Reproductive Abnormalities: How to Optimize Future Fertility
Interesting Case RGM

Beth W Rackow, MD
Case RGM

- 16 year old female, star soccer player
- Dysmenorrhea since menarche at age 12
- Regular monthly menses lasting 7 days
- 2 year history of worsening pelvic pain, maximal discomfort in right lower quadrant
- Intermittent diarrhea/constipation
- Dyschezia during menses
- Episodes of frank hematuria
- Chronic fatigue
- Missed 25 days of school last year!
Case RGM

- Multiple MDs involved: Pediatrics, Nephrology, Urology, Gastroenterology, Gynecology, Rheumatology
- Normal imaging: abdominal and pelvic ultrasound, renal ultrasound, pelvic MRI
- S/p laparoscopic appendectomy → no change in pain
- On exam: soft abdomen, no masses, max tenderness RLQ; pelvic examination with diffuse tenderness, max in RLQ, normal adnexa
Based on your assessment of this adolescent, you make a presumptive diagnosis of endometriosis.

For treatment, you recommend:

A. Nonsteroidal anti-inflammatory drugs
B. Laparoscopy
C. Estrogen-progestin contraceptive
D. Depot-leuprolide acetate
E. Psychologic counseling
Case RGM

• An estrogen-progestin contraceptive is initiated, with the plan for continuous use.
• Her pain is minimally better
• Pediatric Urology evaluates her for intermittent frank hematuria
• Proceeded with joint procedure: laparoscopy, cystoscopy, retrograde pyelogram
Presentation of Adolescent Endometriosis

- Range of symptoms:
  - Cyclic or acyclic pain
  - Early age of onset of dysmenorrhea
  - Severe dysmenorrhea
  - Dysmenorrhea refractory to medical treatment
  - Prolonged menstrual bleeding
  - Bowel and bladder problems
  - Dyspareunia
  - Chronic pelvic pain
The patient and her mother are concerned about how endometriosis affects future fertility, and want to know the best treatment protocol to preserve future fertility. You recommend:

A. Pain management referral
B. Oocyte cryopreservation
C. Depot-leuprolide acetate with add-back therapy
D. Continuous estrogen-progestin contraceptives
E. Oral progestins
Diagnosing Endometriosis

- Up to 70% of adolescents with chronic pelvic pain who do not respond to NSAIDs/E-P contraceptives will have endometriosis at laparoscopy.

- Majority of adolescents have minimal-to-mild disease, but up to 1/3 of adolescents may have moderate-to-severe disease.

- Approximately 60% of adults with endometriosis report symptoms prior to age 20.

Fecundability following diagnosis of endometriosis in adolescence

Adolescent Endometriosis: Treatment and Prevention

- Combined surgical and medical management may retard disease progression in adolescents and young adults
  - Decide to do the first laparoscopy
  - Treat disease at the time of surgery
- A clear benefit of one medical therapy over another has not been shown
- No repetitive surgeries!

TAKE HOME POINTS - Adolescent Endometriosis

- Manage pain
- Suppress disease progression
- Decrease the adverse long-term effects of the disease
  - Chronic pain
  - Endometriomas
  - Infertility
- Improve quality of life of adolescents and young women with endometriosis

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- Improve quality of life of adolescents and young women with endometriosis

LEARNING OBJECTIVES

At the conclusion of this interactive session, participants should be able to:

1. Describe treatment options to maximize fertility for girls with various reproductive abnormalities.

2. Determine the best time for intervention to maximize fertility for girls with various reproductive abnormalities.

3. Determine the best diagnostic tests for determining future fertility potential in girls with various reproductive abnormalities.
DISCLOSURES

- Staci E Pollack – nothing to disclose
- Beth W Rackow – nothing to disclose
Reproductive Abnormalities: How to Optimize Future Fertility
Interesting Case SLS

Staci E Pollack, MD MS
Case SLS

- 18 4/12 year-old virginal G0 young woman
- CC: 2° amenorrhea x 6 months + severe acne
- PMH: Obesity, Acne
- GYN history:
  - Menses irregular q4-6 months
  - LMP 6 months ago
- Birth and Pubertal history:
  - Birth weight 5lb 6oz
  - Thelarche 12 years/Pubarche 6.5 years/Menarche 16 10/12 years
- Family history:
  - Mother, MGM, MA, MU: obesity and DM
Case SLS

Physical Exam:
- Height: 5’5”  Weight: 185 lb  BMI: 30.8 (95% for age)
- Tanner 5 Breasts/Tanner 5 Pubic Hair
- Acne on face/chest/back
- Hirsutism: upper lip/chin/abdomen/buttocks
Which of the following symptoms raise a red flag for risk of future PCOS?

A. Precocious Pubarche
B. No menses by age 15
C. No menses within 3 years of thelarche
D. All of the above
Risk Future PCOS

- History of IUGR
- Low birth weight (<5lb 8oz/<2500gm)
- Precocious Pubarche (<8 years)
- No menses by 15 years
- No menses within 3 years from thelarche

Diagnose PCOS or “at risk for PCOS”:
- Risk factors: LBW, PP, no menses by 15
- Symptoms: menses <q90d, hirsutism, acne
- Associated symptoms: obesity
- 1.5 years post-menarcheal
### Diagnostic Criteria for PCOS in Adolescents


#### Abnormal uterine bleeding pattern

<table>
<thead>
<tr>
<th>Abnormal for age q19d, q90d (Year 1)</th>
<th>Persistent 1-2 years</th>
<th>Primary Amenorrhea-By age 15 3 years post-thelarche</th>
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</thead>
</table>

#### Evidence of Hyperandrogenism

<table>
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<tr>
<th>Elevated Total or Free Testosterone</th>
<th>Moderate-Severe Hirsutism Ferriman-Gallwey &gt;15</th>
<th>±Moderate-Severe Acne &gt;10 lesions</th>
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</thead>
</table>

- ≥2 years since menarche
- AUB x 1 year ➔ ~50% risk ongoing (~50% those = PCOS)  
- IF clinical hyperandrogenism ➔ ≥80% AUB at 3 years  

van
Ferriman-Gallwey Score
Hirsutism in Adolescents

- Adult level hirsutism by 2 years
- Girls with severe acne or acne resistant to oral/topical treatment
  → 40% chance PCOS


Diagnose PCOS or “at risk for PCOS”:
- Risk factors: LBW, PP, no menses by 15
- Symptoms: menses <q90d, hirsutism, acne
- Associated symptoms: obesity
- 1.5 years post-menarcheal

Parents worried about her future fertility
Which of the following factors that are associated with PCOS play a role in the future fertility for adolescent girls with PCOS?

A. Anovulation
B. Obesity
C. Both
Future Fertility and PCOS

- Anovulatory Infertility
- SAB
- Increased PT Delivery and IUFD
- Lower # Pregnancies (vs non-PCOS)
- Higher Chance IVF
- Poorer Response IVF
- Obesity independent risk factor for infertility

- Important: Altered QOL depend on: HIRSUTISM and OBESITY

Pasquali R 2006. BJOG 113(10):1148-1159
Case SLS

- Parents want to discuss treatment recommendations
- Options: weight loss/lifestyle modification, OCP, Metformin
When would you consider treating an adolescent who has PCOS with metformin?

A. Strong family history of Diabetes
B. Obesity refractory to lifestyle intervention
C. Pre-Diabetes
D. Type 2 Diabetes
Adolescent PCOS Treatment

- Weight loss/lifestyle modification
  - Improved response/better pregnancy rate to Clomiphene
  - Resumption menstrual function
  - Improved metabolic parameters → Healthier pre-pregnant state
  - Prevent/delay progression PCOS
- OCP
  - Restores menstrual cyclicity
  - Reduce hirsutism
- Metformin
  - ± Resumption menstrual function
  - ± Reduce hirsutism
  - Improved metabolic parameters

Legro R 2016. J Clin Endo Metab
Tang T et al 2006. *Hum Reprod* 21(1)
TAKE HOME POINTS - Adolescent PCOS

- Don’t rush to diagnose definitive PCOS
- Be inclusive to diagnose “at risk for PCOS”

- Treatment to improve future fertility
  - Weight loss/lifestyle modification
  - Metformin may help
Reproductive Abnormalities: How to Optimize Future Fertility
Interesting Case NME

Staci E Pollack, MD MS
Case NME

- 18 8/12 year-old virginal G0 young woman
- 1° amenorrhea/Delayed menarche
- Thelarche 13 years/Pubarche 13 years
- 2 prior Progestin challenge tests: no bleeding (15 and 4 months prior)
- Denies alcohol/tobacco/drug use, extreme exercise, eating issues
- Orthodox Jew
- Family History
  - Sister: late onset congenital adrenal hyperplasia
  - Paternal Uncle: mental retardation
Case NME

- Physical Exam
  - Height: 5’ 1”
  - Weight: 111 lb
  - BMI: 21 (43% for age)
  - Tanner 5 Breasts/Tanner 4 Pubic Hair

- Labs

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Case NME

- Transabdominal Pelvic Ultrasound
  - normal uterus and ovaries
  - follicles seen, Antral Follicle Count 6

➤ DOR/”Impending POI”
What would you discuss and/or offer with regards to her future fertility?

A. Don’t worry about future fertility
B. 10% chance spontaneous ovulation and pregnancy
C. Donor Egg
D. Oocyte cryopreservation
E. Ovarian tissue cryopreservation
Case NME

- Patient chooses IVF + oocyte cryopreservation
  - Ovarian stimulation daily: FSH 450 IU + HMG 150 IU
  - 2 cycles
  - 33 oocytes (20 M2, 8 M1)
- Subsequent hormone replacement with 30 μg ethinyl estradiol combined oral contraceptive pill
Case NME

- 1 year later, presents questioning her fertility
- Labs

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ARS

Which of the following tests affords you the best assessment at predicting this patient’s future fertility for you to counsel her with?

A. FSH + Estradiol
B. AMH
C. Inhibin A
D. Antral Follicle Count
E. Pelvic MRI
AMH Levels in Girls

- Rise during infancy and childhood, then stable
- ~25-30% decline during first 2 years after pubertal onset
- Plateau during adolescence
- Steady decline during adulthood

- < 25 years, AMH 5-6 ng/ml = median
- Potential variability- biology, exposure, laboratory

DOR/“Impending” POI – what we know

- **Turner Syndrome Girls**
  - Karyotypes with worst probability of fertility have (Purushothaman et al 2010 Fert Stert 94(4):1557-1559):
    - Group 1 (poor probability of fertility)
      - 45XO 4
      - 45XO/46Xr(X) 3
      - 46X del(Xq) 1
      - 45XO/46XY 1
    - Group 2 (fair probability of fertility)
      - 45XO/46XX 3
      - 46X del(Xp) 2
  - AMH low or undetectable (Hagan et al 2011 Pediatr Endocrinol Rev. 9, Suppl 1:525-8)
  - AMH < 8 pmol/l (0.56 μg/l) = ovarian failure (Hagen et al 2010 JCEM 95(11):5003-10)
  - 12% healthy Danish girls AMH < 8 pmol/l (Hagen et al 2011 Hum Reprod 27(3):861-6)
  - Fertility preservation with IVF/Oocyte Cryopreservation (Oktay et al 2010 Fert Stert. 94(2):753.e15-19)
DOR/“Impending” POI – what we know

- Female Childhood Cancer Survivors
  - FSH
    - If prepubertal or cranial irradiation → HPO axis quiescent → FSH low
    - FSH late marker
  - FSH detected fewer patients with DOR than AMH
  - AMH marker gonadotoxicity
  - ↑ AMH low risk vs high risk gonadotoxicity treatment

Brougham et al 2012. JCEM 97:2059-67
TAKE HOME POINTS - DOR/“Impending” POI

- AMH *best* marker in pediatric and adolescent population
  - NOT perfect
- Inhibin A potential marker?
- FSH late marker – too late?
- Oocyte cryopreservation potential strategy for fertility preservation