Unknown Cases

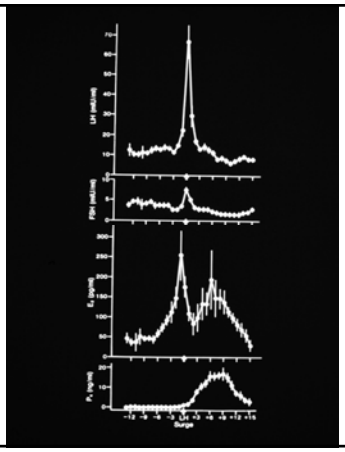
Richard H. Reindollar, M.D.
Dartmouth-Hitchcock Medical Center
Dartmouth Medical School

Case Review

A 32 yo female was referred to you with for infertility evaluation, cycles regular at 22 – 24 days, and a CD 21 FSH of 21 mIU/ml.

Your next step:

A. Obtain CD 3 FSH, "CD 21 was the wrong day."
B. Tell her she likely has reduced ovarian reserve and discuss pros and cons of repeat testing.
C. Tell her this may well be at the LH surge.



For patient who presents with 6 months of amenorrhea and you decide to obtain an FSH level, when do you draw the blood?

A. At her appointment today
B. CD 3 after progestin bleed?

Case 1

A 36 year old patient with 28 day cycles has a CD 3 FSH measured at 15 mIU/ml. A repeat study was performed the next month and the value was 6 mIU/ml. You should tell her that:

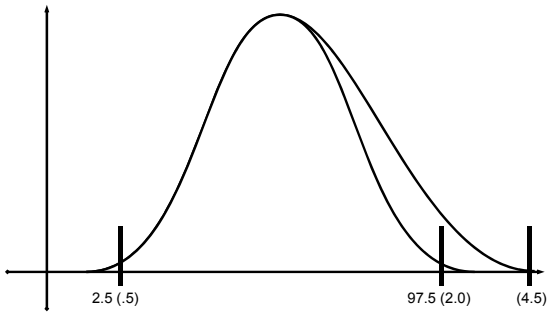
A. the first value was likely an error
B. the highest value tells the story
C. the patient has a normal chance to become pregnant in cycles with normal FSH

Case 2

An 32 year G4P1031 patient completed an evaluation for recurrent abortion. Her TSH value was 3.2 uIU/ml (normal 0.5 – 4.8 uIU/ml). You should:

A. Tell her this is normal and plan a pregnancy
B. Tell her that while in the normal range she likely has hypothyroidism
C. Measure TPO and consider treating if positive for subclinical hypothyroidism

Normal Values for TSH



Adverse Outcomes and Hypothyroidism (reported)

- Increased 1st trimester SAB
- Increased rate of fetal loss: euthyroid women with high TPO antibodies
- Increased rate of pregnancy complications (e.g., preeclampsia, abruption, nonreassuring FHR tracing, low birth weight)
- Subclinical hypothyroidism associated with neuropsychological impairment in some but not all studies (FASTER Trial)

Screening Recommendations For Pregnancy

- ACOG: symptomatic or those with family history
- Endocrine Society: same
- Up to Date: "we suggest universal screening for thyroid dysfunction …"
  - Study of 1560 consecutive pregnancies, targeted screening missed 1/3 of patients with TSH > 4.2 mIU/ml (Vaidya, JCEM 2007;92:203)
- Increase levothyroxine by 30% (an extra tablet 2 days a week)

Thyroiditis and Pregnancy

- Study of Negro et al, JCEM, 2006
  - 115 antibody positive euthyroid patients
  - Randomized to treatment or not
- SAB rates
  - 3.5% TPO positive treated patients
  - 2.4% TPO negative patients
  - 13.8% TPO positive untreated patients
- Premature delivery rates
  - 7% TPO positive treated patients
  - 8.2% TPO negative patients
  - 22.4% TPO positive untreated patients

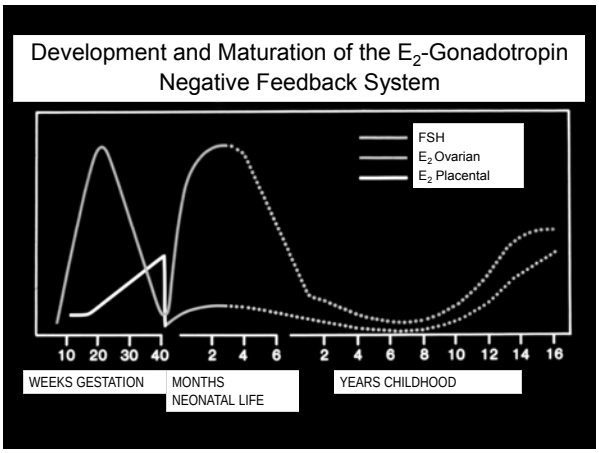
Photo of child with breast development

Case 3

An 18 month old child presents with 6 months of breast development. She remains in the 50% for height and weight. She has no pubic hair.

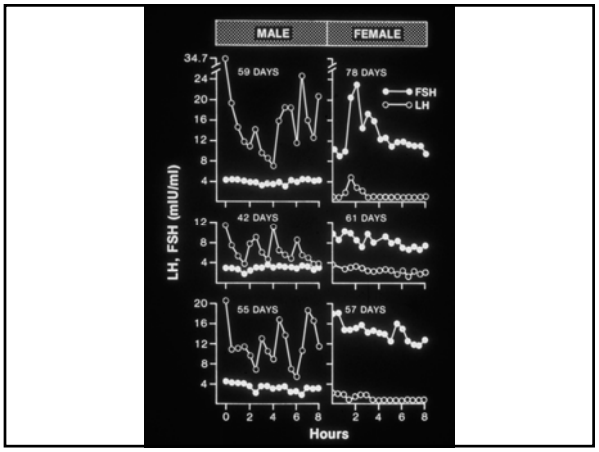
Her premature development is most likely caused by:

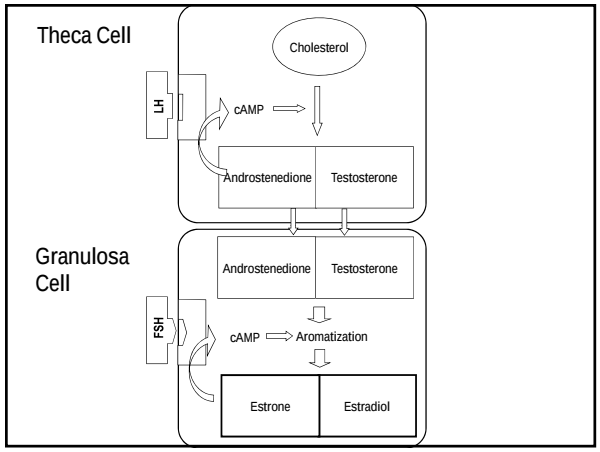
A. Exaggerated response to physiologic events
B. Abnormal autonomous sex steroid production
C. True previous puberty



During the rise of gonadotropins after birth, newborn male infants respond with testosterone production in the lower adult range, but female infants do not. Why?

A. The ovary has absent FSH receptors
B. The primordial follicles do not respond
C. Gonadotropins produced are biologically active for males, not females
D. LH levels are less than FSH levels and limit steroid production in females.





Case 4

Photo of adolescent with absent pubertal development

A 19 year old presents with absent pubertal development. Besides pubertal development shown here (Breast Tanner I and Pubic Hair Tanner II) her exam and evaluation were unrevealing.

The most likely diagnosis is:

A. Constitutional delay of puberty
B. Idiopathic hypogonadotropic hypogonadism
C. Stress related hypothalamic suppression

Idiopathic hypogonadotropic hypogonadism (IHH)

- Absent spontaneous puberty that persists beyond age 18 years.
- Historically diagnosis of exclusion
- Up to 30% gene mutations identified
- Kallmann syndrome (anosmia/ hyposmia)
- Otherwise nIHH (normosmic IHH)

Mutations found in genes:

- Regulate development and migration of GnRH neurons (KAL1, FGHR1, FGF8, PROK2, PROKR2, CHD7)
- GnRH production (GNRH1 gene)
- GnRH processing (PCSK1 gene)
- GnRH secretion (GPR54 gene)

Gene Mutations Associated With Hypogonadotropic Hypogonadism

- Kal1
- GnRH
- GnRH receptor
- DAX1
- PROP1
- HESX1
- LHX3, LHX4
- FGF8
- TAC3, TACR3
- Leptin
- Leptin receptor
- FGFR1 (Kal2)
- GPR54
- NROB1
- Sox2, SOX3
- PCSK1
- CHD7
- NELF

This patient subsequently admitted to having anosmia and was diagnosed with KS. You counsel her that treatment will be needed:

A. Until the normal age of menopause
B. Until age 40
C. Until sexual development is complete
D. Until it is determined by a break in treatment that she has reversal of the disorder

Case 5

A 13 year old adolescent presents with bleeding that has persisted for 10 days, has been excessive and associated for the last 2 days with dizziness. Since menarche, she has had monthly menses that have all been heavy lasting for over 10 days each. Her hemoglobin was 9.8 on admission. She was given a combination ocp q 4 hours and had a syncopal episode becoming hypotensive and tachycardic. Her repeat hgb was 5.9.

The most likely diagnosis is

A. hemophilia A
B. factor V deficiency
C. PCOS
D. AV malformation
E. Von Willebrand disease

What are the current recommendations for screening for VWD?

A. Take off hormonal contraceptives first
B. Do not perform during menses
C. Perform in collaboration with hematologist
D. A and C
E. A, B, and C

CLINICAL OPINION www.AJOG.org

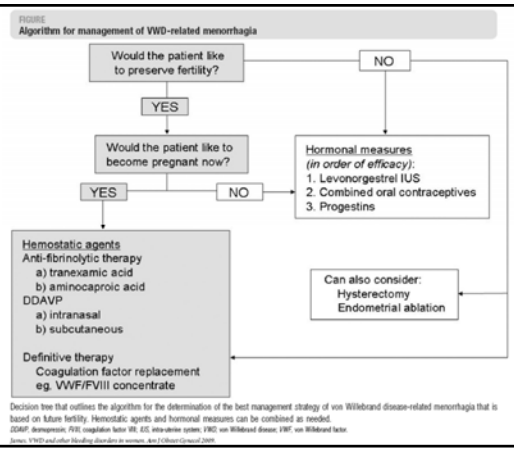
GENERAL GYNECOLOGY Am J Obstet Gynecol 2009;201:12.e1-8.

Von Willebrand disease and other bleeding disorders in women: consensus on diagnosis and management from an international expert panel

Andra H. James, MD; Peter A. Kouides, MD; Rezan Abdul-Kadir, MD; Mans Edlund, MD, PhD; Augusto B. Federici, MD; Susan Halimeh, MD; Pieter W. Kamphuisen, MD; Barbara A. Konkle, MD; Oscar Martinez-Perez, MD, PhD; Claire McLintock, MD; Flora Peyvandi, MD, PhD; Rochelle Winikoff, MD

Summary of Screening Recommendations

- Evaluation in collaboration with hematologist
- Hematologic evaluation: CBC, APPT, PT, and levels of VFW level (assessed with ristocetin cofactor activity and antigen), factor VIII, and fibrinogen
  - Ideally done during menses (levels at lowest); don't delay until then but may repeat then
  - Hormonal contraception can mask type 1 (don't discontinue to measure)
- Point-of-care instruments such as PFA-100 (test of platelet function) of limited use



Decision tree that outlines the algorithm for the determination of the best management strategy of von Willebrand disease-related menorrhagia that is based on future fertility. Hemostatic agents and hormonal measures can be combined as needed.

Menorrhagia in Women without VWD

- 12% of gyn referrals in UK
- > 80 mls blood loss per menstrual cycle
- 80% of women Rx for menorrhagia have no anatomic pathology; 30% of hysterectomy specimens
- Prior treatments (luteal progestins) have been found not to help
- New class of treatments: plasminogen activators

Plasminogen Activator Inhibitors (Antifibrinolytics)

- PA, group of enzymes that cause fibrinolysis
- Ethamsylate and tranexamic acid*
- Prior reluctance in UK because of concern of DVT
- Swedish long term study: no incrased risk over that of general population.

Tranexamic Acid

- Antifibrinolytic agent
- Approved by US FDA 2009 for treatment of menorrhagia
- 1 g three to four times daily during menses, maximum of 5 days
- Reduces blood flow 30 - 55% from baseline; more effective than placebo, NSAIDs and luteal progestins.

Tranexamic acid Cochrane Review 2009

- Objective reduction of menstrual bleeding greater than NSAIDS, oral luteal progestins, ethamsylate, placebo
- Side effects not increased over above Rxs
- Personal report of "flooding and sex life" significantly improved compared to luteal progestins
- No data from RCTs recording frequency of TE evemts

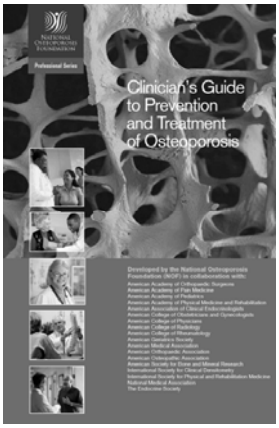
Case 6

A 55 year old Caucasian female presents for her first annual visit with you. Her last menses was at age 48 and while initially bothered by hot flashes they have long gone. She has been healthy, takes no medications, drinks one glass of wine daily, smokes ½ pack per week, and does weight bearing exercise twice weekly. Her mother had moderate osteoporosis. She requests information about DEXA Scan. YOU:

A. Recommend she wait until age 65 for DEXA
B. Order DEXA now
C. Determine her FRAX index and recommend accordingly
D. Reassure her that with appropriate CA and Vitamin D she will be ok

Sources of Information

- WHO
  - WHO Risk Assessment Tool (FRAX Tool)
- NOF (North American Osteoporosis Foundation)
  - Clinician's Guide to Prevention and Treatment
  - FRAX



NOF New: 2008 Guidelines Key Differences

- Expanded guidelines beyond Caucasian postmenopausal women
- Updated Ca and vitamin D
- Discussed the FRAX : a calculation of the 10 year absolute fracture for both hip and other fx taking into account hip BMD and nine other clinical risk factors.

Who to screen

- USPTF:
  - *All women 65 and older
  - Women aged 60 with increased risk of fx
- NOF: (National Osteoporosis Foundation)
- UPDATED IN 2008
  - All women 65 and older (web site: www.nof.org; physician guide available at the website)
  - Postmenopausal women 50-70 WHEN YOU HAVE concern based on risk profile
  - Pts with a fracture

Risk factors:

- These include:
  - personal fx,
  - history fx in first degree relative
  - dementia,
  - poor health/fragility,
  - low body weight (< 127)
  - cigarette smoking,
  - history of estrogen deficiency in premenopausal years
  - hyperthyroidism,
  - medications.

Risk Factors Included in the WHO Fracture Risk Assessment Model

- □ Current age □ Use of oral glucocorticoid therapy
- □ Gender □ Secondary osteoporosis (e.g., rheumatoid arthritis)
- □ Personal history of a fracture □ Parental history of hip fracture
- □ Femoral neck BMD □ Current smoking
- □ Low body mass index (kg/m2) □ Alcohol intake 3 or more drinks/day

2008 guidelines NOF: New Ca and Vit D recommendations

- 50 and older: 1200 mg Ca
  - Above 1500 no evidence of additional benefit. Real threshold is probably in 800-1000mg day so probably best aim for 1200-1500 day.
  - This ideally should be taken in 2 divided dosages and at mealtime.
  - Calcium and vitamin D have been proven to decrease fx risk in controlled trials
- *800-1000IU of vitamin D3 (cholecalciferol) **old one was 400-800**

2010 NOF Recommendations Who to Consider Treating?

- "A hip or vertebral (clinical or morphometric) fracture
- T-score ≤ 2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes
- Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or spine) **AND** a 10-year probability of a hip fracture ≥ 3% **OR** a 10-year probability of a major osteoporosis-related fracture ≥ 20% based on the US-adapted WHO algorithm
- Clinician's judgment and/or patient preferences may indicate treatment for people with 10-year fracture probabilities above or below these levels "

This patient was found to have osteoporosis and was initiated on bisphosphonate therapy. She asks how long she will need to take this medication? You tell her that current evidence suggests that:

A. There is no long term limit
B. Maximum 5 years
C. Maximum 10 years
D. Maximum 20 years
E. Indefinite therapy may not be wise

Bisphosphonate-Related Osteonecrosis of the Jaws (BRONJ)

- IV Bisphosphonates
  - 0.8 – 12%
- Oral Bisphosphonates
  - 0.7/100,000 person/years of exposure
  - 0.01% - 0.04%

AAOMS POSITION PAPER

J Oral Maxillofac Surg 65:369-376, 2007

American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws

BRONJ Risk Factors

- Potency (IV vs. Oral)
- Duration (Longer greater risk)
- Dentoalveolar surgery (extractions, implants, periapical surgery, periodontal surgery involving osseous injury)
- Site (Mandible > maxilla – 2:1)
- Concomitant oral disease
- Demographics
  - Age, Race (Caucasian)
- Systemic factors
  - Cancer (MM, BC), osteopenia/porosis + cancer

AAOMS POSITION PAPER

J Oral Maxillofac Surg 65:369-376, 2007

American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws

Prevention and Treatment Guidelines spelled out

Long Term Bisphosphonate RX and Increased Fx Risk

- **Ing-Lorenzini K** et al. **Low-energy femoral fractures associated with the long-term use of bisphosphonates: a case series from a Swiss university hospital.** Drug Saf. 2009;32(9):775-85.
- Goddard MS , et al. **Atraumatic bilateral femur fracture in long-term bisphosphonate use.** Orthopedics, 2009; Aug 32:607