Controversies in Reproductive Endocrinology and Infertility
October 15, 2015

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Frank De Leon MD
Objectives

- **Infertility Evaluation**
  - Which tests are not necessary
  - In vitro fertilization When to refer? Success rate?

- **Polycystic Ovarian Syndrome (PCOS)**
  - When does PCOS start
  - Risk for glucose intolerance
  - Investigation for diabetes in the asymptomatic patient
  - Appropriate tests, diagnosis and management
  - Long-term effects
  - Strategy for helping patients with PCO achieve pregnancy

- **Endometriosis with chronic pelvic pain in the young patient**
  - Appropriate management
  - Medical
  - Surgical

- **Uterine Fibroids**
  - Medical versus surgical treatment
  - alternate treatments for fibroids
• Mrs Jones has been trying to get pregnant for three years. She is 31 g0p0 and in excellent health. Periods are regular, with mild to moderate dysmenorrhea for which she takes ibuprofen prn. Husband is 33 and in excellent health. ROS and PMH is noncontributory.
<table>
<thead>
<tr>
<th>Routine INFERTILITY evaluation</th>
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<tbody>
<tr>
<td><strong>Male factor</strong></td>
</tr>
<tr>
<td><strong>Ovulation</strong></td>
</tr>
<tr>
<td><strong>Cervical</strong></td>
</tr>
<tr>
<td><strong>Tubal/Uterine</strong></td>
</tr>
<tr>
<td><strong>Peritoneal</strong></td>
</tr>
<tr>
<td><strong>Endocrine/immunological</strong></td>
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<tr>
<td></td>
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<tr>
<td><strong>Peritoneal factor</strong></td>
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</tbody>
</table>
The overall response rate was 84%.

- semen analysis (99.9%), an
- assessment of ovulation (98%)
- postcoital test (PCT, 79%),
- hysterosalpingogram, (HSG; 96%)
- antisperm antibody testing (24%).
- laparoscopy (89%)
Based on clinical evidence and recommendations by Choosing Wisely, how many of these tests/procedures are not routinely recommended for the initial infertility evaluation?

• semen analysis  
  a. 1
• assessment of ovulation  
  b. 2
• postcoital test  
  c. 3
• hysterosalpingogram  
  d. 4
• antisperm antibody testing  
  e. 5
• laparoscopy  
  f. 6
Based on clinical evidence and recommendations by Choosing Wisely, how many of these tests/procedures are not routinely recommended for the initial infertility evaluation?

- semen analysis
- assessment of ovulation
- postcoital test
- hysterosalpingogram
- antisperm antibody testing
- laparoscopy for unexplained infertility
Choosing Wisely

Don’t perform routine diagnostic laparoscopy for the evaluation of unexplained infertility

Don’t perform a postcoital test (PCT) for the evaluation of infertility.

Don’t perform advanced sperm function testing, such as sperm penetration or hemizona assays, in the initial evaluation of the infertile couple.

Don’t routinely order thrombophilia testing on patients undergoing a routine infertility evaluation.

Don’t perform immunological testing as part of the routine infertility evaluation.
Unexplained infertility

• Sometimes we do all of the tests to evaluate a couple’s fertility and they all come back normal.

• Unexplained infertility means that there is a fertility issue, but we are unable to determine the exact cause of the infertility
Treatment of unexplained infertility

a. Empiric clomid

b. Clomid with insemination

c. IVF

d. Laparoscopy
• IVF indications in 2015
• Results
• Costs
• Patients over 40
• Polycystic Ovarian Syndrome (PCOS) is an endocrine (hormonal) disorder that affects 5-10% of all women.
• PCOS can affect women of all races and ethnic backgrounds.

most frequent symptoms

1) Excessive facial or body hair (Hirsutism)
2) Acne
3) Irregular periods
4) Obesity
Symptoms of PCOS most often appear in the

- Mid-teens
- 20’s
- 30’s
- 40’s
• My name is Amanda and I have had very irregular periods since my late teens.
• When I was 18 I went on birth control which caused my hormones to regulate and my period started to come like clockwork. It was light and painless. When I was 23 I decided that I didn’t want to be on synthetic medications anymore and I stopped taking birth control.
• That was when I realized that something was terribly wrong with me. My period completely stopped and did not come back for almost 4 years. I started getting hair in strange places. I gained weight easily and had terrible acne. but every time i would go to the doctor they would tell me they couldn’t find anything wrong with me.

I am now 25 years old and my symptoms are getting worse . I have noticed thickened dark areas on my neck , and have been gaining quit a bit of weight
• DIAGNOSIS
Most likely diagnosis

- Congenital adrenal hyperplasia
- Hypothyroid
- PCOS
- Symptoms due to obesity
Diagnosis of PCOS

1) Excessive facial or body hair (Hirsutism)
2) US appearance of polycystic ovary
3) Irregular periods
4) Obesity
5) Elevated LH/FSH ratio
6) Increased Testosterone
Diagnosis of PCOS

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## Criteria for diagnosis of PCOS

<table>
<thead>
<tr>
<th></th>
<th>NIH 1990</th>
<th>Rotterdam 2003 (2 out of 3 required)</th>
<th>Androgen excess Society 2006 (HA+iof two required)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both required</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hyperandrogenism</td>
<td>R</td>
<td>NR</td>
<td>R</td>
</tr>
<tr>
<td>Oligomenorrhea or amenorrhea</td>
<td>R</td>
<td>____NR</td>
<td></td>
</tr>
<tr>
<td>Polycystic ovaries</td>
<td>____NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Health implications of PCOS

**Short term**
- Infertility
- Hirsutism
- Acne
- Irregular periods
- hyperplasia

**Long term**
- Heart disease
- Diabetes
- Metabolic syndrome
- Uterine cancer
- Breast cancer

![Image of skin condition](image1.png)
![Ultrasonic scan image](image2.png)
Health implications of PCOS

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- Breast cancer
Endometrial adenocarcinoma in teenagers
Dale W. Stovall, Ralph J. Anderson, Frank D. De Leon
1989

• Adenocarcinoma of the endometrium is an extremely rare finding in the teenage population. Two case reports of 17-year-old teenagers with endometrial carcinoma are presented. Both patients have a history of prolonged periods of anovulation which supports the association between unopposed prolonged estrogen effect and the development of endometrial carcinoma
Appropriate workup for PCOS

**Laboratory Evaluation when Considering PCOS**
- TSH
- Prolactin
- LH and FSH
- Total and free T
- 17 OH Progesterone
- DHEA-S
- pelvic ultrasound
- Endometrial biopsy
- Case by case: cortisol
- 17OHProgesterone

**Screening for Metabolic Complications of PCOS**
- Oral glucose tolerance test with fasting glucose, insulin, and 2-hour glucose and insulin levels
- Hemoglobin A1c
- Fasting lipid panel
- Liver tests - AST, ALT, GGT
- Waist circumference measurement
- Blood pressure measurement
- BMI calculation
Treatment

What can you do?

• Birth control pills (Oral Contraceptives)
• Anti-androgen Drugs
• Insulin Sensitizers
• Weight loss
• Excessive Hair Growth - Vaniqa
• Fertility meds

Multidisciplinary Approach to PCOS

• Reproductive endocrinologist
• Internist
• Pediatrician
• Nutritionist
• Exercise coach
• Behavioral therapist
PCOS/Conclusions

• We have an obligation to have an impact on the quality and quantity of life to be experienced by the PCOS patients.
• Early identification in adolescence, intervention and counseling for patients with PCOS may prevent the emergence of co-morbid medical conditions.
• It is most prevalent and severe in those with PCOS phenotype involving hyperandrogenism and chronic anovulation
• Multidisciplinary Approach to PCOS
Endometriosis
Misconceptions

- Endometriosis occurs in patients primarily in their thirties and older
- Patients tend to be white
- Goal oriented, career minded, delayed childbearing
- Rare in Blacks
When does endometriosis begin?

Most teens with endometriosis have suffered from pelvic pain with negative workup for several years before diagnosis is made.

1980- lag time 12-15 years
1998- lag time 9 years

Presently young girls are getting diagnosed earlier because mothers have suffered from this condition or are aware of endometriosis.
Endometriosis

2004;18:201-218
Chronic pelvic pain in adolescents

- **Endometriosis** 66
- Postoperative adhesions 18
- **Uterine anomalies** 12
  - Pelvic inflammatory disease 10
- Hemoperitoneum 6
- Functional ovarian cyst 5
- Serositis 4
- No pathologic diagnosis 19

- **TOTAL** 140

Goldstein et al. Pediatric and Adolescent Gynecology 1990
Reasons for early diagnosis

• Accurate diagnosis
• More prompt relief of symptoms (pain)
• Avoid progression that may impair fertility
Patient A is a 15 year old teenager who complains of increasing pelvic pain with periods which is now more persistent. Presently unresponsive to analgesics. Her mother has a history of endometriosis. After completing a complete H & P, your next step is

- oral contraceptives
- depot lupron
- laser laparoscopy
- exploratory laparotomy
• After trial of oral contraceptives for two months her pain continues.

• At this time you would recommend

GnRh therapy
Laparoscopy
depoprovera
Danazol
Different presentations of Endometriosis

Treatment options? Fulgarate, laser, resect
Presentation of Endometriosis at Laparoscopy in Adolescents

- Lesion type noted at laparoscopy in 48 adolescent girls with endometriosis

  - Lesion type                                Percentage(%)  
    Red                                      81.6
    Pigmented (blue/black)                    75.5
    Superficial                               98.0
    Vesicular                                 40.8
    White                                     8.1
    Deep                                      12.2
    Pocket                                    18.4

Reese KA. J Pediatr Adolesc Gynecol 1996 Aug
Evolution of the Color of Endometriosis Lesions With Age

<table>
<thead>
<tr>
<th>Lesion color</th>
<th>No. patients</th>
<th>Mean age (range), y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear only</td>
<td>6</td>
<td>21.5 (17–26)</td>
</tr>
<tr>
<td>Clear + others</td>
<td>14</td>
<td>23.4 (17–31)</td>
</tr>
<tr>
<td>Red only</td>
<td>6</td>
<td>26.3 (16–38)</td>
</tr>
<tr>
<td>Red + others</td>
<td>22</td>
<td>26.9 (17–43)</td>
</tr>
<tr>
<td>All nonblack</td>
<td>55</td>
<td>27.9 (17–42)</td>
</tr>
<tr>
<td>White only</td>
<td>8</td>
<td>29.5 (20–39)</td>
</tr>
<tr>
<td>Black only</td>
<td>48</td>
<td>31.9 (20–52)</td>
</tr>
</tbody>
</table>
• Is biopsy required to make the diagnosis of endometriosis?

• Recommended surgical treatment; fulgaration vs excision or both

• Does complete laparoscopic excision of endometriosis in teenagers really occur?
Is medical therapy indicated following surgical removal of endometriosis in teenagers? Which agent?

- NSAID
- Noncyclic oral contraceptives
- GnRh analogues
- Depoprovera
- Danazol
- Cyclic oral contraceptives
Adolescents with pelvic pain should be fully assessed to determine if they have endometriosis. (early laparoscopy)

Early diagnosis and treatment can decrease disease progression, allow patients to return to normal psychosocial development and self-esteem, improve academic performance, and facilitate return to normal daily activities.

The possibility of infertility later in life is of particular concern in young, symptomatic patients; (inverse relationship between stage of disease at diagnosis and later fecundity)

Consider uterine anomalies in adolescents
Uterine Fibroids: Treatment Options

- Most common tumor of female genital tract. 
  1 in 3 women >35 yrs. of age.
- As high as 75% in reproductive age African-American women.
- 1/3 are symptomatic
- Tend to regress after menopause (51.8 years)
- Incidence of malignancy is < .3%
- Most common indication for (>600,000) hysterectomy in the U.S. 
  (hysterectomy 2nd most common surgical procedure in the US).
- Costs: $5 billion/year spent in U.S. for fibroids (primarily on the cost incurred from hysterectomy).
Clinical Impact

• Chronic pelvic pain
• Abnormal bleeding
• Reproductive function
Treatment of Uterine Fibroids

- Surgical
- Medical
- Expectant
- Other options?
Patient E.N.

• **Chief complaint:** 23 y/o AAF G0P0 c/o increasing abdominal size and abdominal pain over 1 year

• Abdominal pain began approx one year ago, was intermittent and mild.
• Over last 3 months pain occurring almost every day requires hydrocodone. Also increased abdominal size and firmness noted over last 6 months
• **Meds:** Ortho TriCyclen Lo OCPs
• hydrocodone, indomethacin
Patient E.N.

- **BP:** 112/64  ht. 5’6”  wt. 155.6 lbs
- **Gen:** thin AAF in NAD, flat affect
- **Abdomen:** soft, mass at 2 cm above umbilicus (FH approx 23 wks.)
- **GU:** hymen intact, small introitus
• H/H  12.5/ 39.9
• Pelvic Ultrasound:
  uterus 16.9 x 9.8 x 16.3 cm
  Multiple fibroids, 2 largest 10.5 x 10.9 cm one intramural stripe 7.3 mm
  MRI; 3 distinct fibroids noted
Treatment recommended?

- Myomectomy
- Hysterectomy
- Uterine artery embolization
- MRI guided ultrasound
- Laparoscopic radiofrequency (acessa)
- Hormonal treatment
Myomectomy
Pathology Report: fragments of leiomyoma tissue weighing 757.3 gm with focal degeneration
Laparoscopic approach
Dehiscence following Laparoscopic Myomectomy

• Several case reports exist of uterine dehiscence during pregnancy following laparoscopic myomectomy

• First reported in 1992 in a young G1 at 34 weeks gestation

• Incidence thought to be higher following laparoscopic myomectomy
Minilap vs laparoscopy

- Minilaparotomy <5cms
- Outpatient or 23 hour observation
- Multilayer closure
- Easier application of barrier for adhesion prevention
- Faster than laps
ACESSA

- Radiofrequency
- Needle array
- 7cms fibroids
- 50% vol reduction
- 90% satisfaction
Medical therapy for fibroids (pain, menstrual dysfunction)

- GnRh agonists
- Progesterone antagonist
- Selective estrogen receptor modulators (SERMS)
- Selective Progesterone receptor modulators
- Lupron
- Mifepristone
- Raloxiphene, tamoxifen
- Asoprisnil
Ulipristal acetate

• Dose
  5 or 10 mg of daily oral UPA during two 3-month courses

• Results
  63-72% amenorrhea
  50% volume reduction
  improvement in pain
  estradiol levels midfollicular level

Untoward effects
  bleeding returned within 28 days of stopping meds,
  LDL increased during the treatment
  size of fibroid returned to original size within 6 months
With the advent of selective progesterone receptor modulators, what is the place of myoma surgery in current practice?

Jacques Donnez, M.D., Ph.D., Olivier Donnez, M.D., Ph.D., Marie-Madeleine Dolmans, M.D., Ph.D.

Fertility and Sterility
Volume 102, Issue 3, Pages 640-648 (September 2014)
DOI: 10.1016/j.fertnstert.2014.06.041
Submucous fibroid

- OTHER SURGICAL OPTIONS
- ROLE OF MEDICAL THERAPY
- PRECAUTIONS WITH HYSTEROSCOPY
THANK YOU