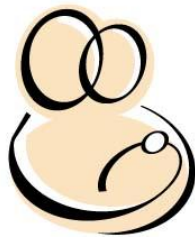


Amenorrhea

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FERTILITY
ASSOCIATES
of MEMPHIS

William H. Kutteh, MD, Ph.D Raymond W. Ke, MD



Objectives

- To know the definition and criteria for amenorrhea
- To understand the diagnostic algorithm for amenorrhea
- To be aware of the treatment of amenorrhea based on specific diagnosis

Case

- 19 yo Go Caucasian female
- Experienced one episode vaginal bleeding age 13. None since.
- Denies pelvic pain
- Difficult social situation
 - Estranged from parents, lives with Grandfather
 - Attempted suicide as 15 yo
- Denies medications, sexual activity

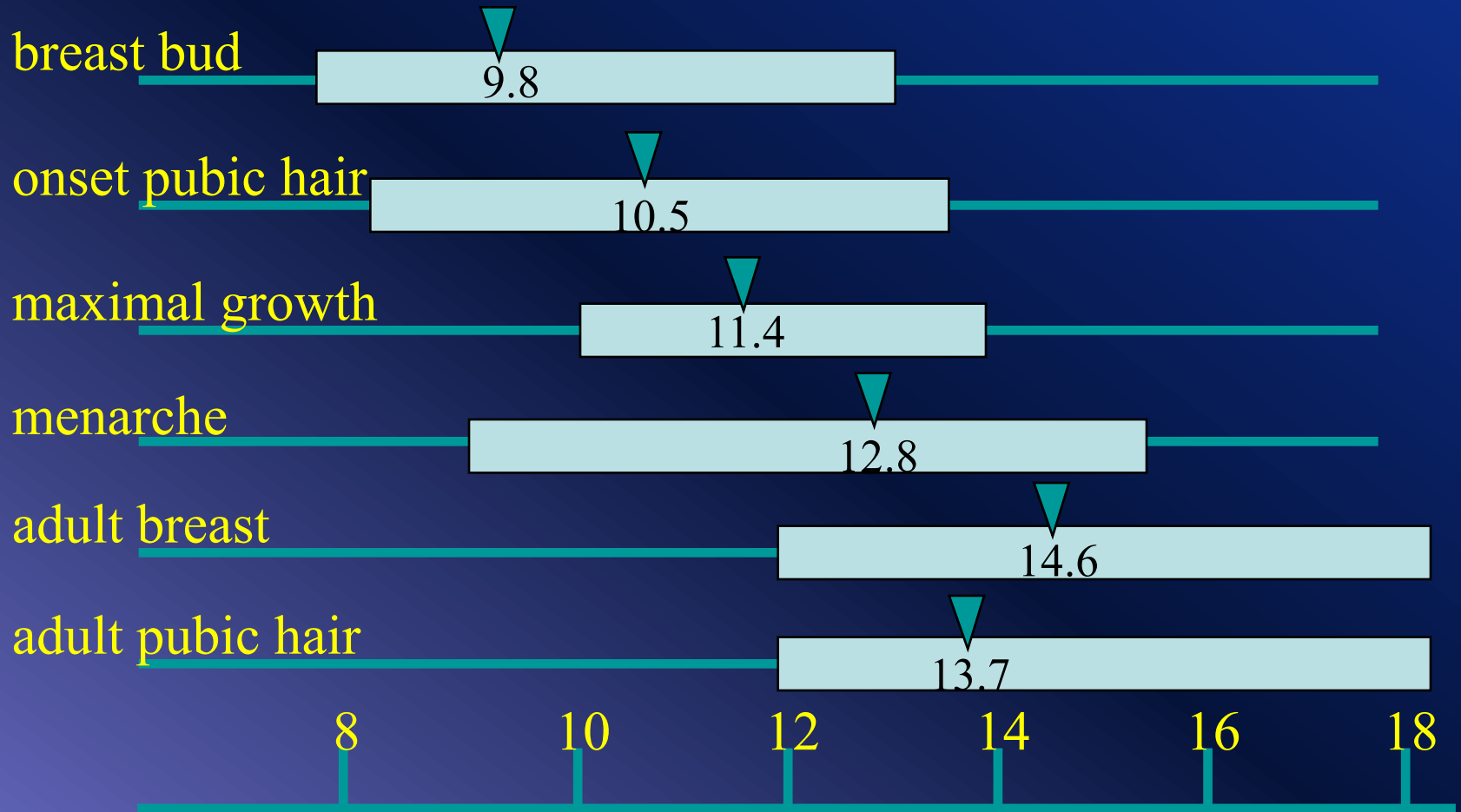
Basics

“Absence of menses”

- Primary
 - Menarche has not occurred by 15 years old
 - No menarche by 13 years in the absence of growth or secondary sexual characteristics
 - No menarche within 3 years from start of breast development
- Secondary
 - After starting menstruation, no menses for an interval of time equal to 6 months or the equivalent of 3 cycle lengths



Puberty Timeline



Adapted from Speroff, 9th Ed

Hypothalamus

GnRH

LH
FSH

estradiol
progesterone

estradiol/progesterone
inhibin/activin

Pituitary

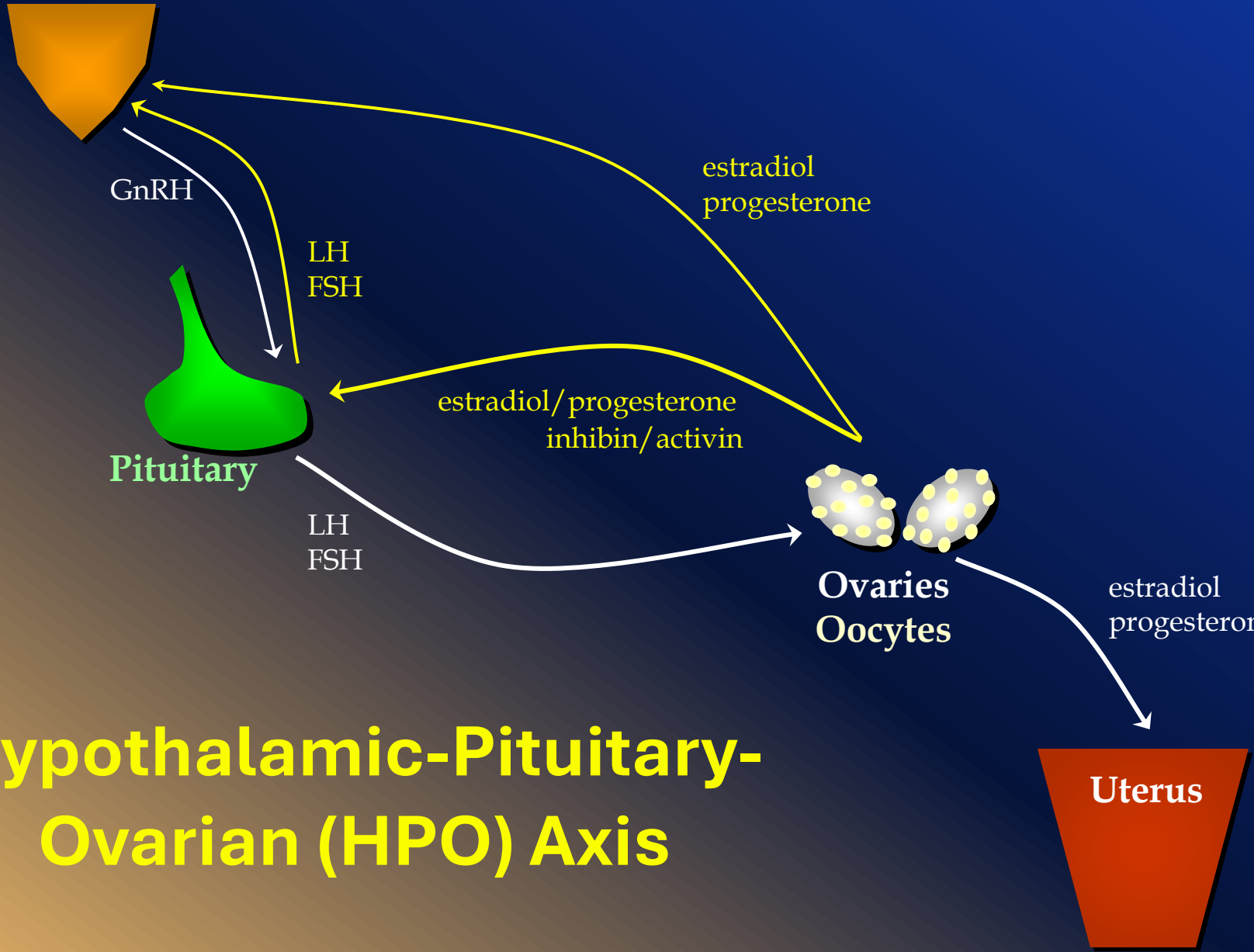
LH
FSH

Ovaries
Oocytes

estradiol
progesterone

Uterus

Hypothalamic-Pituitary-Ovarian (HPO) Axis



Basics

- Eugonadism

- Normal ovarian function, specifically estrogen production
- Estrogen is required for vaginal bleeding and pubertal development

- Hypogonadism

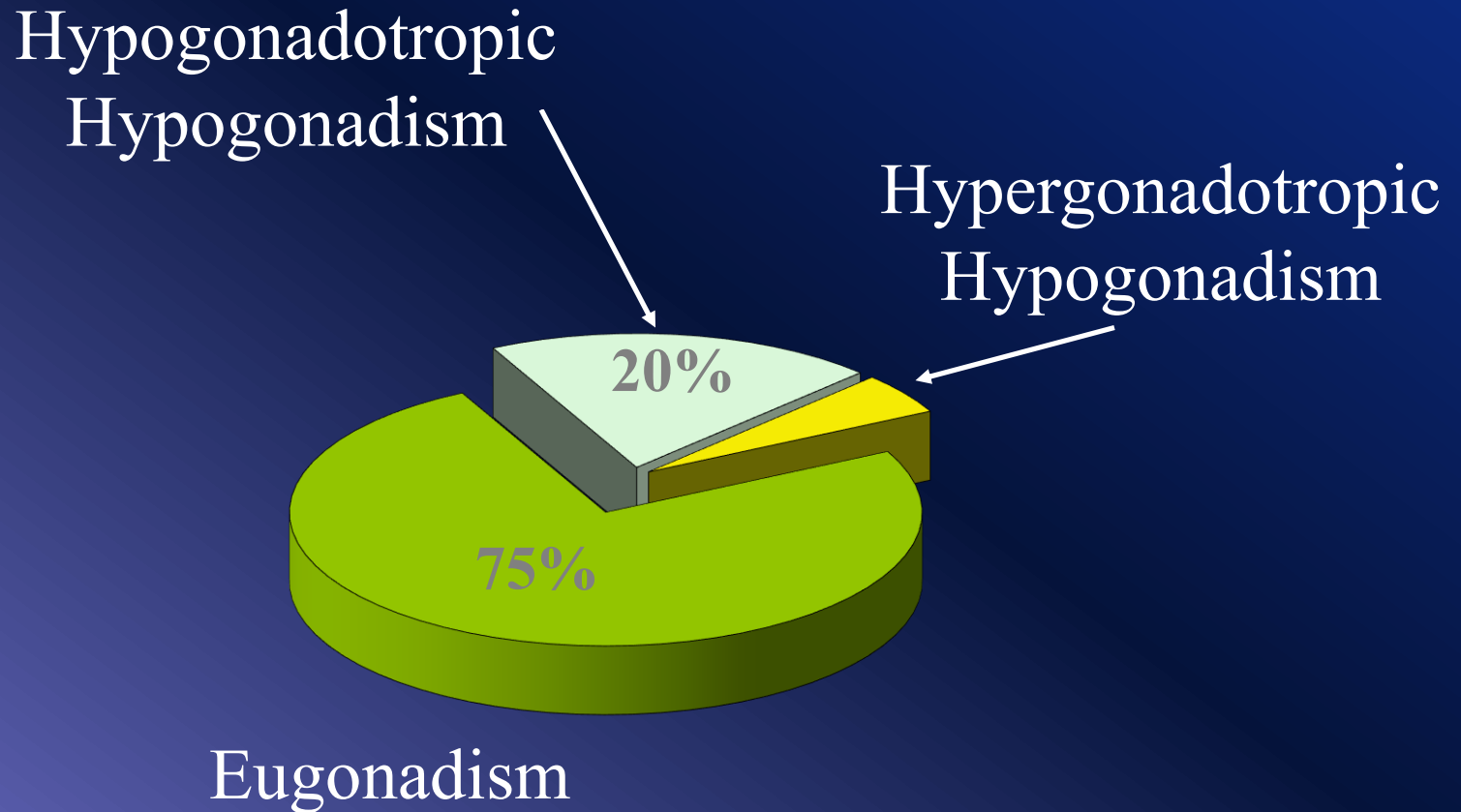
- Hypergonadotropic
 - » Elevated circulating FSH
 - » In the setting of amenorrhea, suggests a gonadal cause
- Hypogonadotropic
 - » Normal or decreased FSH levels
 - » In the setting of amenorrhea, suggests a pituitary/hypothalamic/CNS cause

Serum Gonadotropin Levels in Clinical Perspective

	Serum FSH* (IU/L)	Serum LH* (IU/L)
Normal reproductive age female	5-20 (except at midcycle)	5-20 (except at midcycle)
Hypogonadotropic state: Pre-pubertal, hypothalamic or pituitary defect	< 5	< 5
Hypergonadotropic state: Menopause, ovarian failure	> 20	> 20

* Repeat if abnormal

Cause of Secondary Amenorrhea



Secondary Amenorrhea

Eugonadal Causes

- Polycystic ovary syndrome
- Hyperprolactinemia
- Hypothyroidism
- Anatomic
 - Post surgical
 - Asherman's syndrome
 - Cervical stenosis

Secondary Amenorrhea

Hypogonadal Causes

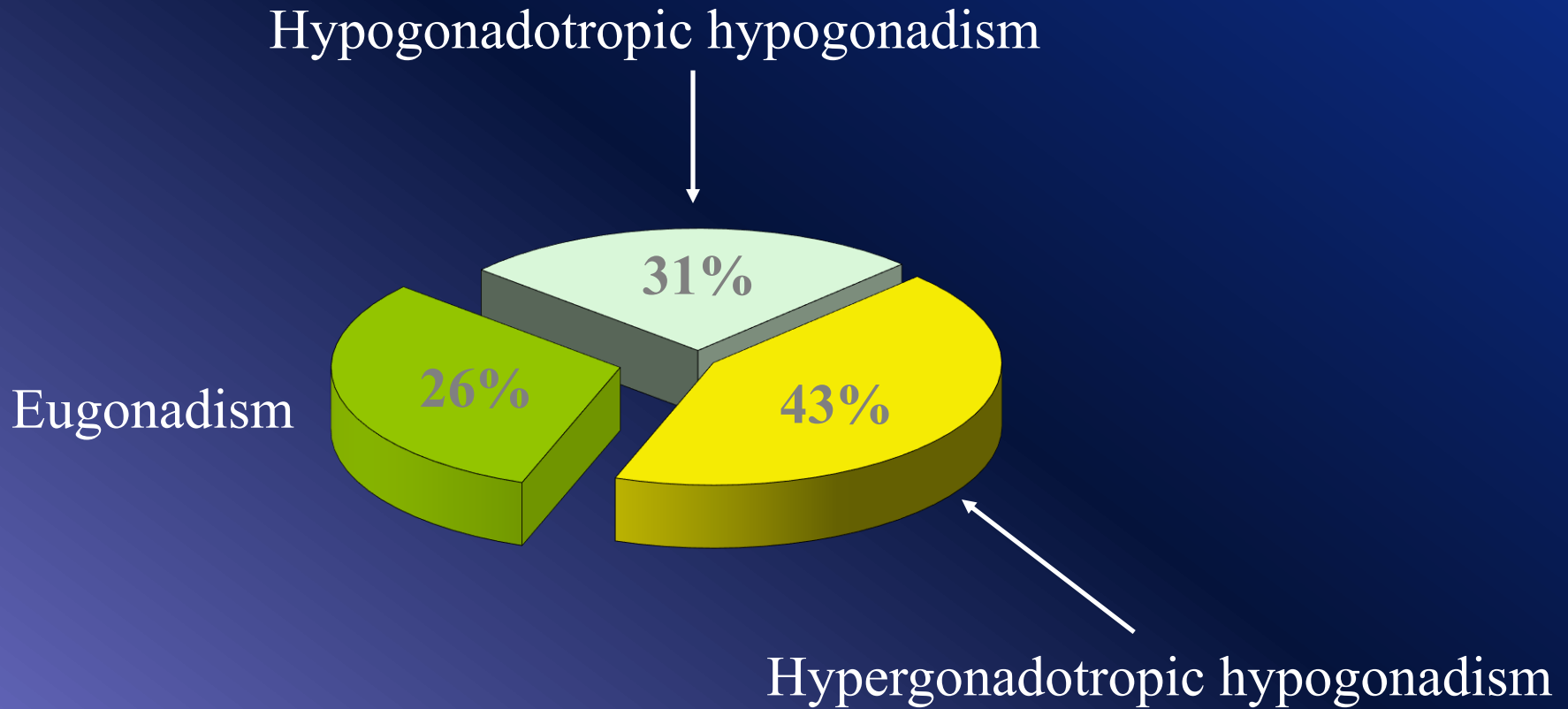
Hypergonadotropic Elevated FSH

- Menopause
- Iatrogenic
- Premature ovarian insufficiency (POI)

Hypogonadotropic Normal/Low FSH

- Functional hypo-hypo
- Hyperprolactinemia
- CNS neoplasia or lesions
- Traumatic brain injury
- Systemic disorders

Cause of Primary Amenorrhea



Primary Amenorrhea

Eugonadal Causes

- Anatomic
 - Mullerian agenesis - Meyer Rokitansky Kuester Hauser (MRKH) syndrome
 - Imperforate hymen
 - Transverse vaginal septum
 - Androgen insensitivity syndrome (AIS)
- Polycystic ovary syndrome
- Hyperprolactinemia
- Hypothyroidism

Primary Amenorrhea

Hypogonadal Causes

Hypergonadotropic Elevated FSH

- Gonadal dysgenesis
 - X chromosome deprivation
45XO
 - Mixed
- Premature ovarian insufficiency (POI)
- Swyer syndrome 46XY
- 17-hydroxylase deficiency
- Galactosemia

Hypogonadotropic Normal/Low FSH

- Physiologic delay
- Kallman's syndrome
- Endocrine diseases
- CNS neoplasia or lesions
- Systemic disorders

First Step

- History
 - Confirm amenorrhea
 - Cyclic mastalgia or pelvic pain
 - Chronology of pubertal development
 - Review of systems:
 - medications
 - galactorrhea and hirsutism
 - weight changes, exercise
 - psychosocial and dietary changes
 - Prenatal, pediatric, and family history

First Step

- Physical
 - Complete physical with pelvic is necessary
 - Height and weight
 - Breast and pubic hair Tanner staging
 - Examine thyroid, skin, spine, heart sounds, extremities
 - Pelvic: vaginal rugae, caliber and depth; cervix

Initial Testing

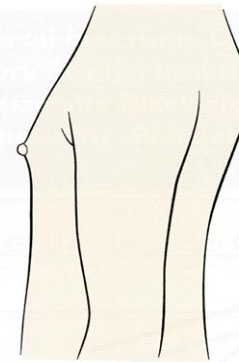
- Pregnancy test
- FSH, LH
- TSH, prolactin
- Vaginal ultrasound
- ? Estradiol
- ? Karyotype

Bioassays for Estrogen Effect

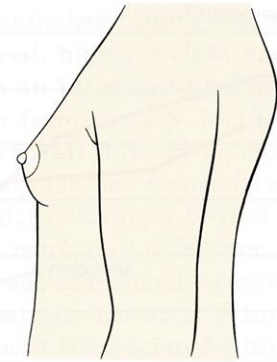
- Tanner staging of breasts for primary amenorrhea
- Progestin withdrawal
 - Give short-acting progestin for 10 days and await menstruation within 7 days of discontinuation
 - Do NOT give if outflow tract is absent/obstructed
- Endometrial thickness $> 5.0\text{mm}$

• Nakamura et al. Obstet Gynecol 1996

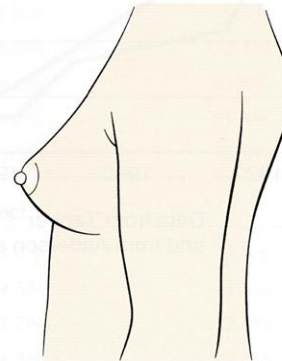
Stages of Breast Development Tanner staging



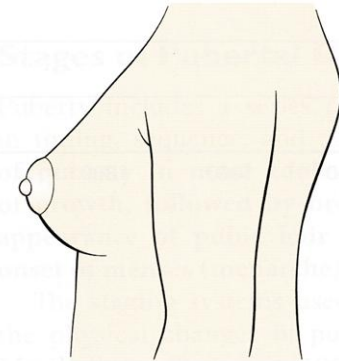
1 Prepubertal



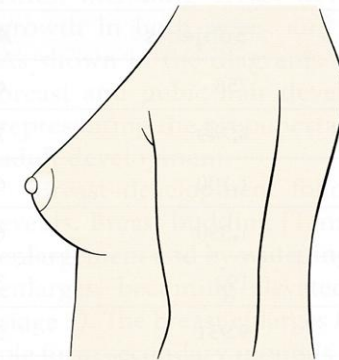
2 Breast bud



3 Breast elevation



4 Areolar mound



5 Adult contour

From Speroff 9th Edition

Pregnancy Test

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graph TD; A[Pregnancy Test] --> B[Physical exam and initial labs]; B --> C[Normal vagina and cervix<br/>Tanner 2-5 breasts]; B --> D[Normal vagina and cervix<br/>Tanner 1 breasts]; B --> E[Absent or shortened<br/>vagina];
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Physical exam and initial labs

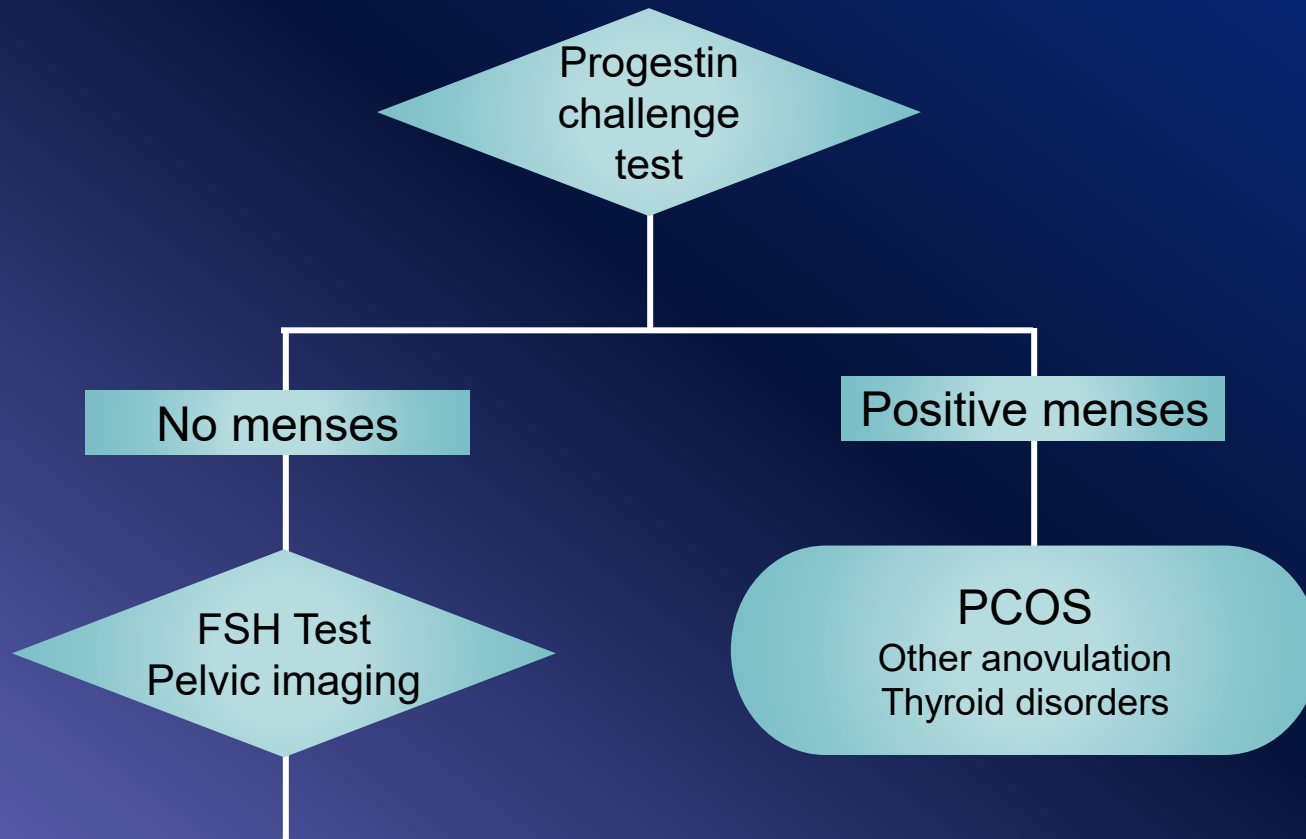
**Normal vagina and cervix
Tanner 2-5 breasts**

**Normal vagina and cervix
Tanner 1 breasts**

**Absent or shortened
vagina**

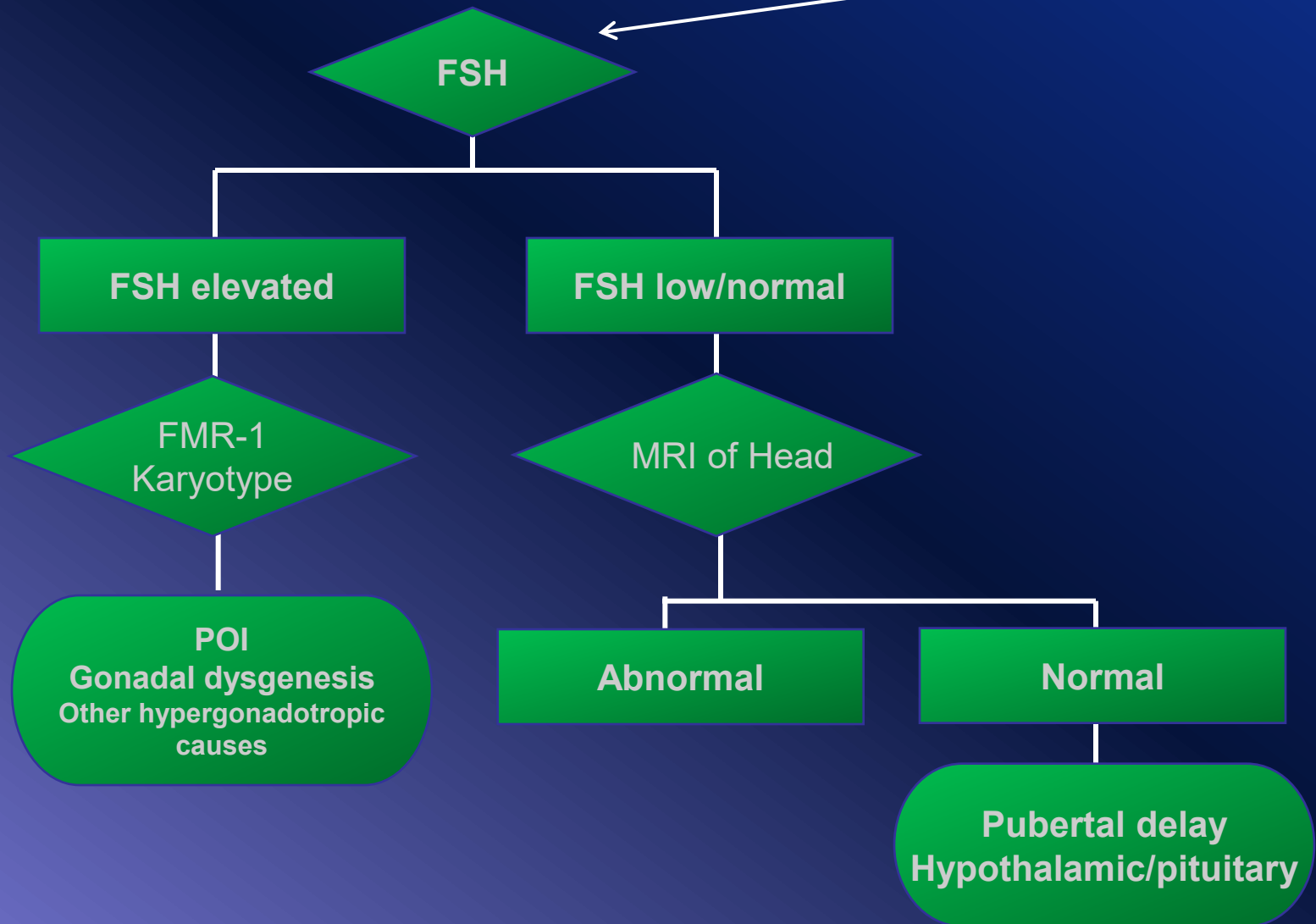
Normal vagina and cervix

Tanner 2-5 breasts



Normal vagina and cervix

Tanner 1 breasts



Premature Ovarian Insufficiency (POI)

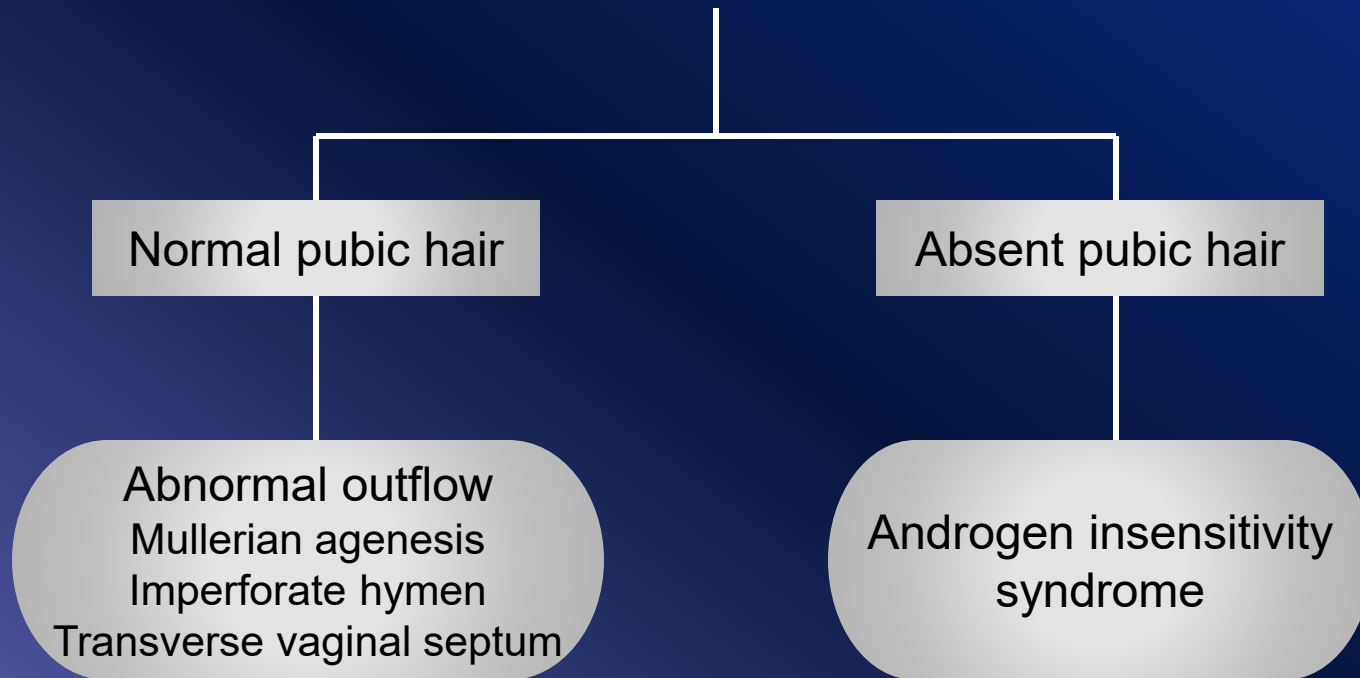
- Amenorrheic
- Hypergonadotropic
- POI = “POF” or “premature menopause”
- Due to premature follicular depletion of ovarian reserve
- General etiologies are genetic and autoimmune

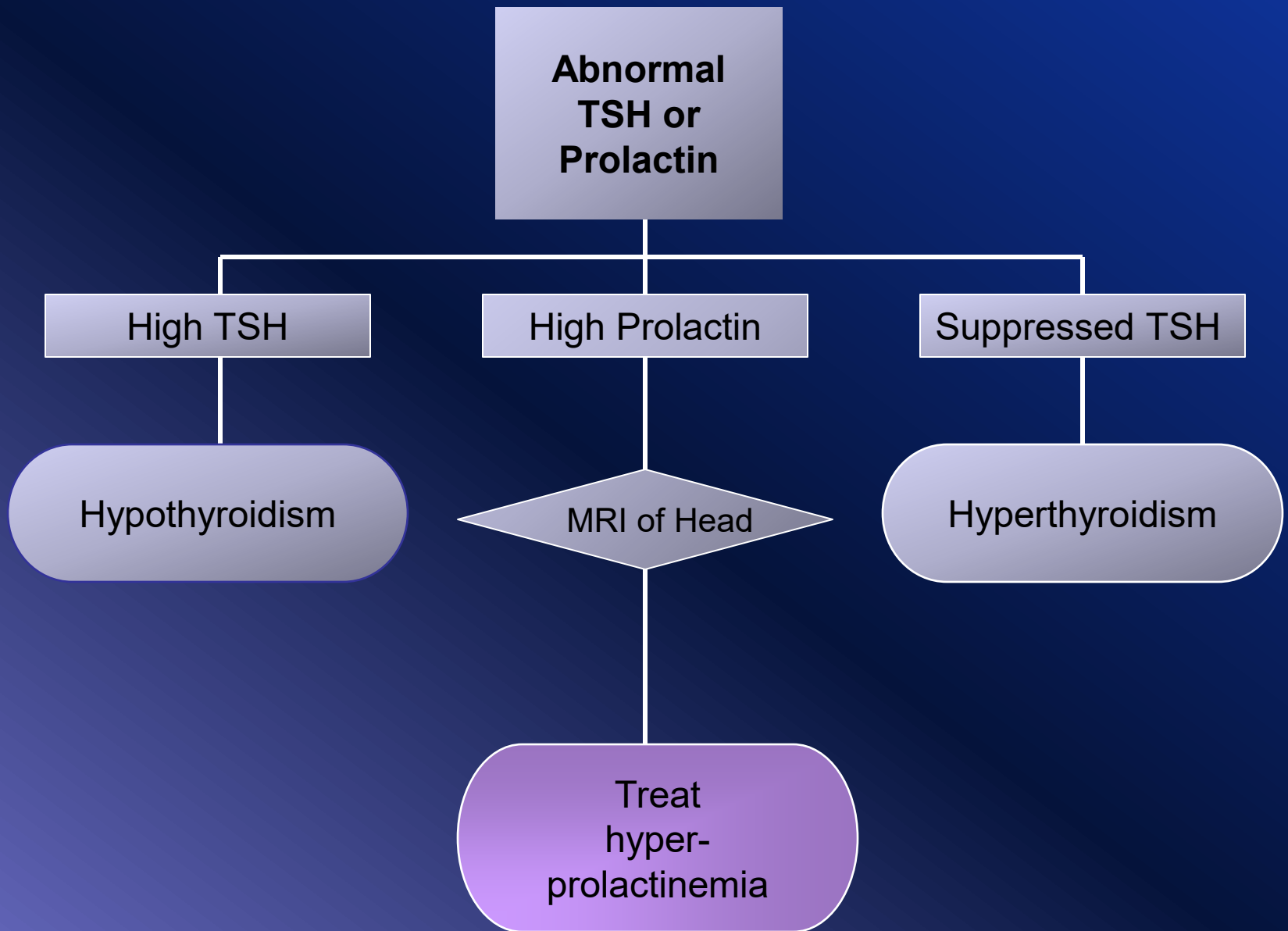
Premature Ovarian Insufficiency (POI)

- For primary amenorrhea:
 - Karyotype to evaluate:
 - X chromosome
 - Presence of Y chromosome
- For secondary amenorrhea:
 - Karyotype for X chrom. mosaicism
 - Fragile X (FMR1) Premutation
 - Wittenberg MD et al. Fertil Steril 87, 2007
 - Autoimmunity
 - Anti-CYP21 antibodies
 - Welk CK Ann NY Acad Sci. 1135, 2008

Absent or shortened vagina

No cervix





Case

- 19 yo Go Caucasian female
- Experienced one episode vaginal bleeding age 13. None since
- Denies pelvic pain
- Difficult social situation
 - Estranged from parents
 - Lives with Grandfather
 - Attempted suicide as 15 yo
- Denies medications, sexual activity

Case

- Height 59 in, 92 lbs, BP 108/77
- Pregnancy test negative
- Tanner stage 1/2 breasts, stage 3/4 pubic hair
- Normal thyroid
- Patent vagina, small cervix seen

[illegible]








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Summary

- Primary vs secondary etiologies
- History, physical and determination of estrogenization will identify most causes of amenorrhea
- Most patients should have FSH, prolactin and TSH obtained