Subclinical Hypothyroidism

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PENNSYLVANIA ACADEMY OF FAMILY PHYSICIANS FOUNDATION

Disclosures

CONFLICTS OR INTEREST

NONE

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Question #1

- 24 yo female who presents complaining of a 6 month history of fatigue, fluid retention, dry skin, constipation. On PE has a small firm mobile goiter.
- TSH 50 mIU/L, free T4 0.4 ng/dl (0.8-2.8 ng/dl)
- What is the most likely diagnosis?
- Any further evaluation needed?
- How would you treat?

Question #2

- 32 yo female presents with no complaints. PE-normal. She has 3 healthy children and is post BTL. FMHx is positive for hypothyroidism in her mother.
- Screening TSH – 4.5 mIU/L
- Any further evaluation?
- Any treatment?

Question #2

- Same 32 yo female, however she is currently undergoing infertility evaluation and therapy.
- TSH 4.5 mIU/L
- Further evaluation?
- Treatment?

Question #3

- 49 yo female for initial evaluation.
- PHMx- T2DM, HTN, CAD/LVD, Dyslipidemia, hypothyroidism
- Meds- #19, including LT4 25 ucg daily, amiodarone, metformin, MDI insulin
- Labs- TSH 3.9 mIU/L, A1C- 12.4%, CC- normal, 7 TSH levels since 2014, 5 normal, high level 7.2 and treatment initiated
- No history of thyroid disease, PE- normal thyroid exam

Question #3

- Since 2014- 102 radiologic studies, 10 contrast CT studies, multiple admissions, multiple cardiac contrast studies
- Does she have thyroid disease?
- What is the cause of periodic TSH elevation?
- Do you recommend any further evaluation or continuation of thyroid hormone replacement therapy?
- Her weight is 72Kg, BMI- 27, what is her estimated thyroid hormone replacement dose?

Question #4

- You are seeing a 82 yo male in follow up. He has no history of thyroid disease. Screening TSH was 6.7 mIU/L. He feels well other then chronic fatigue and dry skin
- You recommend LT4 replacement secondary to symptoms.
- You tell him at 82 years he should be tired and do not recommend LT4 therapy.
- You tell him that symptoms are most likely not related to thyroid disease and that a TSH of 6.7 is in a normal range for his age.

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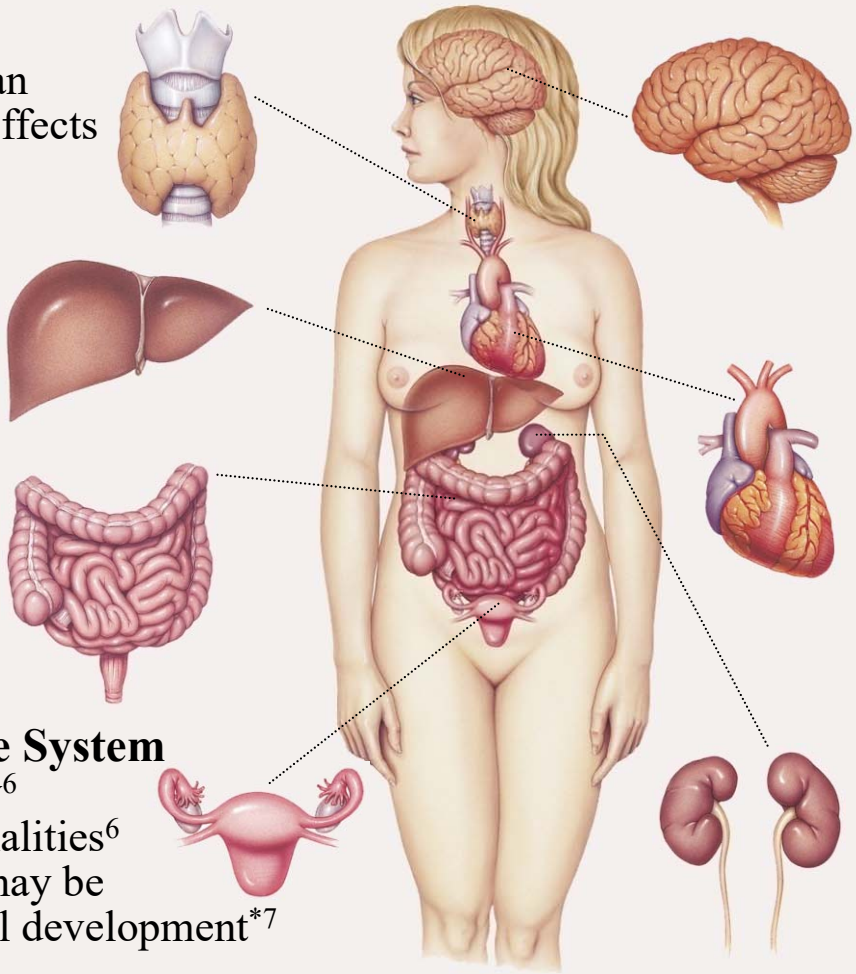
Understanding Thyroid Disease

The Thyroid
- Thyroid disease can have widespread effects

The Liver
- Increased LDL cholesterol[2]
- Elevated triglycerides[2]

The Intestines
- Constipation[4]
- Decreased GI activity[4]

The Reproductive System
- Decreased fertility[6]
- Menstrual abnormalities[6]
- Hypothyroidism may be detrimental to fetal development*[7]



The Brain
- Depression[1]
- Decreased concentration[1]
- General lack of interest[1]

The Heart
- Decreased heart rate[3]
- Increased/decreased blood pressure[3]
- Decreased cardiac output[3]

The Kidneys
- Decreased function[5]
- Fluid retention and edema[5]

References:
1. Nemeroff CB. Clinical significance of psychoneuroendocrinology in psychiatry: focus on the thyroid and adrenal. *J Clin Psychiatry*. 1998;59(suppl1):13-20.
2. Klausen IC, Nielsen FE, Hegedüs L, Gerdes LU, Charles P, Faergeman O.Treatment of hypothyroidism reduces low-density lipoproteins but not lipoprotein (a) *Metabolism*. 1992;41:911-914.
3. Polikar R, Burger AG, Scherrer U, Nicod P. The thyroid and the heart. *Circulation*. 1993;87:1435-1441.
4. Vassilopoulou-Sellin R, Sellin JH. The gastrointestinal tract and liver in hypothyroidism. In:Braverman LE, Utiger RD, eds. *Werner and Ingbar's The Thyroid*. 7th ed. Philadelphia, Pa: Lippincott-Raven Publishers; 1996:816-820.
5. Moses AM, Scheinman SJ. The kidneys and electrolyte metabolism. In:Braverman LE, Utiger RD, eds. *Werner and Ingbar's The Thyroid*. 7th ed. Philadelphia, Pa: Lippincott-Raven Publishers; 1996:812-815.
6. Emerson CH.Thyroid function and disease in the female. In: Gold JJ, Josimovich JB, eds. *Gynecologic Endocrinology*. 4th ed. New York, NY:Plenum Publishing Corp; 1987:109-133.
7. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregancy and subsequent neuropsychological development of the child. *N Engl J Med*. 1999;341:549-555.

Recent Studies

Prevalence of Thyroid Disease

The Colorado Study[1]

At a statewide health fair in Colorado (N=25,862), participants were tested for TSH and total T_4 levels.

- 9.5% of subjects had elevated TSH; most were subclinically hypothyroid (in this study, normal T_4 with TSH >5.1)
- Among the subjects already taking thyroid medication (almost 6% of study population), 40% still had abnormal TSH levels
- Among patients not taking thyroid medication, 9.9% had a thyroid abnormality that had been unrecognized
- There may be in excess of 13 million cases of undetected thyroid gland failure nationwide. In addition, there are nearly 14 million patients on thyroid hormone replacement

1. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med*. 2000;160:523-534.

Recent Studies

Prevalence of Thyroid Disease

Thyroid Disease and Aging

The incidence of thyroid disease increases with age.[1]

The Colorado Study

Percent of Elevated TSH (Age)

	18	25	35	45	55	65	75
Male	3%	4.5%	3.5%	5%	6%	10.5%	16%
Female	4%	5%	6.5%	9%	13.5%	15%	21%

– adapted from Canaris, et al.

Physiological changes in organ systems and higher prevalence of other diseases may make older patients more vulnerable to consequences of even mild thyroid deficiency.[2]

1. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med.* 2000;160:523-534.
2. Jayme JJ, Ladenson PW. Subclinical thyroid dysfunction in the elderly. *TEM.* 1994;5(2):79-86.

Population Based Studies

- 4-15% if populations have thyroid disease
- NHANES III- 4.3% of cohort of 16,533
- Prevalence increased with rising age
- Higher in areas of iodine sufficiency
  - 4.2% iodine deficient areas
  - 23.9% iodine sufficient areas
- Hollowell etal. NHANES III. JCEM 2002;87:489. Biondi etal. JAMA 2019;322:153

Thyroid Auto Antibodies Specific for which disease?

TSH Receptor	Graves'	97-99%
TSH Receptor	Hashimoto's	10-15%
TPO	Graves'	70-80%
TPO	Hashimoto's	90-95%
Tg	Graves'	20-40%
Tg	Hashimoto's	30-50%

Major causes of hypothyroidism

Primary hypothyroidism
Chronic autoimmune thyroiditis
Iatrogenic
Thyroidectomy
Radioiodine therapy or external irradiation
Iodine deficiency or excess
Drugs - thionamides, lithium, amiodarone, interferon-alfa, interleukin-2, perchlorate, tyrosine kinase inhibitors
Infiltrative diseases - fibrous thyroiditis, hemochromatosis, sarcoidosis
Transient hypothyroidism
Painless (silent, lymphocytic) thyroiditis
Subacute granulomatous thyroiditis
Postpartum thyroiditis
Subtotal thyroidectomy
Following radioiodine therapy for Graves' hyperthyroidism
Following withdrawal of suppressive doses of thyroid hormone in euthyroid patients
Congenital thyroid agenesis, dysgenesis, or defects in hormone synthesis
Central hypothyroidism
TSH deficiency
TRH deficiency
Generalized thyroid hormone resistance

TRH: thyrotropin-releasing hormone; TSH: thyroid-stimulating hormone.

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Etiology of Subclinical Hypothyroidism

- Same as those of overt hypothyroidism
- Most common Hashimoto's thyroiditis (TPO+)
- Prior ablation or antithyroid drug therapy
- Prior partial thyroidectomy
- External radiation therapy
- Inadequate LT4 replacement
- Drugs impairing thyroid function

- Bondi etal. JAMA 2019; 322:153

Clinical Findings

- Most patients have TSH <10 mIU/L and asymptomatic
- May have vague symptoms, especially elderly
  - Dry skin, constipation, low energy
- Prospect. Study of 558 pts screened at 85th birthday
  - 5% had subclinical
  - No assoc. between TSH and cog. Function, disability
  - Increased TSH assoc. with slower decline in function

- Gusselkoo J etal. JAMA 2004; 292:2591

Diagnosis

- Based on biochemical testing alone
- Defined as:
  - Normal serum free T4 with elevated TSH
- May occur in presence or absence of mild symptoms
- If initial TSH is elevated, should repeat with free T4 after 1-3 months before making the diagnosis
- Exception is pregnancy or undergoing infertility evaluation and/or treatment. Immediately repeat and treat is TSH elevation confirmed

What represents an elevated TSH?

- Upper normal 4-5 mIU/L in most labs
- Healthy young 2.5-3.0 mIU/L, some experts
- Healthy octogenarians 6-8 mIU/L
- Pregnant or attempting – either specific lab defined trimester ranges or
  - 1st trimester- <2.5 mIU/L
  - 2nd and 3rd - <3.0 mIU/L
  - ATA Guidelines- 2017

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Subclinical Hypothyroidism

- Defined biochemically as a normal serum free thyroxine (T4) concentration in the presence of an elevated thyroid stimulating hormone concentration (TSH).
- Although some patients may have vague, nonspecific symptoms of hypothyroidism, attempts to identify patients clinically have not been successful. Thus, this disorder can only be diagnosed on the basis of lab results.

- Beuden DA. J Fam Pract. 1994;38:583. Bell DJ et al. Clin. Endo. 2007;66:548

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DDx of TSH Elevation

- Recovery phase of non-thyroid illness
- Recovery from thyroiditis- subacute, PP, silent
- Assay variability
- Heterophilic antibodies – assay interference, RF
- “Macro TSH”- IGG complexes, otherwise euthyroid
- TSH producing pituitary adenoma- pt hyperthyroid
- Thyroid hormone resistance- elevated T4/T3
- Central hypothyroidism- low free T4
- Morbid obesity- centrally mediated high TSH

Identify Cause of TSH elevation

- Any history of symptoms or history of thyroid disease
- Review recent history, admissions, stress, procedures
- Review medications
- PE- goiter or physical manifestations of thyroid disease
- Consider measuring TPO antibodies if that data will aid in treatment decision

Consequences of Subclinical Hypothyroidism

- Progression to hypothyroidism
  - Prospective studies 10-20 yr f/u- cumulative incidence 33-55%, yearly incidence 2-4%
  - Related to initial TSH level and TPO status
  - TSH >10, +TPO = increased progression
  - 82 women with TSH – 4-6 mIU/L, zero progression over 9.2 years
  - TSH normalization also occurs, TSH <10, neg. TPO
  - Diez JJ etal. JCEM 2005;90:4124

Consequences

- CVD
  - Increase CAD/LVF with TSH >10, increase stroke risk in pts <49, increase cholesterol TSH >10
- Reproductive abnormalities
  - Risk not well defined, ATA no stance on therapy
- NAFLD- some data on increased prevalence
- Neuropsychiatric symptoms- no clear association

- Chake L etal. JCEM 2015;100:2181

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Case Study 1

- You are seeing a 85 yo male in follow up. PMHx, controlled T2DM on oral agents, HTN, asymptomatic CAD, DJD. Recent TSH level was 7.56 uIU.
- He is complaining of dry skin, constipation and fatigue.
- What is your recommendation on treatment?

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Case Study 1

- ATA guidelines for 70-80 yo patients is TSH of 4-6 uIU
- JAMA- prospective study on 251, 80+ yo patients, mean TSH 5.1 – 7.2 uIU
- Randomly assigned LT4 vs placebo and assessed symptom score
- Treatment not significantly associated with hypothyroid symptom score or fatigue
- JAMA 2019; 322(20):1977

Treatment - Levothyroxine

- All professional groups recommend treatment in patients with TSH >10 mIU/L
- In patients with levels 4.5-10 mIU/L studies have generally not shown benefit. Consider treatment with TSH >8.0, TPO + status, prior history of thyroid disease

ATA, AACE, ETA Guidelines

- TSH >10 mIU/L- Treatment suggested due to risk of progression and atherosclerotic risk
- TSH 7.0-9.9 mIU/L- Treat patients < 65-70 years due to reports of increased CV mortality
- TSH upper normal – 6.9 mIU/L- treat pts younger than 65-70 with convincing symptoms, TPO + status, pts with goiter. Suggest against treating pts >70 due to upper limit of normal TSH may be as high as 6-8 mIU/L
- Suggest initiating LT4 in women with infertility and attempting pregnancy

Treatment Hypothyroidism- ATA 2014 Guidelines

- Use of brand name or same generic preparation
- If tolerance or absorption problems consider gel capsules (Tirosint)
- Fasting am or HS, caution with other meds, vitamins, supplements
- If high dose requirement think malabsorption, H. pylori, atrophic gastritis, celiac disease
- Starting dose of LT4, consider weight, lean body mass, pregnancy status, 1.6- 1.8 ug/kg, suppression 2.1-2.7 ug/kg
- Initiate at full dose or partial replacement with gradual titration, assessment TSH at 4-6 week intervals after dose change

Treatment of Hypothyroidism- 2014 ATA Guidelines

- Avoid over/under replacement, i.e., elderly, persistent symptoms
- Suspect non adherence, consider trial once weekly dosing
- Secondary hypothyroidism – free T4 goal is upper half of normal range, start at 1.6 ug/kg and adjust
- Strongly recommend against use of LT4 in euthyroid patients
- LT4 considered as routine care, do not recommend use of thyroid extracts or combined LT4/LT3 regimens
- Recommend against use of compounded thyroid hormone products, dietary supplements

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American Thyroid Association

- Recommends replacement with synthetic levothyroxine products
- Suggests raising TSH goal to 4-6 mIU/L in people 70 to 80 years of age

- ATA Guidelines for Treatment of Hypothyroidism. March 2015

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Case 2

- 20 yo male complex PMHx, being seen for hypothyroidism and delayed puberty
- Lives in group home. History of autism, schizoaffective disorder, obesity, gynecomastia.
- Complains of delayed puberty, poor terminal hair growth.
- Meds: Depakote, Colace, calcium/D, famotidine, hydroxyzine, trazodone, LT4 88 ucg daily, metformin
- Labs: TSH- range 3.07- 7.56 mIU, TPO- neg, Thyroid US- normal, Free T4- normal
- How do you want to proceed?

Case 2

- Due to no clear diagnosis of etiology of hypothyroidism and no clear TSH elevation. Levothyroxine held with repeat TSH in one month
- 01/2020- TSH – 3.51 uIU, free T4- 0.90 ng/dl
  02/2020- TSH – 3.724 uIU, free T4- 1.00 ng/dl
- Remains off thyroid hormone

Liradas S etal. LT4 overuse. Thyroid. Nov. 2018; 10.1089 epub

- LT4 one of most prescribed drugs worldwide- #1 US, #3 UK
- Once started 90% of pts continue long term therapy
- Study goal- to determine need for LT4 therapy
- Study cohort – 291 subjects, 84% women, age 48 +/- 19 yrs. On LT4 without solid dx of hypothyroid etiology
- At entry assessed TSH/Free T4, stopped LT4 and reassessed TSH/Free T4 and performed thyroid US at 6-8 weeks
- Consider hypothyroid if f/u TSH > 4.5 mIU/L

Lirada S etal. Continued

- Results in 291 subjects
  - 114 (39.2%) became hypothyroid – Gp A
  - 177 (60.8%) remained euthyroid – Gp B, p <0.001
  - Groups comparable for sex, FMHx, Age, TPO status, duration of therapy
  - Group A had a higher prevalence of inhomogeneous echo pattern on US evaluation, p <0.001

Liradas S etal. - Continued

- Conclusions
  - Found significant overuse of LT4
  - Need to establish firm diagnosis prior to initiating therapy
  - Need to undertake periodic evaluation of all patients on chronic therapy when dx is unclear to determine need to continue
  - Is rational to introduce 6-8 week period of LT4 withdrawal with TSH monitoring when dx is unclear as approach to decrease LT4 overuse.

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LT4 Overuse- Time for about face? Lancet Endo. Vol 5, April 2017

- 25% of UK population had TSH tested yearly
- 1/3 of patients with subclinical hypothyroidism placed on LT4 with only one abnormal TSH
- 62% of pts with TSH 5.5-10 mIU/L normalized without intervention
- No good correlation between symptoms and thyroid hormone status
- In patients >65 years taking LT4, 40-50% had TSH levels < 0.45 mIU/L increasing risk of arrythmia, angina, bone loss/fracture

Question #1

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Summary – Subclinical Hypothyroidism

- Commonly identified process defined at elevated TSH level with normal free T4
- A biochemical diagnosis, not clinical diagnosis
- Always confirm with additional testing prior to treatment
- Define etiology prior to treatment
- Treatment- pregnancy, young, +TPO/ AITD
- Suspect over treatment
- Consider trial off therapy when no clear etiology identitied

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Adrenal Nodules and Aldosterone

Andrea Manni, MD

March 6, 2020

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Disclosure

- Nothing to disclosure.

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Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors

ADRENAL INCIDENTALONOMAS

- An adrenal incidentalonoma is an asymptomatic adrenal mass detected on imaging not performed for suspected adrenal disease.
- Most, but not all adrenal incidentalonomas are non functioning adrenal cortical adenomas.
- The purpose of this guideline is to provide clinicians with best possible evidence-based recommendations in the following areas.
  - How to assess the risk of malignancy
  - How to determine whether the tumor is functioning
  - Who should be treated surgically
  - What follow up is indicated if the adrenal incidentalonoma is not surgically removed

Tumor entity	Median (%)	Range (%)
Series including all patients with an adrenal mass*		
Adenoma	80	33–96
Nonfunctioning	75	71–84
Autonomously cortisol-secreting	12	1.0–29
Aldosterone-secreting	2.5	1.6–3.3
Pheochromocytoma	7.0	1.5–14
Adrenocortical carcinoma	8.0	1.2–11
Metastasis	5.0	0–18
Surgical series**		
Adenoma	55	49–69
Nonfunctioning	69	52–75
Cortisol-secreting	10	1.0–15
Aldosterone-secreting	6.0	2.0–7.0
Pheochromocytoma	10	11–23
Adrenocortical carcinoma	11	1.2–12
Myelolipoma	8.0	7.0–15
Cyst	5.0	4.0–22
Ganglioneuroma	4.0	0–8.0
Metastasis	7.0	0–21

*Data from references: (2, 6, 14); **Data from references: (2, 3, 6, 7, 10, 14, 17, 18).

ASSESSMENT OF THE RISK OF MALIGNANCY

- Non contrast CT is the imaging technique of choice. If the non contrast CT is consistent with a benign adrenal mass (Hounsefield units < 10) that is homogeneous and smaller than 4 cm (based on clinical experience) no further imaging is required.
- The above applies to patients with no known extra-adrenal malignancy. In patients with extra-adrenal malignancies, 7% of cases with non contrast HU < 10 turned out to be malignant.
- MRI has the advantage of avoiding ionizing radiation. However, this test is not sufficiently standardized to make recommendations about defining the benign or malignant nature of the tumor.

ASSESSMENT OF THE RISK OF MALIGNANCY

- If an adrenal mass is indeterminate on non contrast CT, three options should be considered by a multidisciplinary team.
  - Immediate additional imaging with another modality
  - Interval imaging in 6-12 months
  - Surgery without further delay
- Contrast CT with assessment of washout. A washout >60% is indicative of a benign lesion
- FDG-PET/CT has the advantage that the risk of false negative results is quite low. However, the procedure is more expensive and has the disadvantage that several benign adrenal tumors (e.g. functional adenomas) may be FDG-positive.

ASSESSMENT OF THE RISK OF MALIGNANCY

- The panel recommend against the use of an adrenal biopsy, unless there is a history of extra-adrenal malignancy.
- This recommendation is particularly strong in patients suspected to have an adrenal carcinoma because of the risk of tumor dissemination, thus precluding the possibility of a curative resection.

ASSESSMENT FOR HORMONE EXCESS

- Every patient with an adrenal incidentalonoma should undergo careful assessment including clinical examination for symptoms and signs of adrenal hormone excess suggesting:
  - Cushing
  - Primary aldosteronism
  - Pheochromocytoma
  - Androgen producing tumors

ASSESSMENT OF HORMONE EXCESS

- The panel recommend excluding pheochromocytoma by measurement of plasma free metanephrines or urinary fractionated metanephrine.
- Metanephrines should be measured in normotensive patient as there are clinically silent pheochromocytomas which may cause hemodynamic instability during surgery.
- Measurement of metanephrine may be avoided when imaging criteria are typical for lipoid rich adenoma.

ASSESSMENT OF HORMONE EXCESS

- The panel recommends the use of the aldosterone/renin ratio to exclude primary hyperaldosteronism in patients with hypertension or unexplained hypokalemia.
- The panel suggest measurement of sex hormones and steroid precursors in patients with imaging or clinical features suggestive of adrenal corticol carcinomas. They include measurement of DHEA-S, androstenedione, 17-hydroxy progesterone, testosterone in women, extradiol in men and postmenopausal women.

ASSESSMENT FOR HORMONE EXCESS

- All patients with adrenal incidentalonomas should undergo a 1mg overnight dexamethasone suppression test
- They recommend to use a post-dexamethasone cortisol level of < 1.8 ug/dL to exclude autonomous cortisol secretion.
- This cut-off is supported by studies showing that patients with post-dexamethasone cortisol values > 1.8 ug/dL have increased morbidity and mortality.

ASSESSMENT OF HORMONE EXCESS – Role of additional tests to rule out autonomous or excess cortisol secretion

- Late night salivary cortisol
- 24-hour urinary free cortisol

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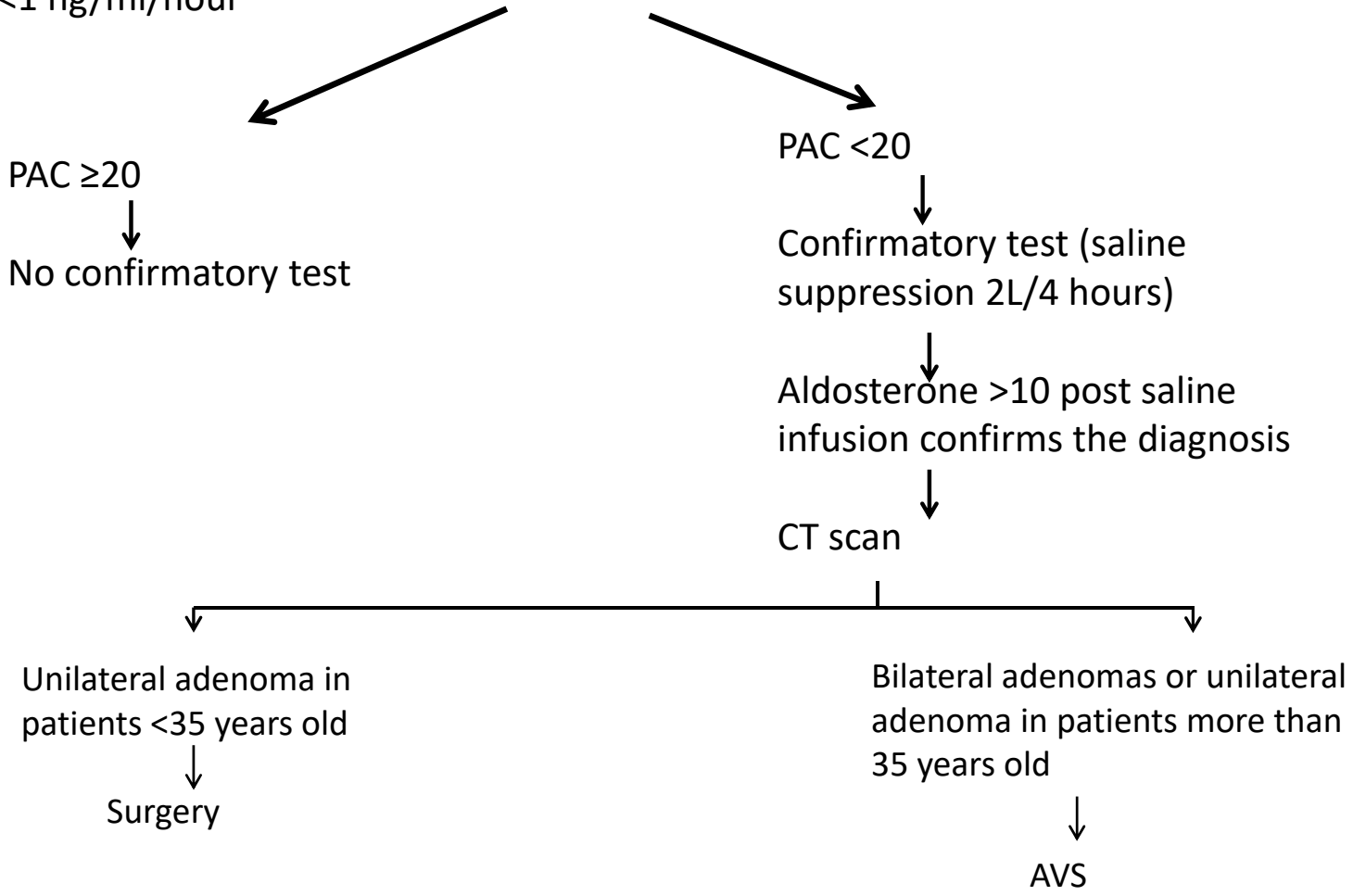
SCREENING FOR CO MORBID CONDITIONS

- The panel recommends screening patients with “possible autonomous cortisol secretion”, or autonomous cortisol secretion for hypertension and type 2 diabetes.
- The association with dyslipidemia is less proven, although biologically plausible.
- The panel recommends screening patients with “autonomous cortisol secretion”, for asymptomatic vertebral fractures.
- This can be accomplished by re-evaluating available images (e.g. CT scan when performed) or by plain X-rays. No consensus was reached about recommending DEXA.

DIAGNOSIS OF PRIMARY HYPERALDOSTERONISM

- Plasma aldosterone/renin ratio >20-40 provided PAC ≥10 ng/dL and PRA <1 ng/ml/hour



ASSESSMENT OF HORMONE EXCESS

- DHEA-S
- Testosterone in women
- Estradiol in men

SURGICAL TREATMENT

- The panel recommends adrenalectomy as the standard of care for unilateral adrenal tumors with clinically significant hormone excess.
- The panel recommend against performing surgery in patient with an asymptomatic, non-functioning unilateral adrenal mass with obvious benign features on imaging studies.
- There was consensus that a tumor < 4cm with benign imaging features does not require surgery. An individualized approach is suggested for tumors > 4cm.

FOLLOW UP OF PATIENTS NOT UNDERGOING ADRENAL SURGERY

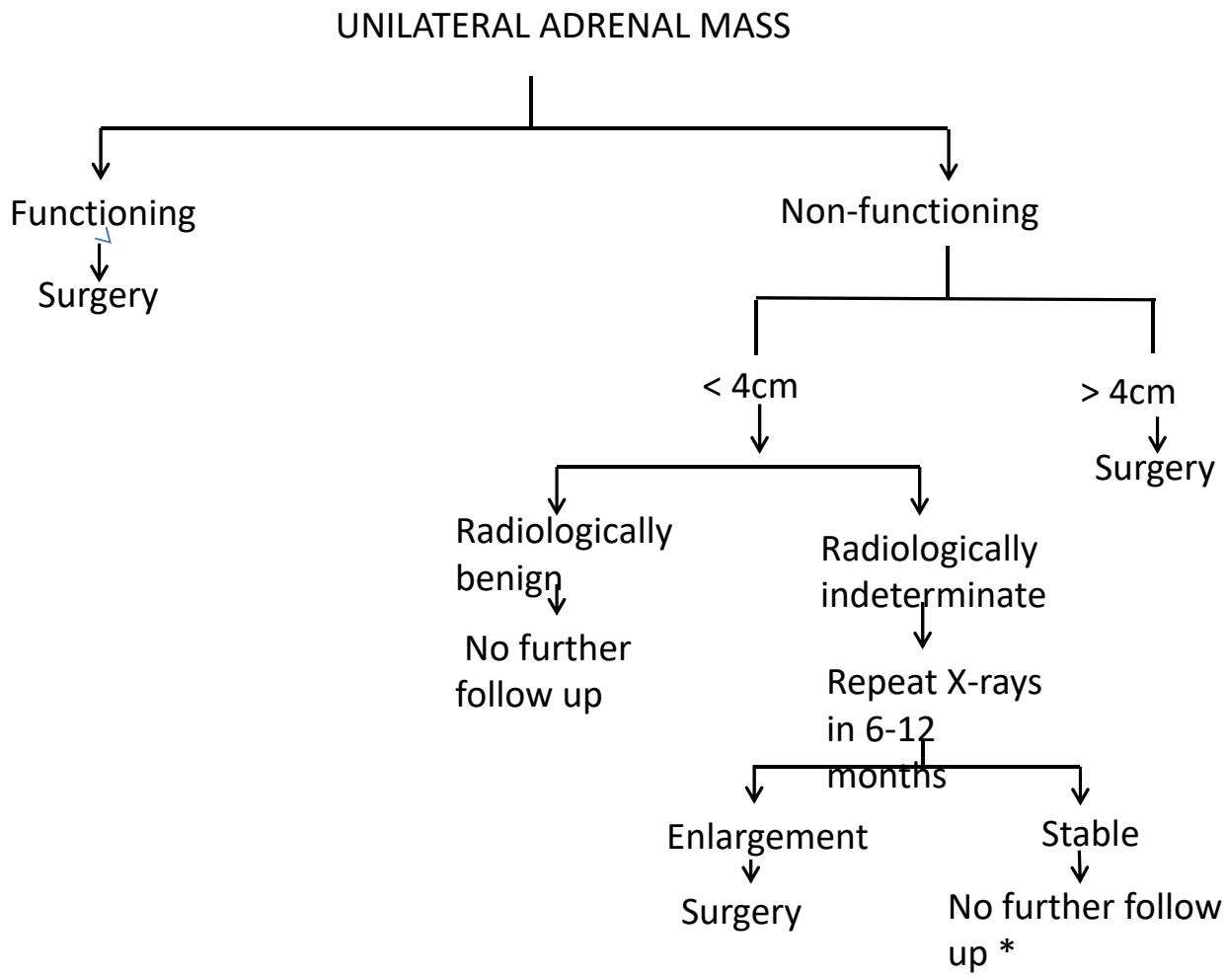
- The panel suggests against further imaging during follow up in patients with an adrenal mass < 4cm with clear benign features on imaging studies.
- No report of occurrence of adrenal malignancy has been described in over 2,300 patients in this category.
- The literature on follow up of non-operated larger adrenal incidentalonomas is scarce (as many patients undergo surgery).
- Some panel members argued that one follow up imaging after 6-12 months might be considered in lesions > 4cm.

FOLLOW UP OF PATIENTS NOT UNDERGOING ADRENAL SURGERY

- In patients with indeterminate adrenal masses (by imaging) who opt not to undergo adrenalectomy following initial assessment, the panel suggests to repeat non-contrast CT or MRI after 6-12 months.
- Surgical resection is indicated if the lesion enlarges by more than 20% in its largest diameter, together with an absolute increase of at least 5mm.
- If there is growth of the lesion below this threshold, additional imaging might be performed after 6-12 months.

FOLLOW UP OF PATIENTS NOT UNDERGOING ADRENAL SURGERY

- The panel suggests against repeated hormonal work up in patients with a normal hormonal work up at initial evaluation unless
  - New clinical evidence of endocrine activity appears.
  - There is worsening of comorbidities (e.g. hypertension and type 2 diabetes).
- The risk of developing clinically relevant hormonal excess is below 0.3% in patients with an initial negative hormonal work up.



* Lack of growth of an adrenal mass over a period of 6-12 months makes a malignant mass highly unlikely.

Evaluation and Management of Amenorrhea

Andrew Lutzkanin, MD, FAAFP
Penn State College of Medicine
March 6, 2019

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Learning Objectives

- Examine the different causes of amenorrhea
- Describe a structured approach to the initial evaluation and workup of amenorrhea
- Develop appropriate management plans for patients with amenorhea

Disclosures

No conflicts of interest for this presentation

Definitions

- Primary amenorrhea:
  - No initiation of menses at age >15
  - Or 3 years post thelarche
- Secondary amenorrhea:
  - No menstruation for >3 months with history of regular (21-34 day) cycles
  - No menstruation for >6 months with history of irregular cycles

What causes amenorrhea?

- Physiologic: pregnancy, breastfeeding, menopause
- Outflow tract abnormalities:
  - Congenital: Mullerian agenesis, 5$^{\alpha}$-reductase deficiency, imperforate hymen
  - Acquired: Asherman's, cervical stenosis
- Primary ovarian insufficiency:
  - Turner syndrome,
  - chemo/radiation

But wait….there's more!

- Hypothalamic or pituitary disorders:
  - Functional hypothalamic amenorrhea: eating disorder, excessive exercise, stress
  - Hyperprolactinemia: adenoma, medications, CKD
  - Other: infarction, infection, trauma, tumor, radiation, gonadotropin deficiency
- Other endocrine disorders: PCOS, Thyroid, Cushing, Adrenal insufficiency
- Chronic disease: Celiac disease, IBD
- Iatrogenic: birth control, other medications

So where do I begin?

- Start with a detailed history including:
  - Menstrual history – age of onset, average cycle length, duration of period
  - Review of past/current medications, surgeries, other therapies
  - Family history

- Physical exam:
  - Growth charts, BMI
  - Tanner staging
  - Pelvic exam

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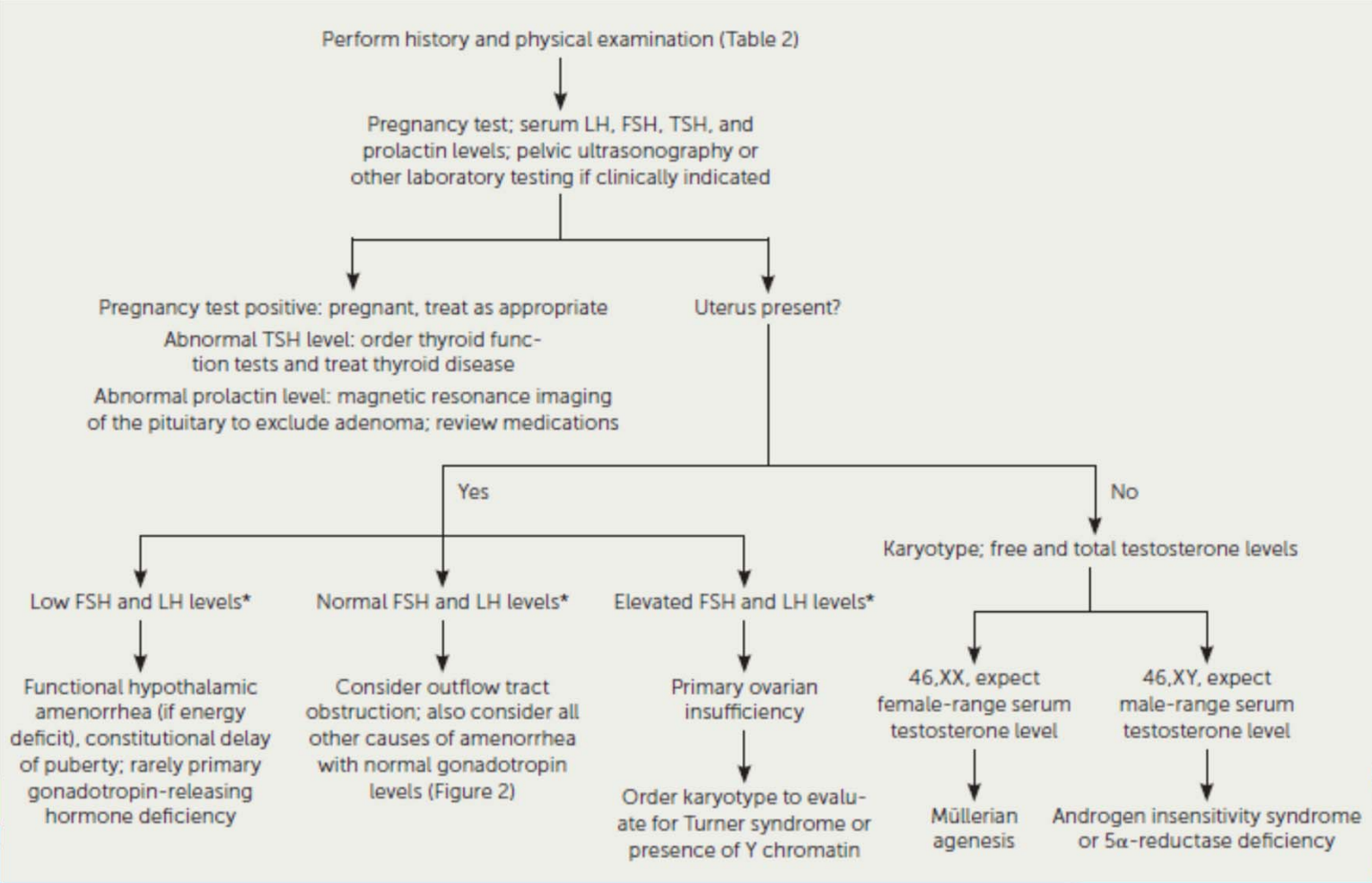
Initial bloodwork

- Pregnancy test
- TSH, LH, FSH, Prolactin levels

- Consider determining estrogen status:
  - 5-10mg progesterone x 10 days → positive if bleeding occurs w/in 2-7 days

Primary Amenorrhea



Klein DA, Paradise SL, Reeder RM "Amenorrhea: A Systematic Approach to Diagnosis and Management" Am Fam Physician. 2019; 100(1): 39-48.

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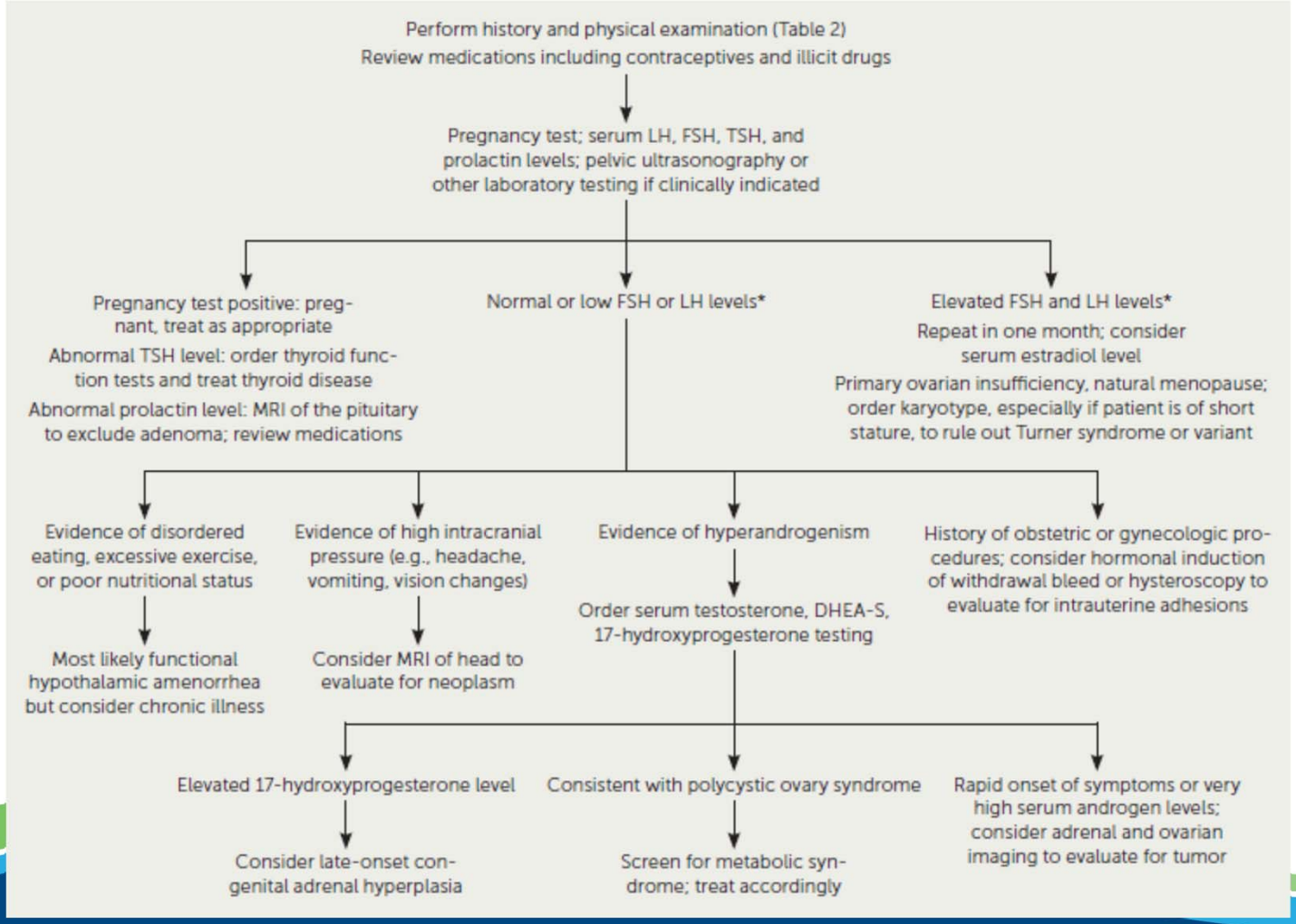
Secondary Amenorrhea



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Management

- Outflow Abnormalities
- Ovarian Insufficiency
- Hypothalamic and Pituitary Causes
- Other Endocrine Causes

Outflow Tract Abnormalities

- Müllerian agenesis
  - 1/5000 females, accounts for 15% of cases
  - associated with skeletal and urologic abnormalities
- Transverse septum/imperforate hymen
  - cyclic pelvic pain
  - can dx with pelvic exam and US
  - refer for surgery
- Asherman's/cervical stenosis
  - occurs post instrumentation/pregnancy
  - refer to OB/GYN

Outflow Tract Abnormalities

- Androgen insensitivity
  - 46XY genotype
  - female phenotype (testosterone resistant)
- 5α-reductase deficiency
  - 46XX genotype
  - female phenotype but develop male characteristics at puberty
- Both are relatively rare
  - dx with enzyme assays vs genetic testing
  - may need prophylactic gonadectomy

Primary Ovarian Insufficiency

- Occurs in about 1/100 females, most cases idiopathic
  - Other causes: tumor, chemo, radiation, infection, autoimmune
- Menopausal sx: vaginal dryness, hot flashes
- Diagnosis:
  - age <40
  - need 2 FSH levels in menopause range (>25) one month apart
- 1/3 pts with 1° amenorrhea have abnormal karyotype (Turner syndrome)

Primary Ovarian Insufficiency

- Hormone Replacement Therapy
  - 100mg transdermal or 0.625mg oral estrogen with 200mg progesterone x12 days each month
  - Decreases vasomotor sx, CV risk, bone loss
  - Continue to age 50-51
  - 10% retain fertility – can use OCP instead but need higher estrogen dose
- Calcium + vitamin D
- Test for FMR 1 gene – risk of fragile x in children
- Thyroid and adrenal antibodies frequently co-exist

Hypothalamic and Pituitary Causes

- Functional Hypothalamic Amenorrhea
  - suppression of hypothalamic-pituitary axis
  - excessive exercise, stress, weight loss (think Female Athletic Triad)
  - treat based on cause
- Hyperprolactinemia
  - pituitary adenoma: dx on MRI, tx with dopamine agonist or surgery
  - psychiatric medications – antipsychotics
  - pregnancy

Other Endocrine Causes

- Polycystic Ovarian Syndrome (PCOS)
  - ovulatory dysfunction + androgen excess + polycystic ovaries (on imaging)
  - Rotterdam Consensus Criteria: 2 of the 3 above
  - Androgen Excess Society: signs of androgen excess + one other from above
  - Pts often develop metabolic syndrome with insulin resistance
    - Screen BP and BMI with each visit
    - Lipids and 2-hr glucose tolerance (A1c) every other year
  - Treatment:
    - Aggressive lifestyle management – weight loss can restore normal cycles
    - OCPs – restore cycles, decrease acne/hirsutism, prevent endometrial cancer
    - Metformin – treat insulin resistance, can restore normal cycles
    - Letrozole over clomiphene for infertility

Other Endocrine Causes

- Hyperthyroidism or hypothyroidism
- Cushing syndrome
  - 24-h urine cortisol, dexamethasone suppression test
- Congenital adrenal hyperplasia (21-hydroxylase deficiency)
  - 17-hydroxyprogesterone level elevated → confirm with adrenocorticotropic hormone stimulation test
- Androgen-secreting tumors (adrenal or ovarian)
  - Suspect with rapid onset virilization or highly elevated androgen levels
  - Very rare

Summary

- Pts presenting with amenorrhea should be evaluated
  - Start with pregnancy test
  - Check TSH, Prolactin, FSH, LH levels
- History and Physical can help point to many diagnoses
  - Outflow tract abnormalities
  - Signs of androgen excess
- Treat primary ovarian failure with HRT through age 50
- Treat underlying cause in functional hypothalamic amenorrhea
- Monitor metabolic status of patients with PCOS

References

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QUESTIONS?

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