

Screening For Endocrine Disorders of the Adrenal, Pituitary, & Gonads

Richard J. Auchus, MD, PhD, FACE
Division of Metabolism, Endocrinology & Diabetes
Departments of Internal Medicine & Pharmacology
University of Michigan

Disclosures

- **Contracted Research**
 - Neurocrine Biosciences
 - Novartis Pharmaceuticals
 - Strongbridge Biopharma
- **Consultant**
 - Laboratory Corporation of America
 - Corcept Therapeutics
 - Janssen Pharmaceuticals
 - Novartis Pharmaceuticals
 - Tokai Pharmaceuticals
 - Viamet Pharmaceuticals
 - Alder BioPharmaceuticals
 - Spruce Biosciences

Topics & Objectives

- Adrenal
 - Insufficiency
 - Primary Aldosteronism
 - Pheochromocytoma
 - Cushing's
- Pituitary
 - Hypopituitarism & Hormone Excess
- Gonadal/Reproductive
 - Male Hypogonadism
 - Amenorrhea First Steps

Adrenal Insufficiency Symptoms

- | | |
|------------------------|-------|
| • Weakness, fatigue | 100% |
| • Anorexia | 100% |
| • Nausea | 86% |
| • Vomiting | 75% |
| • Abdominal pain | 31% |
| • Salt craving | 16% |
| • Postural dizziness | 12% |
| • Muscle or joint pain | 6-13% |

Adrenal Insufficiency

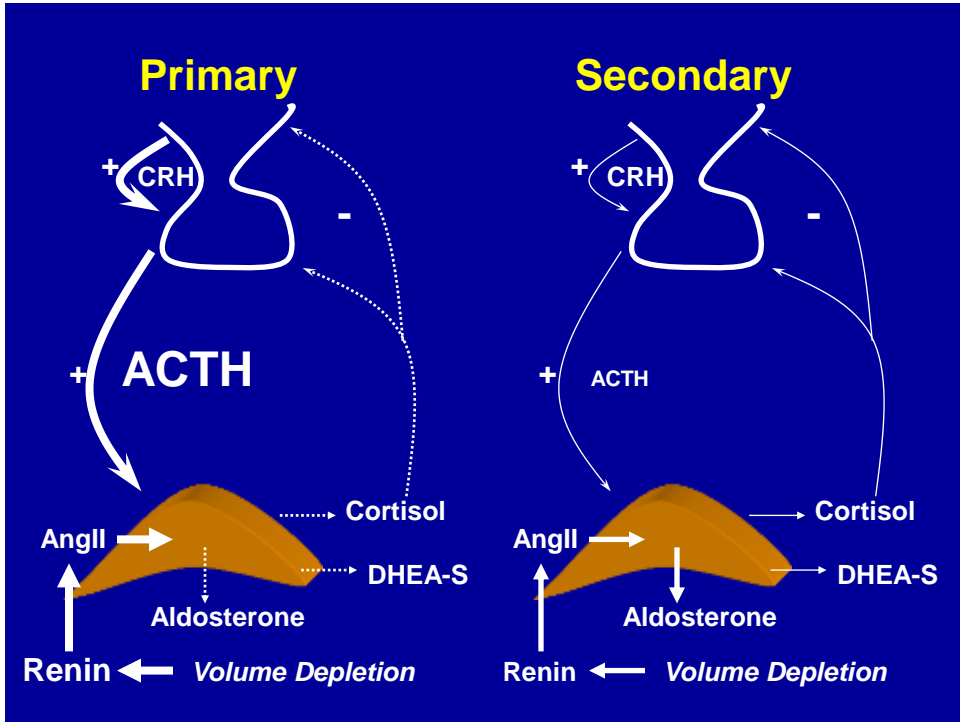
Signs & Labs

- Weight loss 100%
- Hyperpigmentation 94% (primary)
- Hypotension 88-94%
- Viteligo 10-20%
- Hyponatremia 88% (↓ Cortisol)
- Hyperkalemia 64% (↓ Aldosterone)

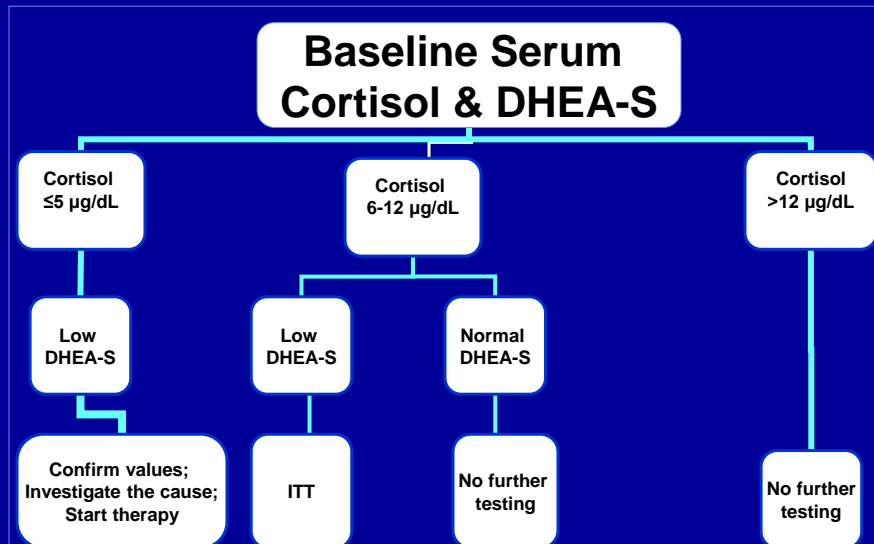
Adrenal Insufficiency

Diagnosis

- Basal (0800) Hormones Useful
 - Cortisol: <5 µg/dL Low; >15 µg/dL Normal
 - DHEA-S: >60 µg/dL Normal
 - ACTH: Low (<10 pg/mL) or High (>100)
 - Renin & Aldosterone
 - Primary AI: High Renin, Low Aldosterone
 - Secondary AI: Both Normal or High
- Cosyntropin Stimulation Test
 - 250 µg ACTH¹⁻²⁴ IM/IV
 - Cortisol@30-45 min: >18-20 µg/dL Normal



Diagnosis of Central AI: Ambulatory Setting



Primary Aldosteronism Whom To Screen?

- HTN + Spontaneous Hypokalemia
- Patients With Resistant HTN
- Patients With HTN At Age < 40
- Considering Secondary Causes
- HTN + Known Adrenal Mass

Primary Aldosteronism Screening Procedure: Stop Drugs?

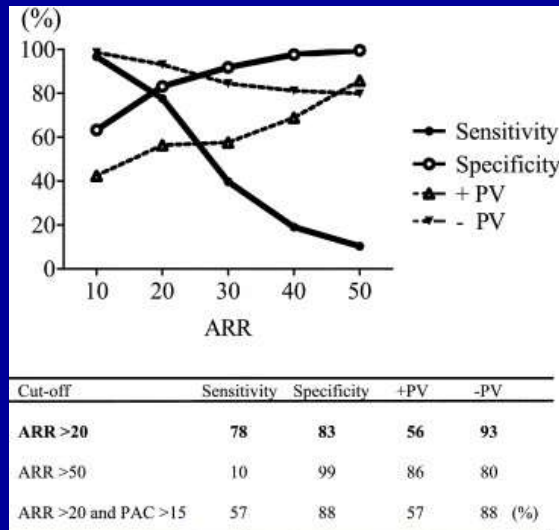
- Most Drugs OK for Screening
 - Most Drugs \uparrow PRA & Aldo (β -Blockers \downarrow PRA)
 - If PRA is Suppressed, Screen is Valid
- Up to 6 Wk: Spironolactone, Eplerenone
- Best: α_1 -Blocker + Verapamil
- Can Always Rescreen After Off Drugs

Primary Aldosteronism Screening Tests

- Random PAC/PRA or “ARR”
 - Try To Stimulate Renin Production in AM
 - PAC > 15 ng/dL AND PRA < 1 ng/mL·h
 - **PAC/PRA Dominated By Low PRA ($\div 0$)
- 24 h Urine Na, K
 - Adequate Na Intake, NO K Supplements
 - K > 30-40 meq/d + Na > 100 meq/d
 - Useful if Hypokalemic

Pearl #3: Screening is more about whether renin is suppressed than about whether aldosterone is high

ARR Sensitivity & Specificity



Nishizaka 2005 Am J Hypertens 18:805

Who Has Primary Aldo? ARR Interpretation

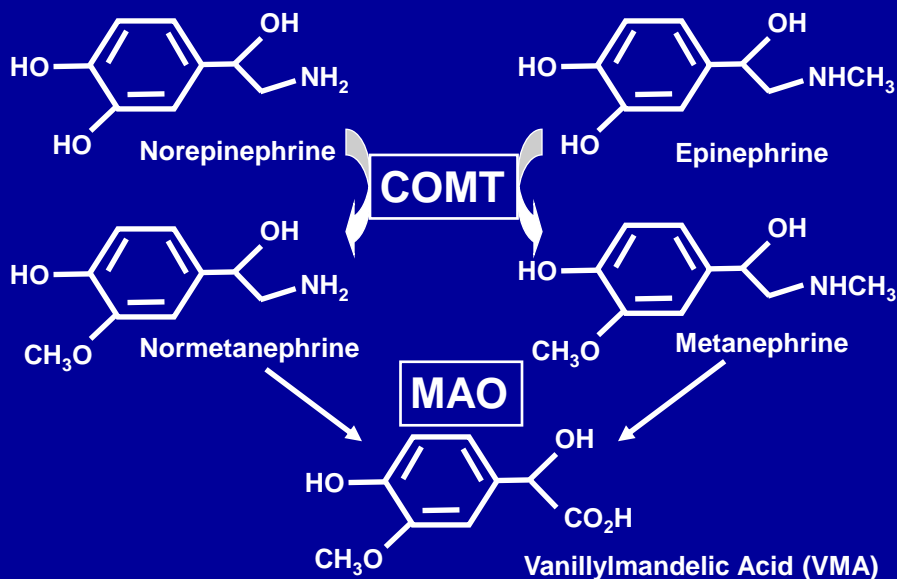
Aldo (ng/dL)	PRA (ng/mL/h)	ARR (meq/L)	Serum Potassium (meq/L)	Interpretation
14	3.5	4	4.2	Low ARR, not PA
4	0.1	40	4.0	Low aldo, not PA
21	0.6	35	4.1	Positive screen, go to confirmatory testing
12	0.6	20	3.3	Probably PA, supplement K, rescreen
38	2.0	19	3.7	Probably PA, stop meds & rescreen

Pheochromocytoma

Clinical Features

- Pressure: Sustained HTN + Spikes
- Pain: Throbbing HA, Chest Pain
- Perspiration: Heavy, Generalized
- Palpitations
- Pallor
- Other: Hyperglycemia, Weight Loss, Tremor, Orthostasis, Hypercalcemia, Fatty Liver, Cardiomyopathy
- 5-10% Asymptomatic(!!)

Catecholamine Catabolism



Pheochromocytoma

Screening Tests

- **24 h Urine Metanephrines & Catecholamines**
 - MN >400 μg , NMN >900 μg ; Epi >35 μg , NE >170 μg
- **Plasma Metanephrines: More False Positives**
 - Seated 5 Min; Indwelling Catheter Best
 - NMN >0.9 nM ~ 150 pg/mL, MN >0.5 nM ~ 60 pg/mL
 - No Caffeine, Acetaminophen, TCA, SSRIs, Labetalol, Sotalol, Phenoxybenzamine (Although Usually OK)
- **Grossly Positive Screen Sufficient (Clonidine)**
- **Most Slightly Abnormal Screens Not Pheo**

Pearl #1:
Pheo Symptoms
Correlate With
Catecholamine
Elevations

**Pearl #2:
Pheos Do Not
Hide on CT
Scans**

CT: Pheochromocytoma



Cushing Syndrome – Exam **Discriminatory Features**

- Proximal Muscle Weakness/Myopathy
- Wide, Purple, Nonblanching Striae
- Easy Bruising
- Dermal Atrophy
- Disproportionate Supraclavicular Fat
- Poor Sleep
- Unexplained Hyperglycemia or Osteoporosis

➤ *Findings Increase Pre-Test Probability*

Cushing Syndrome **Principles of Testing**

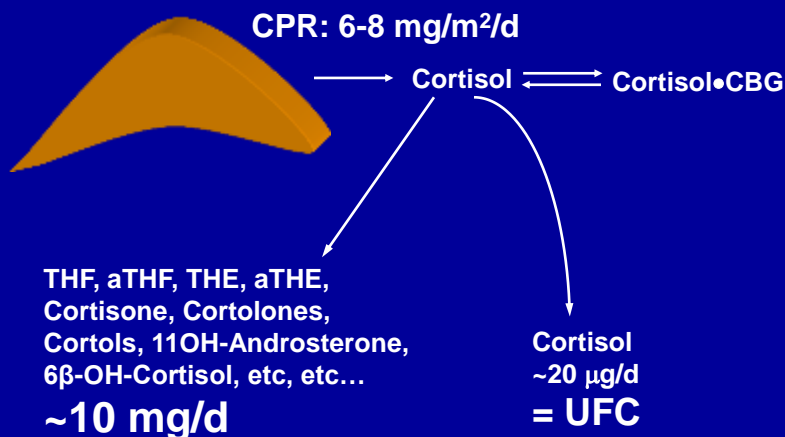
- Cortisol Production is Elevated
 - Urinary Free Cortisol
 - Not Always High, Varies With Assay
- Cortisol Production is Not Suppressible
 - Dexamethasone Suppression
 - Most Sensitive for ACTH-Independent
- The Diurnal Rhythm is Blunted
 - Nocturnal Serum or Saliva Cortisol
 - Saliva Cortisol Now Routine

Cushing Syndrome

Screening Tests: 24 h UFC

- Cortisol Cleared Only When Concentration Exceeds Plasma Binding Capacity
- “Free” Cortisol Not CBG-Bound
- False Positives: High Urine Volumes
 - Pseudocushing: EtOH, Obesity, Stress, Psyc
- False Negatives: Undercollection, Early Dz

UFC: What Are We Measuring?



Cushing Syndrome

Screening Tests: Dexamethasone

- 1 mg Overnight DST
 - 1 mg Dexamethasone at 2300
 - 0800 Cortisol $>1.8 \mu\text{g/dL}$ (Prior $>5 \mu\text{g/dL}$)
- False Positives:
 - Pseudocushing States; Estrogen (CBG)
 - Rapid Dex Metabolism (Rifampin)
- False Negatives: CYP3A4 Inhibitors

Cushing Syndrome

Nocturnal Cortisol Testing

- Late Night Cortisol Sampling
 - Midnight Cortisol $>7.5 \mu\text{g/dL}$ Diagnostic (?)
 - Requires Admission, IV Catheter
- Outpatient Saliva Cortisol
 - Reflects Plasma Free Cortisol
 - Normally Obtain 2-3 at 2300-2400
 - Values $<100 \text{ ng/dL}$ Normal
 - Values $>250 \text{ ng/dL}$ C/W Cushing's



Pituitary Testing

General Principles

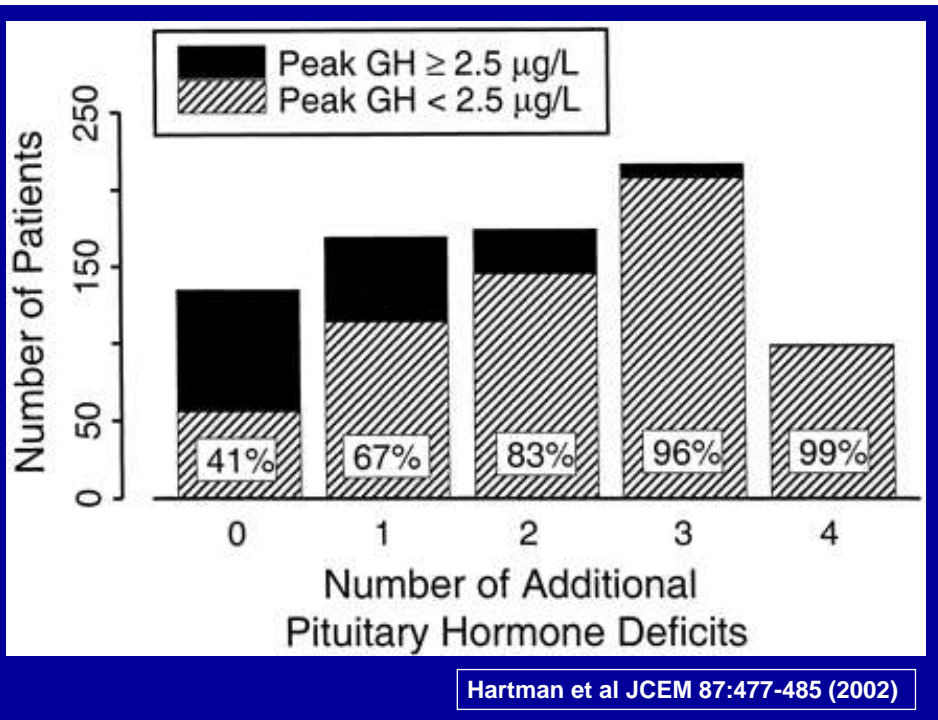
- **If You Think It Is High, Try To Suppress**
 - Or Measure When It Should Be Low
- **If You Think It Is Low, Try To Stimulate**
 - Or Measure When It Should Be High
- **Normative Data Or Lack Thereof**
 - Assays & Populations Used For Data
- **Typical Loss-of-Function Order w/Tumor**
 - GH>LH/FSH>TSH>ACTH; AVP Hypothalamus

Central Hypothyroidism

- Pitfall of Screening with TSH Only
- Inappropriate Normal/Low TSH + Low FT4
- TSH Receptor is “Noisy”
 - Free T4 Rarely Falls to <0.5 ng/dL

Growth Hormone Deficiency Basal Testing

- IGF-1: Good Screen
 - Age, Gender, Tanner Stage Ranges
 - May Be Sufficient, Especially If MPHD
 - Normal Value Does Not Exclude GHD
- IGFBP3: Slightly More Specific
 - Utility In Children Only
- Random GH of No Utility in Adults



Vasopressin Deficiency (DI)

- Neurogenic (Central)
 - Parital
 - Complete
- Nephrogenic
 - Parital
 - Complete
- Dipsogenic Polydipsia
 - Dipsogenic (Thirst)
 - Psychogenic (No Thirst)

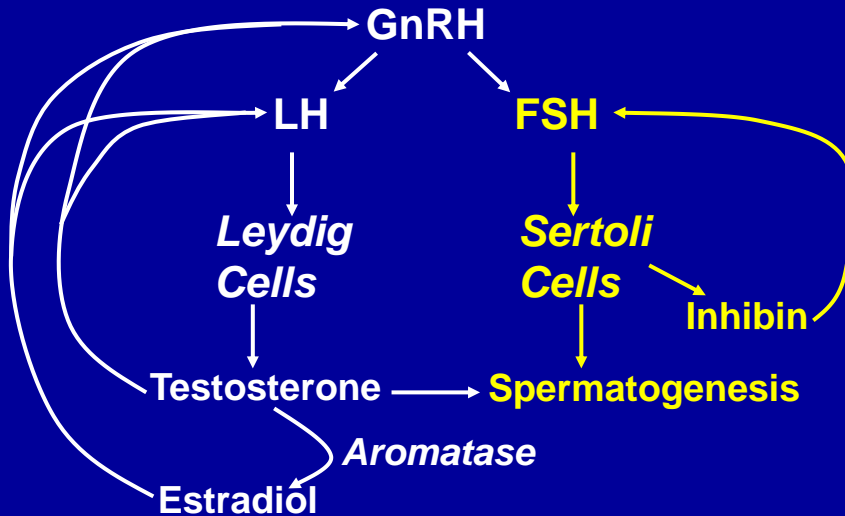
Diagnosis of DI

- Complete DI
 - Inability to Concentrate Urine
 - $S_{osm} > U_{osm}$ and $> \sim 300$ mOsm/kg
 - Thirst Center Activated 292 mOsm/kg
 - Dehydration Test Rarely Necessary
- Partial DI
 - $U_{osm} > S_{osm}$ and < 295 mOsm/kg
 - ***The Ability to Concentrate Urine Does Not Exclude a Deficiency of Vasopressin***

Hormone Excess

- Prolactin: Basal Only (Stress FP)
- GH: Basal IGF-1 +/- GH
- TSH: Non-Suppressed + High T4
 - FAS/TSH Molar Ratio > 1
 - $= [FAS (\mu\text{g/L}) / TSH (\text{mU/L})] \times 10$
- LH/FSH: “Non-Secreting Tumors”

Male Reproduction Physiology



Circulating Testosterone Fractions

Total T = Free T + Albumin-bound T + SHBG-bound T
 “Bioavailable T” or
 “Non-SHBG-bound T”

	Normal Range (ng/dL)	Deficiency (ng/dL)
Total T:	250 - 900	<250
Free T:	5 - 20	<5
Bioavailable T:	100 - 400	<100

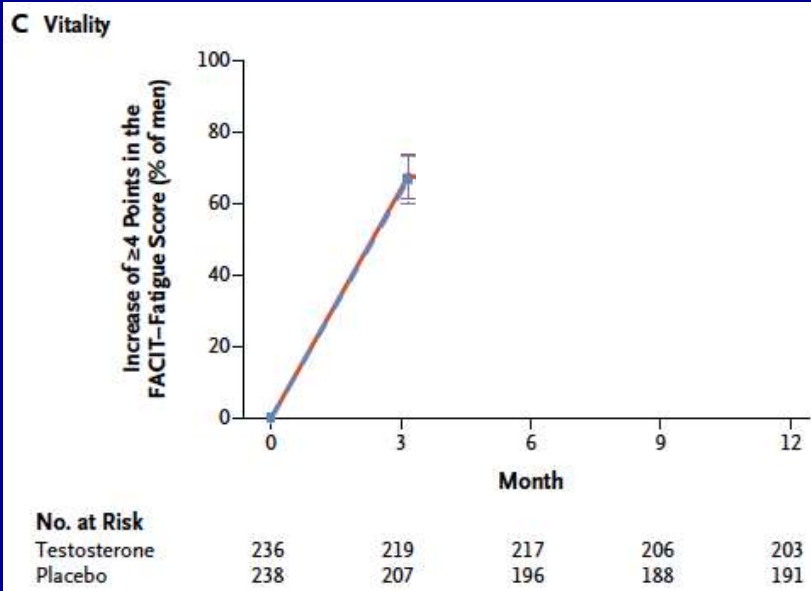
Free/Bioavailable T:

- Aging (high SHBG)
- Obesity (low SHBG)
- Borderline Total T (200-300)

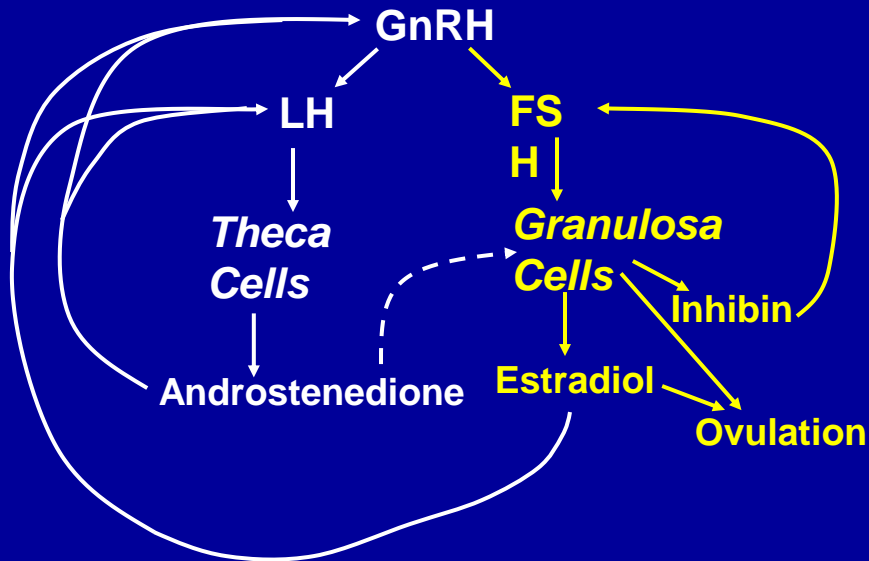
Diagnosing T Deficiency

- Screening Test:
 - Total Serum Testosterone by 0900
- If Abnormal or Low-normal, Repeat:
 - Free Testosterone and/or SHBG
 - Bio-T By Calculation <100 ng/dL
 - <http://www.issam.ch/freetesto.htm>
 - LH and FSH
 - Prolactin

Before You Start...



Female Reproductive Axes



Oligo- Amenorrhea Definitions

- **Primary: No Menses By Age 16**
 - Or By Age 14 Without Secondary Sex Char
- **Secondary: No Menses For 3 Mo**
- **Categories:**
 - Anatomic Defect
 - Ovarian Failure
 - Chronic Anovulation With Estrogen
 - Chronic Anovulation Without Estrogen

Oligo- Amenorrhea

Sites Of Dysfunction

- Hypothalamus & Higher Brain Centers
- Pituitary
- Ovaries
- Uterus
- Outflow Tract

Oligo- Amenorrhea

History

- Puberty, Prior Menses & Pregnancies
- PMH, Meds, STDs
- D&C – Why, Volume Removed
- Minimal Sx
- Infections, Trauma, Contraception
- Weight Change, Virilization
- Galactorrhea, Hot Flashes, Vision

Oligo- Amenorrhea

Physical Exam

- Ht & Wt; Tanner Stage; Turner Stigmata
- Visual Fields, Galactorrhea
- Virilization, Hirsutism, Striae, Acne
- Carotenemia, Acanthosis Nigricans

Oligo- Amenorrhea

Laboratory

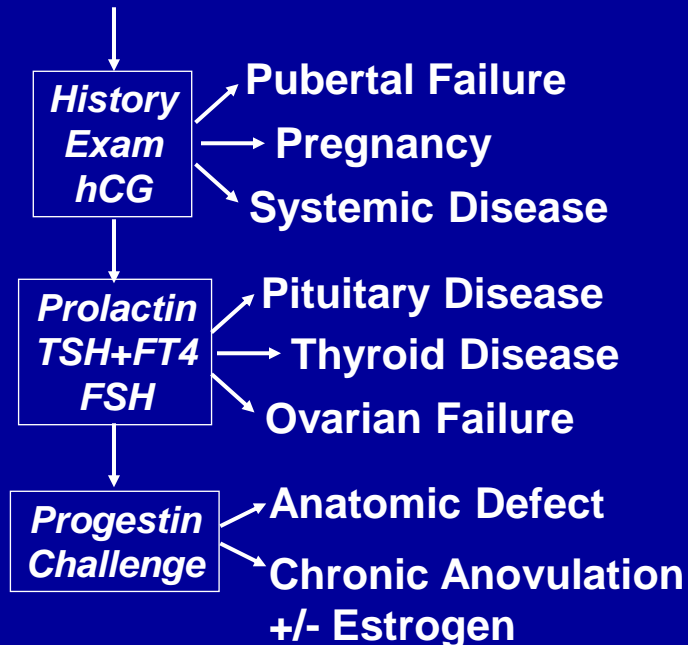
- hCG, hCG, hCG
 - ON EVERYBODY, NO EXCUSES
- FSH, Prolactin, TSH/FT4
- Karyotype If Short
- Basal Body Temperature Very Useful
- Progestin Challenge (Tanner 4-5)
 - 5 mg MPA x 10 d or 10 mg x 5 d
 - Micronized Progesterone 200 mg x 12 d

Oligo- Amenorrhea

Progestin Challenge

- **Withdrawal Bleeding Indicates**
 - Estrogen Exposure
 - Functional Endometrium
 - Patent Outflow Tract
 - Suggests Ovarian Or Partial Central D/O
- **No Withdrawal Bleeding Indicates**
 - No Estrogen Production (Trial OCP) –OR–
 - Outflow Tract Obstruction

Amenorrhea



Summary

- **Basal Testing Useful if Performed Well**
- **Primary Aldosteronism is Common**
- **Cushing's is Difficult**
- **Amenorrhea Initial Evaluation**