal layer, and the trilaminar appearance is therefore no longer evident.

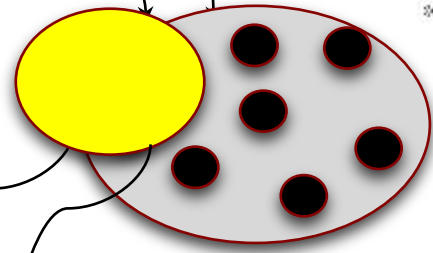


GnRH



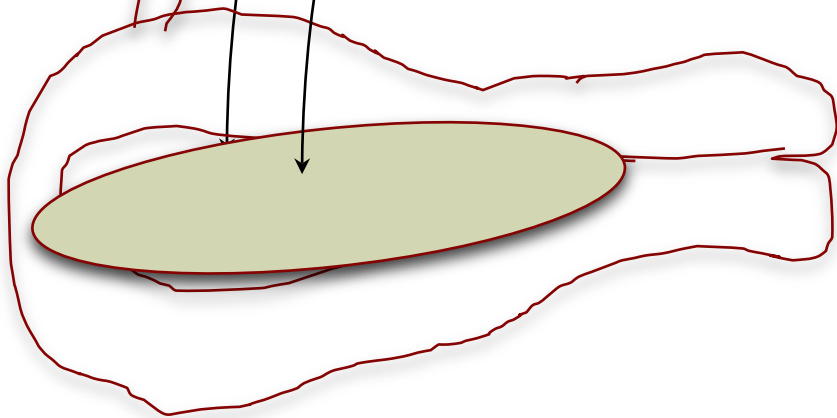
LH

FSH

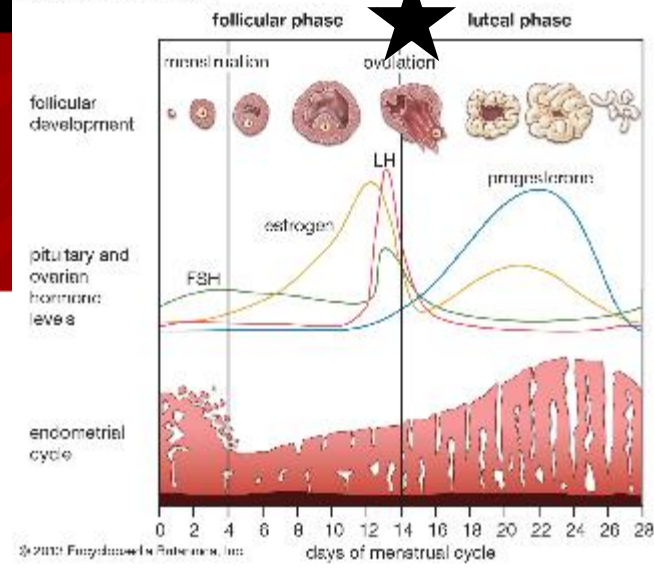


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The menstrual cycle



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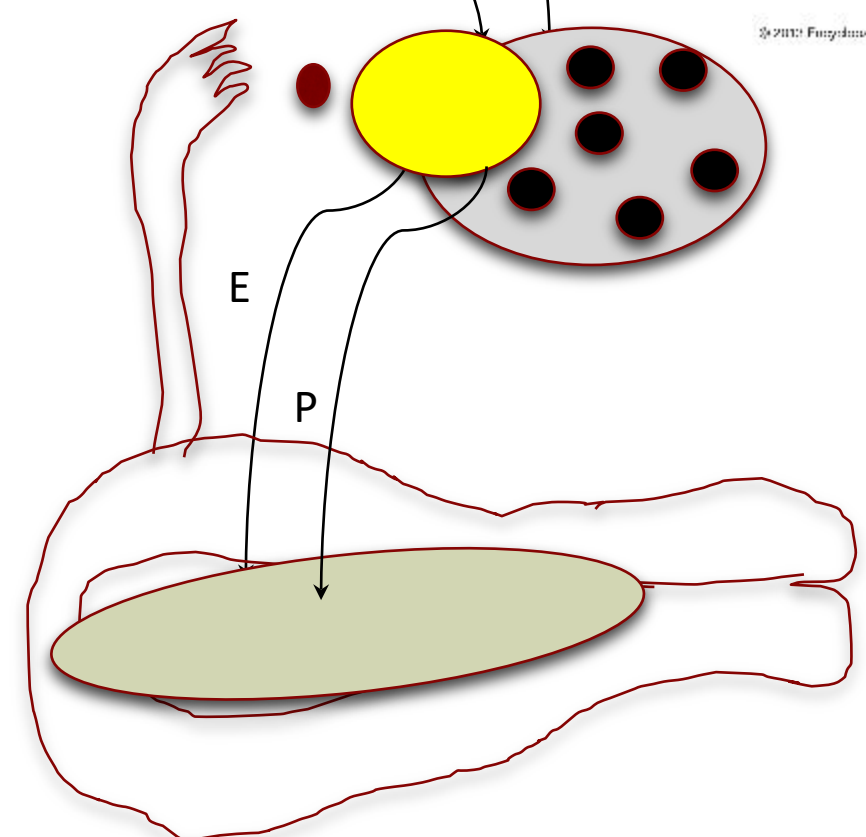


GnRH

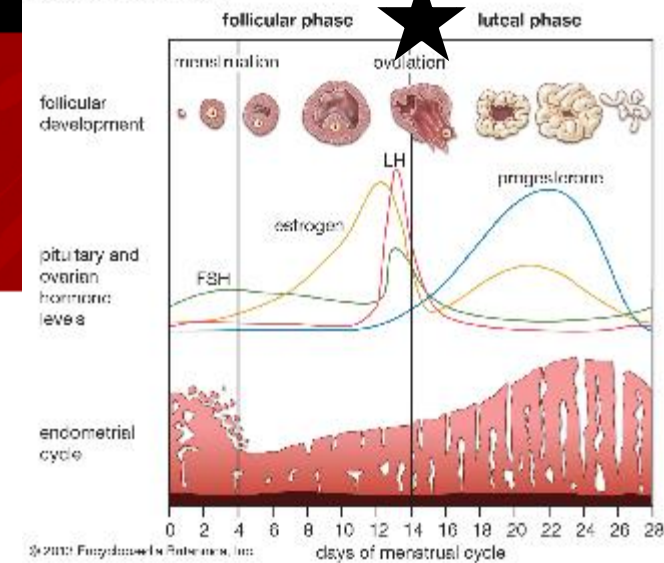


LH

FSH



The menstrual cycle



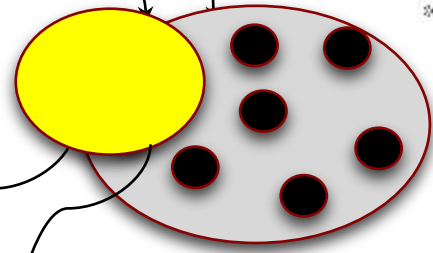


GnRH



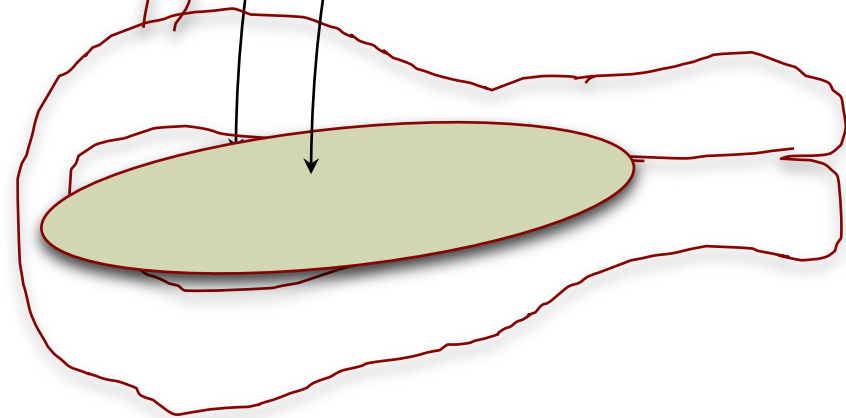
LH

FSH



E

P

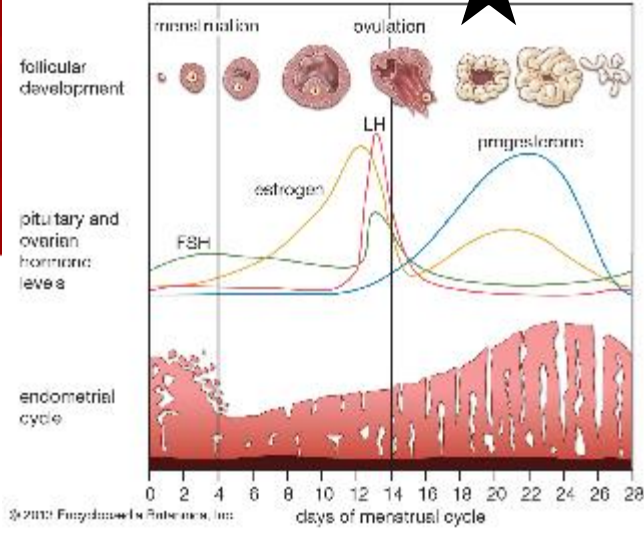


The menstrual cycle

follicular phase



luteal phase



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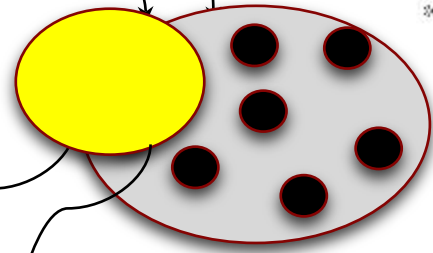


GnRH



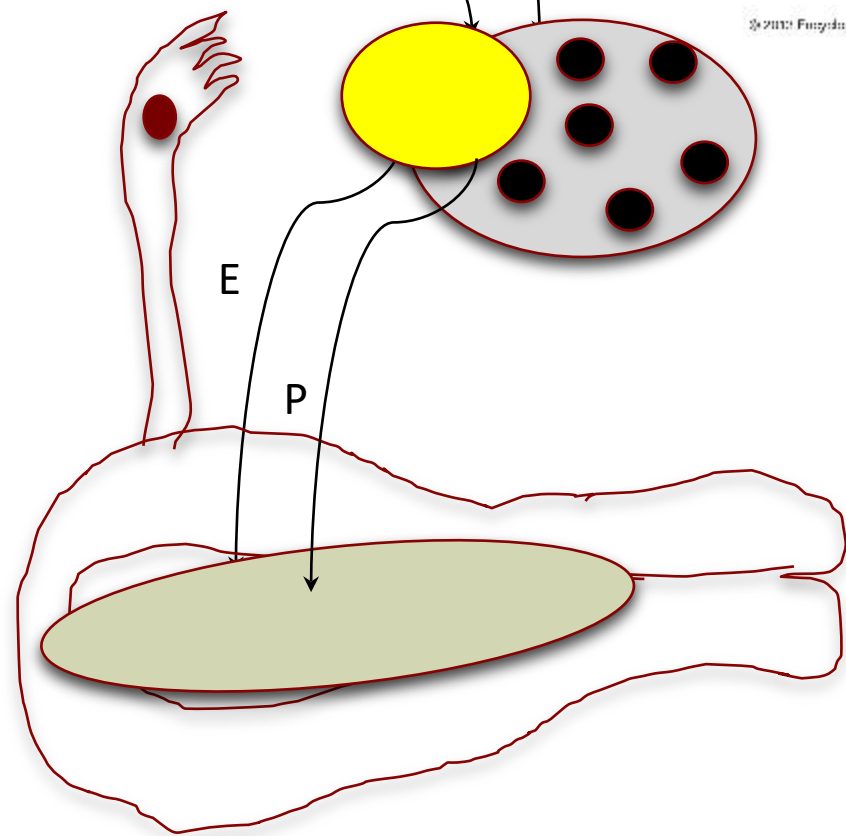
LH

FSH



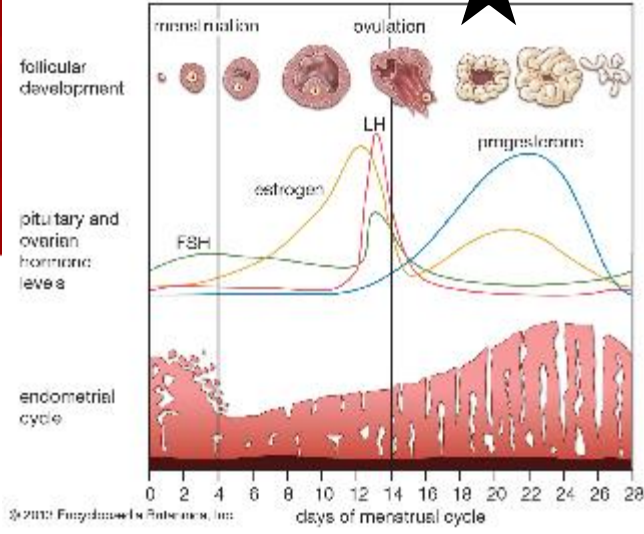
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The menstrual cycle

follicular phase luteal phase



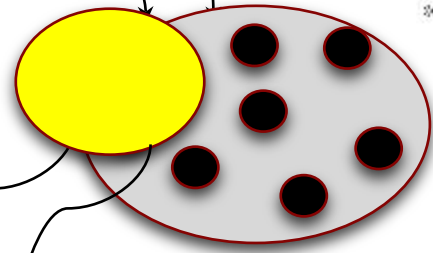


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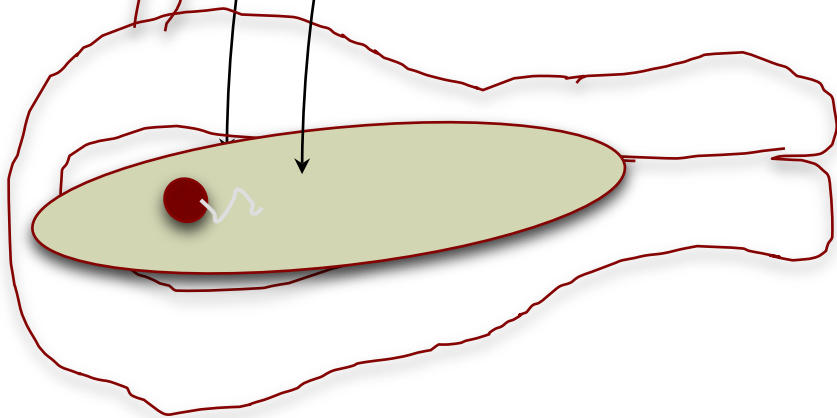
LH

FSH



E

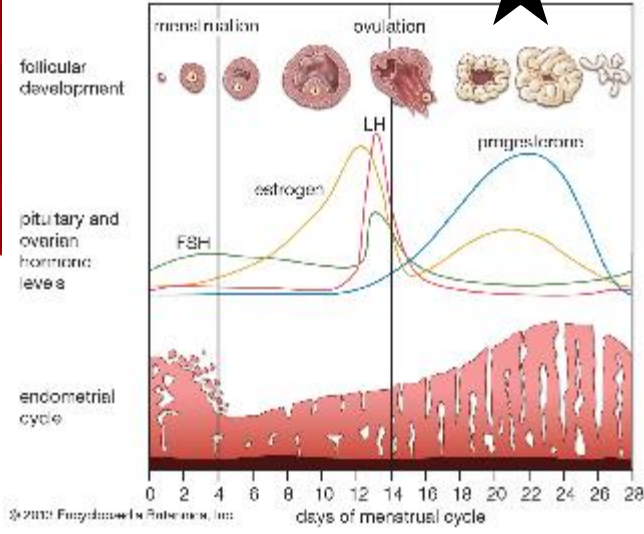
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The menstrual cycle

follicular phase

luteal phase



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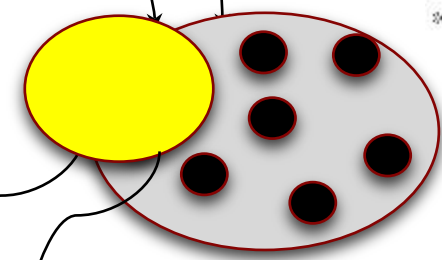


GnRH



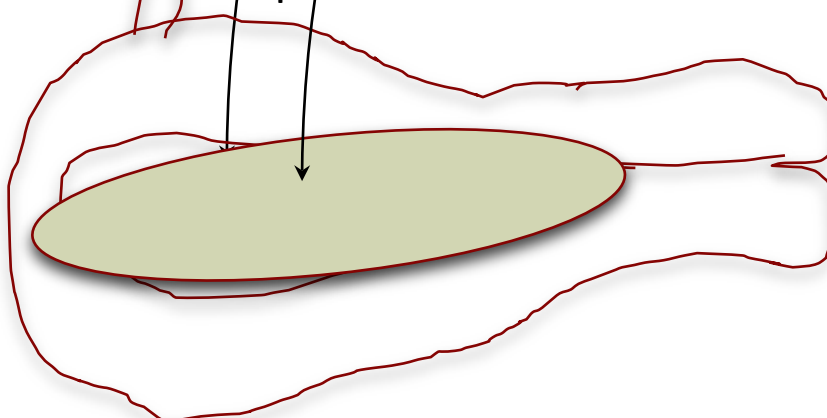
LH

FSH

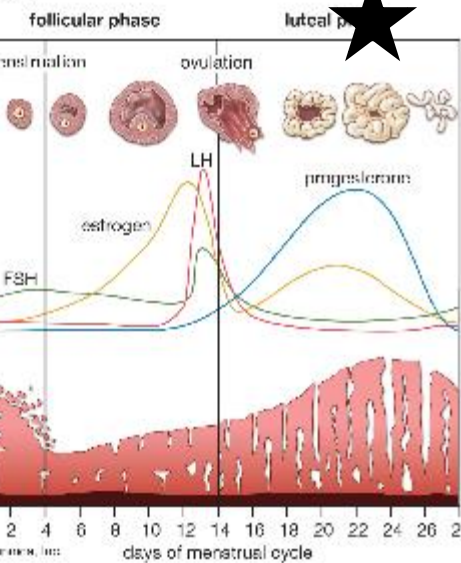


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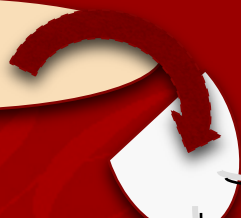
The menstrual cycle



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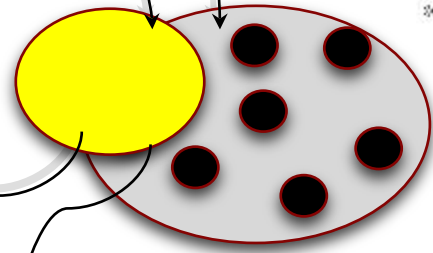


GnRH



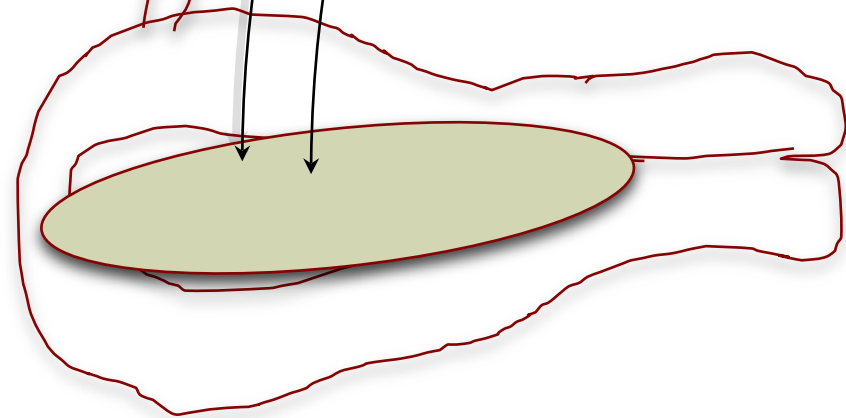
LH

FSH



E

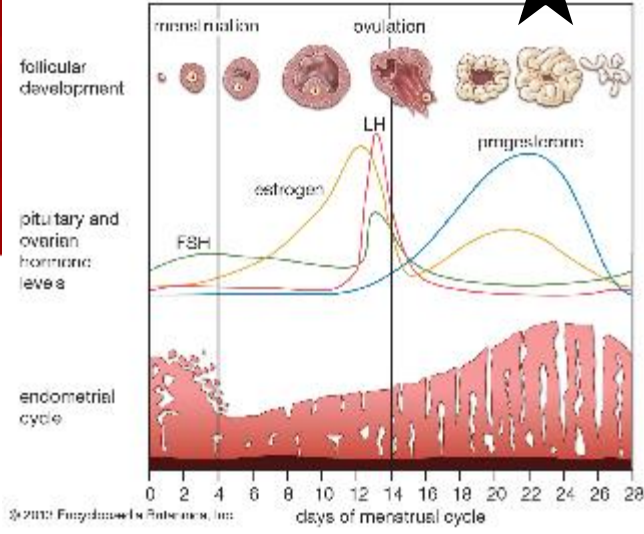
P



The menstrual cycle

follicular phase

luteal phase



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GnRH

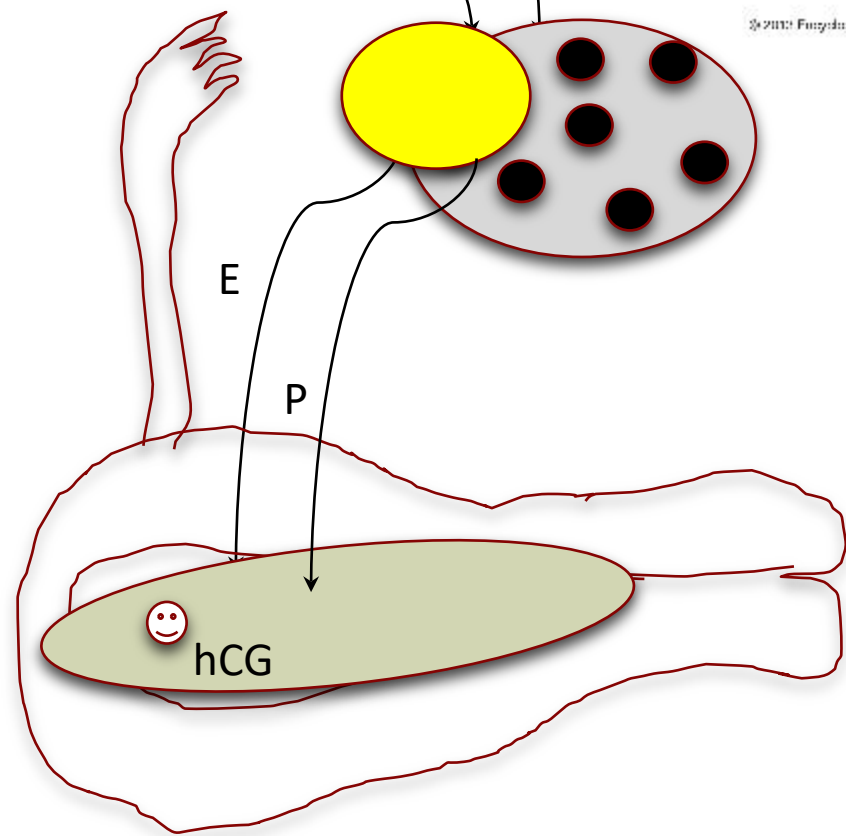
LH

FSH

E

P

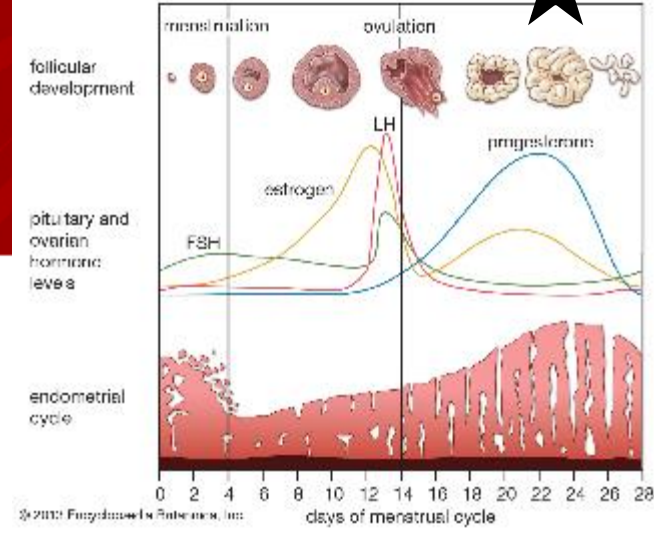
hCG



The menstrual cycle

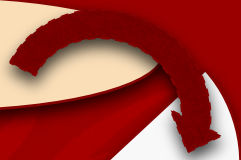
follicular phase

luteal phase



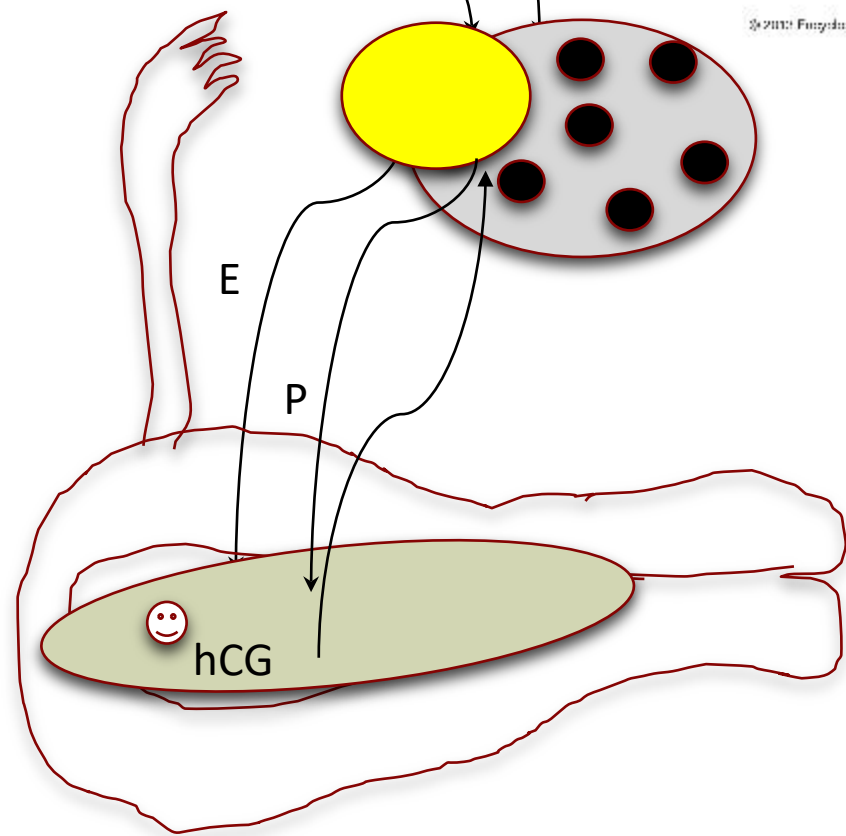


GnRH



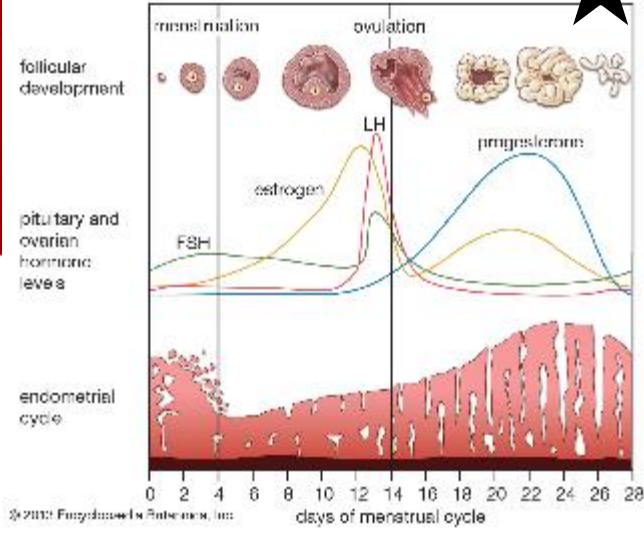
LH

FSH



The menstrual cycle

follicular phase luteal phase



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Background-Infertility



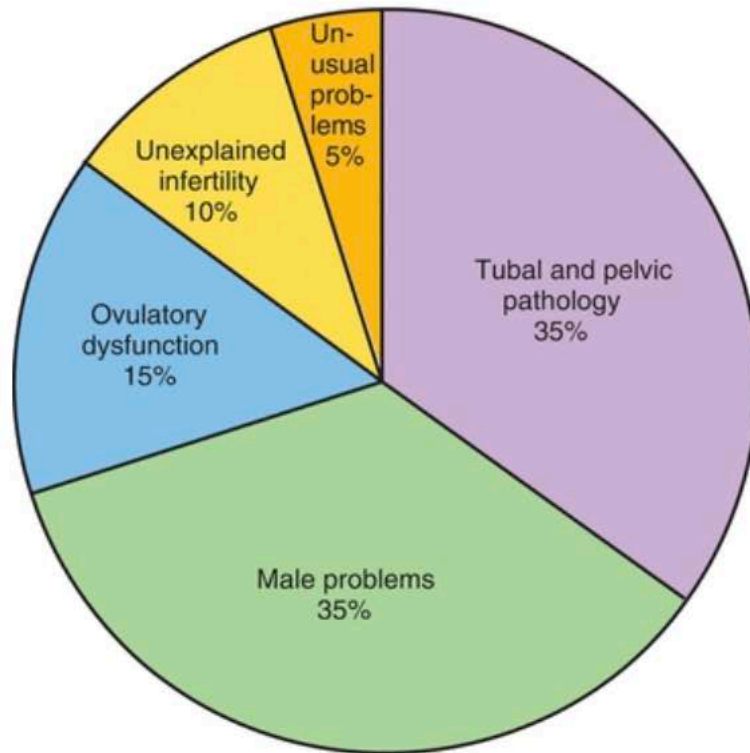
- Defined as > or equal to 12 months of time intercourse or TDI without conception (6 months if 35 or greater)
- 1/8 couples
- Immediate eval indicated:
 - Oligomenorrhea, amenorrhea
 - Known/suspected uterine or tubal disease
 - Stage III/IV endometriosis
 - Suspected male infertility
 - > 40 yrs of age

Months of Exposure	% Pregnant
3 mo	57%
6 mo	72%
1 y	85%
2 y	93%

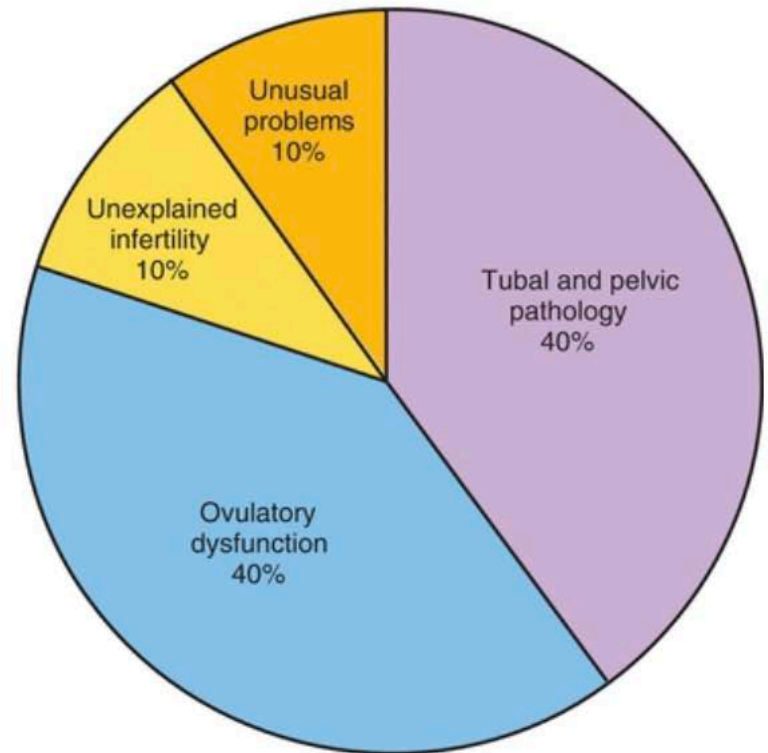
Data from Osterman, AP. Factors affecting natural conception. JAMA. 1968; 200: 1002.



Causes of Infertility



Couples



Women



Table 1. Basic Infertility Evaluation

Female

History

Physical

Prepregnancy evaluation*

Additional evaluation for etiology of infertility

Diminished ovarian reserve

- Antimüllerian hormone or basal follicle-stimulating hormone plus estradiol
- Transvaginal ultrasonography with antral follicle count

Ovulatory dysfunction

Ovulatory function test (eg, serum progesterone measurement)

Tubal factor

- Hysterosalpingography
- Hysterosalpingo-contrast sonography

Uterine factor

- Transvaginal ultrasonography
- Sonohysterography
- Hysteroscopy
- Hysterosalpingography

Male

History

Semen analysis

*See the following document for guidance on prepregnancy evaluation: Prepregnancy counseling. ACOG Committee Opinion No. 762. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2019;133:e78–89.



History of Patient: Female



- Age
- Menstrual Hx: monthly? Irregular?
- Pregnancy Hx?
- Discuss both partner's reproductive history
 - Hx of STI's? Pelvic surgery?
- Family history
 - POF? Fragile X/mental retardation?
Endometriosis?



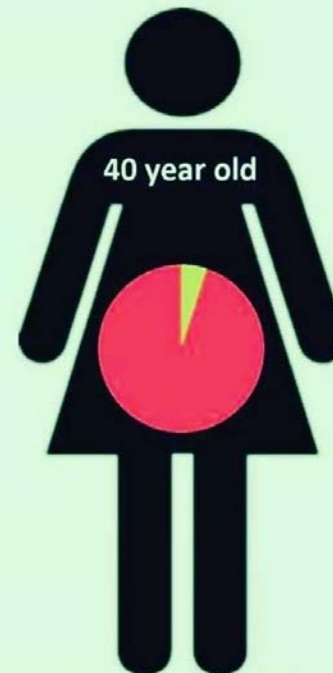
Fertility Declines with Age



Your chance of pregnancy each month declines with age



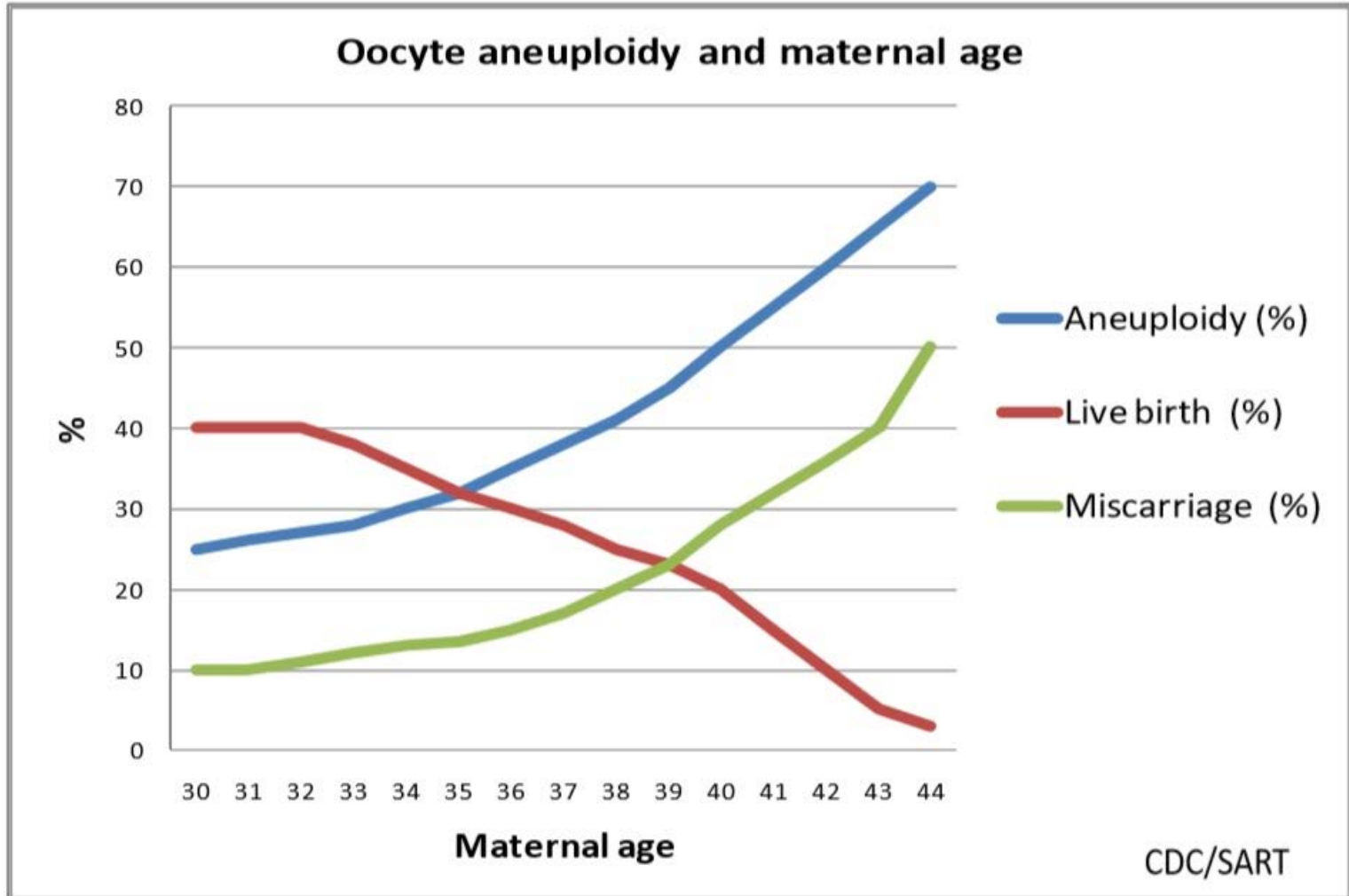
A healthy 30-year old woman has about a **20%** chance of getting pregnant each month.



A healthy 40-year old woman has about a **5%** chance of getting pregnant each month.

Female age is the single most important predictor of fecundity!

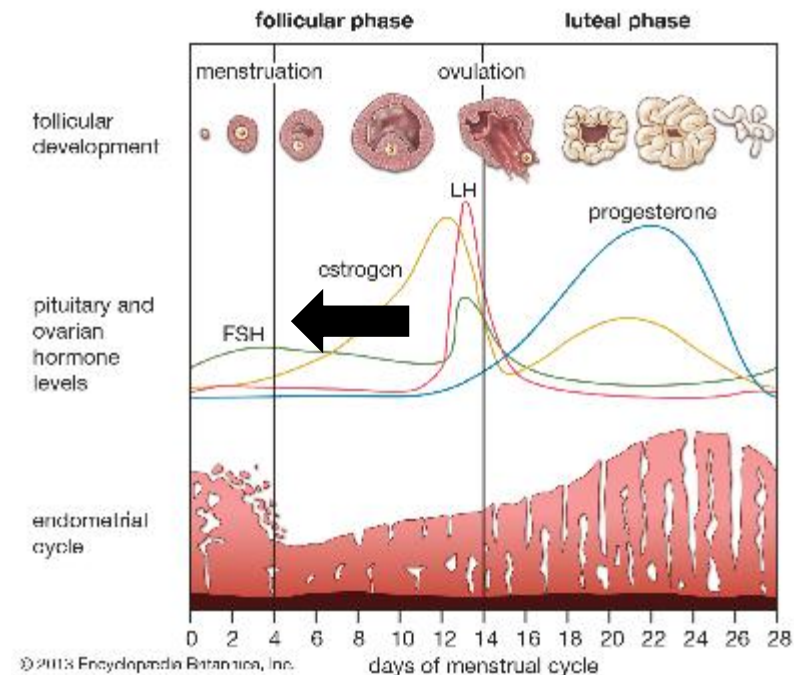
Pregnancy Outcomes in Relation to Maternal Age



Ovarian Reserve Testing

- Cycle Day 3 FSH/Estradiol
 - Normal FSH: < 10 mIU/mL,
Borderline: 10-15 mIU/mL
High: > 15 mIU/mL
 - E2 should be < 60-80 pg/ml
- Anti-mullerian Hormone (AMH)
 - Direct correlation to follicular granulosa cell function
 - Can test on any day of cycle, low cycle-to-cycle variability
- Antral follicle count (TVUS)

The menstrual cycle





Diminished Ovarian Reserve

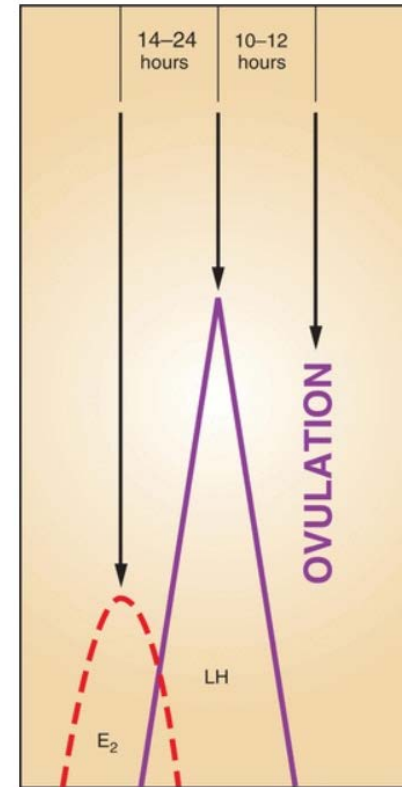


- Predictors of poor ovarian stim, but not live birth
- AMH < 1 ng/mL
- AFC < 5-7
- Baseline FSH > 10 IU/L
- Poor prior IVF stim (< 4 oocytes at retrieval)
- Elevated baseline E2



Ovulation

- E2 feedback ($\geq 200\text{pg/mL}$) sustained for > 50 hours
 - Ovarian signal to initiate mid-cycle gonadotropin surge
- Serum LH starts to rise approx. 36 hours and peaks approx. 10-12 hours before ovulation
- Urine LH detectable approx. 12 hours after serum
 - Therefore urine-LH kits are positive approx. 24 hours prior to ovulation

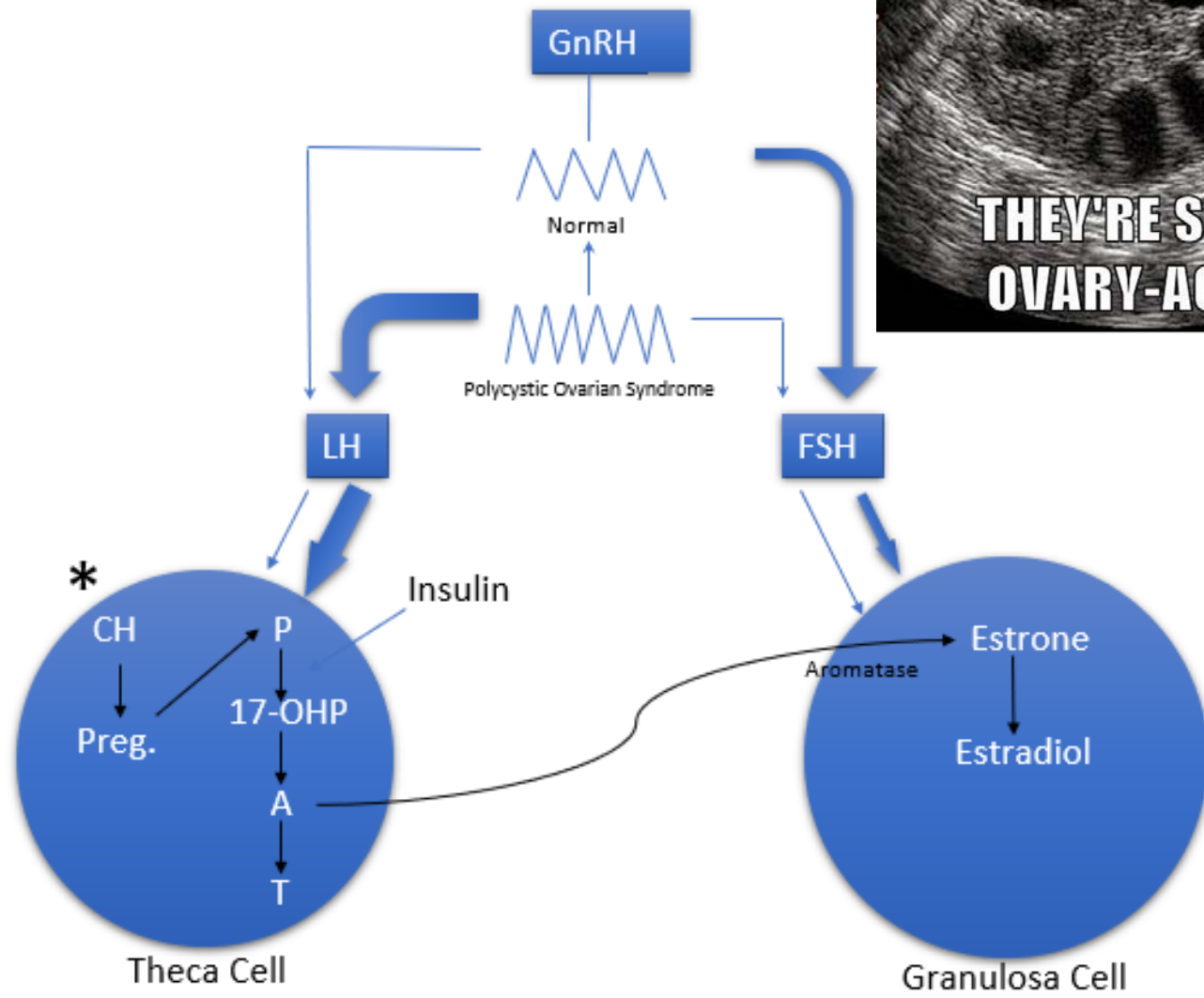
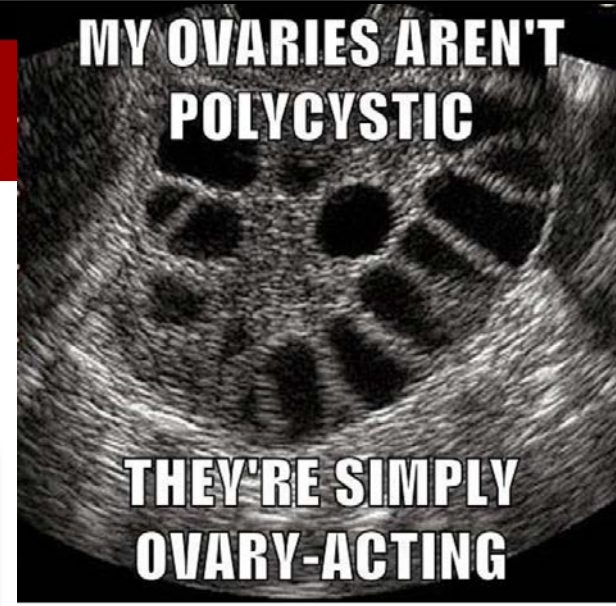


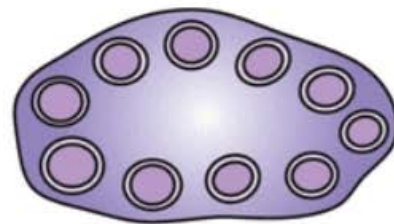


Luteal Phase

- P4 begins to rise 12 hours before the LH surge
 - Prepares endometrium
 - Peak P4 secretion is ~1 week post LH surge
 - LH = highly pulsatile. P4 can fluctuate SEVENFOLD over a few hours. Minimum of 3 confirms ovulation. Should not assess luteal phase quality
- Luteo-placental shift begins around 6-7 weeks (EGA)
 - Loss of corpus luteum prior to this = miscarriage. Must supplement with exogenous P4
- *LH stimulation required = those without pituitary function need luteal support*







FSH & LH IU/L	Estradiol pg/mL	Progesterone 17-OHP ng/mL
20	500	10
18		9
16	400	8
14		7
12	300	6
10		5
8	200	4
6		3
4	100	2
2		1
0	0	0

#1 OB-GYN Recommended Brand

Clearblue

ADVANCED DIGITAL Ovulation Test

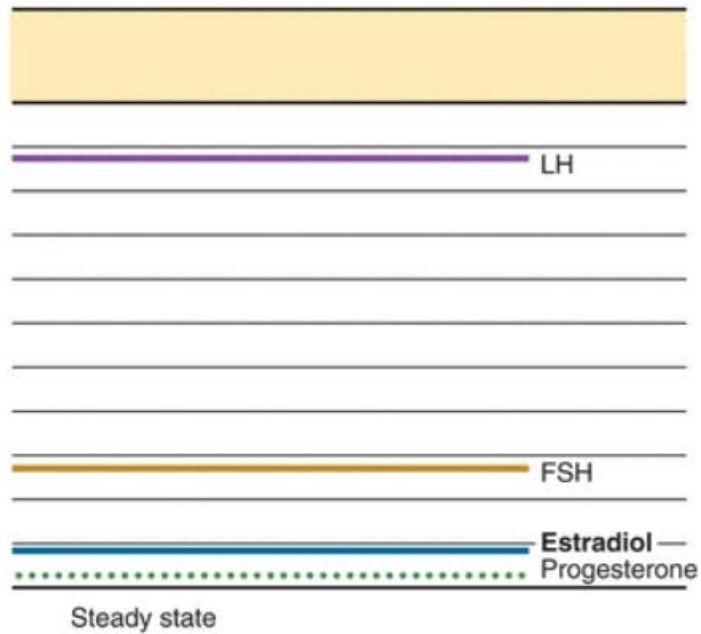
4 Typically Identifies or More Fertile Days²

At Least 2X The Days vs. Other Tests

Over 99% Accurate*

Proud to support **march of dimes**
A RIGHT TIME CHANCE FOR EVERY BABY

10 Tests



Persistent anovulation



PCOS – Dx Criteria



Criteria	National Institute of Health (NIH) Criteria 1990	Rotterdam Criteria 2003	Androgen Excess and PCOS Society Criteria 2006
1 Irregular periods ^b	1 and 2 ^a	Any 2 of 3 ^a	1 and 2 ^a
2 Elevated serum androgens or Hyperandrogenism Hirsutism Acne Androgenetic alopecia			or 2 and 3 ^a
3 Polycystic ovarian morphology (PCOM) or polycystic ovary (PCO) ^c			

^aDifferential diagnoses that can mimic clinical presentation must be excluded.

^bEight or less menses per year.

^cOvarian volume >10 mL³ and/or >12 follicles between 2 and 9 mm in size in at least one ovary.

Other causes of anovulation: obesity, thyroid disorder, hyperprolactinemia, POI, anorexia, stress, androgenic disorders





Infertility tests that should not be routinely ordered, unless specifically indicated (33).

- Laparoscopy for unexplained infertility
- Advance sperm function testing (e.g., DNA fragmentation testing)
- Postcoital testing
- Thrombophilia testing
- Immunologic testing
- Karyotype
- Endometrial biopsy
- Prolactin
- Progesterone
- Estradiol
- Follicle-stimulating hormone
- Luteinizing hormone

ASRM. Fertility evaluation of infertile women. Fertil Steril 2021.



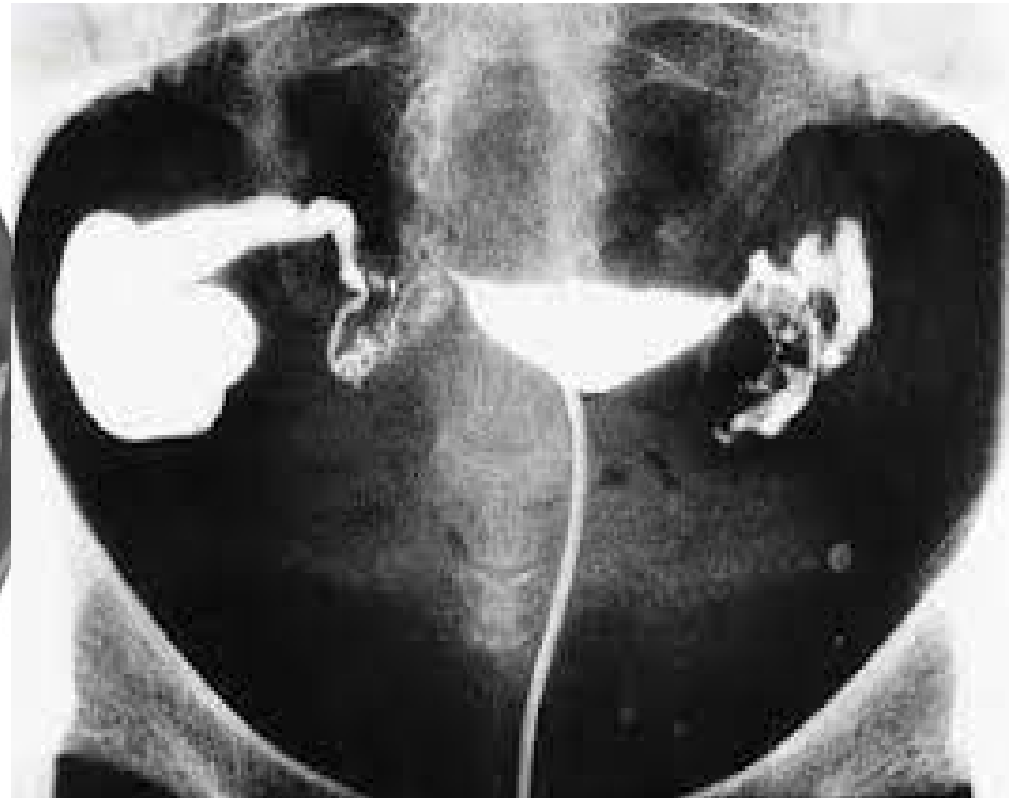
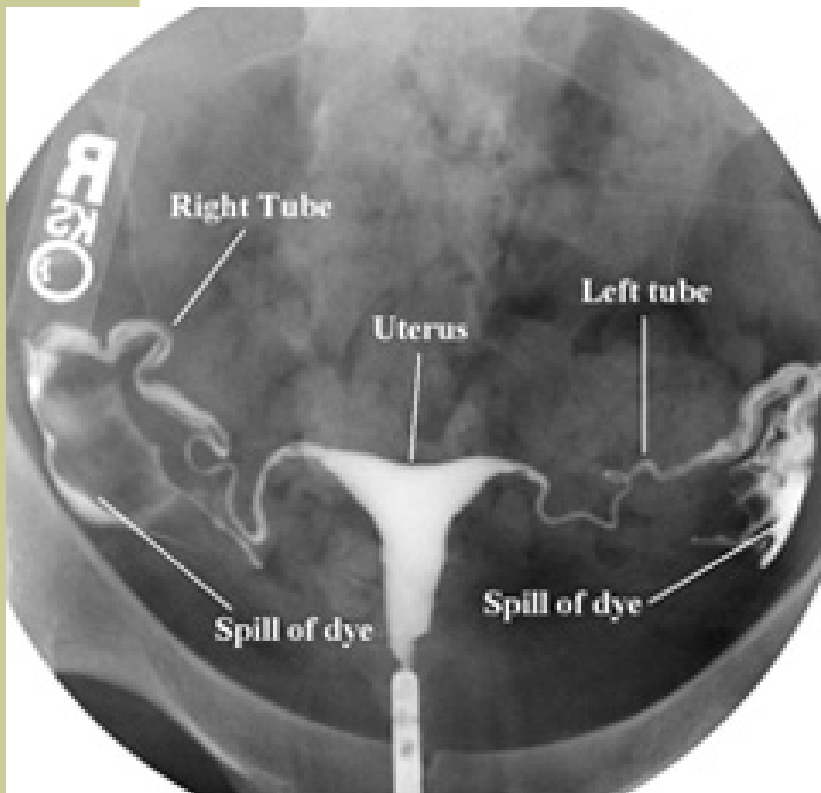
Tubal Disease



- Prior ectopic
 - Salpingostomy? Salpingectomy?
- Pelvic surgery: adhesions
- Hx of pelvic infections (GC, CT, TB)
- Endometriosis
- Tubal sterilization procedure



Hysterosalpingogram



- PPV and NPV for HSG are 38% *and* 94%, respectively
- Sensitivity of detecting cavity polyps is only 50%

<https://www.drmoomy.com/blog/hsg>

<http://www.abivf.com/blog/hydrosalpinx/hydrosalpinx-ivf-and-surgery-by-richard-chetkowski-m-d/>



Chromopertubation





Uterine Factors



Spent years worrying
about birth control only
to find out my uterus
was child proof all
along.



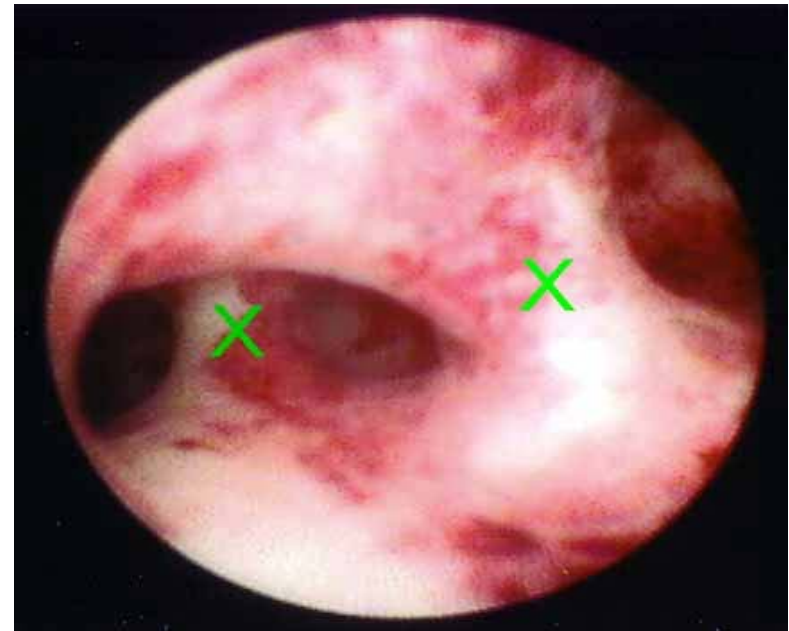
somee cards
user card



Uterine Factors



- Uterine cavity evaluation
 - Fibroids
 - Polyps
 - Mullerian anomalies
 - Uterine synechiae/Asherman's Syndrome





Endometrial polyps and their implication in the pregnancy rates of patients undergoing intrauterine insemination: a prospective, randomized study

Tirso Pérez-Medina¹, José Bajo-Arenas, Francisco Salazar, Teresa Redondo, Luis Sanfrutos, Pilar Alvarez and Virginia Engels

Department Of Gynaecology, Santa Cristina University Hospital, Universidad Autónoma de Madrid, C/O'Donnell 59, 28009 Madrid, Spain

	Polypectomy		p value
	Study (n=101)	Control (n=103)	
Pregnant	Number (%)	Number (%)	<0.001
Yes	64 (63.4)	29 (28.2)	
No	37 (36.6)	74 (71.8)	

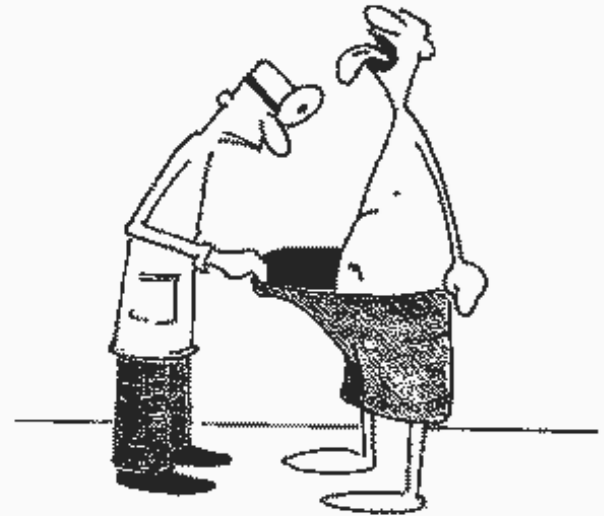
Pérez-Medina T, Bajo-Arenas J, Salazar F, et al. Endometrial polyps and their implication in the pregnancy rates of patients undergoing intrauterine insemination: a prospective, randomized study. *Hum Reprod.* 2005;20(6):1632–1635.



History of Patient: Male



- 40-50% of couples
- Medication/Steroid use?
- Abnormal pubertal history?
- Childhood illnesses?
- Testicular surgery?
- Occupational risk exposures?
- Vasectomy?





SPERMATOGENESIS



- 300 thousand spermatogonia/gonad during embryogenesis
- 600 million/testis by puberty
- In adulthood: 4.4 million sperm/gram of testis tissue/day x 15 and 15 grams of testis tissue = 132,000,000 sperm per day
- More than 1 trillion sperm during normal reproductive life span
- Assuming a 60 bpm heart rate about 1,500 sperm per heart beat!





Male Factor: Semen Analysis



TABLE 26.3 Semen Analysis: Lower Reference Limits (95% CI) in Fertile Men

Volume	1.5 (1.4-1.7) mL
Sperm concentration	15 (12-16) million/mL
Total sperm number	39 (33-46) million/ejaculate
Total motility	40 (38-42) %
Progressive motility	32 (31-34) %
Normal morphology	4 (3-4) %
Vitality	58 (55-63) %

- 1.5, 15, 40%, 4%





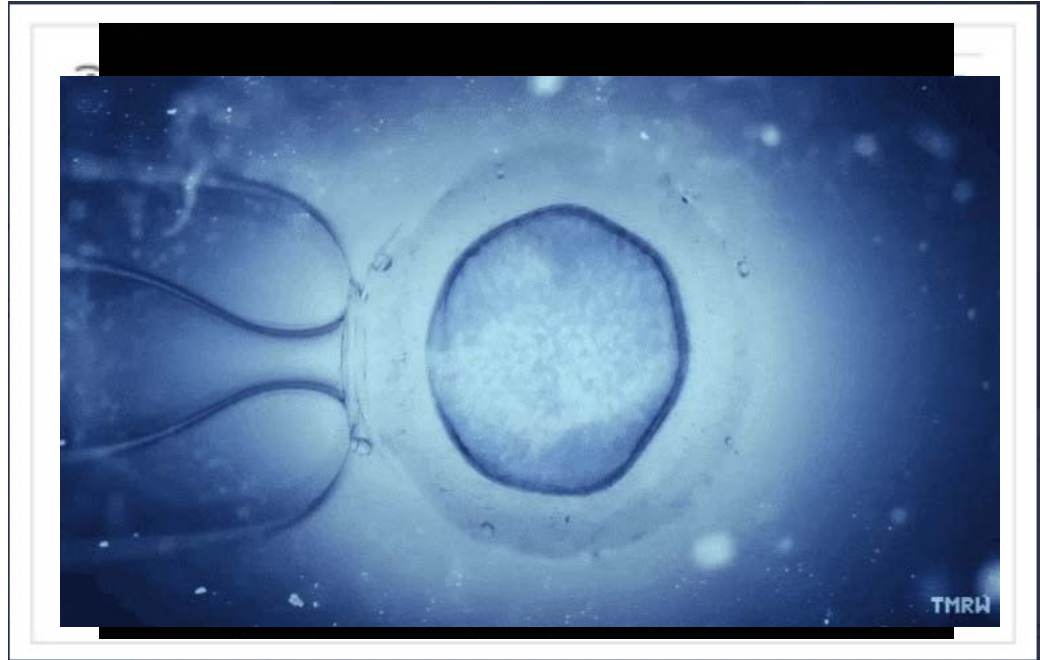
Male Factor Infertility

- Insufficient sperm quantity or quality
 - Idiopathic (40%)
 - Pre-testicular (1%)
 - Hypogonadotropic hypogonadism
 - Kallman Syndrome, anabolic steroids, pituitary mass, prolactinoma, idiopathic
 - Testicular (40%)
 - Klinefelters Syndrome, Y chromosome deletion, chemo/radiation, trauma/torsion, varicocele
 - Post-testicular (20%)
 - CBAVD (congenital bilateral absence of vas deferens): in cystic fibrosis gene carrier, obstruction, retrograde ejaculation, erectile dysfunction, vasectomy

How much is needed?



- **IUI**- ideally 9 million, but possible with 250k
- **Conventional IVF**- 50,000 to 100,000 sperm per oocyte
- **ICSI** – 1 sperm per oocyte



Intrauterine insemination performance characteristics and post-processing total motile sperm count in relation to live birth for couples with unexplained infertility in a randomised, multicentre clinical trial

Karl R. Hansen^{1,*}, Jennifer D. Peck^{1,2}, R. Matthew Coward^{3,4}, Robert A. Wild^{1,2}, J.C. Trussell⁵, Stephen A. Krawetz⁶, Michael P. Diamond^{7,8}, Richard S. Legro⁹, Christos Coutifaris¹⁰, Ruben Alvero^{11,12}, Randal D. Robinson¹³, Peter Casson^{14,15}, Gregory M. Christman^{16,17}, Nanette Santoro¹¹, and Heping Zhang for the NICHD Reproductive Medicine Network¹⁸

- Secondary analysis of 2,462 cycles from AMIGOS trial
- TMC grouped into categories of 5 M **live birth** based on TMC:
 - 15-20: 14.8%
 - < 5: 5.5%
 - <1 million: 5.1%
- Time from HCG to IUI was not significantly different





Treatment: Infertility



- **Treat underlying cause**
 - Hypothyroidism – thyroid replacement
 - Hyperprolactinemia – Dopamine agonist
 - Surgical – uterine (polyps, fibroids, etc.)
- **Anovulatory -> ovulation induction**
 - Clomiphene Citrate (Clomid)
 - Letrozole
 - Exogenous gonadotropin injections
- **Male Factor**
 - Intrauterine Insemination
 - IVF with ICSI
 - Possible use of Donor Sperm
- **Tubal Factor**
 - Possible surgical correction
 - IVF
- **Unexplained infertility**
 - Ovulation induction with Intrauterine Insemination
 - Clomid or Letrozole
 - 3-4 cycles then move to IVF
- **Failure of Prior Treatments, DOR etc.**
 - IVF ± ICSI
 - Donor oocyte, donor embryo, adoption
 - Surrogacy (uterine factor, maternal morbidity)





Ovulation Induction Agents



Clomiphene Citrate

- Selective Estrogen Receptor Modulator (SERM)
 - Work at level of hypothalamus
 - Inhibits normal negative feedback
 - Causes increase of GnRH secretion
 - Subsequently FSH/LH
- Dose: 50mg x 5 days
 - Can increase to 100mg or 150mg
- 2 isomers
 - Zuclomiphene (38%)
 - Enclomiphene (62%) – *isomer responsible to ovulation induction actions

Letrozole

- Aromatase inhibitor
 - Nonsteroidal, competitive
 - Work peripherally
 - Blocks conversion of androgens to estrogens
 - Perceived low estrogen levels
 - Causes increase of GnRH secretion
 - Subsequently FSH/LH
- Dose: 2.5mg x 5 days
 - Can increase to 5mg or 7.5mg
- Considered 1st line for tx of anovulation
 - Higher ovulatory and pregnancy rates compared to Clomiphene
 - *not FDA approved for this indication





Exogenous Gonadotropins



- Uses:

- Gonadotropin deficient (hypothalamic hypogonadism)
- Failure of less complicated forms (clomid, letrozole)



- FSH

- Recombinant hormones – from Chinese hamster ovary cell line

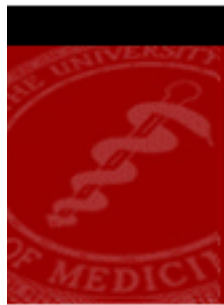
- HMG (human menopausal gonadotropins)

- Equal amounts of FSH and LH
- Urine of post menopausal women
- Recombinant forms available

- Risks:

- Multiple gestation
 - Selective multifetal reduction
- OHSS
- Breast and ovarian cancer
 - No causal relationship
 - Prolonged treatment best avoided





What are my odds trying naturally?

- Monthly chance of pregnancy or "fecundity": **20-25%**
 - 85% of couples will achieve pregnancy after 1 year of trying
 - 15% of couples will have diagnosed infertility
- Monthly chance of pregnancy after 1 year of trying: **3%**

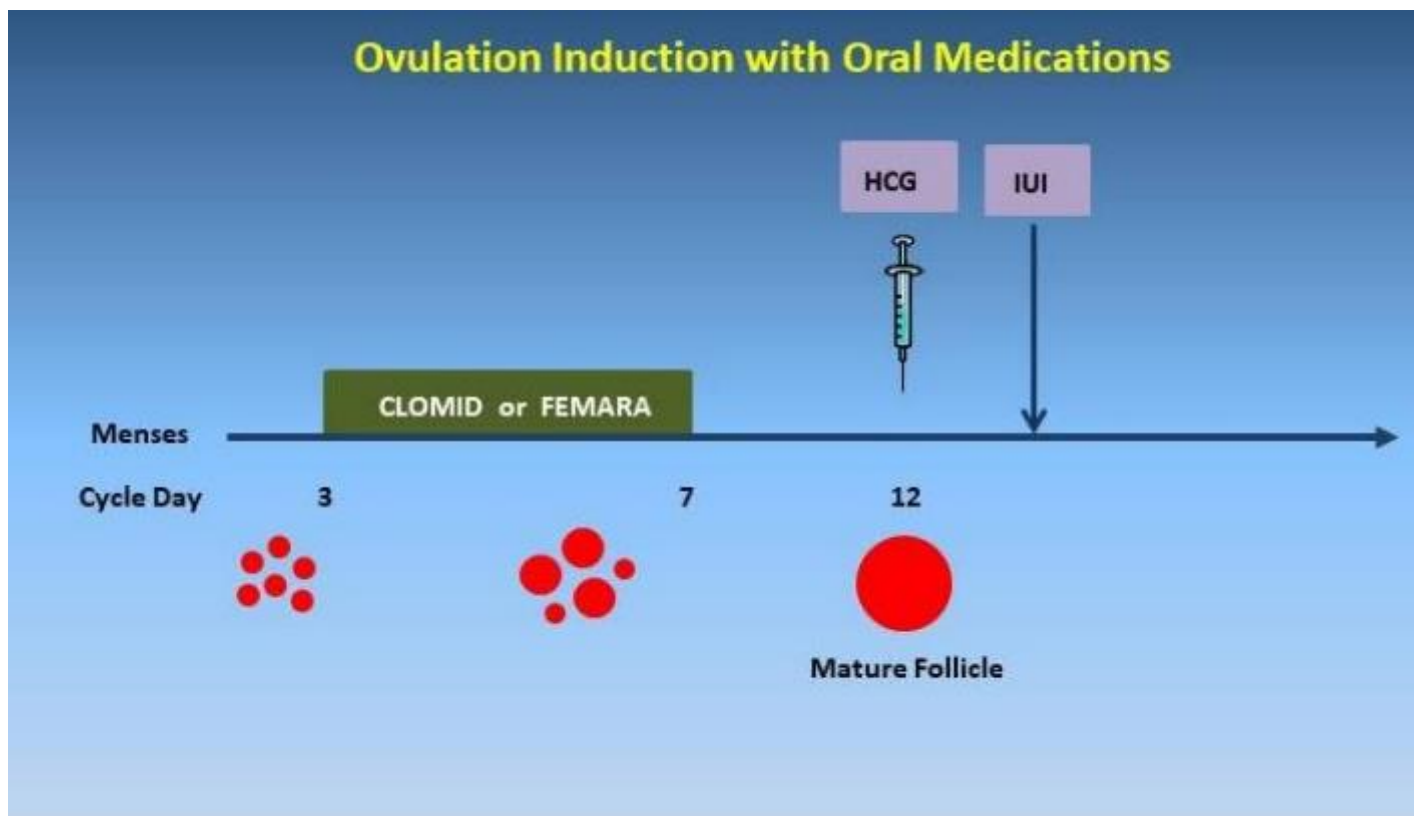
Treating Unexplained Infertility

Method	Success rate	Twin Risk	Cost
"Timed Intercourse"	3% / month	1-2%	0
IUI + Medication (Clomid/Letrozole)	8-10% / cycle 3 cycles: 25-30%	5-10%	+
IVF	60% per transfer (depending on female age / embryo quality / genetic testing / etc.)	2% (transfer ONE embryo at a time)	+++ (depending on insurance)

*all percentages are approximate

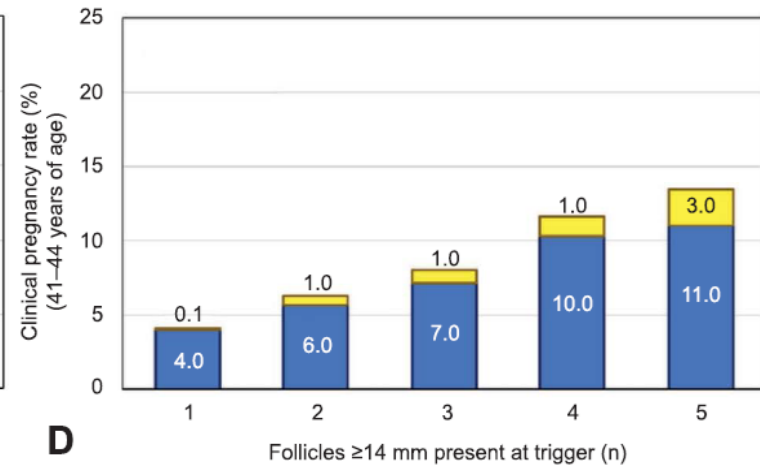
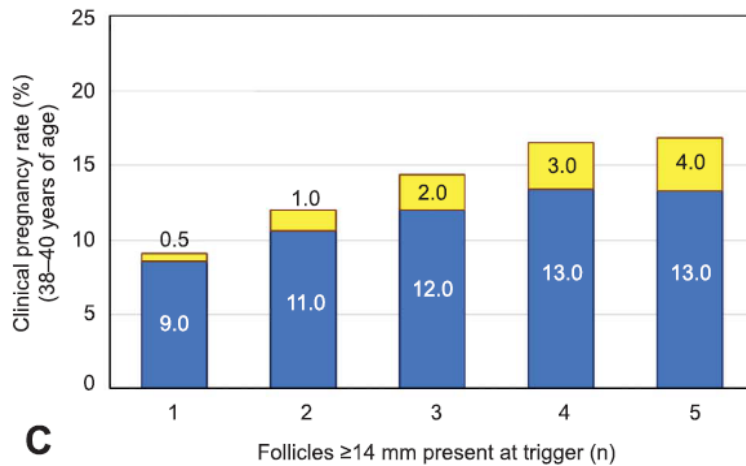
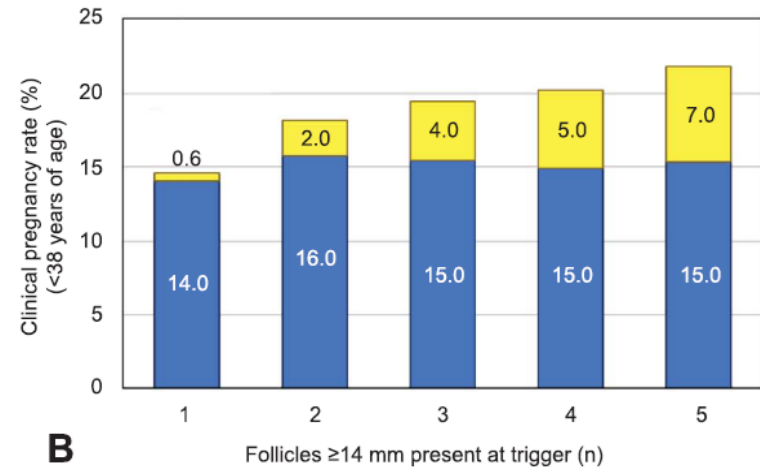
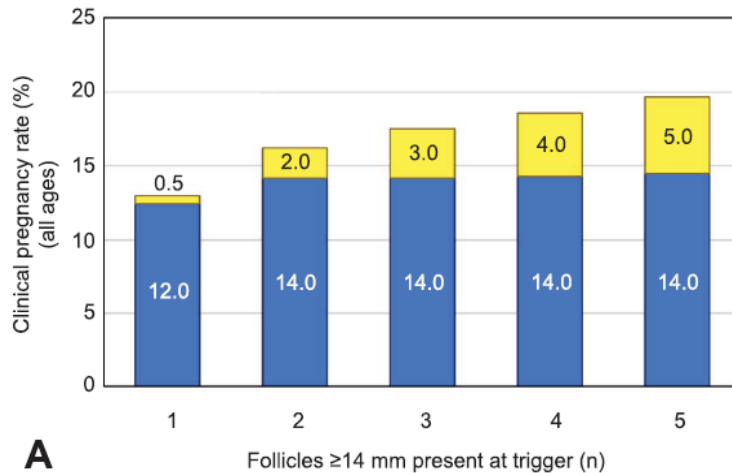


Ovarian Stimulation - Intrauterine Insemination



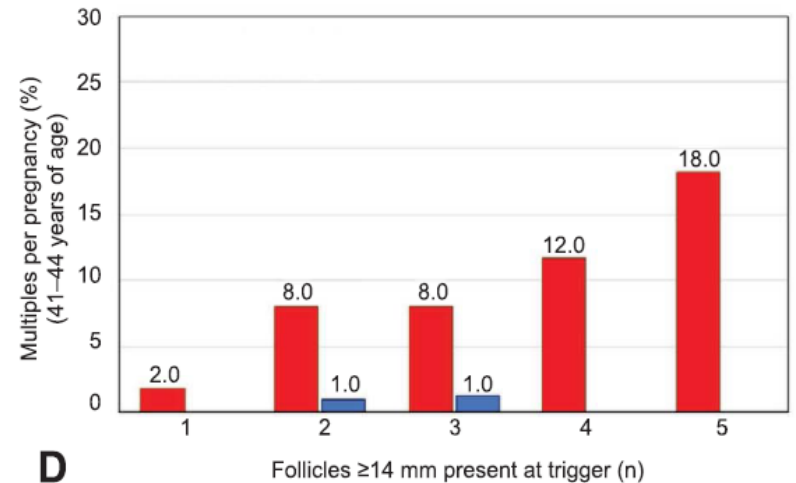
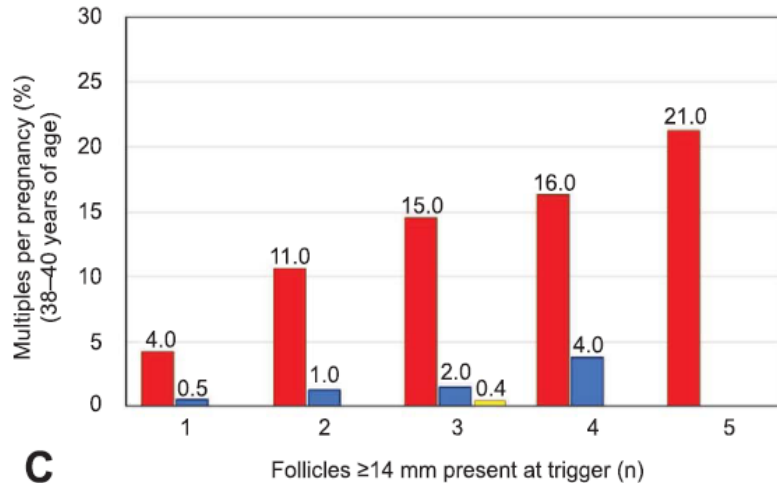
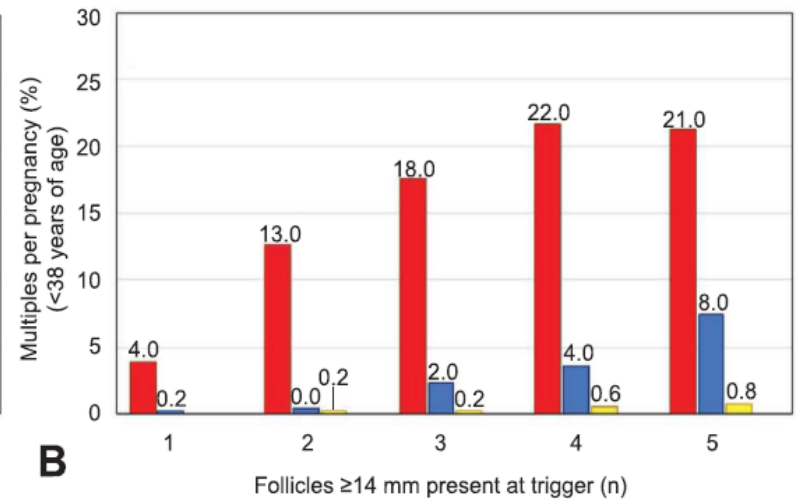
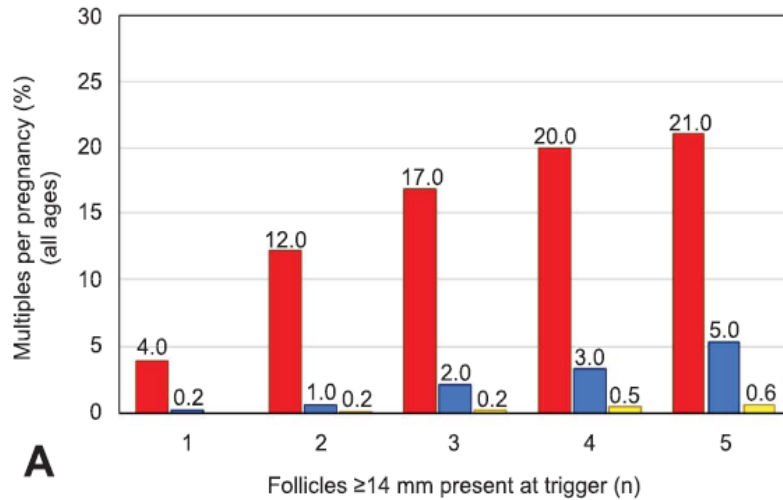


Clinical Pregnancy Rates per IUI Cycle – Age/Follicle



Multiple Singleton

Multiple Pregnancy Risk per Pregnancy

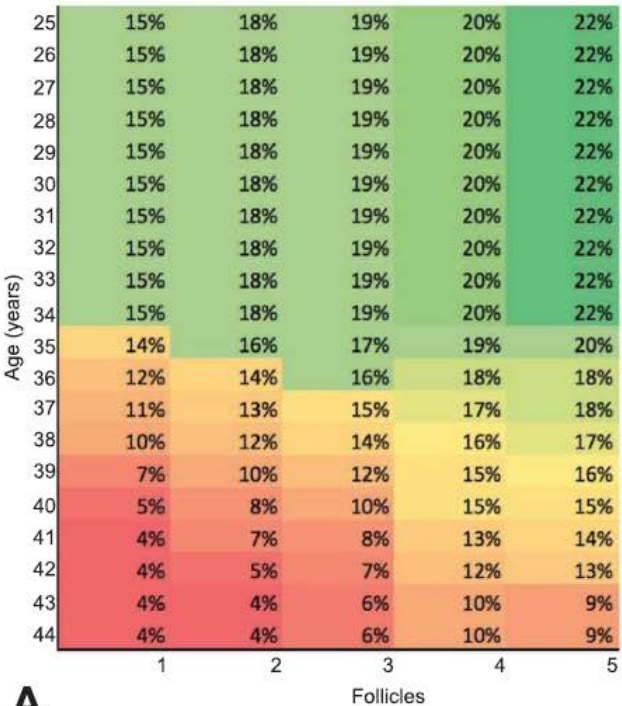


■ Twin ■ Triplet ■ Quadruplet

Heat Map Counseling Tool for Ovarian Stimulation/IUI Cycles



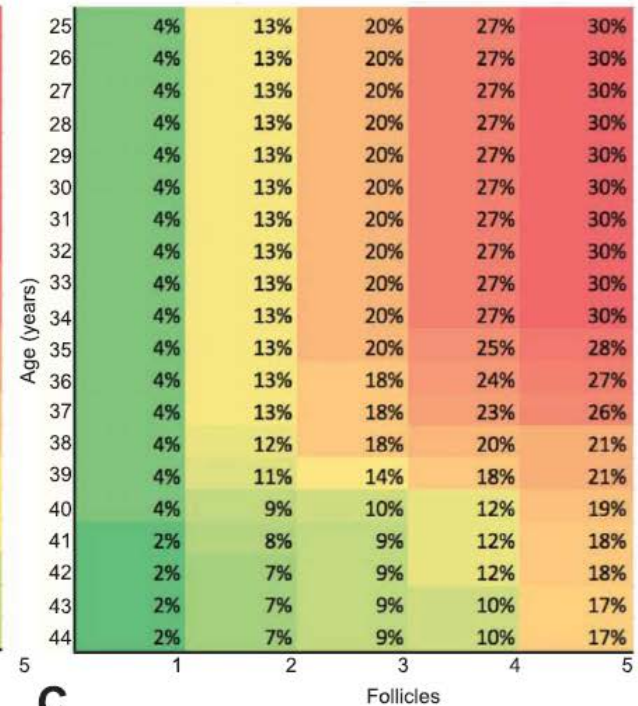
Clinical pregnancy rate



Absolute multiple risk (multiples/IUI)



Relative multiple risk (multiples/clinical pregnancy)



A

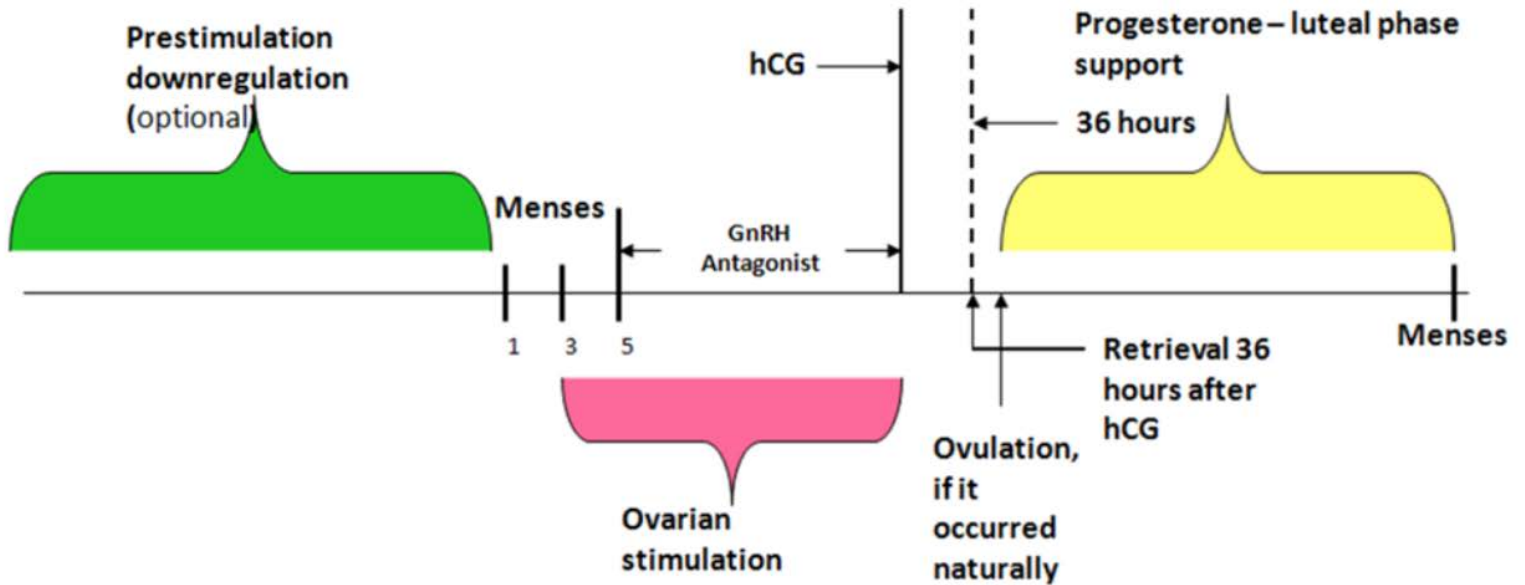
B

C

- Highest success in acquiring a pregnancy or lowest risk of multiple pregnancy
- Moderate pregnancy success or multiple pregnancy risk
- Low pregnancy success or high risk of multiple pregnancy

A GnRH Antagonist Protocol

Example Protocol



Oocyte Retrieval

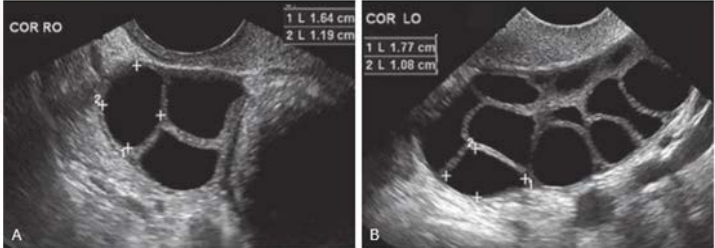
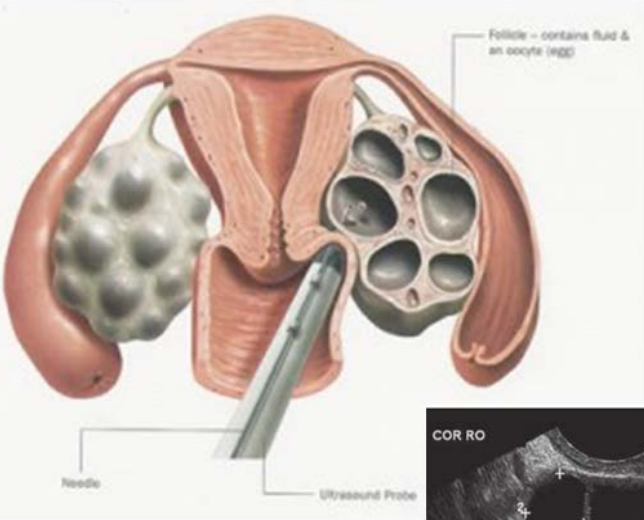
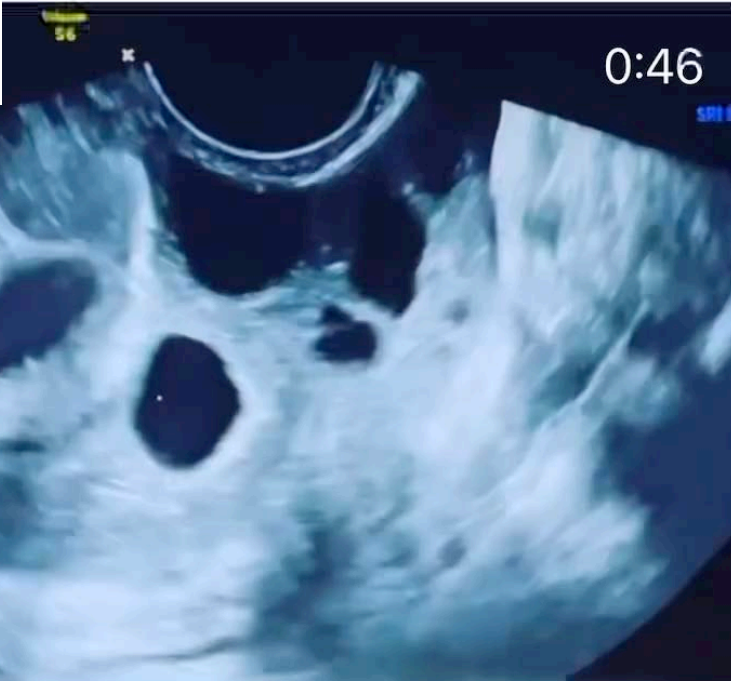
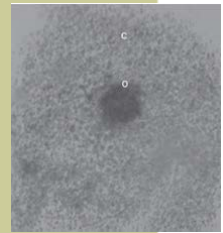


FIG 32-18 Variable appearance of ovaries on follicular monitoring studies. A, Three follicles are shown within the right ovary, measuring up to 16 mm in diameter (calipers). B, In a different patient, undergoing treatment as an egg donor, the follicular monitoring study shows at least 10 follicles within the left ovary, with an average follicle measuring approximately 18 × 11 mm (calipers).



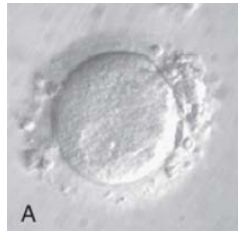


Egg Isolation and Examination

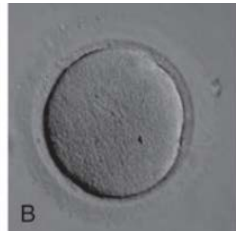


Retrieved Egg
(Cumulus
Oocyte
Complex)

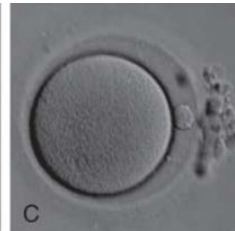
Denudation
for Egg
Freezing or
ICSI



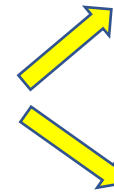
Germinal
Vesicle (GV)



M1 Egg



M2 Egg



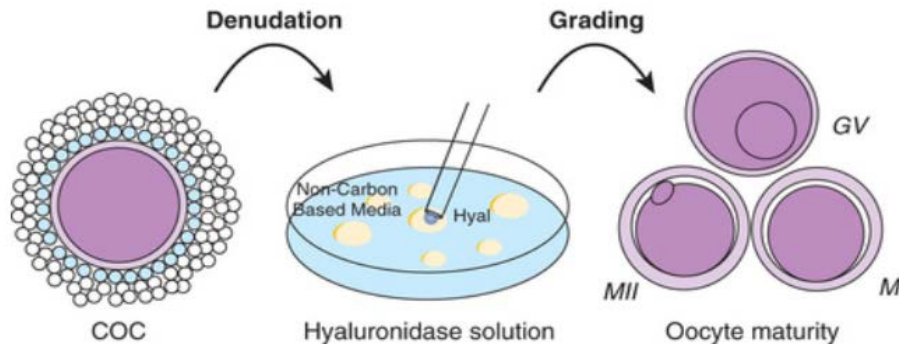
Egg
Freezing



Fertilization
with ICSI



Fertilization with
Conventional
Insemination

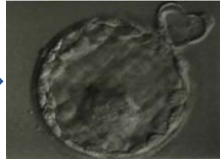
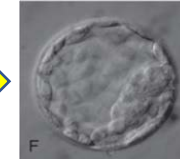
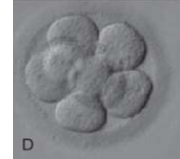
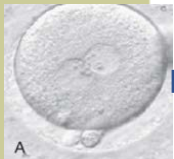




Embryo Development



Day 1



Day 3

Cleavage
Stage
Embryo

Day 5

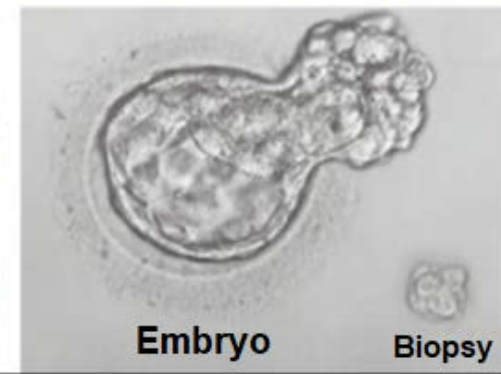
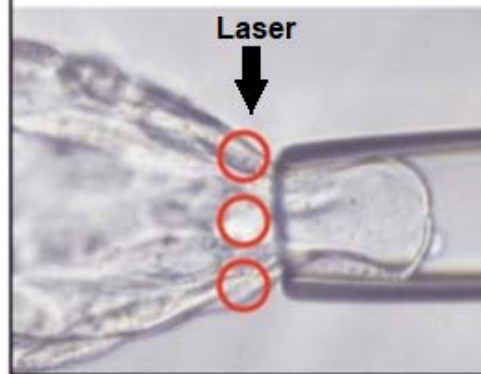
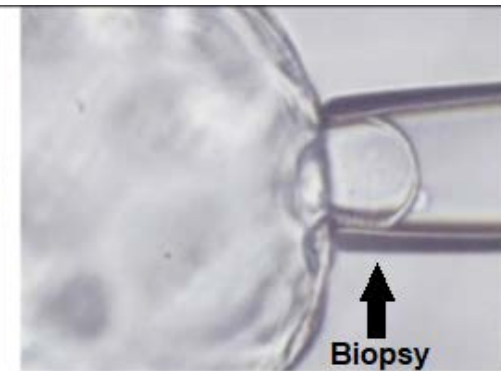
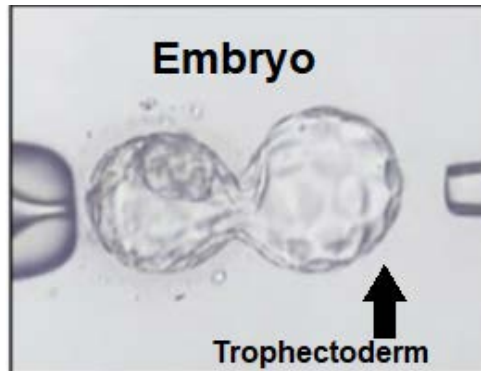
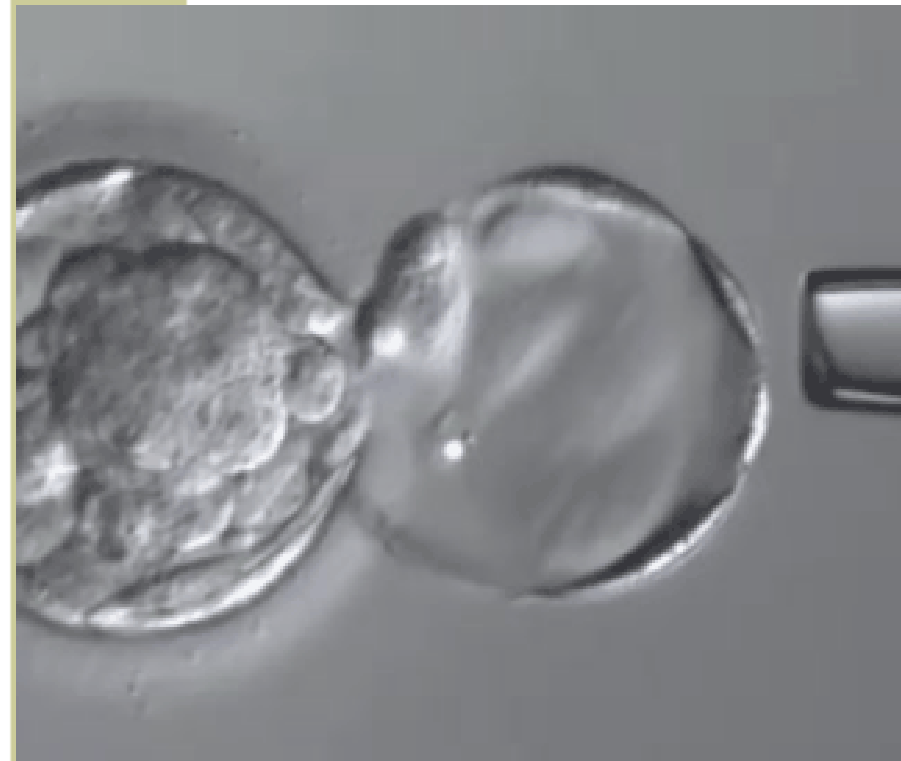
Blastocyst

Hatching
Blastocyst

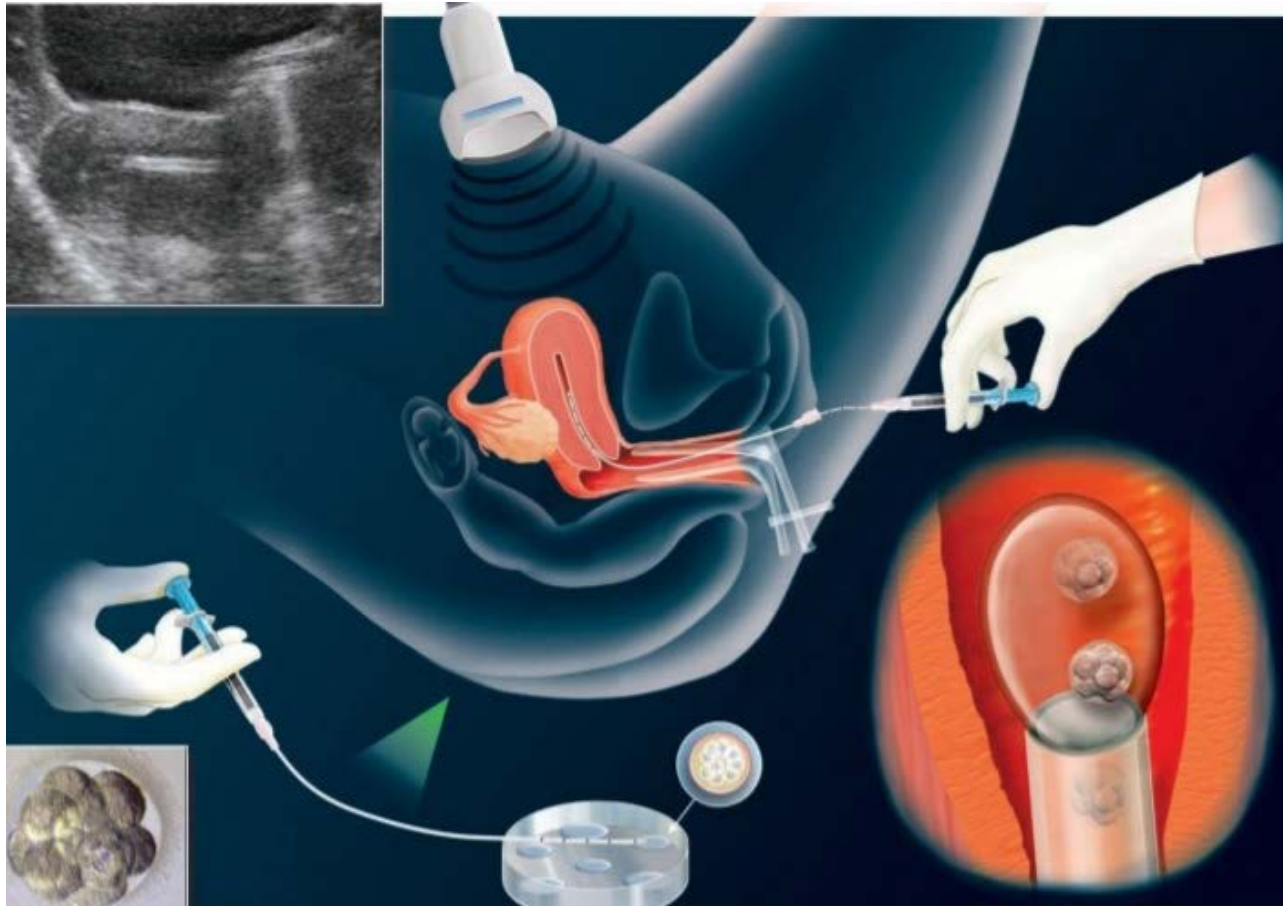
Fertilized
Egg



Embryo Biopsy for PGT-A



Embryo Transfer Procedure





Fibroids and Infertility

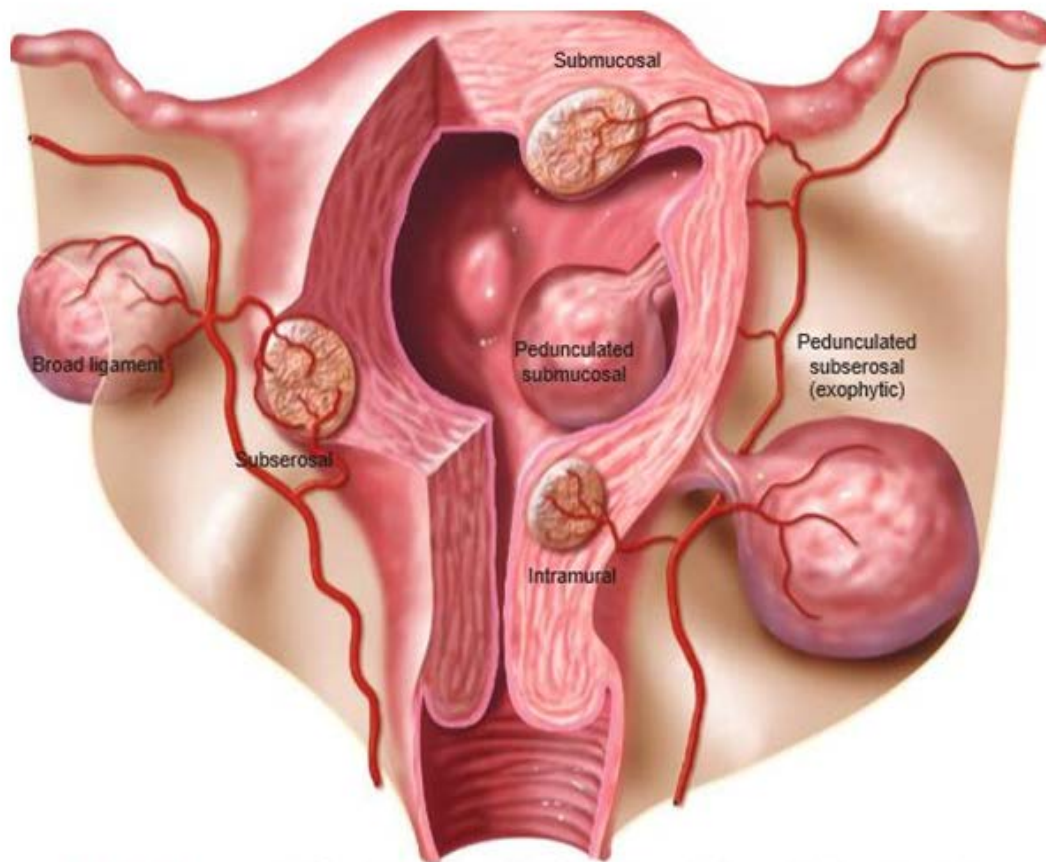
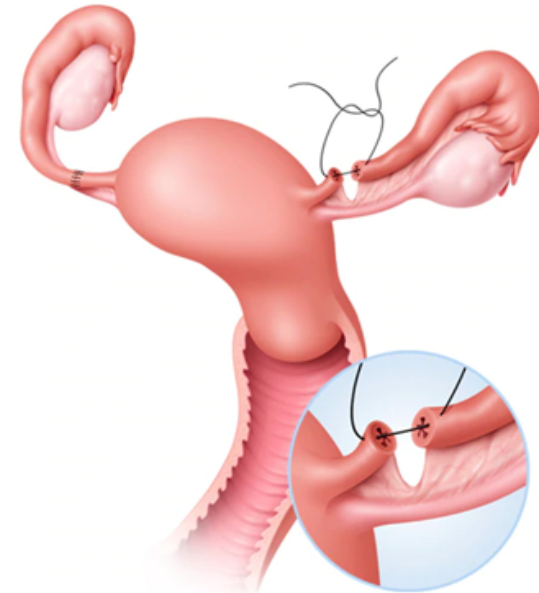


FIG 28-19 Common locations of leiomyomas. (Illustration by James A. Cooper, MD, San Diego, CA.)



Tubal Reversal

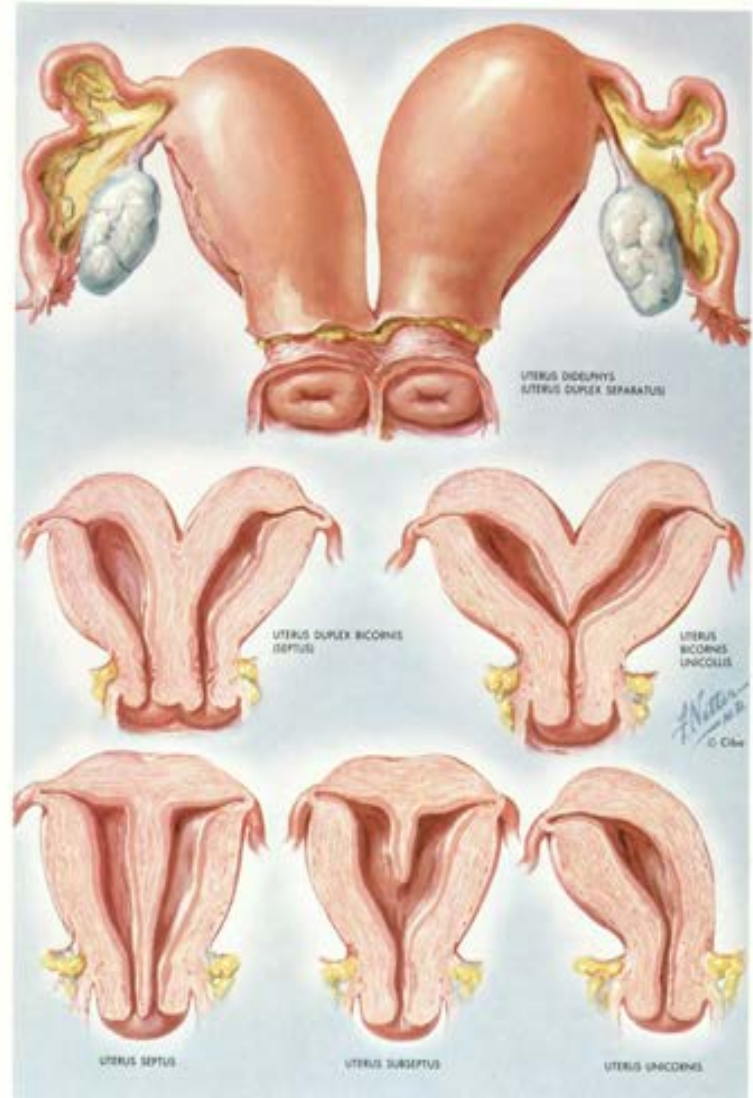
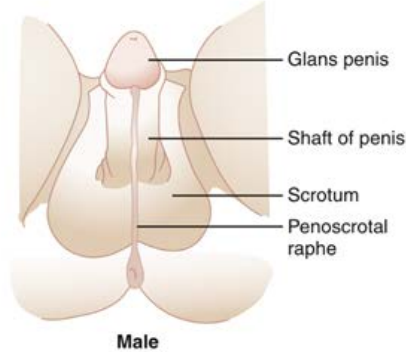
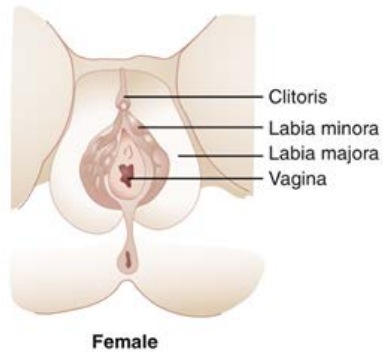
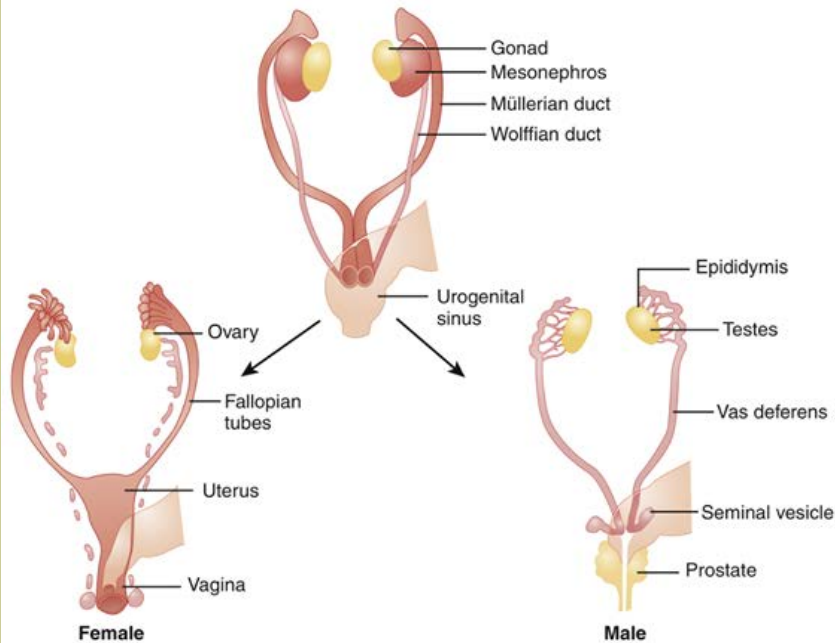
- Success Rates: Clips>Rings>Pomeroy>Cauterization
- Need 4 cm of tube
- 50-75% success rate within 1 year



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Uterine Anomalies





Questions?



**If you're going to question my
credentials as a gynecologist
get the hell out of my office
van.**

