Current Concepts in Galactorrhea and Hyperprolactinemia

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Disorders of prolactin (PRL): PRL made in anterior pituitary; normal level <20 ng/mL; other hormones from anterior pituitary include thyrotropin (TSH), adrenocorticotropic hormone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH); unlike other hormones from anterior pituitary, PRL controlled by inhibitory hormone (dopamine) from hypothalamus; PRL rises when any process interrupts pituitary stalk, which can result in galactorrhea, changes in menses, and infertility

Prevalence of galactorrhea: varies from <1% to 30%, depending on population; more common in women with irregular menses or history of pregnancy

Causes of galactorrhea: pituitary tumors — prolactinoma most common tumor causing galactorrhea; also caused by tumors that secrete growth hormone; when galactorrhea present but PRL level normal, other symptoms, such as headache (HA), may lead to diagnosis; parapituitary — other conditions that affect dopamine include empty sella syndrome, tumors, sarcoidosis, and infiltrating disorders; medications — oral contraceptives (OCs) and other drugs can cause galactorrhea; other causes — include neurogenic causes, breast stimulation, and idiopathic; ~20% of women with galactorrhea have pituitary tumor; imaging can reveal infiltrative disorders, such as sarcoidosis and hemochromatosis, and infections, such as tuberculosis; section of pituitary stalk uncommon, but can occur in motor vehicle accident; meningioma, craniopharyngioma, and empty sella syndrome associated with high levels of PRL

Hypothyroidism: included in differential diagnosis of galactorrhea; 20% of patients with hypothyroidism have elevated PRL, but most do not have galactorrhea; checking PRL level unnecessary in patients with hypothyroidism; thyrotropin-releasing hormone stimulates both TSH and PRL

Drugs: OCs — elevated PRL common in women on OCs; of these, 30% have galactorrhea; condition improves when OCs stopped; other drugs — agents that act on central nervous system (CNS) affect PRL, including selective serotonin reuptake inhibitors, tricyclic agents, trazodone, valproate, methyldopa (Aldomet), and H2 blockers; recreational drugs (eg, opiates, cocaine, marijuana) and several herbs can cause galactorrhea

Neurogenic stimulation: includes direct stimulation by breastfeeding child or partner, or indirect stimulation from skin lesions such as herpes zoster or surgical lesions

Idiopathic: accounts for 40% to 60% of galactorrhea; PRL often normal or minimally elevated; most common etiology in women with normal menses and normal level of PRL; no additional evaluation required

Case: woman discontinued breastfeeding, but observed recurrence of lactation and sometimes spontaneously wet her blouse

History: patient should be asked about neural and local stimulation, menstrual and obstetric history, medications, herbs, and CNS symptoms (eg, HA); patient reported new onset of irregular menses and increase in migraine HAs; galactorrhea found in 80% to 90% of patients with prolactinoma; HA more common with large tumors (occurs in 75% of patients with large prolactinomas); 70% to 80% of patients with pituitary tumors have amenorrhea

Physical examination: galactorrhea usually involves multiple ducts; may occur spontaneously or only with manipulation; physician should look for galactorrhea in women with amenorrhea; galactorrhea sometimes unilateral; fluid appears milky or clear; fluid from single duct may indicate local disease or tumor; patient or physician should try to elicit discharge; fat stain or water stain used to look for globules of fat; intraductal carcinoma may present with clear or bloody discharge, usually from localized area; cytologic examination may be helpful

Laboratory evaluation: physician should check TSH and morning PRL level; in hypothyroidism, galactorrhea usually resolves within 3 to 6 mo of starting treatment; check PRL level in morning to detect highest value; in case presented above, TSH normal and PRL elevated; these findings and irregular menses suggest need to evaluate pituitary; incidence of pituitary tumor 50% when PRL >100 ng/mL, ~100% when PRL >300 ng/mL, and 0% to 33% when PRL <100 ng/mL; in patients with slightly elevated PRL (<50 ng/mL) and regular menses, observing menstrual cycle and repeating PRL level in 3 mo reasonable approach

Imaging: if menses irregular or PRL level rises, patient needs magnetic resonance imaging (MRI); in case presented, imaging revealed 12- to 11-mm pituitary macroadenoma compressing dura mater in suprasellar area

Other evaluations: patients with suprasellar tumors should have evaluation of visual fields by ophthalmologist and referral to endocrinologist; additional evaluation in patient with adenoma includes assessment of other anterior pituitary hormones and adrenals by endocrinologist; patients at risk for osteoporosis should have dual-energy x-ray absorptiometry

Educational Objectives
The goals of this program are to improve diagnosis and treatment of gynecologic endocrine disorders. After hearing and assimilating this program, the clinician will be better able to:

2. List the indications for treatment of galactorrhea.
3. Use the Rotterdam criteria to diagnose polycystic ovary syndrome (PCOS).
4. Evaluate metabolic disorders in patients with PCOS.
5. Diagnose the cause of and provide treatment for hirsutism.

Faculty Disclosure
In adherence to ACCME Standards for Commercial Support, Audio Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, members of the faculty and planning committee reported nothing to disclose. In his lecture, Dr. Sakiyama presents information that is related to the off-label or investigational use of a therapy, product, or device.
Indications for treatment: galactorrhea without other findings does not require treatment if discharge is not spontaneous or bothersome; 95% of microadenomas do not grow to macro-adenomas, so MRI may be repeated in 2 to 3 yr; treatment indicated for infertility, change in menses, elevation of PRL in presence of osteoporosis or abnormal bone resorption, disabling galactorrhea, or symptoms related to CNS

Treatment: surgery — performed via sphenoid sinus; not ideal as primary treatment because cure rates low (40%-50%); radiation therapy — used only for large tumors; medication — effectively reduces micro- to macroadenomas; medical therapy associated with high rates of cure and decreases in symptoms and level of PRL; bromocriptine and cabergoline — dopamine agonists that downregulate lactotrophs and decrease secretion of PRL from anterior pituitary; bromocriptine D; receptor agonist; cabergoline (Dostinex) more specific and more effective than bromocriptine and has long half-life, which allows once-or twice-weekly dosing.

Outcomes with medical treatment: microadenomas may disappear; macroadenomas may shrink but do not disappear completely; goals of therapy to normalize PRL, shrink tumor, improve gonadal function, restore fertility, and, for large tumors, reduce CNS symptoms; stopping medication may result in increase in PRL level and growth of tumor, even if tumor previously disappeared on MRI; 10% to 20% of patients with microadenomas have spontaneous cure, but ongoing therapy required because identification of patients likely to be cured not possible; because cabergoline more specific for dopamine receptor than bromocriptine, normalization of PRL level more likely; side effects — long-term treatment with these drugs associated with valvular heart disease; patients should be followed with echocardiography

Polycystic Ovary Syndrome

Dr. Sakiyama

Polycystic ovary syndrome (PCOS): present in 5% to 10% of reproductive-age women; present in 1 out of 3 women with secondary amenorrhea and 75% of women with anovulatory infertility; severity varies from classic syndrome of hirsutism, amenorrhea, obesity, and large, cystic ovaries (previously called Stein-Leventhal syndrome) to presentations with fewer manifestations of disorder

Rotterdam criteria: 2 of 3 criteria required for diagnosis; first criterion — oligoovulation or anovulation, which may present as irregular menses or infertility; second criterion — clinical or biochemical evidence of high levels of androgens; third criterion — polycystic ovaries

Pathophysiology: underlying cause of PCOS unknown; most cases sporadic, not familial; key features obesity and insulin resistance; hyperinsulinemia often associated with increased waist circumference and decreased sex hormone-binding globulin (SHBG); androgens — SHBG binds testosterone (T) and prevents it from entering cells; unbound T of hormone constitutes free or bioavailable T; total level of T may be normal, but if SHBG low, free T high; gonadotropins — in most anovulatory women with PCOS, LH levels exceed FSH levels; LH stimulates thecal cells to produce androgens; FSH stimulates granulosa cells to convert androgens to estrogens; pathogenesis of cysts unknown

Insulin resistance: common in patients with PCOS, even in nonobese women; after controlling for weight, incidence of type 2 diabetes (DM) in patients with PCOS elevated 2- to 5-fold; risk for DM 8-fold higher in patients with PCOS, compared with controls; patients may be screened with fasting glucose or hemoglobin A1c (HbA1c); blood pressure and lipid panel used to screen for metabolic syndrome if patient obese or has other risk factors; incidence of metabolic syndrome 23% in general population and ≥33% in women with PCOS

Ovulatory disorders: 70% to 75% of women with PCOS have irregular menses; in most cases, menarche normal but irregular menses begin in teens, 20s, or early 30s

Elevated androgen levels: present as hirsutism, excessive acne, or male pattern hair loss; hirsutism characterized by dark terminal hair in midline distribution (not forearms) on lip, chin, upper chest, abdomen, or upper pubic area; measurement of free T more useful than total T

Acanthosis nigricans: usually indicates insulin resistance; commonly observed in armpits or neck area; areas dark brown or blackish and feel like velvet; affected areas raised rather than hyperpigmented

Prevalence of findings in PCOS: two-thirds of women with PCOS have hirsutism, ≥25% have acne, and 35% to 80% obese; 25% of patients have amenorrhea, 50% have oligomenorrhea, and 25% have regular menses

Diagnostic evaluation: focus on menstrual history, hyperandrogenism (acne or hirsutism), acanthosis nigricans, and obesity; patients with irregular menses or hirsutism should be screened for other disorders of androgens that affect adrenals and ovaries

Clinical laboratory evaluation: includes free T, LH and FSH helpful in patients with irregular menses; screening blood glucose and lipid panel also desirable

Red flags: other disorders should be considered in patients with high level of T and such masculinizing characteristics as clitoral hypertrophy, deepening of voice, loss of breast fat, or muscular development

Ovarian cysts: usual finding in PCOS 10 to 12 peripheral cysts per ovary, each measuring 3 to 9 mm; volume of stromal tissue in ovary may be high because high LH stimulates stromal cells to produce androgens; 90% of women with PCOS have ovarian findings, but 25% of normal women may have similar sonographic findings at some time in their lives

Laboratory findings: free T high in two-thirds of patients and total T high in 30%; dehydroepiandrosterone sulfate (DHEAS) marker of adrenal activity; 17-hydroxypregosterone (17-OHP) used to test women with hirsutism for congenital adrenal hyperplasia (CAH); tests for Cushing syndrome, PRL, TSH, androstenedione, estrone, and SHBG not necessary in all patients; ratio of LH to FSH typically >1; ratio >3 diagnostic for PCOS; DHEAS — may be slightly elevated

Androgen-secreting tumors: 1 in 300 to 400 patients with hirsutism have tumor; use total T to screen; adrenal or ovarian tumor possible if total T >200 ng/dL; in this situation, elevated DHEAS suggests need to evaluate adrenals with computed tomography; normal DHEAS suggests ovarian tumor

Congenital adrenal hyperplasia: present in 1% to 10% of hirsute women; nonclassical CAH affects enzyme that converts 17-OHP to 21-OHP (unlike classical CAH, appears in adolescence or early adulthood as hirsutism or irregular menses); CAH treated with prednisone; normal 17-OHP <2 ng/mL in morning; refer patient with abnormal test to endocrinologist

Cushing disease: affects ≥1 in 1,000,000 people (so routine screening impractical); signs include rapid weight gain and vertical striae; testing — screen with 24-hr urinary cortisol (normal value <50 µg; values >100 µg indicate Cushing disease); overnight dexamethasone suppression test performed by giving 2 mg dexamethasone at 11 PM and checking morning cortisol (values ≥25 µg abnormal)

Management of PCOS: physician should assess uterine lining, treat acne or hirsutism as primary manifestation, and address fertility issues or insulin resistance; lifestyle — loss of 7% of body weight and regular exercise can reduce levels of androgen, insulin, and LH, and probably improves hirsutism and ovulatory dysfunction; women with PCOS who undergo bariatric surgery experience normalization of most endocrine disorders and improvement in hirsutism and ovulatory function, which suggests many problems in patients with PCOS related to weight and insulin resistance; unopposed estrogen — patients
should use OCs, cyclic progestin, levonorgestrel-releasing intrauterine device (Mirena, Skyla), or progestin-only contraceptives; OCs — primary treatment for hirsutism and acne; newer progestins with less androgenic potential (eg, norgestimate, desogestrel, drospirenone [found in Yasmin and Yaz]) not found to be superior to older progestins for patients with PCOS; drospirenone associated with deep venous thrombosis (DVT); spironolactone (Aldactone) — antiandrogen and potassium-sparing diuretic used off-label for hirsutism; improves hirsutism in 60% to 70% of women; 3 to 6 mo required for effect to become evident; initial dose of 50 mg twice daily can be increased to 100 mg twice daily if electrolytes normal and patient tolerating drug; most common adverse effects HA and fatigue; hyperkalemia uncommon; OCs and spironolactone good combination for treating hirsutism and acne.

**Other medications:** often have excessive side effects; finasteride (Propecia, Proscar) — blocks conversion of T to dihydrotestosterone; category X in pregnancy and may affect male fetus; flutamide — toxic to liver; cyproterone — progestin similar to drospirenone, but with antiandrogenic effects; combination of cyproterone plus estrogen (Diane, Dianeette) not available in United States; associated with DVT; eflorenithine (Vaniqua) — topical agent that inhibits ornithine decarboxylase (enzyme that stimulates hair growth); produces marked improvement in 25% of women with hirsutism and some improvement in 25%; may cause irritation of skin.

**Metformin:** improves sensitivity to insulin; may improve hirsutism and menstrual cycle, but patients rarely lose weight; improves hirsutism more than ethinyl estradiol plus cyproterone; although hirsutism improves in 50% of women taking metformin, drug not used for hirsutism alone; may be used for patients at high risk for DM to prevent progression to DM; although known to prevent cardiovascular disease in patients with DM, similar effect in patients with PCOS unproven; not approved for treatment of PCOS; adding metformin to clomiphene (Clomid, Serophene) does not significantly increase live birth rates; metformin may cause ovulation to resume in obese women; clomiphene preferred over metformin for treatment of infertility in women with PCOS.

**Suggested Reading**


**Acknowledgements**

Dr. Sakiyama was recorded at Office Gynecology/Women’s Health for Primary Care, sponsored by the Office of Continuing Medical Education, David Geffen School of Medicine at University of California, Los Angeles, and the UCLA Department of Family Medicine, and held July 31 to August 3, 2014, in Anaheim, CA. For information on upcoming CME programs sponsored by the David Geffen School of Medicine at UCLA, please visit cme.ucla.edu. The Audio Digest Foundation thanks Dr. Sakiyama and the sponsors for their cooperation in the production of this program.

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**Estimated time to complete the educational process:**

- Review Educational Objectives on page 1: 5 minutes
- Take pretest: 10 minutes
- Listen to audio program: 60 minutes
- Review written summary and suggested readings: 35 minutes
- Take posttest: 10 minutes
1. Approximately what percentage of women with galactorrhea have a pituitary tumor?
   (A) 1%  (B) 20% ** (C) 30%  (D) 60%

2. Which of the following is an example of an indirect neurogenic stimulation that may produce galactorrhea?
   (A) Stimulation of breast by sexual partner  
   (B) Stimulation of breast by nursing infant  
   (C) Use of herbs or recreational drugs that act on central nervous system  
   (D) Herpes zoster

3. The most common etiology of galactorrhea is:
   (A) Macroadenoma  (B) Microadenoma  (C) Oral contraceptives  (D) Idiopathic

4. Patients who have _______ and no other findings need not be treated for galactorrhea.
   (A) Osteoporosis  (B) Elevation of prolactin  (C) Infertility  (D) Headache

5. Which of the following is the initial treatment for a pituitary macroadenoma?
   (A) Medical therapy  (B) Transsphenoidal surgery  (C) Radiotherapy

6. The Rotterdam criteria for polycystic ovary syndrome (PCOS) include:
   1. Elevated androgen levels  
   2. Insulin resistance  
   3. Polycystic ovaries  
   4. Obesity  
   5. Ovulatory disorder
   (A) 1,2,3  (B) 1,3,4  (C) 1,3,5 **  (D) 3,4,5

7. The incidence of metabolic syndrome in patients with PCOS is at least:
   (A) 23%  (B) 33% **  (C) 50%  (D) 70%

8. An androgen-secreting tumor should be considered in any woman with PCOS who has:
   (A) Clitoral hypertrophy ** (B) Elevated luteinizing hormone  
   (C) Elevated free testosterone  (D) Acanthosis nigricans

9. In addition to evaluation for PCOS, a woman with signs of PCOS who has rapid weight gain and vertical striae should undergo assessment of:
   (A) Dehydroepiandrosterone sulfate  (B) Urinary cortisol  
   (C) Total testosterone  (D) 17-hydroxyprogesterone

10. Which of the following is known to be true about metformin?
    (A) Is an appropriate primary treatment for hirsutism  
    (B) Is superior to clomiphene alone for treating anovulatory infertility 
    (C) Prevents progression to diabetes in patients with risk factors for diabetes 
    (D) Prevents cardiovascular disease in patients with PCOS

Answers to Audio Digest Obstetrics/Gynecology Volume 61, Issue 20: 1-C, 2-B, 3-D, 4-A, 5-D, 6-C, 7-D, 8-A, 9-A, 10-D