ADVANCED REPRODUCTIVE AGE AND INFERTILITY

Maria Giroux, HBSc, MD

Outline

1. Ovarian reserve
2. Age-related fertility decline
3. Ovarian reserve testing
4. Benefits and risks of advanced maternal age
5. Prevention of age-related fertility decline
6. Management of age-related fertility decline

Tips for presenters [Digital image]. (n.d.). Retrieved from https://ezuce.com/presenter-pc-suggestions/

How old was the oldest mother to conceive naturally? With IVF?

Oldest Mothers

Oldest natural mother

- Dawn Brooke
- Delivered at 59yo
- Delivered 1997, UK

12 Oldest Mothers Who Have Given Birth. (2018, March 16). Retrieved from http://wojournals.com/12-oldest-mothers-who-have-given-birth.html/page11

Guinness World Records. (n.d.). Retrieved from https://en.wikipedia.org/wiki/Guinness_World_Records

Oldest Mothers

Oldest mother with IVF
- Maria del Carmen Bousada Lara
- Delivered at 66 years 358 days old
- IVF in America (she told doctors she was 55yo) after being rejected for IVF in Spain
- Twins delivered in 2006, Barcelona, Spain
- Passed away in 2009

Guinness World Records. (n.d.). Retrieved from https://en.wikipedia.org/wiki/Guinness_World_Records

Maria del Carmen Bousada de Lara. (2018, May 13). Retrieved from https://alchetron.com/Maria-del-Carmen-Bousada-de-Lara

Epidemiology

- Increase in child-bearing age in Canada and worldwide
  - Canada: >50% of births in women >30yo

Upward trend [Digital image]. (n.d.). Retrieved from https://pngtree.com/freepng/upward-trend_1028204.html

Average age of 1st child
- 1970: 23.7
- 2011: 28.5

% 1st time mothers >30
- >30yo
 - 1987: 11%
  - 2005: 26%
- >35yo
  - 1987: 4%
  - 2005: 11%
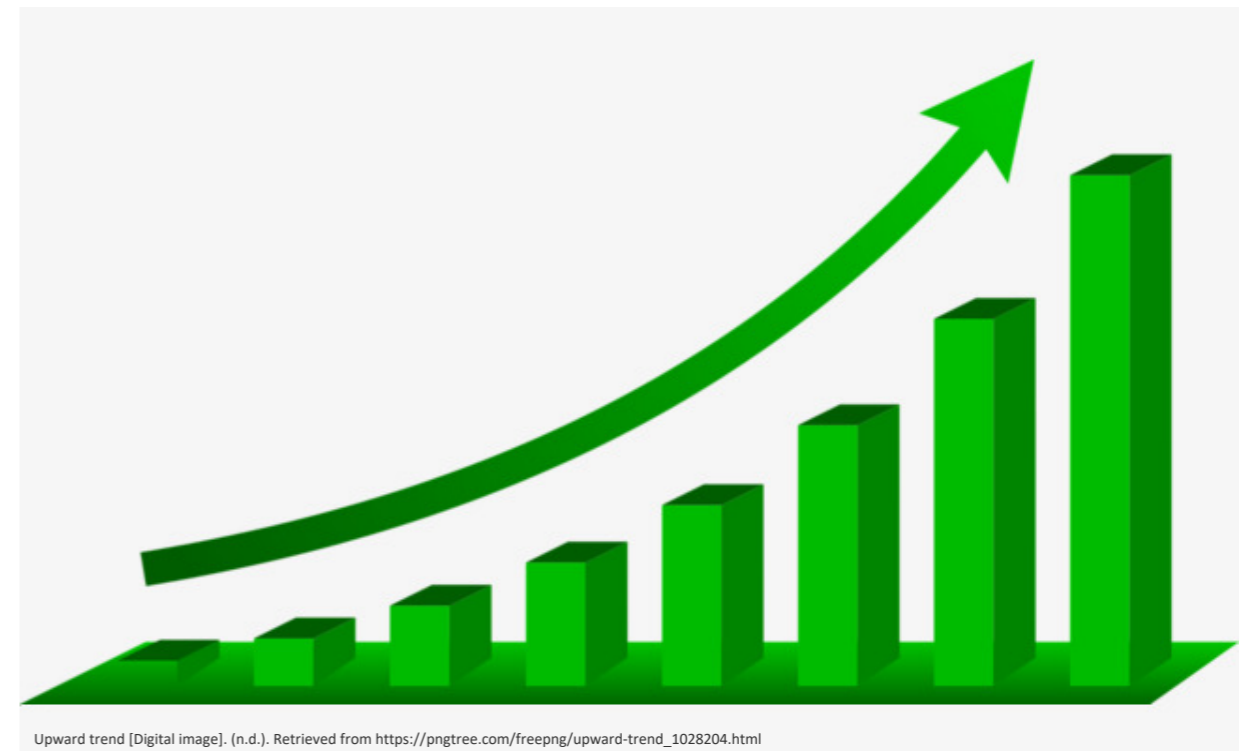
Reasons for the trend:
- **Improved contraceptive methods**
- **Social changes**: economic, professional, educational, personal changes
- **Increased options for fertility treatment and ART**

Ovarian Reserve

- Ovarian function decreases with age
  - Decreased quantity and quality of oocytes
- **20w:** highest number of oocytes (6-7mil)
- Then ovarian follicular pool decreases
- **At birth:** 1-2mil
- **Puberty:** 300,000-500,000
- **Reproductive years**
  - Most oocytes are lost via apoptosis
  - **Only 400-500 oocytes are ovulated**
  - Same rate of loss until menopause
- **Menopause:** few hundred oocytes left
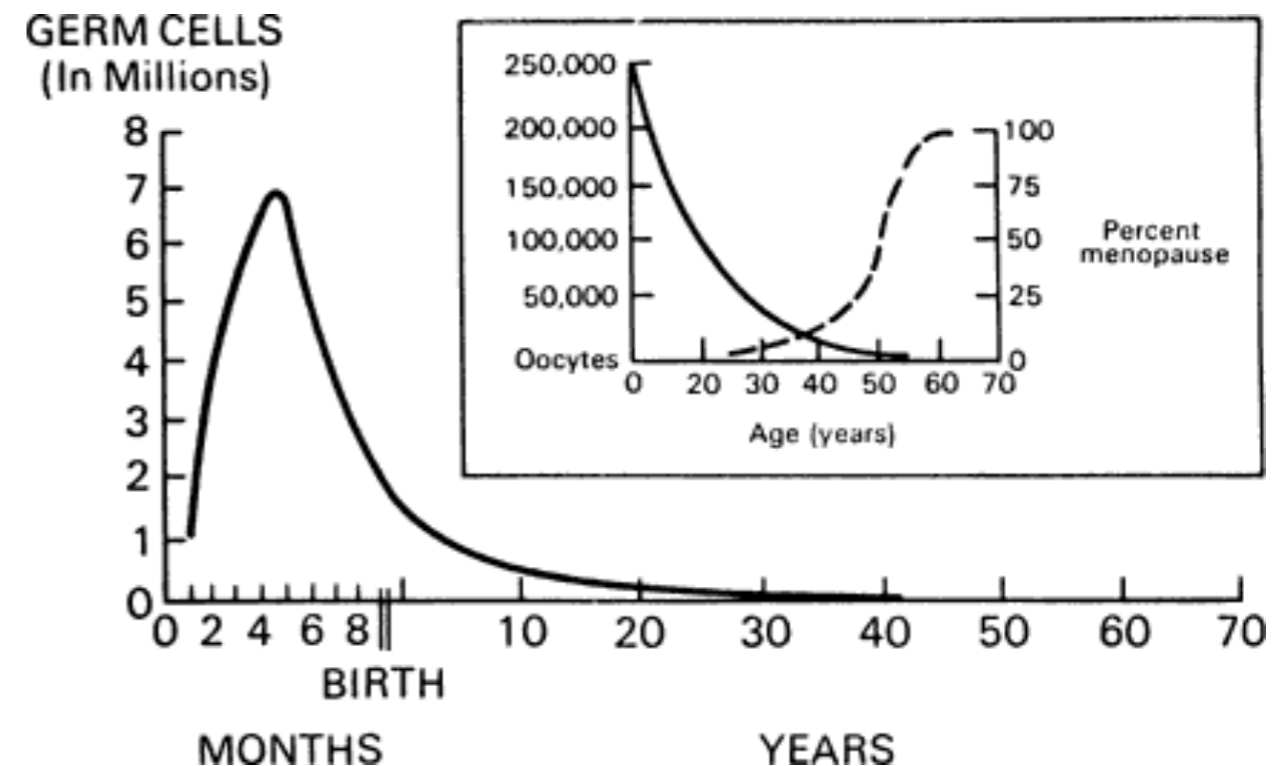
Mattison, D. (1980). Relationship between the number of oocytes and age. Inset shows the relationship of oocyte number, age, and menopause [Digital image]. Retrieved from https://www.glowm.com/resources/glowm/cd/pages/v5/ch088/framesets/001f.html
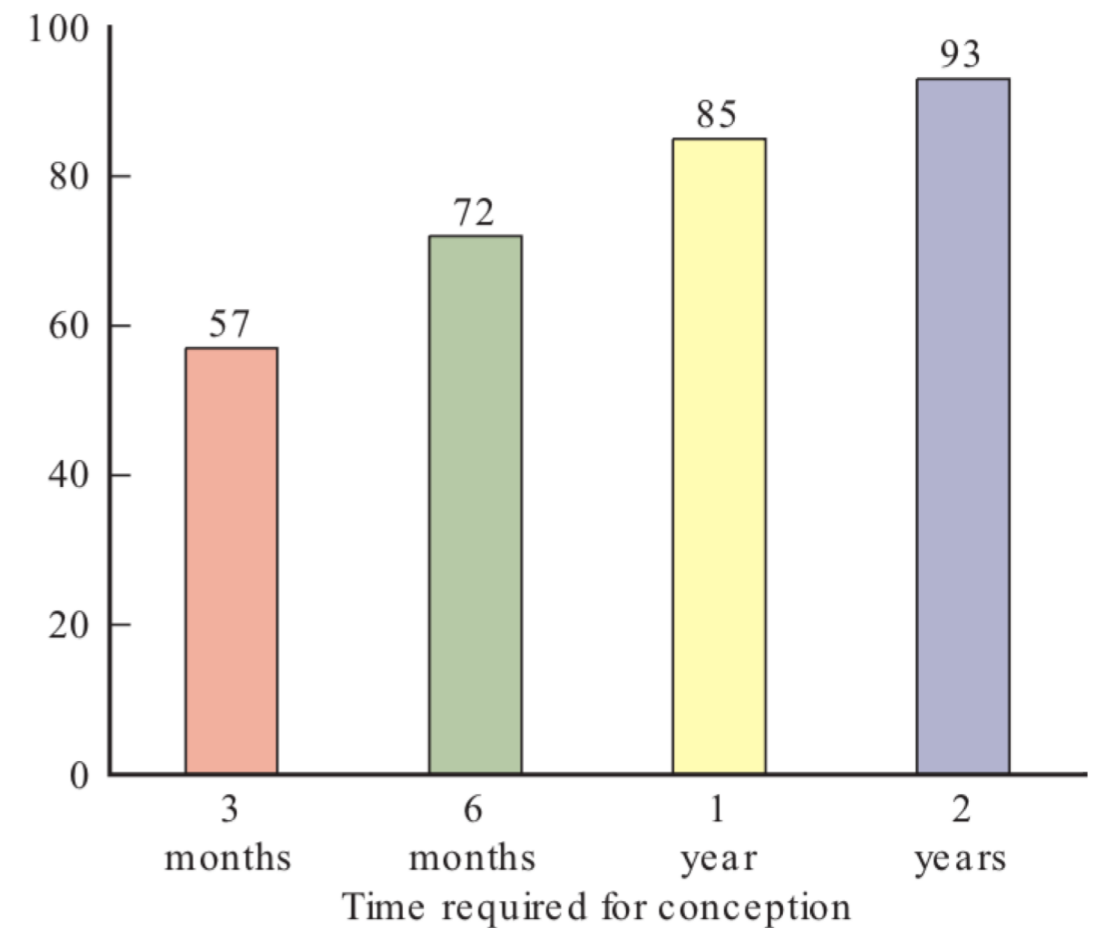
Definitions

- **Infertility-** no pregnancy after 1 year of regular unprotected intercourse
- **Primary infertility-** no previous pregnancies
- **Secondary infertility-** infertility after at least 1 previous pregnancy

Fecundability

- **Fecundability-** ability to conceive
  - 1 month: 20-25%
  - 3 months: 50%
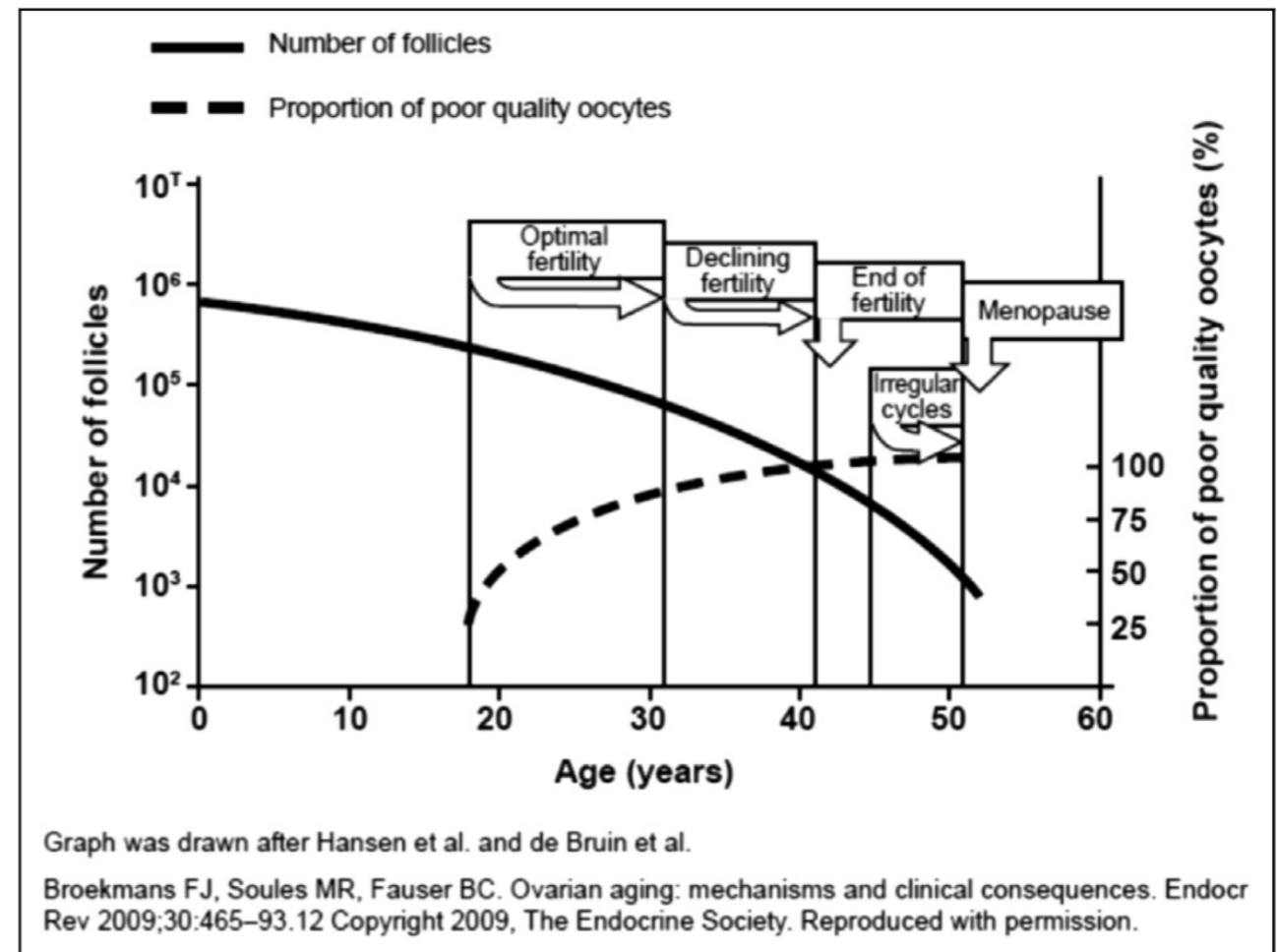 - 6 months: 75%
  - 1 year: 85%
  - 2 years: 93%

FIGURE 19-1 Time required for conception.

Hoffman, B., Schorge J., Bradshaw K., Halvorson L., Schaffer J., Corton M. (2016). William's gynecology. 3rd ed. New York. McGraw-Hill Education.
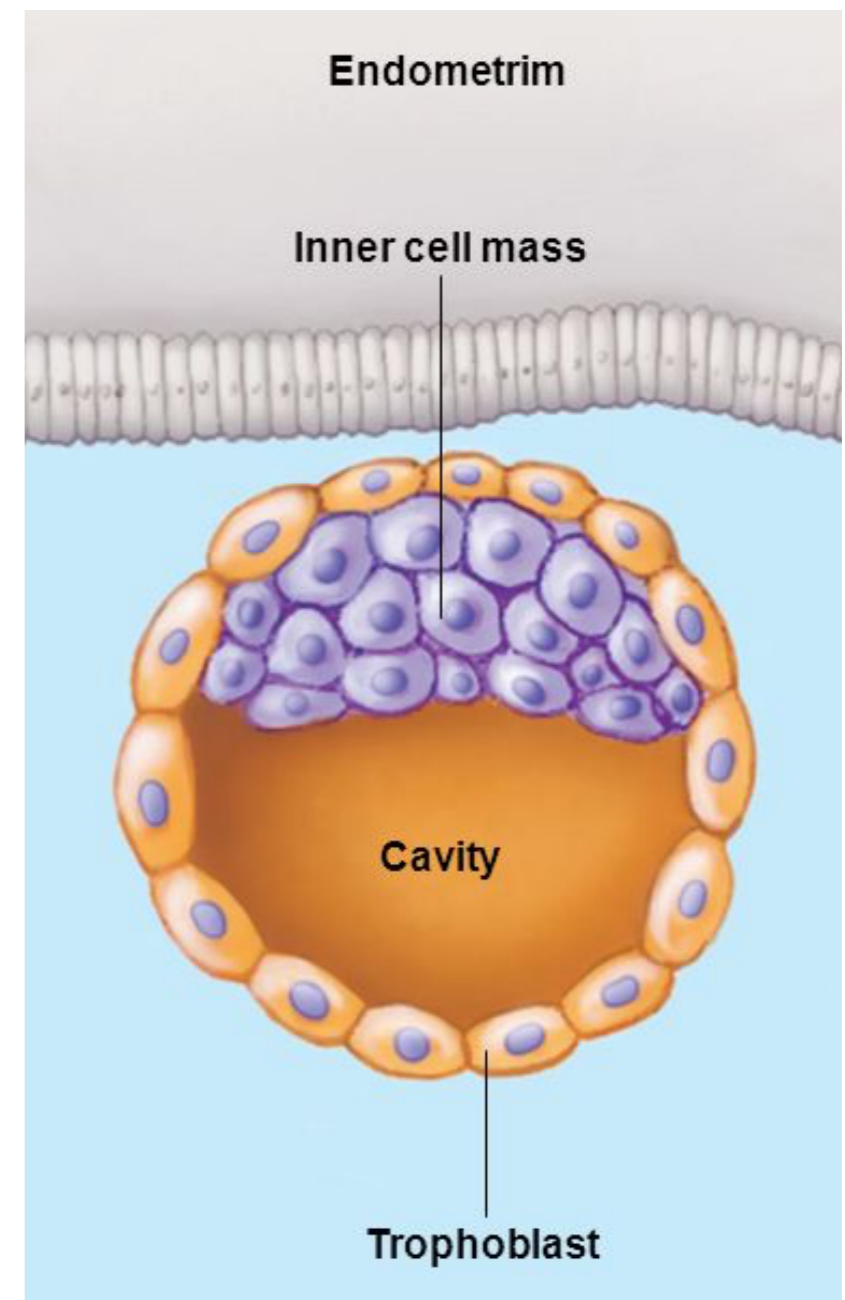
Age-Related Fertility Decline

- Decreased fertility with age due to decrease in oocyte quantity and quality
- As age of female increases
  - **It takes longer to conceive**
  - **↑ infertility and sterility**

Graph was drawn after Hansen et al. and de Bruin et al.

Broekmans FJ, Soules MR, Fauser BC. Ovarian aging: mechanisms and clinical consequences. Endocr Rev 2009;30:465–93.12 Copyright 2009, The Endocrine Society. Reproduced with permission.

Endometrium

- **Age does not affect how endometrium responds to hormones**
- Endometrium can maintain pregnancy throughout and beyond reproductive years
  - Age of patient using egg donor does not affect pregnancy rate

Campbell, Reece, Taylor, & Simon. (n.d.). [Digital image]. Retrieved from https://slideplayer.com/slide/4404381/

Age-Related Fertility Decline

- Average age of last child: 41yo
  - Range: 23-51yo
- Women who conceive >35yo may be biologically younger
  - Longer telomere length in women who are pregnant >35yo than women who do not become pregnant

SOGC guideline risk of infertility:
- 20-24yo: 6%
- 30-34yo: 16%
- 40-44yo: 64%

Hutterite population:
- 34yo: 11%
- 40yo: 33%
- 45yo: 87%

TABLE 19-6.	Female Aging and Infertility
Female Age (years)	**Infertility**
20–29	8.0%
30–34	14.6%
35–39	21.9%
40–44	28.7%

Hoffman, B., Schorge J., Bradshaw K., Halvorson L., Schaffer J., Corton M. (2016). William's gynecology. 3rd ed. New York. McGraw-Hill Education.

Timeline of Age-Related Fertility Decline

Consistent despite age of menopause:

- **Asymptomatic decrease in fecundity**
  - ↓ total # of remaining follicles
    - Usually occurs 35-40yo
  - Pt may have **regular cycles and continue to ovulate** → no clinical signs/symptoms of ovarian aging
    - Pts may present with infertility
  - Investigate with markers of ovarian reserve to assess for pt's fertility potential and ovarian aging

Timeline of Age-Related Fertility Decline

- **Sterility: child-bearing typically stops 10yrs prior to menopause**
  - Sterile before complete cessation of menses
- **Cycles become irregular 6-7yrs before menopause** (about 10,000 follicles remaining)
  - Cycles become shorter, then lengthen and become irregular
- **Menopause: complete cessation of menses >12m**
  - Ovarian estrogen and progesterone production continues for 1st year after menopause
  - **Premature ovarian failure-** cessation of menses <40yo
  - **Note Fx of age of menopause!**

OVARIAN RESERVE TESTING

Ovarian Reserve Testing

- Not a screening tool
- Pts may have ovarian reserve inconsistent with chronological age
    - Sooner than average decline in fertility or good ovarian function at an older age

Consider in:
- >35yo to assess for age-related infertility
- <35yo and RF for decreased ovarian reserve
    - Single ovary
    - Hx ovarian surgery
    - Poor response to FSH
    - Hx exposure to chemo/radiation
    - Unexplained infertility
    - Unexplained change in menstrual cyclicity
    - Fx early menopause

Ovarian Reserve Testing

- May be done prior to ART
- Used to predict **egg quantity, ovarian response to stimulation, prognosis** with fertility treatments and IVF
- **Not for predicting pregnancy rates** in pts <35yo
    - Not used to predict oocyte quality, infertility, time to infertility
- Results are used for counselling and to assist with decision-making

What are the markers of ovarian reserve testing?

Brain Thinking Clipart [Digital image]. (n.d.). Retrieved from
https://www.clipartmax.com/middle/m2i8i8H7N4d3Z5K9_clipart-of-brain-thinking-black-and-white/

Ovarian Reserve Testing

Markers for decreased ovarian reserve:
- **Day 3 FSH, estradiol**
  - **↑ FSH is the 1st sign of declining ovarian function that can be detected**
  - FSH can be drawn days 2-5
  - **↑ FSH (>14 IU/L) and ↓ estradiol (60-80 pg/ml)** in DOR, POF, and menopause
- **↓ Serum Antimullerian hormone (AMH)**
- **↓ Ovarian TVUS for antral follicle count (AFC)**
  - In early follicular phase measure AFC
    - Better prognostic factor than basal FSH for ovarian stimulation
  - Also perform endometrial assessment

- No longer used:
  - luteal phase endometrial biopsy
  - Inhibin B
  - +/- clomiphene citrate challenge test (CCCT)
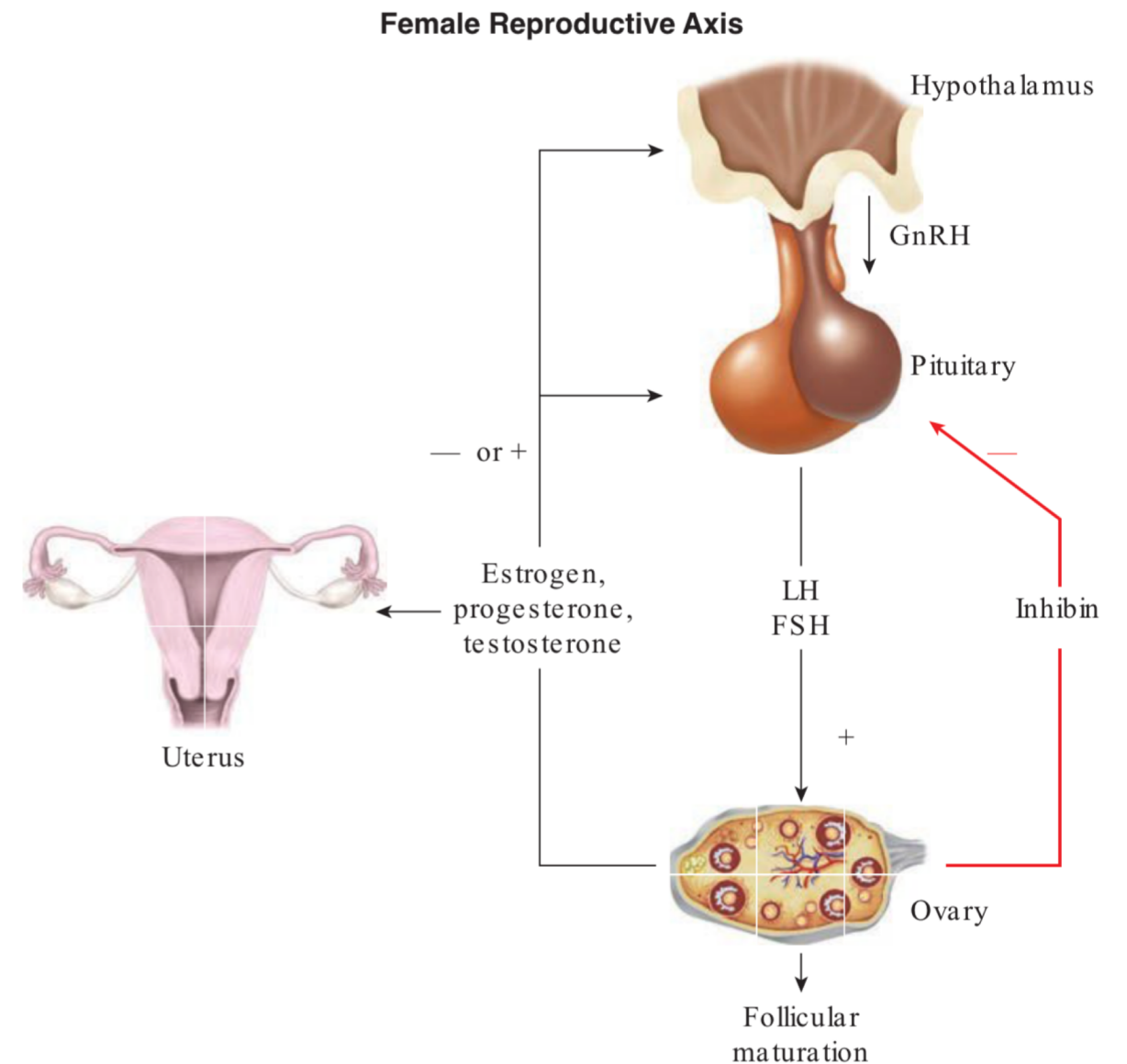   - No benefit over day 3 FSH or AFC

Day 3 FSH

- Aka basal FSH level
- **↑ FSH (>14 IU/L) is the 1st sign of declining ovarian function that can be detected**
  - FSH varies from cycle to cycle, but if consistently elevated, then poor prognosis for fertility
  - If extremely elevated, can be used to predict poor response to ovarian stimulation and no pregnancy
    - Issue: only fraction of pts will have very high levels
    - Less predictive of pregnancy in <35yo
  - False+: 5%

Hypothalamic-Pituitary-Ovarian Axis

Normal Reproductive Years:

- **Hypothalamus:** GnRH neurons produce GnRH in a **pulsatile fashion**
- **Anterior pituitary gland:** GnRH binds to gonadotropic cells of anterior pituitary gland → stimulates **pulsatile** release of glycoprotein **gonadotropins** (LH, FSH) into peripheral circulation

Female Reproductive Axis

Hypothalamus

GnRH

Pituitary

— or +

Estrogen, progesterone, testosterone

LH
FSH

Inhibin

Uterus

Ovary

Follicular maturation

Hoffman, B., Schorge J., Bradshaw K., Halvorson L., Schaffer J., Corton M. (2016). William's gynecology. 3rd ed. New York. McGraw-Hill Education.

Hypothalamic-Pituitary-Ovarian Axis

Normal Reproductive Years:

- **Ovaries:** LH and FSH bind to theca and granulosa cells, stimulate
    - Production of **sex steroid hormones** (estrogen, progesterone, androgens)
        - Important to prepare endometrium for implantation
    - Production of **gonadal peptides** (activin, inhibin, follistatin), GF
   - **Folliculogenesis** (follicular development)
    - **Ovulation**
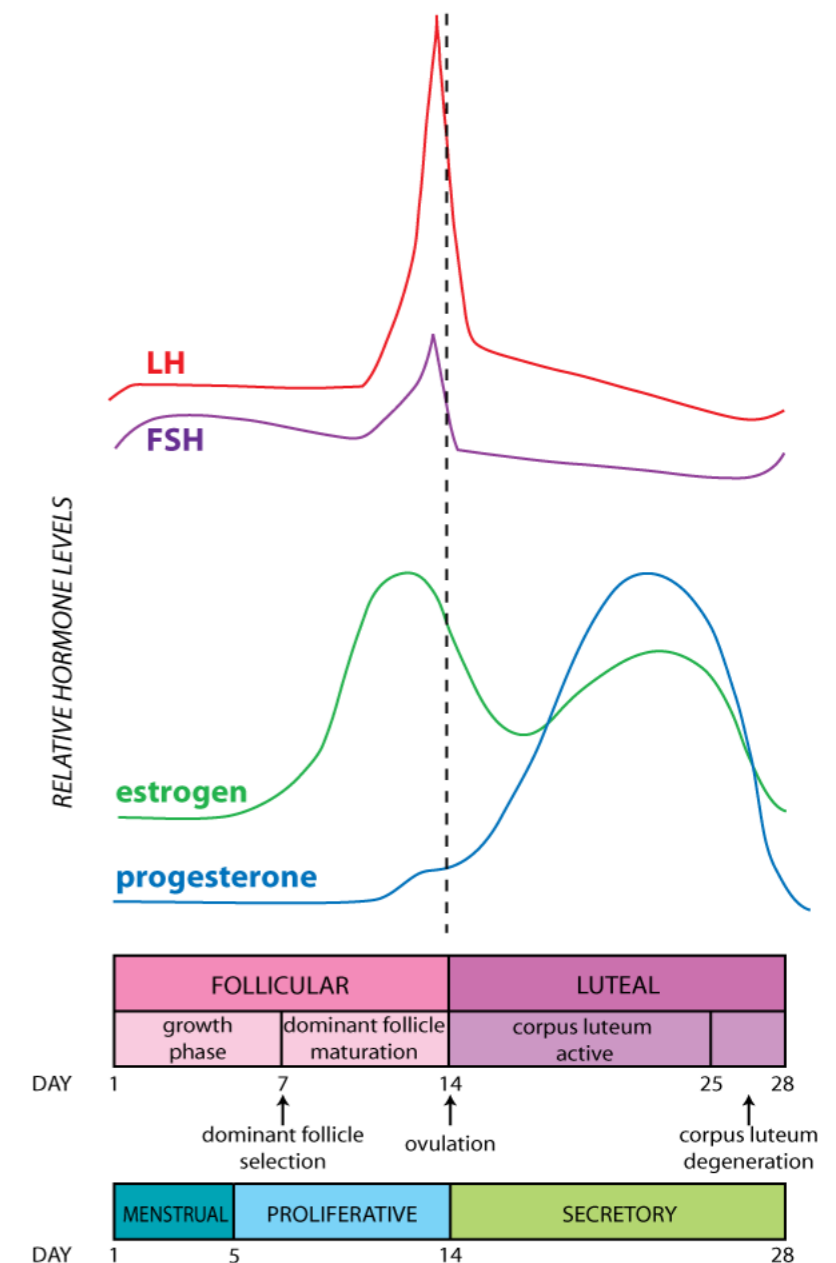
Female cycle [Digital image]. (n.d.). Retrieved from
https://www.google.com/url?sa=i&rct=j&q=&esrc=s&source=images&cd=&cad=rja&uact=8&ved=2ahUKEwjzq8H319rfAhWG34MK
HQ2FCxUQjhx6BAgBEAM&url=https://courses.washington.edu/conj/bess/female/female.html&psig=AOvVaw0tXct8kaP0MHlhS7e3
j3OR&ust=1546916676280615

Hypothalamic-Pituitary-Ovarian Axis

Normal Reproductive Years:

- Estrogen and progesterone and inhibin B cause
  - **Negative feedback** to **hypothalamus** and **pituitary gland** → decrease GnRH production → decrease FSH
  - Increased GnRH and LH/FSH secretion at midcycle surge
 - Prepare endometrium for placental implantation if pregnancy occurs
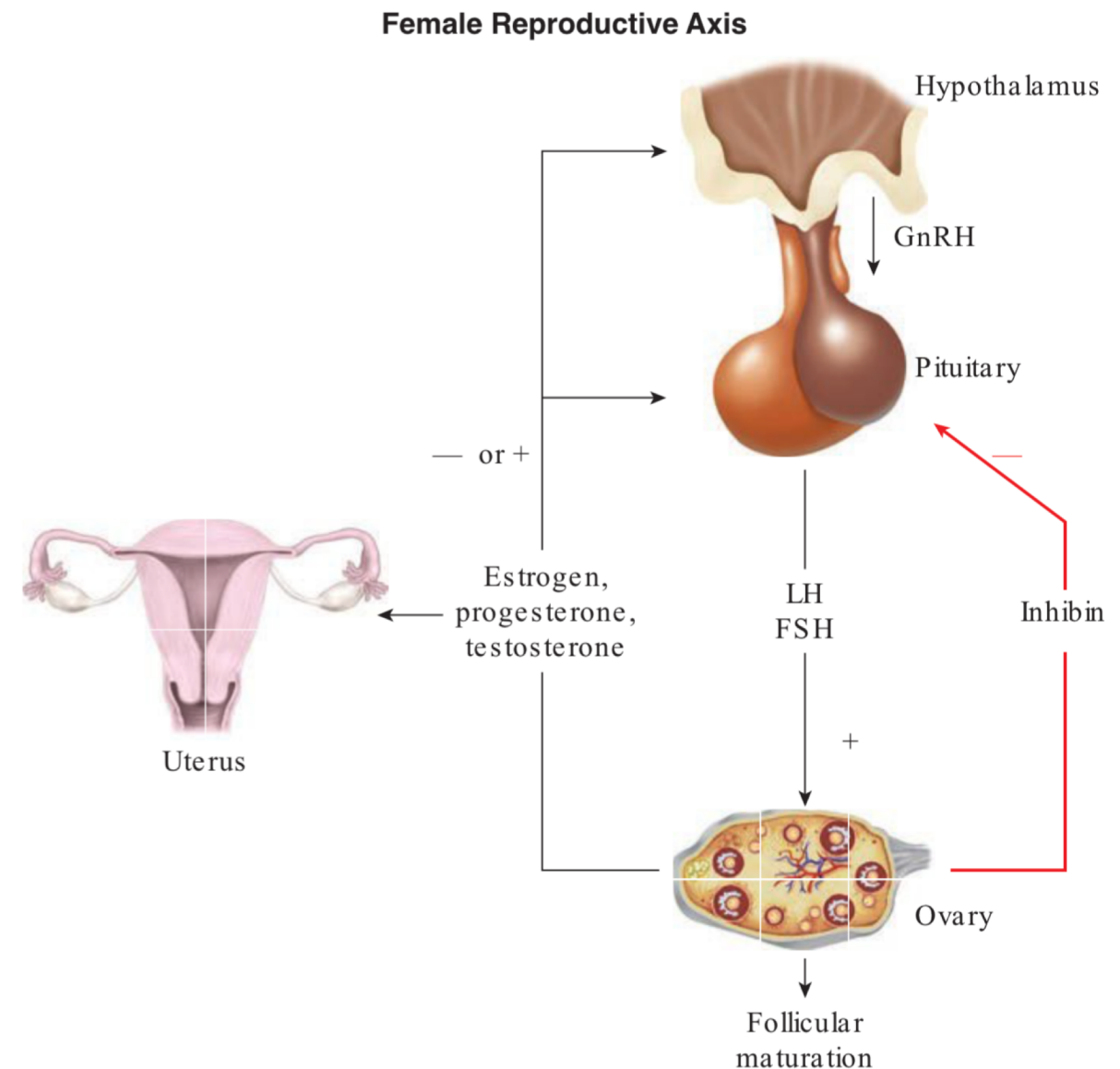
Female Reproductive Axis

Hoffman, B., Schorge J., Bradshaw K., Halvorson L., Schaffer J., Corton M. (2016). William's gynecology. 3rd ed. New York. McGraw-Hill Education.

Day 3 FSH

Perimenopause- ↑ FSH :

- Rapid loss of ovarian follicles→ ↓ inhibin B production by granulosa cells in follicular phase→ open negative-feedback loop
  - ↑ GnRH→ ↑ **FSH in early follicular phase** (4 times higher than reproductive years) → ↑ ovarian follicular response → ↑ estrogen (initially) → negative feedback to ↓ FSH
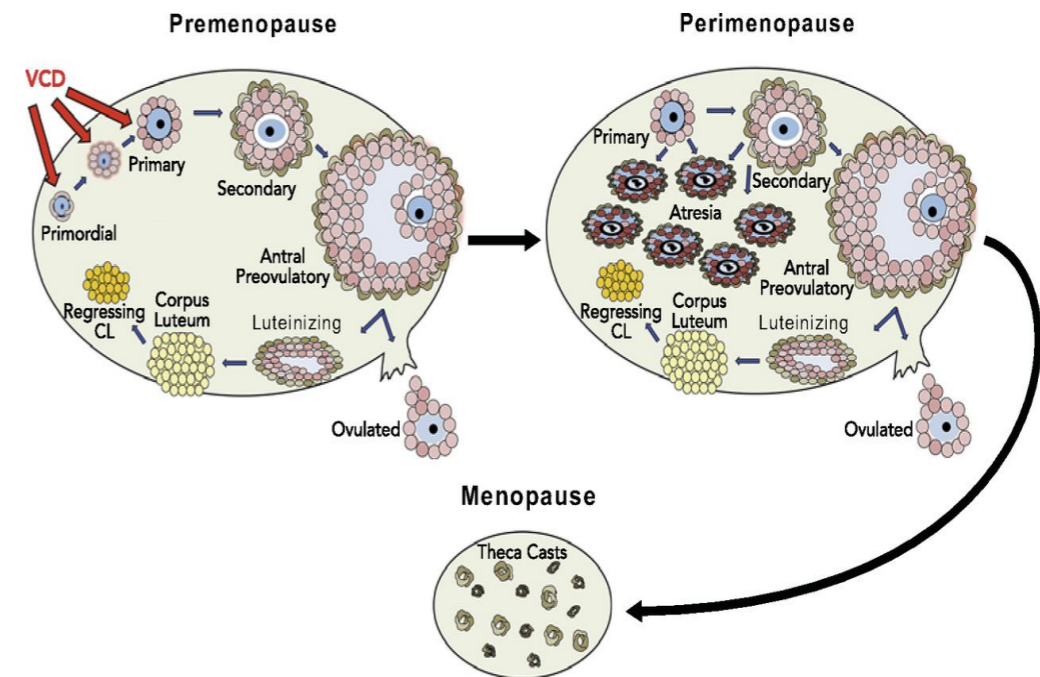
Brooks, H., Pollow, D., & Hoyer, P. (2016, June 1). Ovarian follicular development and VCD action on primordial and primary follicular populations [Digital image]. Retrieved from http://physiologyonline.physiology.org/content/31/4/250
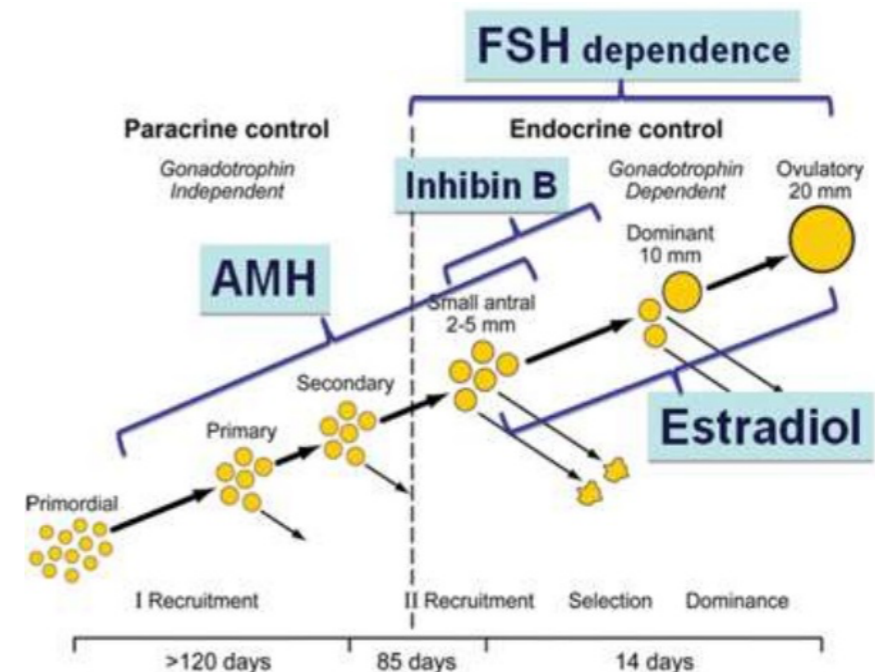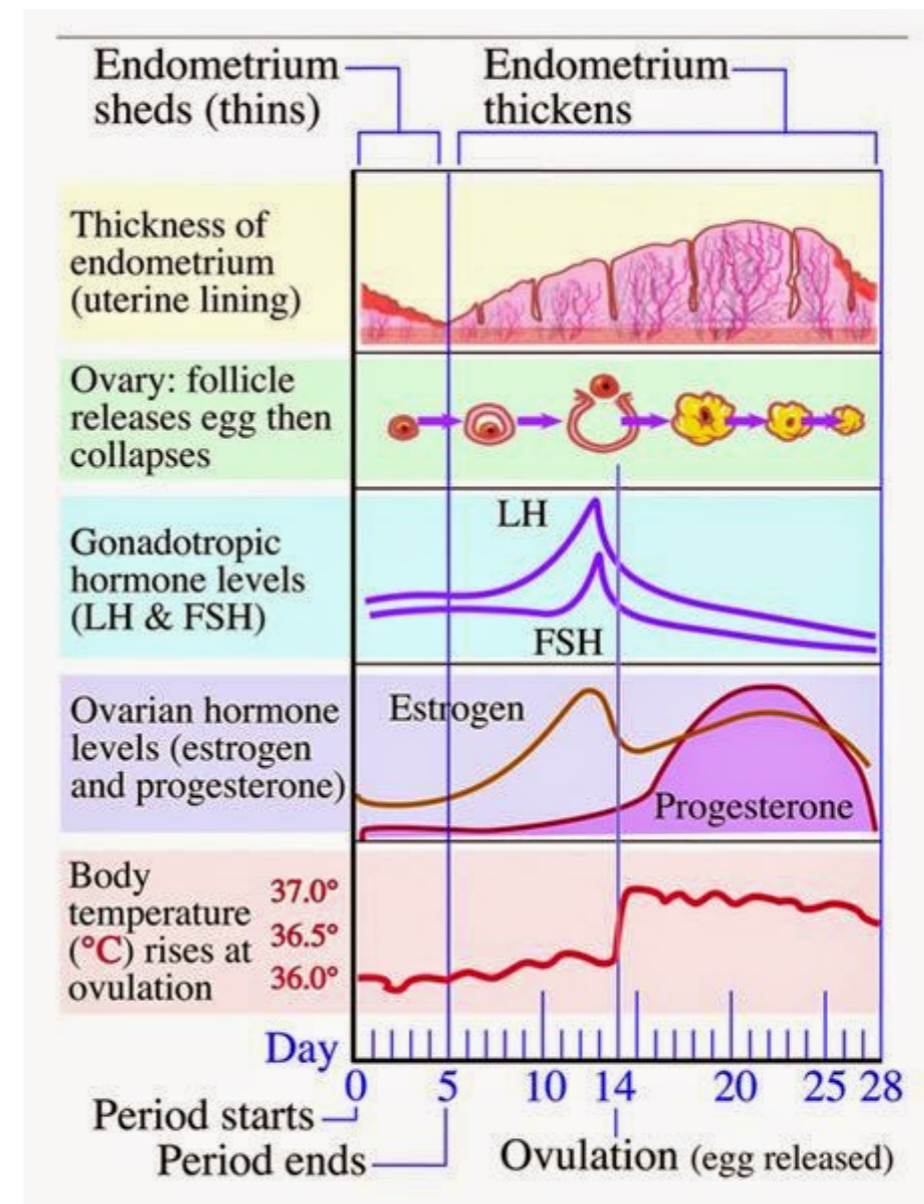

Smith, D. (2015, January 21). Ovarian reserve and infertility [Digital image]. Retrieved from https://www.slideshare.net/drangelosmith/ovarian-reserve-and-infertility
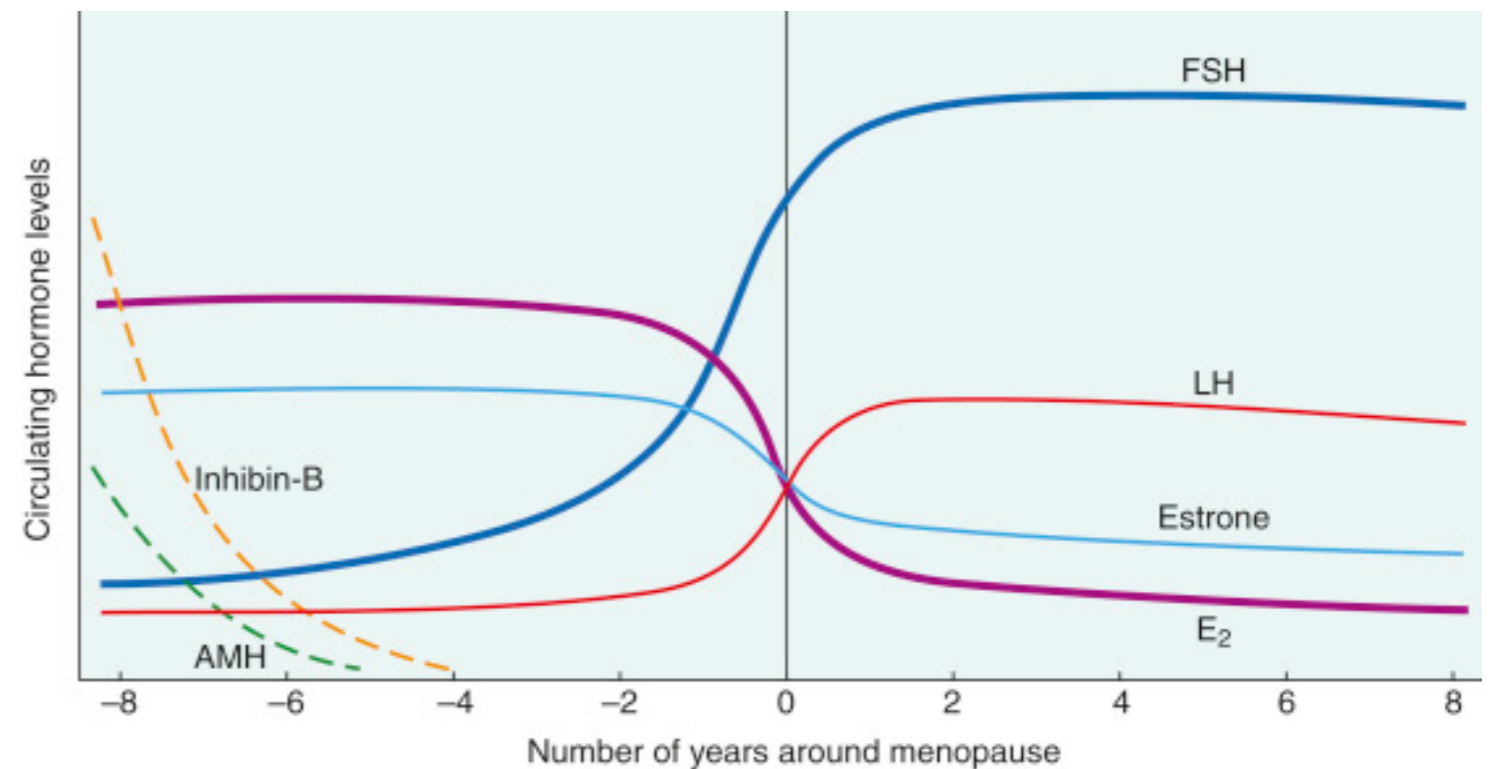
Day 3 Estradiol

- Used to confirm correct timing within the menstrual cycle
- Estradiol is low on day 3
- If estradiol is high, then can negatively inhibits FSH production → falsely suppresses FSH levels

[Digital image]. (2015, May 22). Retrieved from http://sleepyheadcentral.blogspot.com/2015/05/women-sleep-hormones-how-could-you.html

FSH and Estrogen in Perimenopause

- At first, both FSH and estrogen levels will fluctuate
- Once the number of ovarian follicles ↓ significantly (late menopausal transition)
  - FSH ↑
  - Estrogen ↓
- ↓ Estrogen → thinning of endometrial lining → cessation of menses

Avis, N. (2001). Circulating levels of FSH, LH, estradiol (E2), estrone, AMH, and inhibin-B in women before, during, and after menopause [Digital image]. Retrieved from https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/perimenopause
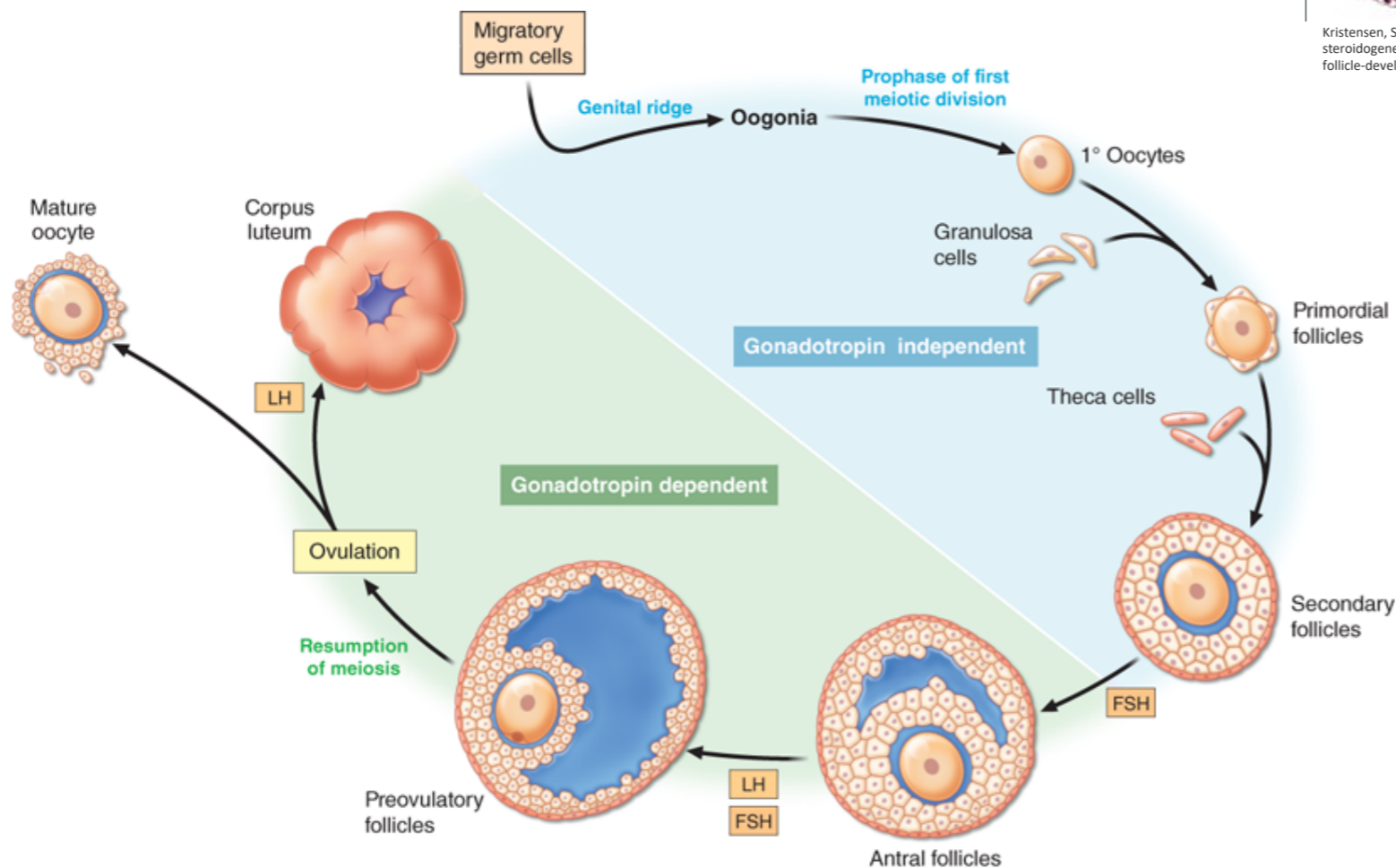
Antral Follicle Count (AFC)

Antral follicles:
- 2-10mm follicles
- Sensitive to FSH
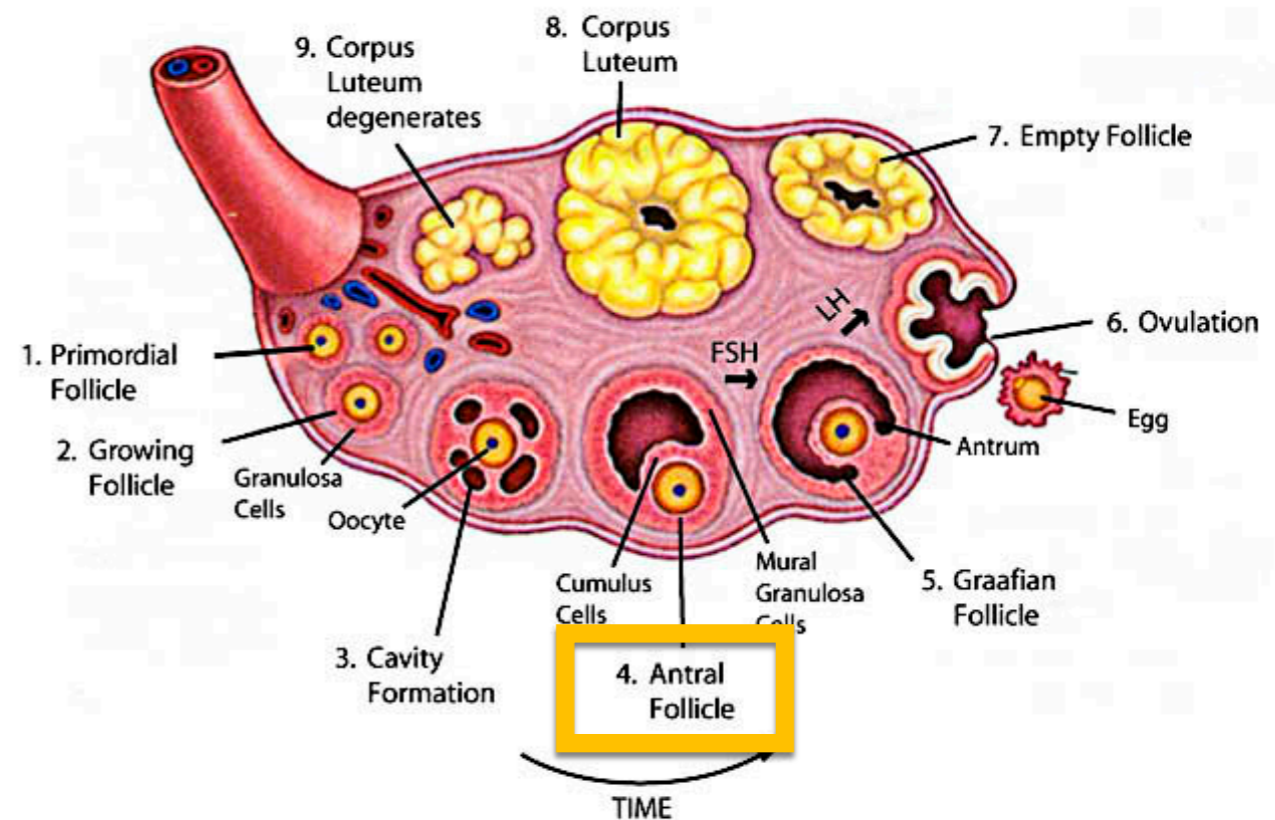- Correlates with # of primordial follicles available in ovary
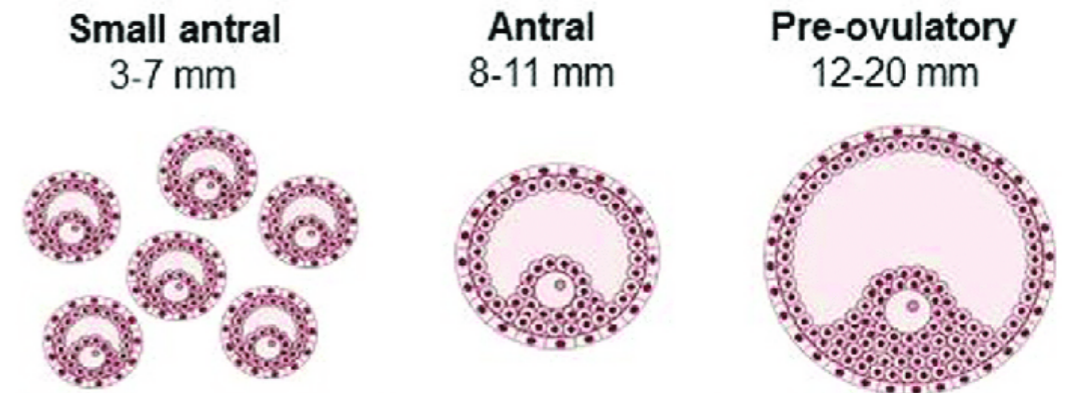
Kristensen, S., Mamsen, L., Jeppsen, J., & Andersen, C. (2018, January). Hallmarks of human small antral follicle development: Implications for regulation of ovarian steroidogenesis and selection of the dominant follicle [Digital image]. Retrieved from https://www.researchgate.net/figure/Hallmarks-of-human-small-antral-follicle-development-implications-for-regulation-of_fig3_322429316

Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition.
www.accessmedicine.com
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Antral Follicle Count (AFC)

- Count # of antral follicles
  - No corpus luteum, not more than 10mm
  - Issues
    - Inter-observer measurement variability
    - Inter-cycle variability
- Relatively stable throughout the menstrual cycle
  - Same predictive value regardless of when measured in the cycle

9. Corpus Luteum degenerates
8. Corpus Luteum
7. Empty Follicle
1. Primordial Follicle
2. Growing Follicle
Granulosa Cells
Oocyte
3. Cavity Formation
Cumulus Cells
4. Antral Follicle
Mural Granulosa Cells
5. Graafian Follicle
Antrum
Egg
6. Ovulation
FSH
LH
TIME

[Digital image]. (n.d.). Retrieved from http://www.ihrivf.net/antral-follicle-count/

Antral Follicle Count (AFC)

- Decrease in AFC indicates
    - Ovarian aging → AFC decreases with age, less retrievable eggs
    - Decreased ovarian response to stimulation
    - Perimenopause
- Can be used to predict poor ovarian response with IVF
- Not a good predictor of pregnancy
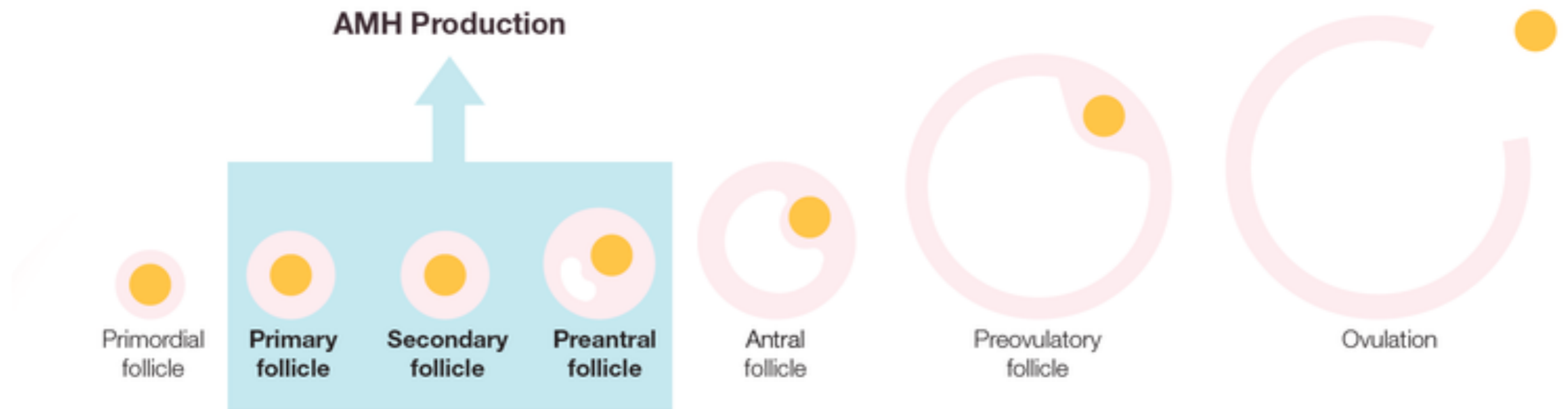   - Decline in fertility may be less than decline in AFC
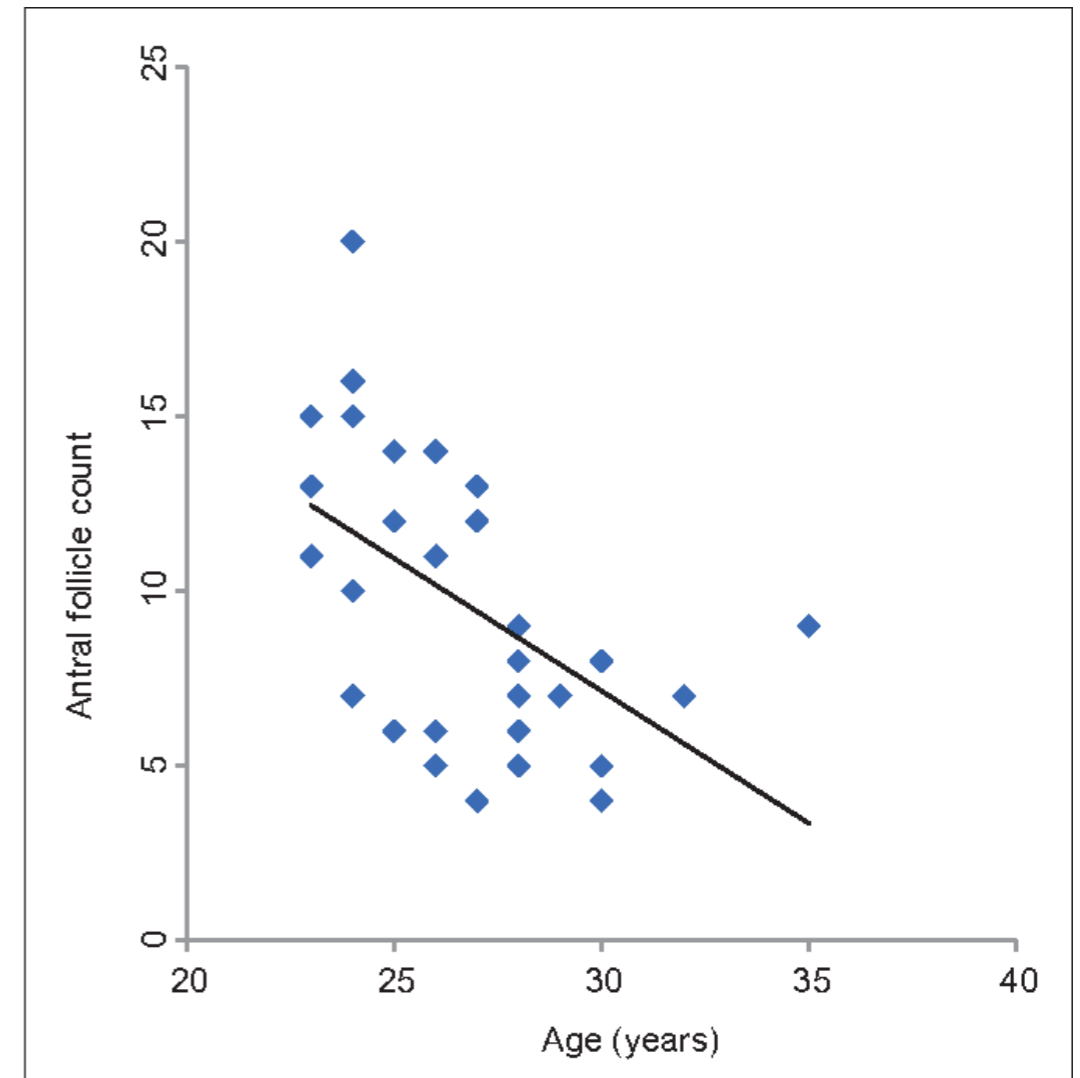
Figure 3: Scatter diagram showing age versus AFC in infertile group

Agarwal, A., Verma, A., Agarwal, S., Shukla, R., Jain, M., & Srivastava, A. (2014). Scatter diagram showing age versus AFC in infertile group [Digital image]. Retrieved from https://www.semanticscholar.org/paper/Antral-follicle-count-in-normal-(fertility-proven)-Agarwal-Verma/4ed87cb49fbf76f90b9bd09637f11be50f828d33

Antimullerian Hormone (AMH)

- Produced by granulosa cells of small preantral follicles; limited expression in large follicles
    - Has a role in dominant follicle recruitment

AMH Production

Primordial follicle | Primary follicle | Secondary follicle | Preantral follicle | Antral follicle | Preovulatory follicle | Ovulation

Epitope Diagnostics is proud to present a robust AMH ELISA kit with the following specifications: [Digital image]. (2017, December 29). Retrieved from http://www.epitopediagnostics.com/news/new-anti-mllerian-hormone-elisa-kit-launched/2017/12/29

Antimullerian Hormone (AMH)

- Levels correlate with the number of primordial follicles
  - Patients with **PCOS have higher AMH** levels at baseline (since more early follicles)
  - **# of follicles decreases with age → AMH levels decrease**
    - Levels drop before observable changes in FSH
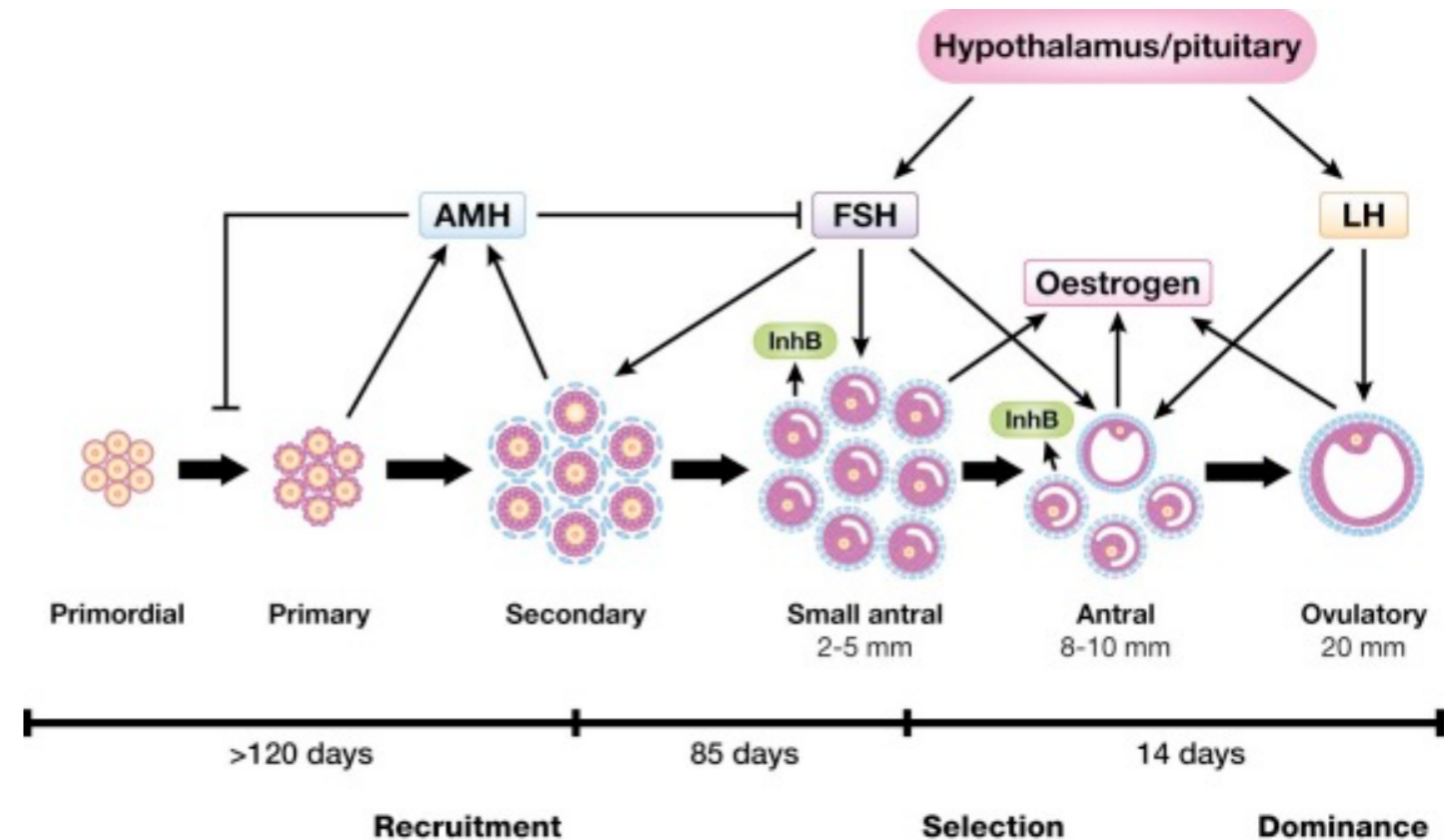
Fleming, R., Seifer, D., Frattarelli, J., & Ruman, J. (2015, October). [Digital image]. Retrieved from https://www.sciencedirect.com/science/article/pii/S1472648315003119

Antimullerian Hormone (AMH)

- Levels can be measured at any time during menstrual cycle
  - Relatively stable levels across menstrual cycle and between cycles
  - This is an advantage compared to FSH (however new studies show fluctuations)

Disadvantages:
- Variability between available assays
- Cannot compare AMH levels between different assays
- Affected by contraceptive use (decreased AMH and AFCs by up to 20%)

Antimullerian Hormone (AMH)

- May be a better marker for assessing age-related decrease in follicles and poor response to ovarian stimulation
    - Can be used to predict poor ovarian response with IVF
    - **Low AMH predict poor response to controlled ovarian stimulation**
- AMH levels may be used to adjust dose of gonadotropin meds

BENEFITS AND RISKS OF AMA

What are some benefits of advanced maternal age?

Brain Thinking Clipart [Digital image]. (n.d.). Retrieved from
https://www.clipartmax.com/middle/m2i8i8H7N4d3Z5K9_clipart-of-brain-thinking-black-and-white/

Benefits of AMA

Benefits:
- Better outcomes with multiple gestation
- Better SES
- More motivated

What are some risks of advanced maternal age?

Brain Thinking Clipart [Digital image]. (n.d.). Retrieved from
https://www.clipartmax.com/middle/m2i8i8H7N4d3Z5K9_clipart-of-brain-thinking-black-and-white/

Complications of AMA

- ↑ risk of adverse outcomes, especially >40yo

Mother	Baby
Infertility - Decreased ovarian reserve, endometriosis, fibroids ↑ **SA-** ↑ rate of chromosomal abnormalities - For both spontaneous and stimulated cycles <30yo: 7-15% 30-34yo: 8-21% 35-39yo: 17-28% ≥40yo: 34-52% - After IVF <35yo: 5.9% 35-39yo: 8.3% ≥40yo: 9.5% **Medical comorbidities during pregnancy** ↑ pre-existing medical conditions ↑ HTN, pre-eclampsia ↑ diabetes ↑ placenta previa and placental abruption (attributed to multiparity, not age) **During L&B** ↑ need for augmentation ↑ OVD ↑ C/S rate ↑ **maternal death**	**Chromosomal abnormalities** (trisomies, aneuploidy) and mitochondrial deletions **PTB** **IUGR, LBW** **IUFD, neonatal death** 35-39yo: 2.5 per 1,000 - Age 35-44: 1.0 per 1,000 stillbirth if HTN present - Age 35-44: 0.6 per 1,000 stillbirth if diabetes present 2.5 times the risk if HTN is present; 2.9 times the risk of diabetes is present

AMA and Aneuploidy

- **The rate of aneuploidy and SA increases with age**
  - **Due to issues with formation and function of spindles**
    - Spindles are more diffuse → error during meiosis
  - **Due to poor oocyte quality**
    - Decreased oocyte selection process → poor quality oocytes that should have undergone atresia may develop into dominant follicles or become selected for IVF cycles

Most common chromosomal conditions associated with AMA:
- Trisomies 13, 18, 21, X

All chromosomal anomalies:
- 20yo: 1 in 526
- 30yo: 1 in 384
- 35yo: 1 in 204
- 40yo: 1 in 65
- 45yo: 1 in 2

T21:
- 20yo: 1 in 1477
- 30yo: 1 in 939
- 35yo: 1 in 353
- 40yo: 1 in 85
- 44yo: 1 in 39

Prevention of Age-Related Fertility Decline

- Attempt conception at a younger age
- Donor
    - Sperm
    - Egg
    - Embryo
- Cryopreserving own oocytes (egg freezing) to use for ART in the future

TREATMENT OF AGE-RELATED INFERTILITY

Goal of Treatment

- Increase monthly fecundity
- Decrease time to conception
- Increase # of mature oocytes to balance decreased oocyte quality
  - Do not fix oocyte quantity or quality

Treatment Options

- Controlled ovarian hyperstimulation (COH) + IUI
  - Clomiphene citrate
  - Gonadotropins (ex. FSH)
- IVF
- Oocyte donation
  - **Only effective treatment of decreased oocyte quality!**

Controlled Ovarian Hyperstimulation

- Low pregnancy and live birth rates in >40yo
- Move onto IVF if do not conceive in 1-2 cycles

Success rates:
- Pregnancy rates of clomiphene citrate + IUI:
  - 38-40yo: 7%
  - 41-42yo: 4%
  - >42yo: 1%
- Live birth rates of gonadotropins + IUI:
  - 38-39yo: 6%
  - >40yo: 2%
  - All live births occurred in first 1-2 cycles

IVF

- **Age is the most important prognostic factor of success of IVF**
  - Due to decreased ovarian reserve
- As age increases, success decreases, SA increases
  - Higher chance of pregnancy than COH
  - Lower pregnancy rates than oocyte donation

Success rates (no egg donor):
- Significantly lower in late 30s and 40s, declines with age
- Need more cycles of treatment for pts ≥35yo
- Live birth rates after IVF
  - <35yo: 41%
  - 35-39yo: 30.9%
  - >40yo: 12.3% per cycle
  - 40-42yo: 1.1%
  - ≥42yo: <5%
  - Significant decrease ≥43yo
  - ≥43yo: 1.1%
  - ≥45yo: no live births

IVF

- **Own cryopreserved eggs:** success **depends on the age of egg when it was cryopreserved**
- **Donor eggs:** success depends on the **age of donor egg,** not the age of recipient

Oocyte Donation

- Many older pts achieve pregnancy only with donor eggs
- **The only effective treatment for ovarian aging**
    - Higher pregnancy rates than COH or IVF
- Egg is donated, pt carries pregnancy
    - Egg donors are altruistic (ex. Close friends, family, colleagues)
    - May use frozen donor oocytes from anonymous egg donors → from donor egg banks in US

Canada- Assisted Human Reproduction Act (2004):
- Prohibits sale of eggs/sperm/surrogacy services
- Donors can be compensated for receiptable expenses (meds, parking)

- In US, egg donors may be paid → this is prohibited in Canada

Oocyte Donation

- Use of donor eggs in pts >50yo is controversial due to risks of AMA!
    - Canada: no regulation on the upper age limit
        - Canadian guidelines recommend pts >45yo to have medical assessment and OB consult prior to treatment
    - Many experts think that the natural age of menopause is the max age for oocyte donation

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