Disclosure

- Dr. Jones has no financial interest in the pharmaceutical agents mentioned in this presentation

Objectives

- 1. Manage an adolescent with delayed menarche
- 2. Manage abnormal uterine bleeding in adolescents
- 3. Prescribe safe and effective contraception to adolescents
Question 1

- Which of the following are causes of delayed puberty
  - 1. Mullerian agenesis
  - 2. Fragile X premutation
  - 3. XY gonadal dysgenesis
  - 4. Androgen insensitivity

Question 2

- Which of the following tests are necessary to make the diagnosis of PCOS in adolescence
  - 1. Ultrasound
  - 2. History and physical exam
  - 3. DHEAS level
  - 4. LH/FSH ratio

Question 3

- Which of the following tests is most appropriate in a 14 year old with intermittent severe menorrhagia and anemia
  - 1. Ultrasound
  - 2. Pelvic exam
  - 3. CBC, coags
  - 4. Free testosterone
Question 4

- Which of the following is not an appropriate choice for contraception and cycle control for a 15 year old with Von Willebrand Disease:
  - 1. etonorgestrel implant
  - 2. levonorgestrel IUD
  - 3. DMPA
  - 4. oral combination birth control pills

Overview

- Too Early
- Too Late
- Too Much
- Too Weird

PUBERTY

- The coordination of adrenarche and gonadarche
- The “on center” begins pulsing GnRH at night
- Gonadal steroids rise
- Destructive lesions of the hypothalamus can cause delayed puberty
WHAT MAKES PUBERTY HAPPEN??

- Well.....we don’t really know, exactly
- Some clues from critical body mass reached (the Frisch Hypothesis)
AT BIRTH

- Withdrawal of placental steroids leads to possible bleeding in neonatal girls and "witches milk"
- In boys, testosterone rises for some months
- In girls, GnRH, FSH and estrogens are suppressed….why?
VAGINAL BLEEDING IN CHILDREN

- Not usually a medical emergency
- Often a psychological emergency to the family and pediatrician
- May be a legal emergency

START TOO EARLY

- Not all vaginal discharge is blood
- Foreign body (peanuts, snaps, tissue)
- Vaginitis
- Sexual abuse
- Urethral caruncle
VAGINAL BLEEDING IN CHILDREN

- Not all vaginal bleeding is precocious puberty
- Trauma
- Foreign body
- Tumor
- Exogenous steroids ("who took my pills"?)
- Idiopathic (we never figure it out)

TRUE PRECOCIOUS PUBERTY

- Growth spurt
- (Smells different)
- Pubic hair
- Breast development
- Vaginal bleeding

ISOSEXUAL PRECOCIOUS PUBERTY

- Breast development
- Vaginal bleeding
- No real evidence of pubic hair
- Minimal growth spurt
- Estrogen producing tumor, exogenous estrogens, etc.
TRUE PRECOCIOUS PUBERTY
- Labs – FSH, LH, estradiol, DHEAS
- Bone age
- CT or MRI of the pituitary/hypothalamus
- Refer to pediatric endocrinologist or reproductive endocrinologist
- Most common diagnosis is idiopathic

WHEN IS PUBERTY TOO EARLY
- Breast buds before 8 (or maybe 7)
- Adrenarche before 6
- The earlier the onset, the more likely there is pathology, and not idiopathic or related to a family history of precocious puberty

START TOO LATE
- Delayed menstruation (after 16) and delayed puberty (after 14…in girls) are not necessarily the same
START TOO LATE

- Think systems:
  - Outflow obstruction
  - Ovarian failure
  - Pituitary failure
  - Absence of GnRH (hypothalamus)

OUTFLOW OBSTRUCTION

Looks like a woman

- Imperforate hymen
- Transverse vaginal septum
- Absence of vagina and uterus
  - Mullerian agenesis
  - Androgen insensitivity

OUTFLOW OBSTRUCTION

Looks like a girl

- XY gonadal dysgenesis
OVARIAN FAILURE
- Normal outflow tract
- No withdrawal to progestin
- FSH high
- Check karyotype

PREMATURE OVARIAN FAILURE
- Abnormal karyotpye – XO, XX/XO, XX/XY,
- Autoimmune ovarian failure
- Chemotherapy and/or radiation
- Classical galactosemia
- Idiopathic
- And others

OVARIAN FAILURE
- Normal outflow tract
- No withdrawal to progestin
- FSH high
- Check karyotype
PRIMARY AMENORRHEA

- FSH low LH low
- Prolactin high – pituitary tumor or drugs
- Prolactin normal – assess other pituitary function
- Consider CT or MRI of pituitary

PRIMARY AMENORRHEA

- Need careful history and physical exam for evidence of calorie restriction, excess physical activity, bulimia
- History of medical problems that make calorie intake or absorption limited

START TOO EARLY

- RULE OUT LIFE THREATENING CNS PATHOLOGY
- RULE OUT PELVIC TUMORS
- RULE OUT TRAUMA
- TREAT TO LIMIT SHORT STATURE IN TRUE PRECOCIOUS PUBERTY
START TOO LATE

- RULE OUT OUTFLOW TRACT OBSTRUCTION
- RULE OUT ABNORMAL KARYOTYPE
- RULE OUT PITUITARY AND HYPOTHALAMIC TUMORS
- RULE OUT LIFE THREATENING EATING DISORDERS

START TOO LATE

- INITIATE PUBERTAL DEVELOPMENT SLOWLY
- IT TAKES 2 YEARS OF LOW DOSE UNOPPOSED ESTROGEN TO START TO MAKE A BREAST
- WHEN BREAST TISSUE TO ANT AXILLARY LINE – ADD PROGESTINS
- WHAT ABOUT TESTOSTERONE?????

Abnormal Uterine Bleeding

PALM-COEIN

- Forget the PALM part in adolescents: polyps, adenomyosis, leiomyoma, and uterine malignancy are very rare
- Remember the COEiN part: coagulopathy, ovulatory disorders, endometrial abnormalities, idiopathic, and not otherwise specified
- Coagulopathy and ovulatory disorders are where the money is.
Anovulatory Bleeding

- Immature HPO axis
- May also be associated with
  - Sports participation
  - Stress
  - Eating disorders
  - Endocrine disorders

Anovulatory Bleeding

- Endocrine Disorders
  - Hypothyroidism
  - Hyperthyroidism
  - Diabetes mellitus
  - Cushing syndrome
Anovulatory Bleeding
- Delayed maturation of normal negative feedback
  - Rising estrogen levels do not block FSH
  - FSH increased relative to LH
  - Endometrium proliferates and becomes unstable

Anovulatory Bleeding
- Endometrium lacks stabilizing effect of progesterone
- Thickened endometrium
  - Sloughs when estrogen is withdrawn (estrogen withdrawal bleeding)
  - Sloughs when lining is unstable (estrogen breakthrough bleeding)

Differential
- Anovulatory bleeding
- Endocrine disorders
- Pregnancy-related complications
- Infection
- Bleeding disorders
- Vaginal or cervical abnormalities
- Uterine abnormalities
- Endometriosis
- Ovarian etiology
- Trauma
- Foreign body
- Systemic disease
- Medications
History
- Obtain with and without parent/guardian
- Careful menstrual history
  - Date of first period
  - Usual bleeding pattern
    - Quantify number of pads or tampons changed Q24hrs
    - Indirect measurements of heavy flow
  - Frequency and duration of menses
  - Cramping
  - Other premenstrual symptoms
  - Date of last period

History
- Sexual history
  - Age at first experience
  - Total lifetime partners
  - Gender of partner(s)
  - Use of condoms
  - Use of other contraception
  - Sexually transmitted infections
  - Abuse history

History
- Past Medical History
  - Systemic illness
  - Renal disease
- Family History
  - Bleeding disorders
  - Infertility
  - Menstrual disorders
  - Thyroid disease
  - Diabetes and/or hyperlipidemia
History

- Review of systems
  - PCOS
    - Acne, hirsutism, acanthosis nigricans, weight gain, family history of PCOS, Type II DM, or early puberty or adrenarche
  - Thyroid disease
    - Weight changes, cold or heat intolerance, growth patterns
  - Bleeding disorders
    - Gingival bleeding, epistaxis, bruising, family history, post-op bleeding, lightheadedness, syncope, fatigue
  - Hypothalamic dysfunction
    - Psychosocial stressors, eating-disordered behavior, weight loss, athletics

- Medications
  - Contraceptive methods
  - Psychotropics
  - Aspirin containing medications
  - Other
  - Herbs
  - Dietary supplements
  - Illicit drugs

Exam

- Vitals
  - Also include height, weight, arm span
- Pertinent findings
  - Obesity, hirsutism, acne, acanthosis nigricans, clitoromegaly (PCOS or androgen excess)
  - Thyroid enlargement or nodules (thyroid disease)
  - Bruising or petechiae (bleeding dyscrasias)
Exam

- Breasts
  - Tanner staging of breasts
  - Assessment of galactorrhea
- Abdomen
  - Uterine or ovarian mass
  - External genital exam
    - Clitoral size, Tanner staging, hymen, signs of trauma
- Bimanual and speculum exam
  - Necessary for unexplained or severe bleeding
  - [If unable to perform may use ultrasound and consider examination under sedation]

Laboratory Studies

- Urine hCG
- CBC
  - Iron studies if anemic
  - Reticulocyte count
  - [Platelet count]

Laboratory Studies

- Severe bleeding history
  - PT, PTT
  - Von Willebrand panel
    - Ristocetin factor
    - VWF antigen
    - Factor VIII activity
  - Platelet function assay
Laboratory Studies

- Depending on history and exam findings
  - Gonorrhea and Chlamydia screen
    - Urine or cervical culture
  - TSH
  - Free Testosterone
  - DHEAS (dehydroepiandrosterone sulfate)

Imaging

- Pelvic Ultrasound
  - May be indicated if exam is limited
  - Helpful in evaluating structural abnormalities

Pregnancy

- Must rule out in ALL adolescents
- Any bleeding pattern possible
- Ectopic pregnancy
- Threatened abortion
- Incomplete abortion
- Complications of induced abortion
Anovulatory Bleeding

- PCOS
  - 5-10% of adolescents
  - Overweight
  - Insulin resistance
  - Acanthosis nigricans
  - Hirsutism
  - Acne

Infectious Etiologies

- Cervicitis
- Vaginitis
- Endometritis
- Pelvic inflammatory disease

Trauma

- Acute injuries
  - Waterskiing
  - Gymnastics
  - Horseback riding
- Sexual trauma
Menorrhagia

- Bleeding disorders
  - 19% of acute adolescent menorrhagia later diagnosed with a coagulation abnormality
- Uterine pathology

Bleeding Disorders

- 20% of girls who require hospitalization
- 25% of girls with hemoglobin <10g/dL
- 33% of girls who require transfusion
- 50% of girls who present with menorrhagia from first menses

Bleeding Disorders

- 3% adolescents diagnosed with bleeding disorders
- 13% adolescents presenting with menorrhagia had thrombocytopenia
Bleeding Disorders

- Thrombocytopenia
  - Immune thrombocytopenic purpura
  - Iatrogenic thrombocytopenia

Bleeding Disorders

- Von Willebrand disease
  - Often women present with menorrhagia
  - Family history of menorrhagia
  - 95% of women with vWD experience menorrhagia
  - Accurate diagnosis of vWD sub-type
  - Desmopressin challenge prior to routine use
  - Other available treatments

Metrorrhagia

- Infection
  - Cervicitis
  - Endometritis
  - Pelvic inflammatory disease
Management

Menstrual calendars

Management
Chronic or mild acute bleeding

Mild Bleeding (prolonged menses or more frequent cycling, no anemia)
- Reassurance
- FeSO4
- NSAIDS
- Hormonal therapy
  - Combination oral contraceptive
  - Progestins

Hormone Therapy

Lack of evidence guiding exact treatment regimen
- Monophasic pills
- Examples
  - Norgestrel 0.3mg/ ethinyl estradiol 30mcg
  - Levonorgestrel 0.15mg/ ethinyl estradiol 30mcg
Progestins

- Avoiding combination pills
  - Patients with medical contraindications
  - Parental or patient preference

- Oral progestins
  - Medroxyprogesterone acetate 10mg daily for 12-14 days
  - Norethindrone acetate 5mg daily for 12-14 days

Progestins

- Depot medroxyprogesterone acetate
  - Irregular bleeding for 6 months
  - May ultimately induce amenorrhea

- Levonorgestrel IUD
  - Older adolescents
  - Need to evaluate patients on an individual basis

GnRH Agonist

- Depot Leuprolide
- Extreme cases
  - bone marrow transplantation
  - long-term anticoagulation

- Complete arrest of menstrual cycles

- Add-back therapy necessary to prevent bone loss if used for more than one year

  - Low-dose estrogen/progestin or norethindrone acetate
  - Conjugated estrogen 0.625mg plus norethindrone acetate 5mg daily
    - Prevention of bone loss
    - Reduction in vasomotor symptoms

Hornstein et al., Obstet Gynecol 1998
Management
Acute moderate bleeding

- Moderate bleeding
  - Menses > 7 days or cycle length < 3 wks
  - Hemoglobin 10-11 g/dL
- Treatment
  - One pill 2x/day until bleeding stops
  - Then one pill/day for 21d, then one week of placebo
  - Continue once daily regimen for 3-6 months

Management
Acute severe bleeding

- Hemoglobin 8 to 10 g/dL
- Consider inpatient admission
- One pill 4x/day for 2-4 days
- One pill 3x/day for 3 days
- One pill 2x/day for 2 weeks
  - Consider antiemetic 2hr before each pill when taking 2-4 pills/day
- Follow closely with serial hcts
- Cycle using regular pill pack for 6 months

Management
Acute severe bleeding with severe anemia

- Defined
  - Hemoglobin < 7g/dL
  - Orthostatic
  - Heavy ongoing bleeding with hemoglobin < 10g/dL
- Treatment
  - Admit for inpatient management
  - Consider need for transfusion
  - IV conjugated estrogens (in severe acute hemorrhage only)
  - Oral combination pills
Management
Acute severe bleeding with severe anemia
- IV Conjugated estrogen
  - 25mg Q4hrs for 2-3 doses
- Combination pills
  - One pill Q4hrs until bleeding slows (usually 24-36hrs)
  - One pill 4x/day for 2-4 days
  - One pill 3x/day for 3 days
  - One pill 2x/day for 21 days or until hemoglobin > 30g/dL
  - Use antiemetics pm 2hrs before each pill

Management
- Increased risk of stroke with IV estrogen vs high dose OCPs (note what is "increased" 1/100,000? 1/1,000,000 – the number must be VERY small if the literature cannot give you a number. I usually avoid the use of "increase" and use attributable risk.
- No published data to support/refute this claim

Follow-up
- Perimenarchal bleeding
  - Most females establish regular cycles within 2 yrs of menarche
  - Iron therapy
  - Serial hct
  - Menstrual calendar
  - Long term follow-up important
Special Cases

- Bone Marrow Transplant or Chemotherapy Patients
  - Bleeding risk increases with platelet count < 20,000
  - Depot Lupron or Depot Provera (DMPA)

Special Cases

- Leuprolide
  - BMT pts
  - 7.5mg IM Q28days
  - First injection 4-5wks prior to BMT
  - High amenorrhea rates
- Leuprolide vs. DMPA
  - Pts receiving myelosuppressive chemo
  - Severe or moderate menorrhagia
    - 0/39 Luprolide
    - 9/39 (21%) DMPA
    - 9/20 (40%) no treatment

Epidemiology

- 20% of women experience abnormal bleeding during their lifetime
- Most irregular bleeding occurs within 2-3 years after menarche
  - 85% of cycles anovulatory in first year after menarche
  - Adolescents who have not established a 24-35 day cycle by 3 years after menarche have a 50% chance of having a persistent irregular pattern
Anovulatory Bleeding

- PCOS is a SYNDROME...not a Disease
  - 5-10% of adolescents and women of reproductive age
  - Overweight (much of the time)
  - Insulin resistance (some of the time)
  - Acanthosis nigricans (some of the time)
  - Hirsutism (some of the time)
  - Acne (some of the time)

PCOS

- Anovulatory from puberty
- Usually <6 menses per year
- Periods are unpredictable in timing and amount
- Excessive hair growth is typical
- Most (60%-70%) are infertile
- At risk for diabetes, heart disease (?)
- At risk for sleep apnea, depression

Prevalence

- Appears to be the same range among all races examined to date
- About 6.5% using consensus definition
- About 25% using the 2003 Rotterdam criteria (two of three):
  - Irregular periods
  - Evidence of androgen excess
  - Polycystic ovaries on ultrasound
Ultrasound Criteria....

 >12 follicles 2-9 mm in at least one of the ovaries
 Increased volume (>10cc)

 Excluded are those on OCPs and those with follicle >10mm.
 “Chain of Pearls sign” is not required

If you are using ultrasound criteria...and I don't.

Ultrasound Criteria

 Only 2 of three women with this criteria will have PCOS, and probably even fewer adolescents
 About 25% of ovulatory women have this morphology (most of our good fertile young egg donors)
Consensus Diagnosis of PCOS

- “There is lack of consensus with even the latest consensus statement”
- Obesity is not even part of the diagnostic criteria but it does add to the clinical suspicion

PCOS - 2008

- Hyperandrogenism - (clinical and/or biochemical)
- Ovarian dysfunction – as reflected by oligo-ovulation and/or polycystic appearing ovaries
- Exclusion of other androgen excess disorders


PCOS 2008

- Clinical or biochemical signs of androgen excess are prerequisites of PCOS
- If an adolescent doesn’t have hyperandrogenism, don’t order ultrasound
- (I never order the ultrasound in adolescents)
PCOS

- The diagnostic approach in adolescents should be based on history and physical exam
- Avoid numerous laboratory tests that do not contribute to clinical management

Guzick DA. Clinical Updates in Women's Health Care, ACOG 2009

Million Dollar Workup

- TSH, Prolactin, Total testosterone (female), Free Testosterone, SHBG, androstenedione, DHEAS, Plasma free testosterone, overnight Dexamethasone Suppression test, IGF-1, 17-hydroxyprogesterone in the follicular phase, fasting insulin and glucose
- Ultrasound

Hundred Dollar workup

- Testosterone (female) to rule out tumors (free testosterone may be elevated in the face of normal total but you know that by looking)
- Prolactin and TSH (for other causes of anovulation)
- 17-hydroxyprogesterone in the follicular phase?
- Serum glucose or HgA1c if clinically suspected
PCOS and Insulin resistance
(the chicken and the egg problem)

- Does obesity and insulin resistance cause PCOS …or…
- Does PCOS cause insulin resistance and obesity
- Or a little of both

(note: gastric bypass surgery “cures” PCOS in obese women)

PCOS and Insulin resistance

- Insulin is a growth factor for the ovary
- Women who are obese sometimes have insulin resistance (it takes higher and higher insulin levels to keep glucose in the normal range)
- Fat cells are insulin resistant, but the ovaries are not

Figure 1
Pathophysiology of Polycystic Ovary Syndrome

Source: Rehan RL (2001)
Insulin and PCOS

- 50% of obese teens with PCOS have insulin resistance by the most sensitive tests (insulin euglycemic clamp test)
- 17% of normal weight women with PCOS have insulin resistance by the most sensitive tests

Metformin and Adolescents with PCOS

- No real data on long term use of metformin in adolescents
- One small randomized trial in morbidly obese teens showed improvement in glucose, insulin, BMI, and menstrual cyclicity
- All effects gone within 3 months of discontinuing metformin

Ibanez L. JCEM 2001;86:3595-3598
And in the Face of Clinical Suspicion...

- 24 hour urinary free cortisol to rule out Cushing's
- IGF-1 for acromegaly
- DHEAS for adrenal tumors (but I have never seen one)
- If 17-hydroxyprogesterone is very high (check your lab's normals) and you are sure it was follicular – refer

PCOS Treatment
The complicated way

- The big work up
- The big therapy
  - Metformin
  - Lifestyle modifications

Add OCPs if cycles do not regulate (and they often don't)
Repeat the big workup yearly

PCOS Treatment
The Easy Way

- Diet and exercise
- OCPs
- Check fasting glucose (or two hour post prandial....or random...or HgA1c) if they are still gaining weight

- How do you put the fear of the mirror without creating self loathing?
PCOS and Adolescents

- Prevent severe DUB and endometrial cancer
- Suppress ovarian androgen production and bind up the rest
- Be prepared to detect and treat diabetes

PCOS and Adolescents

- Low dose OCPs
- Any ones will do
- Norgestimate, desogestrel, drospirenone are non-androgenic progestins and have theoretical advantages
Can’t Take OCPs

- Cyclic progestins
- Androgen blocking therapies (spironolactone)

Cosmetic therapy

- OCPs for Acne
- Laser for Hair
- efomithine?

Diet for PCOS

- Some websites and some science suggest low carb (or low glycemic index) high protein, high fat diets are more appropriate for PCOS
- Decrease glycemic load, decrease insulin, decrease androgens
Treatment for Obesity

- Diet – there is evidence in adults that low carb is more sustainable than low fat
- Exercise (good luck) – 2400 calories out a week minimum
- Bariatric surgery – this is what works for morbidly obese adolescents with PCOS

Diets

- Large (811) 2 year randomized trial of various diets with counseling
- No real difference in weight loss (about 6kg at 6 months, about 3.3kg at 2 years)
- Only calories counted….
- Best predictor of success was attendance at group sessions

Sacks et al. NEJM 2009;360:859-73

Lifestyle Changes

- Exercise (good luck) – 2400 calories out a week minimum
- Bariatric surgery is the only thing that reliably works: instant reversal of diabetes, long term success in many
- Bariatric surgery recommended for morbidly obese adolescents
Adolescents

UNPLANNED PREGNANCIES

PERCENT UNPLANNED PREGNANCIES IN FEMALE RESIDENTS

WOMEN NEED PROTECTION FOR MORE THAN ONE YEAR

PERCENT PREGNANCY – 5 YEARS CUMULATIVE RISK

PHelan, Obstetrics and Gynecology, 1988

Contraceptive Technology - 1988
WOMEN NEED PROTECTION FOR MORE THAN ONE YEAR

THE FUTURE WELFARE OF HUMAN KIND RESTS MORE HEAVILY AT THIS POINT IN HISTORY ON THE PROGESTINS THAN IT DOES ON ATOMIC WEAPONS

ROY O. GREEN 1976

A CONTRAINDICATION TO PROGESTINS IS A CONTRAINDICATION TO PREGNANCY
CONTRACEPTION IN EARLY ADOLESCENCE

- No evidence that hormonal methods will delay the maturation of the hypothalamic-pituitary access (and if they did...so would pregnancy...)
- "Pseudo dementia" of adolescence makes risk taking likely
- Coexistence of medical illness (CF, congenital heart disease, type 1 diabetes) makes GOOD CONTRACEPTION PLAN IMPERATIVE!
- Pediatricians may effectively practice "DON’T ASK, DON’T TELL" when it comes to sex