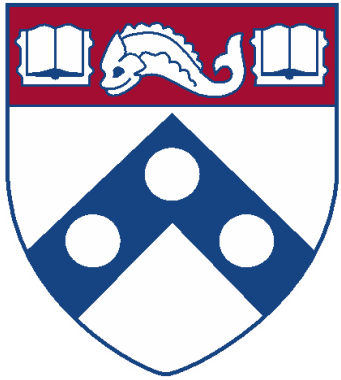


Hormone Replacement Therapy in Males



Christopher Gibson, MD

Assistant Professor, Division of Endocrinology and Diabetes

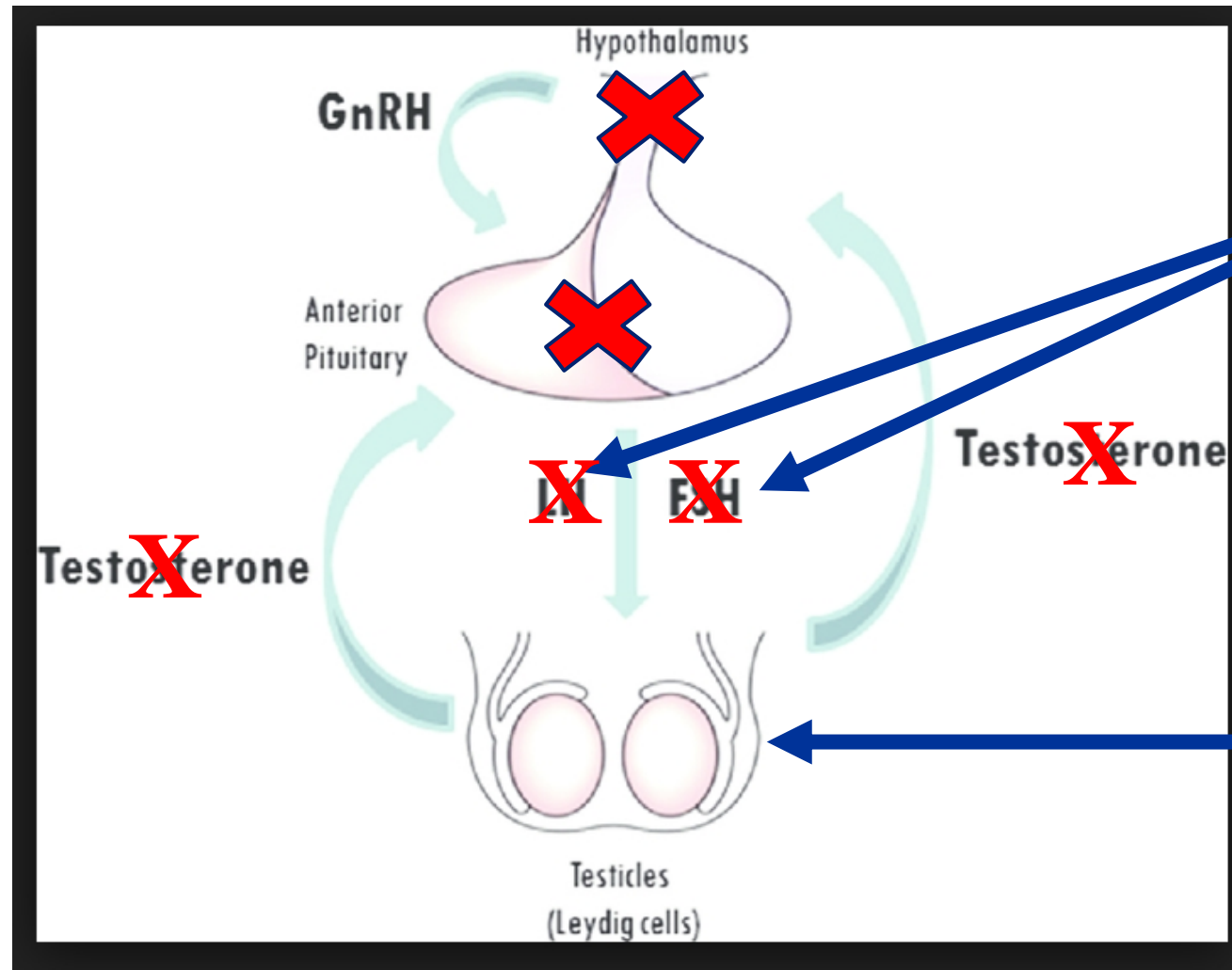
CHOP Neuroendocrine Center Pituitary Education Conference

March 16, 2019

Objectives

- 1. Understand the pituitary gland's role in testicular function**
- 1. Identify the testosterone treatment options for males during puberty and adulthood**
- 1. Recognize the complexities of fertility investigations and treatments utilized in men with hypogonadotropic hypogonadism (HH)**

Hypothalamic-Pituitary-Testicular (HPT) Axis

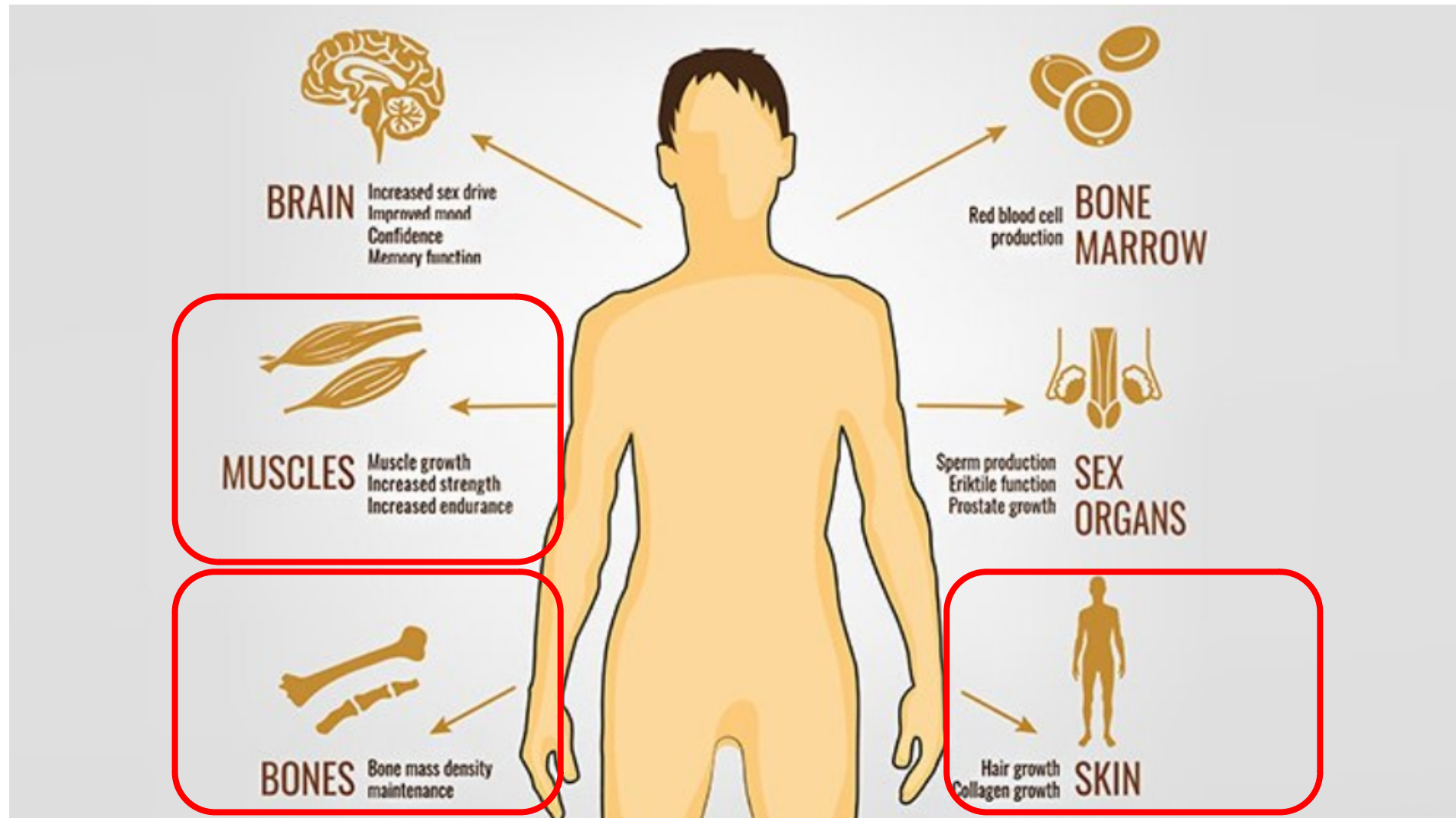


Gonadotropins

“Hypogonadotropic Hypogonadism”

**Gonads
(Testicles)**

Testosterone Effects



Effects of Low Testosterone

- **Pubertal Age –**

- Slower than normal vertical growth (height)
- Lack of secondary sexual characteristics
 - **Pubic and facial hair, deepened voice, musculature development**

- **Adulthood –**

- Fatigue, sleep disturbance, concentration difficulties
- Reduction in libido, erectile dysfunction
- Increased body fat, & decreased muscle mass and bone density
- Type 2 diabetes, metabolic syndrome, cholesterol abnormalities, cardiovascular disease

Testosterone effects in Puberty

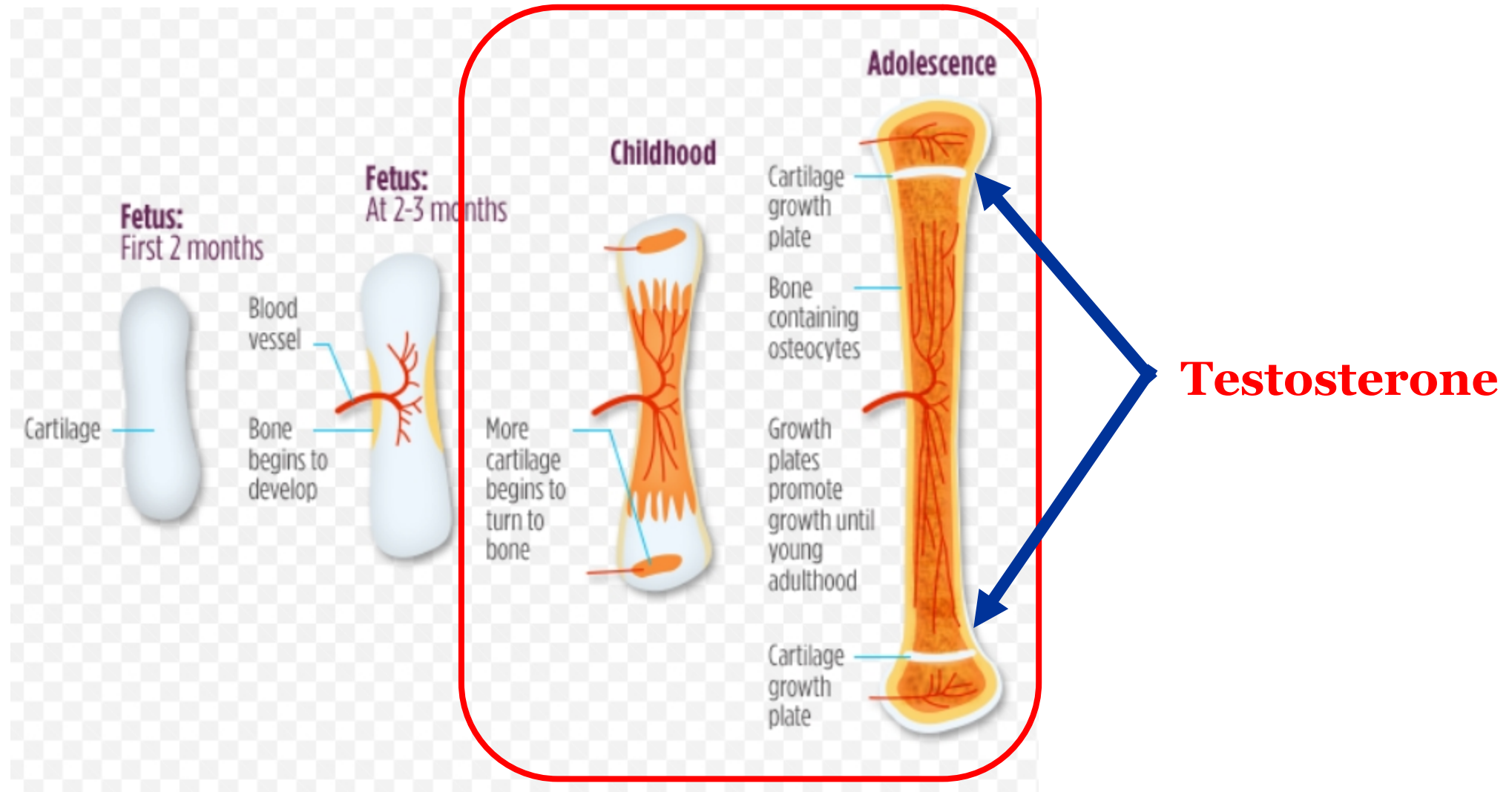
- **Testosterone → Classic male target tissues**

1. Penile growth
1. Sexual hair
1. Scrotal development
1. Sebaceous glands (acne)
1. Muscular development and Lipolysis

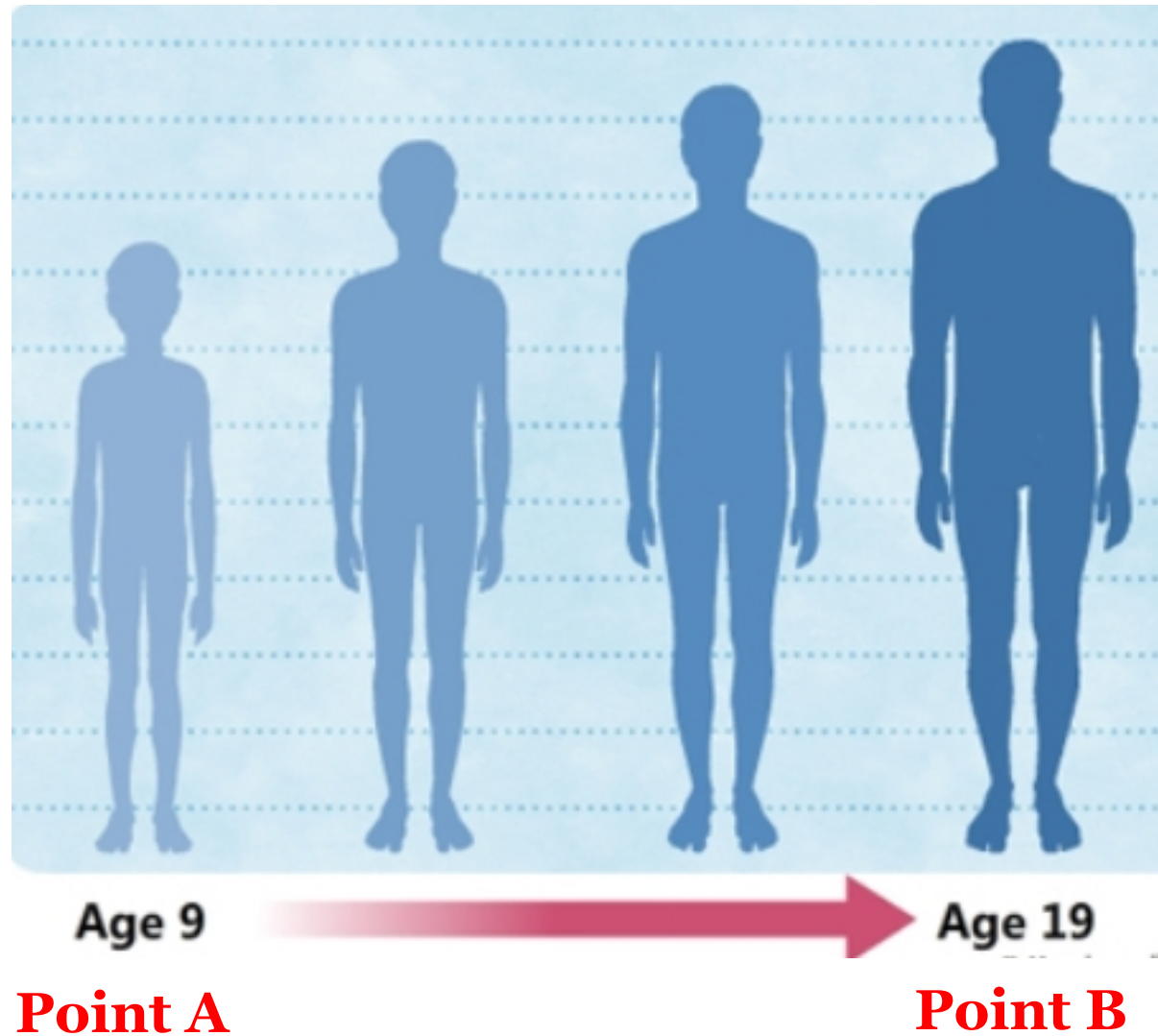
Testosterone in Pubertal & Adult Males

- **Typical adult testicle produces/releases 5-7 mg of Testosterone daily**
- **This amount is far less during the early and mid-stages of puberty**
- **Slowed and sustained release of testosterone paramount to appropriate yearly height progression**

Testosterone in Pubertal Males



How Do We Get from Point A to Point B?



When is Puberty “Delayed?”

- **Delayed puberty –**
 - Generally classification: lack of testicular growth by age 14
 - Clinical definition: “the absence or incomplete development of secondary sexual characteristics bounded by an age at which 95 percent of males of that ethnic background have initiated sexual maturation”
 - Laboratory definition: Decreased first morning LH, FSH and Total Testosterone levels

Testosterone Replacement Therapy (TRT)

- **Replace the hormone that's missing**
- **Intramuscular testosterone –**
 - 1st line treatment
 - Some time between 13 and 14 years of age
 - Dose can be easily adjusted to match requirements at different stages of pubertal development to avoid growth plate closure and bone demineralization

Testosterone Replacement Therapy (TRT)

- **Long-acting Intramuscular Testosterone –**

- Testosterone Cypionate



- Testosterone Enanthate



Testosterone Replacement Therapy (TRT)

- **Example Regimen 1:**

1. 50 mg intramuscularly (IM) once monthly for 6 months
2. 100mg IM once monthly x4-6 months
3. 150mg IM once monthly x4-6 months
4. 200mg IM once monthly x4-6 months
5. 200 mg IM given once every 2 weeks (final dose)

- **Example Regimen 2:**

1. 50–75 mg once monthly x6 months
2. 100–150 mg once monthly over 2.5-3 years
3. 200 mg every 3 weeks after 3–4 years of TRT initiation (final dose)

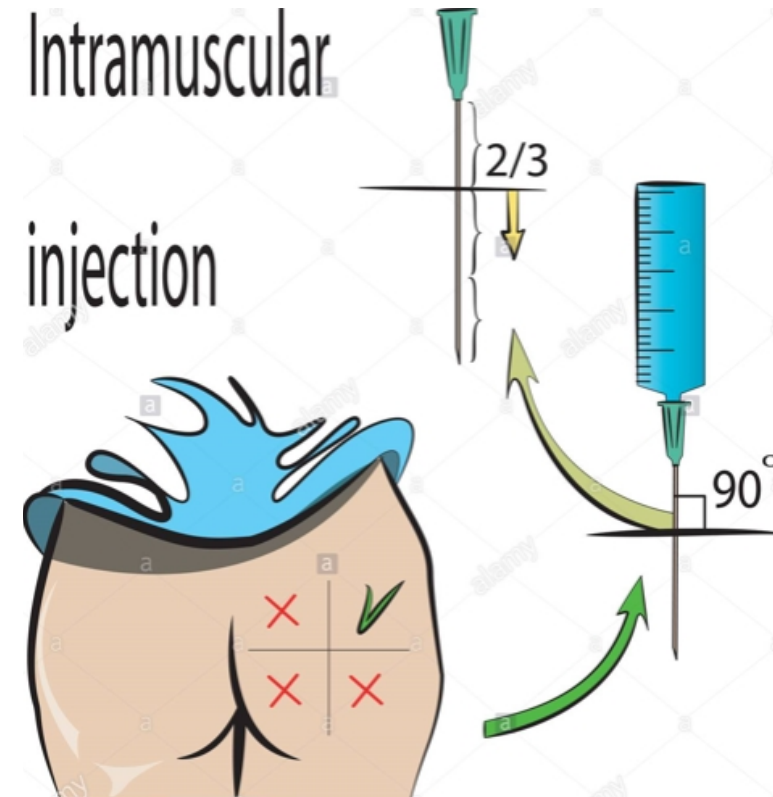
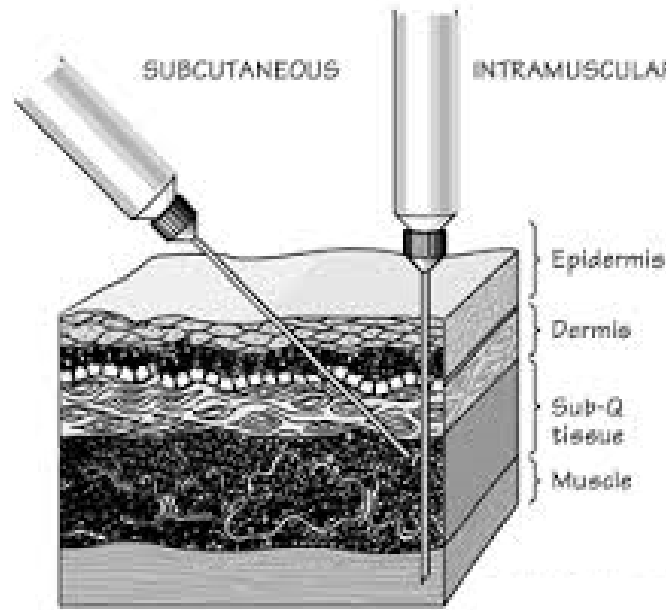
TRT Goals

- 1. Slow and appropriate transition into puberty**
- 1. Acceptable height progression and velocity**
- 1. Avoidance of early growth plate closure**
- 1. Achievement of secondary sexual characteristics**
 - ☐ Pubic and facial hair, deepened voice and muscle development

TRT Side Effects

- **Injection pain**
- **Skin blistering**
- **Acne**
- **Mood Swings**
- **Increased Blood Pressure**
- **Increased Hemoglobin/Hematocrit**
- **Variable Swings in Testosterone Levels**
- **Gynecomastia (nipple/chest enlargement)**
- **Decrease in sperm production (temporary infertility)**

Subcutaneous vs. Intramuscular Injections



TRT Monitoring

- **Endocrinology follow up visits**
 - Close growth curve monitoring
 - Secondary sexual characteristic monitoring
- **Testosterone levels:**
 - Several days after injection (“peak”)
 - Several days before injection (“trough”)
- **Once to twice yearly Hemoglobin/Hematocrit levels**

Alternatives to Intramuscular Testosterone?

- **Topical testosterone gel:**

- Androgel, Androderm, Fortesta
- Typically 2 actuations/pumps applied once daily
- Mostly adult studies performed, demonstrating:
 - Higher patient satisfaction
 - More stable daily testosterone levels
- Offered to males once on finalized IM doses



Intramuscular Injection

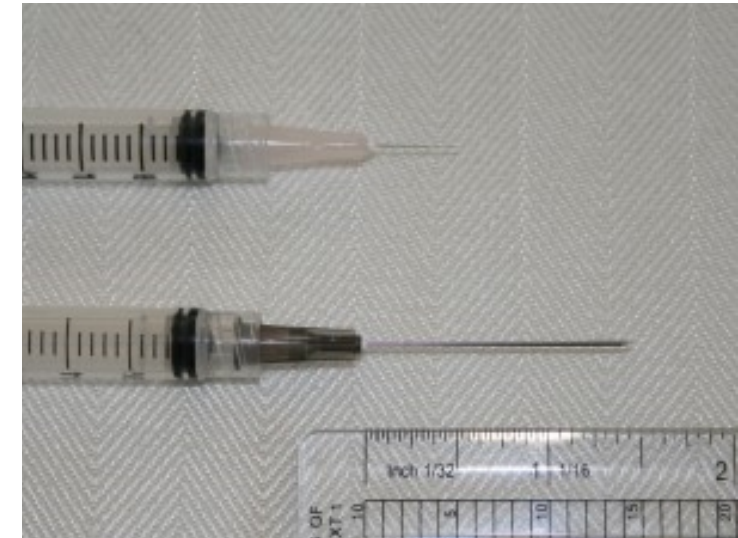
Alternatives to Intramuscular Testosterone?

- **Testosterone patch:** skin irritation, difficult to maintain
- **Nasal & Buccal Mucosa forms:**
Less effective, associated with gum and nasal inflammation
- **Topical pellets:** Painful, every 3-5 month surgical insertion
- **Testosterone pills:** Dosed several times per day; more liver side effect risks
- **Long-lasting intramuscular Testosterone Undecanoate:**
Risk of pulmonary oil micro-embolization



Subcutaneous Testosterone

- **Benefits:**
 - Delivered through smaller syringe and needle into fat (subcutaneous) tissue
 - Can be given by individual/caregiver
- **Drawbacks:**
 - Typically given once weekly
 - No prior studies performed in children/teens
 - Non-FDA approved



Subcutaneous Testosterone

- **First considered in early 2000s in adult men**
- **Studies first performed earlier this decade**
- **Several studies performed already in:**
 1. Adult men with hypogonadism
 2. Adult transgender men (*aka* female-to-male individuals)
- **What are the risks?**
 1. Too little, or too much, absorption through the subcutaneous (fat) tissue
 2. Worsening symptoms of hypogonadism
 3. Increased risk of testosterone side effects

Subcutaneous Testosterone Research Studies

- All in adults
- Small number of research participants
- Wide inter-patient and intra-patient variability
- 50-100 mg of testosterone once weekly?
- Blood work 5 days after first couple of injections?
- What laboratory ranges and targets should be used in pediatric population?
- Long-term studies needed
- Pediatric studies needed

Subcutaneous Testosterone Research Studies

A 52-Week Study of Dose Adjusted Subcutaneous Testosterone Enanthate in Oil Self-Administered via Disposable Auto-Injector

Jed C. Kaminetsky, Andrew McCullough, Kathleen Hwang,
Jonathan S. Jaffe,^{*,†} Christina Wang[†] and Ronald S. Swerdloff

From Manhattan Medical Research (JCK), New York, New York, Lahey Hospital and Medical Center (AM), Burlington, Massachusetts, Division of Urology, Department of Surgery, Brown University (KH), Providence, Rhode Island, Antares Pharma, Inc. (JSJ), Ewing, New Jersey, and Division of Endocrinology, Department of Medicine, Harbor-UCLA Medical Center and Los Angeles Biomedical Research Institute, Torrance (CW, RSS), California

- **2019 *Journal of Urology* study**
- **Open label, single arm, dose blinded, 52-week registration phase study**
- **Efficacy and safety of once weekly 50-mg, 75-mg, or 100- mg subcutaneous testosterone**
- **Administered weekly to 150 men with hypogonadism**

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- **Findings:**
 - Steady total testosterone pharmacokinetic profiles on blood work
 - Small peak and trough fluctuations
 - Safe, well tolerated

Subcutaneous Testosterone Research Studies

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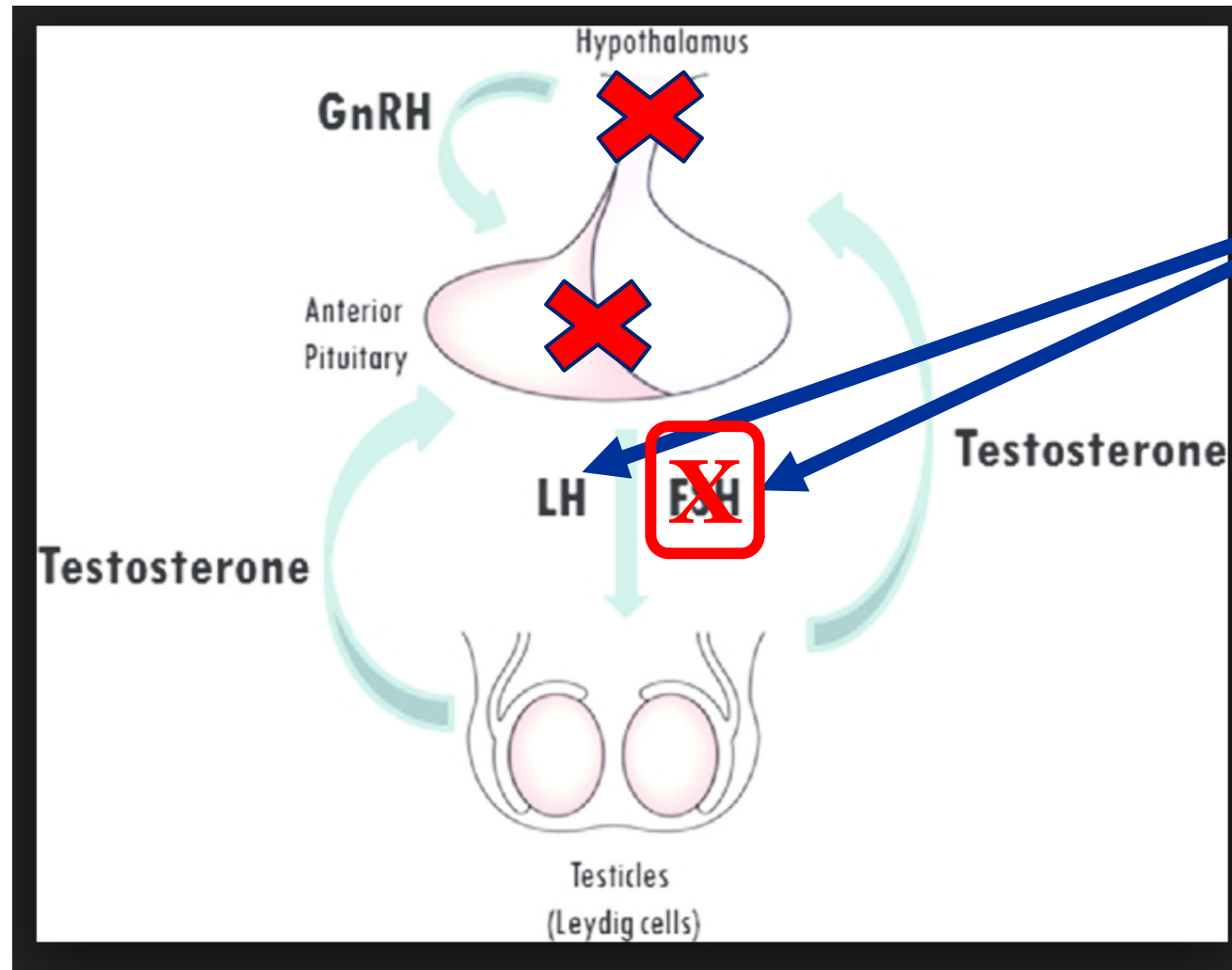
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- **Limitations:**
 - Although 150 men enrolled, only 98 completed 52 week study
 - Only 1 of the 150 indicated to have “secondary hypogonadism” (hypogonadotropic hypogonadism)
 - 30 reported increased hematocrit, blood pressures, and prostate specific antigen (PSA) levels, who had to leave the study

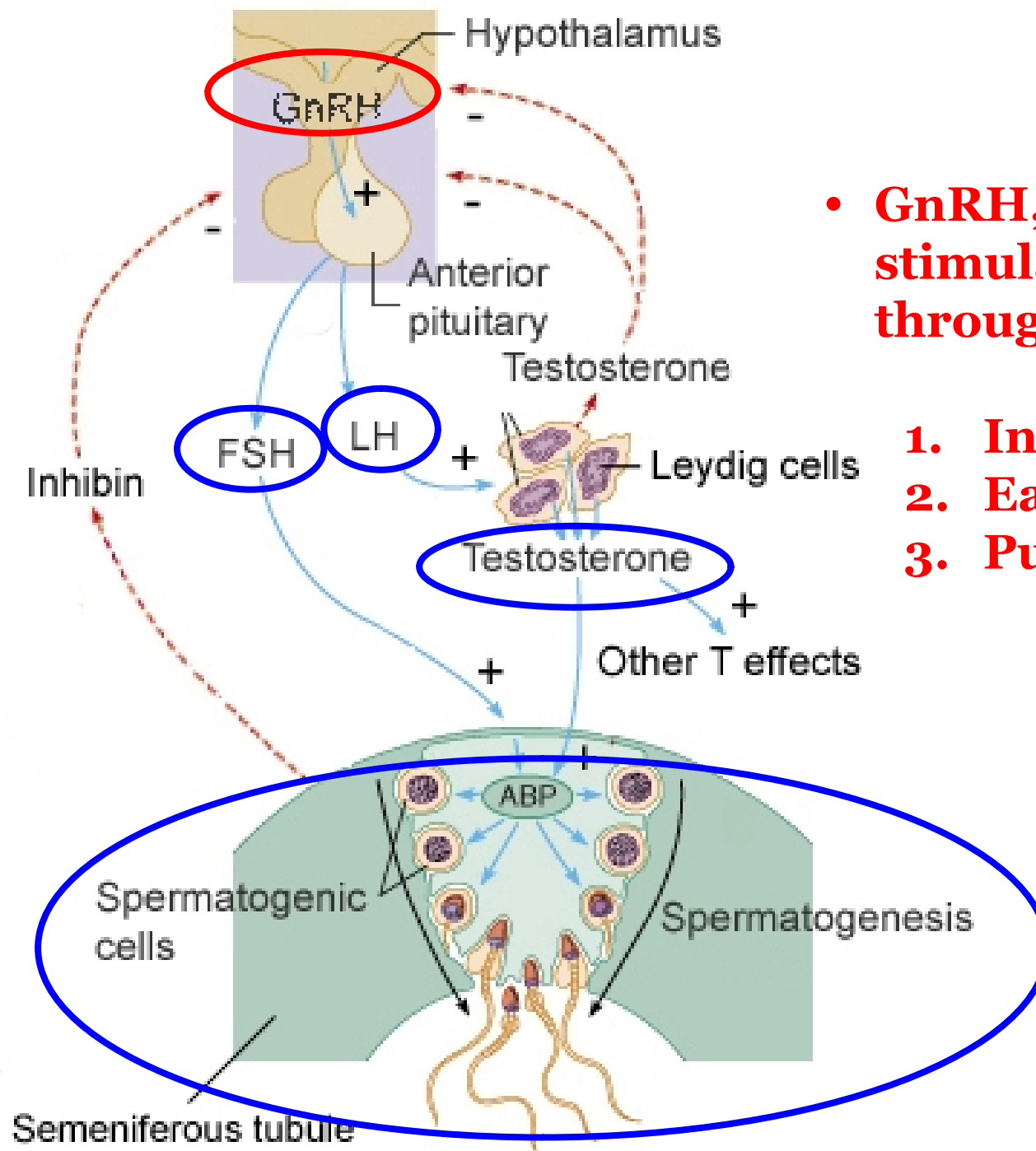
What About Fertility?



Hypothalamic-Pituitary-Testicular (HPT) Axis



Gonadotropins

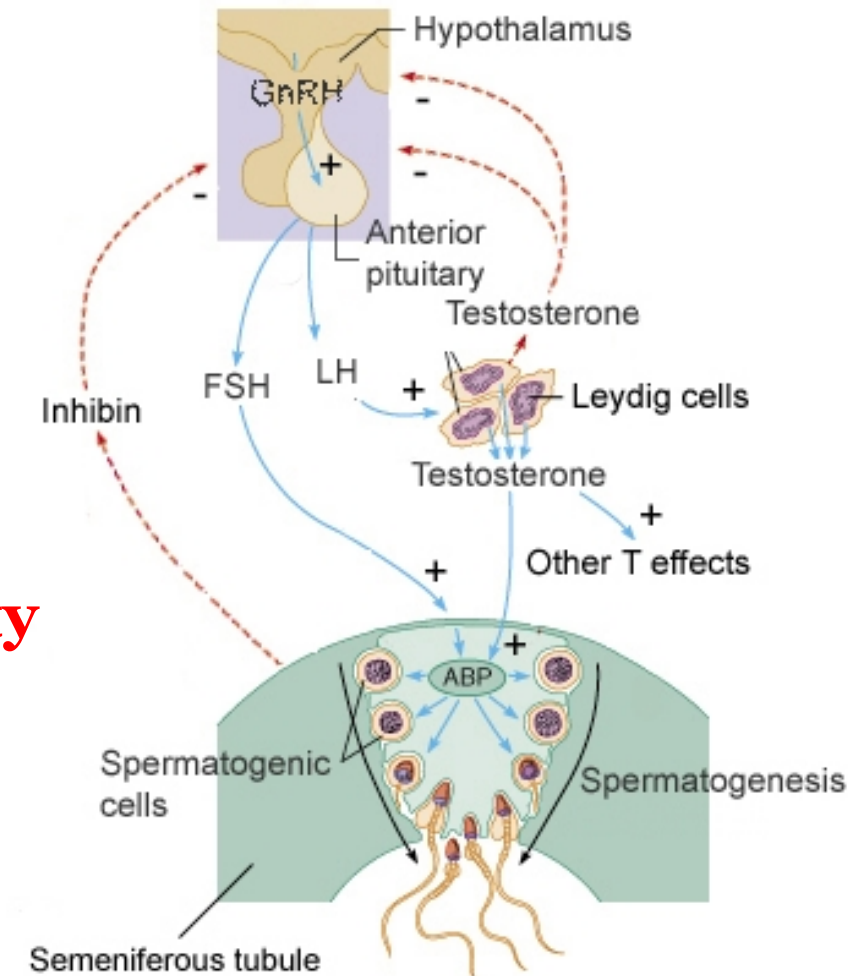


• **GnRH, and FSH/LH stimulation occurring throughout life as follows:**

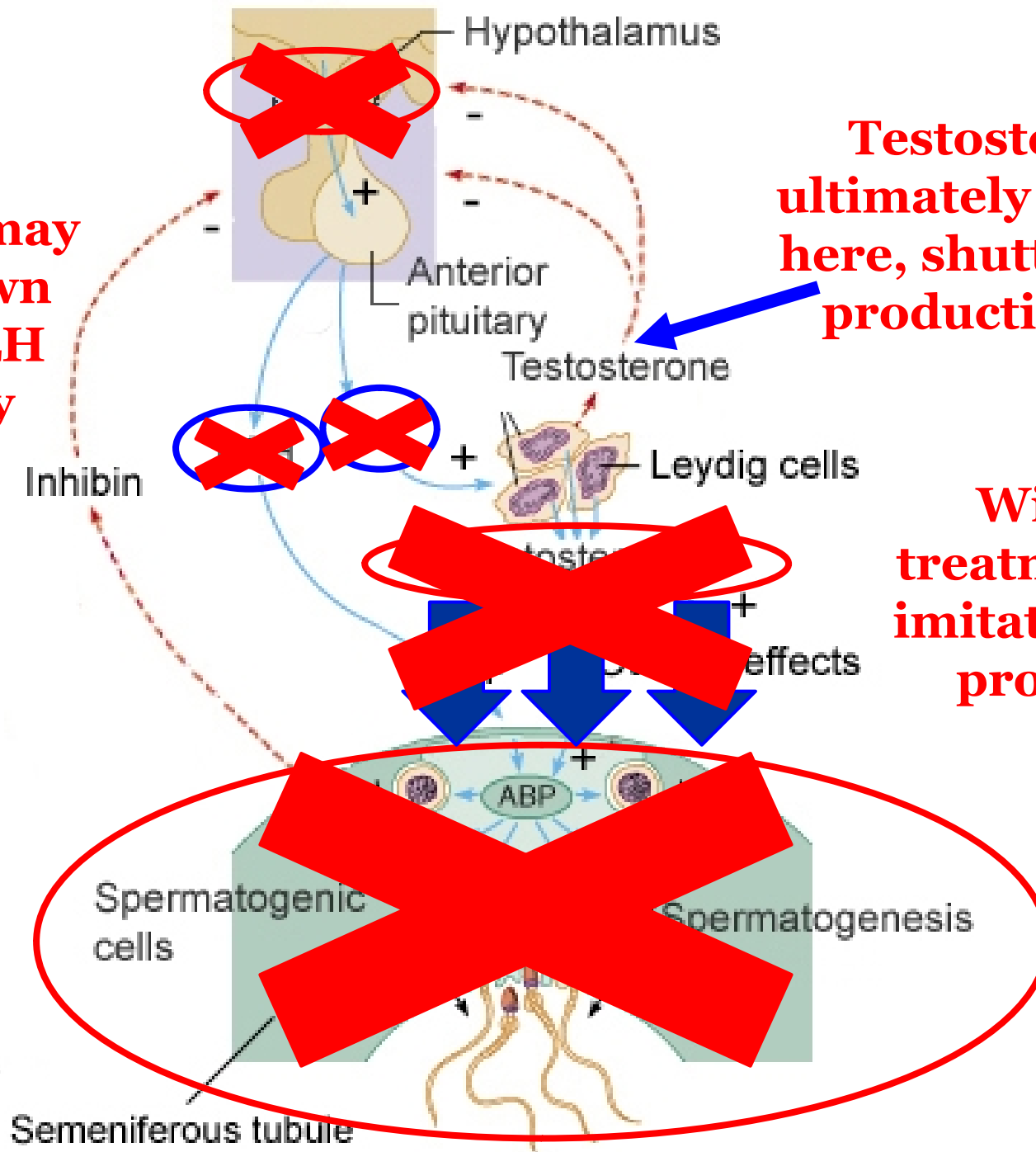
- 1. In utero**
- 2. Early infancy**
- 3. Puberty onward**

“Priming” of Sperm Cells in Fetal/Neonatal Period

- Occurs from 3rd trimester – 6th month of life
- Hormonal changes:
 - Testosterone production
 - Immature Sertoli cell proliferation
- 3-fold testicular volume increase
- No true sperm production
- Dormancy from 6th month of life thru puberty
- Profound effects on future fertility?



Prior brain surgeries may have already shut down the GnRH and FSH/LH mechanisms already



Testosterone treatments ultimately imitate this process here, shutting down testicular production of testosterone

Will testosterone treatments for my child imitate this process and promote their own fertility?

Are there Fertility Preservation Options, or Treatments?



What are the Infertility Risks?

- 1. What was the level of initial brain tumor/lesion?**
- 1. What age were they diagnosed with hypogonadotropic hypogonadism?**
- 1. What is the degree of hypogonadism?**
- 1. Is there a prior history of undescended testicles?**
- 1. Has he ever been on previous testosterone treatments?**

Are there Fertility Preservation Options?

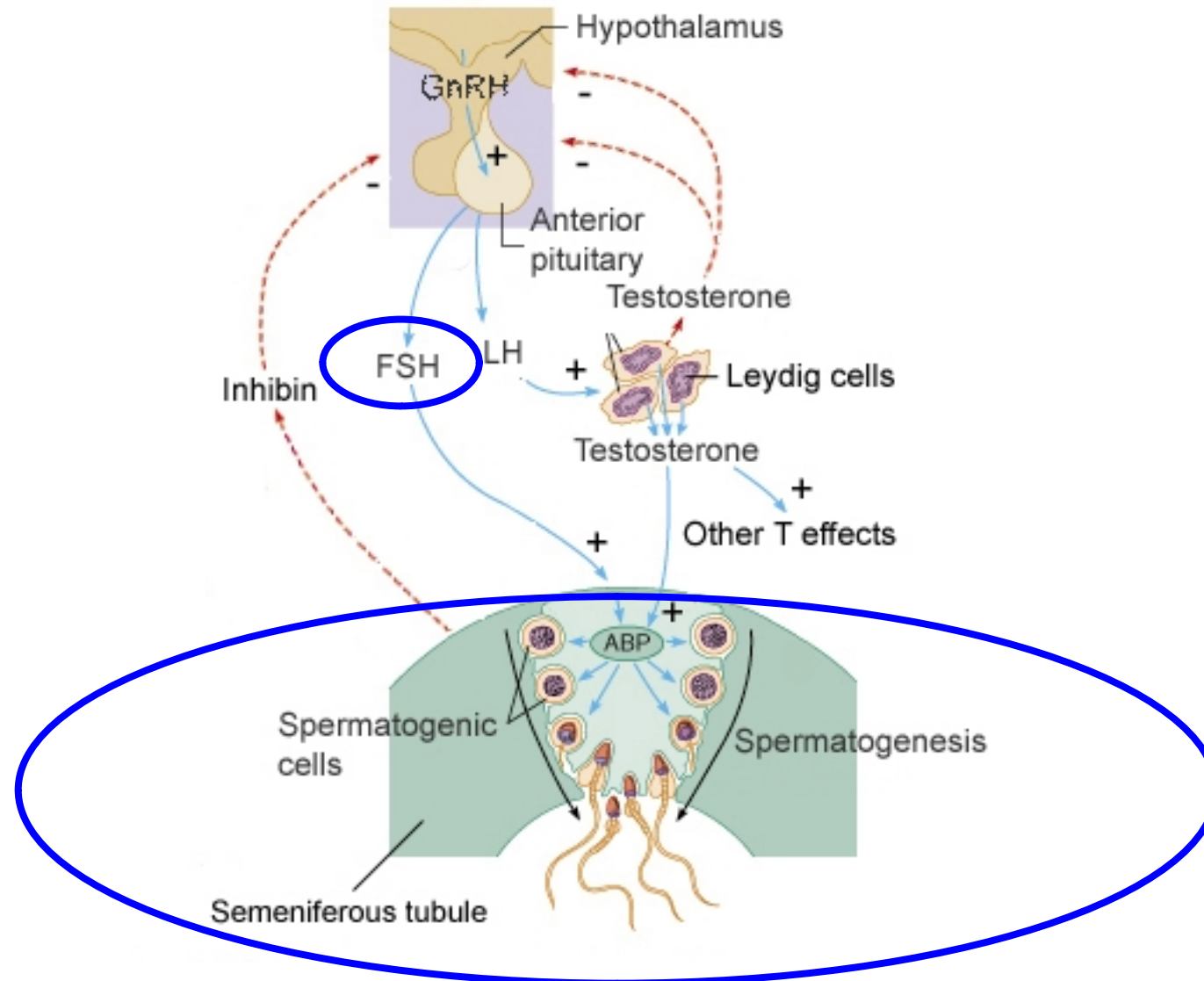
- **Yes, sperm banking (at the right age)**
 - Offered for those who are in puberty, or have completed, and are developmentally appropriate to bank sperm

Preservation Method	Initial Freeze	Yearly Cost	Insurance Coverage
Sperm	\$300	\$200-300	Not always covered

Is Fertility Preservation Necessary?

- **Not necessarily in those in puberty or past puberty**
- **Slightly higher rate of natural conception with partner later on life if:**
 - CNS tumor was diagnosed and removed during or after puberty
- **Consultation with male fertility specialist**
 - Intrauterine Insemination (IUI)
 - Intracytoplasmic sperm injection (ICSI)
 - In vitro fertilization (IVF)
- **But what about those diagnosed during infancy or childhood?**

“Priming” of Sperm Cells in Fetal/Neonatal Period



Fertility Treatment Options and Likely Outcomes Based on Diagnosis Age

```
graph TD; A[Fertility Treatment Options and Likely Outcomes Based on Diagnosis Age] --> B[Post-pubertal]; A --> C[Childhood]; A --> D[Infancy]; B --> E["- Spontaneous fertility<br/>- Single agent fertility treatment"]; C --> F["- 1-2 agent(s) fertility treatment"]; D --> G["- Likely 2-agent fertility treatment"];
```

Post-pubertal

- Spontaneous fertility
- Single agent fertility treatment

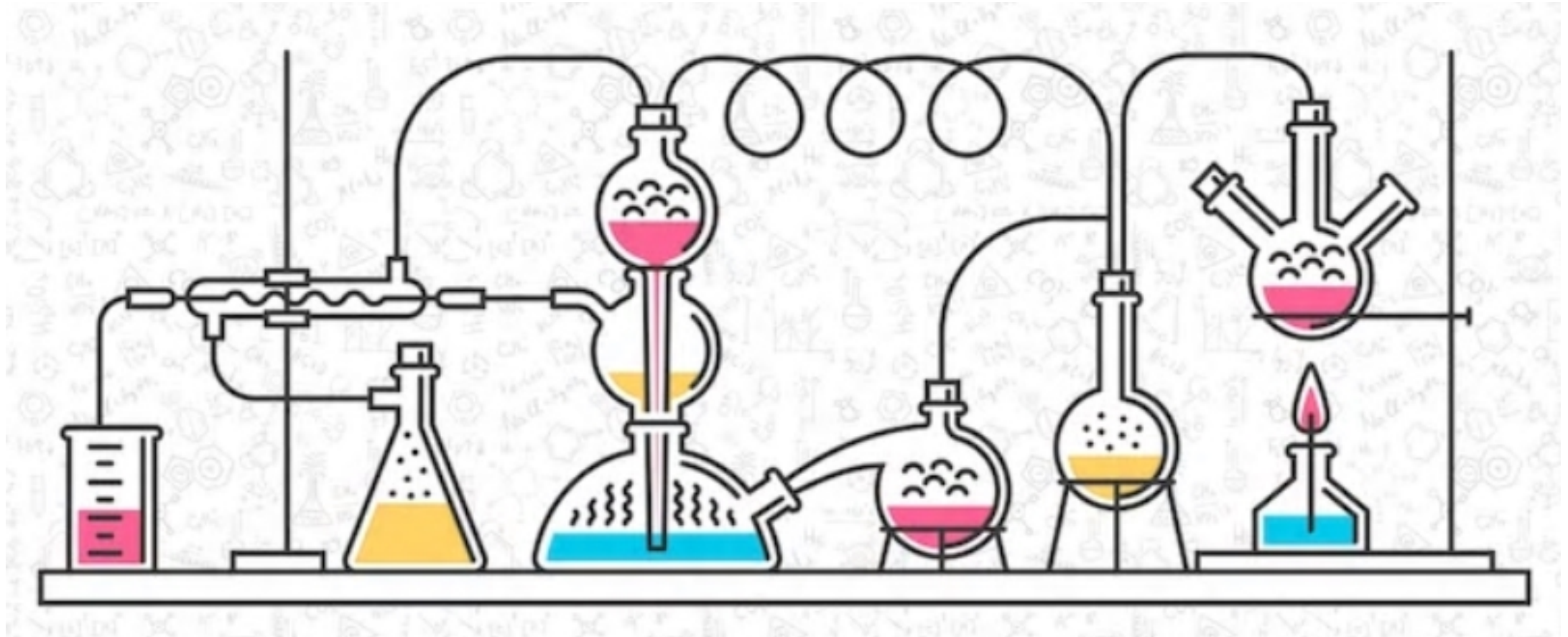
Childhood

- 1-2 agent(s) fertility treatment

Infancy

- Likely 2-agent fertility treatment

So What Are These Adult Fertility Treatments?



Adult Fertility Treatment Options

- **Testosterone often stopped for 3-6 months prior to starting treatments**

GnRH

- Hypothalamic lesions
- Given subcutaneously thru pump
- \$7000 yearly (not offered in U.S.)



Where is your Adolescent at?



Fertility Treatments for the Teen

- **Talk to your child**
- **Have they ever thought about having a family?**
- **If your teenager is only looking for puberty to begin, testosterone therapy is typically the best and easiest option**

Take Home Points

- **The pituitary plays a vital role in testicular development and testosterone release**
- **Intramuscular testosterone is widely used and studied in pubertal induction for hypogonadal males**
- **Close collaboration with Pediatric Endocrinologist is needed to ensure most appropriate progression through puberty**
- **Greater emphasis has been placed on alternative forms of testosterone, but few studies have focused on children/teens**
- **Fertility outlooks & treatments in this population are complex and multi-faceted**

Adult Endocrinology & Research Resources

- **Dr Puneet Masson, MD**
University of Pennsylvania
Division of Urology
Division of Reproductive Endocrinology and Infertility
Director, Male Reproductive Medicine and Surgery
- **Dr Peter Snyder, MD**
University of Pennsylvania, Division of Endocrinology
Medical Director, Penn Pituitary Center
- **Dr William Crowley, MD**
Massachusetts General Hospital, Partners Healthcare, Harvard Medical School
Division of Endocrinology
Founding and Emeritus Chief of Reproductive Endocrine Unit

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3. McFarland J et al. "Serum Testosterone Concentrations Remain Stable Between Injections in Patients Receiving Subcutaneous Testosterone." Journal of the Endocrine Society. 2017 Jul 21; 1(8):1095-1103.
4. Wilson DM et al. "Pharmacokinetics, safety, and patient acceptability of subcutaneous versus intramuscular testosterone injection for gender-affirming therapy: A pilot study." Am J Health Syst Pharm. 2018 Mar 15;75(6):351-58.
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