Optimizing Ovulation and Fertility in the Polycystic Ovary Syndrome (PCOS)

Wendy Chang, M.D., F.A.C.O.G
Scientific Director
Southern California Reproductive Center
Assistant Clinical Professor
UCLA and USC Schools of Medicine
OBJECTIVES

At the conclusion of the presentation, the participant should be able to...

1. Understand the impact of PCOS on anovulatory infertility.
2. Discuss the potential benefits of lifestyle changes on ovulation in PCOS women.
3. Describe ovulation induction options in PCOS.
   - Clomiphene citrate
   - Letrozole
   - Adjuncts & new protocols (metformin, glucocorticoids, CoQ10, myo-inositol)
4. Discuss ovarian drilling in PCOS
5. In vitro fertilization
DIAGNOSIS OF PCOS: Historical Perspective

- Originally described by Drs. Irving Stein and Michael Leventhal at Rush Medical College in 1935.
- Case series of 7 patients (4 obese) with amenorrhea, hirsutism and enlarged, polycystic ovaries on exploratory laparotomy.
- On ovarian biopsy, thickened ovarian tunica thought to impair ovulation.
DIAGNOSIS OF PCOS:
(NIH/NICHD Conference, 1990)

- Clinical hyperandrogenism/hyperandrogenemia
- Ovulatory dysfunction
- Exclusion of other disorders:
  - non-classic adrenal hyperplasia
  - androgen secreting tumors
  - hyperprolactinemia/thyroid disorder
- Presence of polycystic-ovaries was felt to be suggestive, but not diagnostic of PCOS

Zawadski & Dunai, 1992
Presence of at least 2 of 3 criteria:
- Clinical and/or biochemical signs of hyperandrogenism
- Oligo and/or anovulation dysfunction
- Polycystic ovaries on ultrasonography

and

- Exclusion of other disorders:
  - non-classic adrenal hyperplasia
  - androgen secreting tumors
  - hyperprolactinemia/thyroid disorder

Fertility 101: The Basics
Basic Fertility 101

1. Ovarian Function
2a. Tubal Patency

2b. Uterine

3. Sperm

Adapted from Barbieri RL, Reproductive Endocrinology 4th ed. 1999; 562.
Definitions of Infertility

- Infertility: inability to conceive after 12 months of regular intercourse in women less than 35 years of age; and after six months of regular intercourse without use of contraception in women 35 years and older
- Affects approximately 15% of reproductive aged couples in the United States
- History of risks factors should prompt earlier evaluation:
  - Irregular menses
  - Previous pelvic surgery/ injury
  - Previous cancer treatment (chemo, radiation)
  - Significant pain, mass
Causes of Infertility

Collins et al., *Can Med Assoc J* 1984; 130:269.
PCOS and Anovulatory Infertility

- **PCOS is the most common cause of anovulatory infertility**
- Multiple etiologies of ovulatory dysfunction in PCOS
  - Excess intraovarian 5α-reduced androgens inhibit granulosa cell aromatase and inhibit follicle growth
  - Elevated insulin levels worsen follicular arrest
    - Stimulates increased theca cell androgen
    - Promotes premature luteinization, arresting granulosa cell proliferation and follicle growth
  - Overproduction of AMH by granulosa cells antagonizes FSH action in small follicles
### Prevalence of Infertility in PCOS

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>Balen et al.</th>
<th>Franks</th>
<th>Goldzieher et al.</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Menstrual cycle disturbance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligomenorrhoea</td>
<td>47</td>
<td>52</td>
<td>29</td>
<td>547</td>
</tr>
<tr>
<td>Amenorrhoea</td>
<td>19</td>
<td>28</td>
<td>51</td>
<td>640</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>66.2</td>
<td>64</td>
<td>69</td>
<td>819</td>
</tr>
<tr>
<td>Obesity</td>
<td>38</td>
<td>35</td>
<td>41</td>
<td>600</td>
</tr>
<tr>
<td>Acne</td>
<td>35</td>
<td>27</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Alopecia</td>
<td>6</td>
<td>3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>3</td>
<td>&lt;1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Infertility</strong></td>
<td>(primary) 20</td>
<td>42</td>
<td>74</td>
<td>596</td>
</tr>
</tbody>
</table>

**Note:**

- The data for infertility (primary/secondary) is 20/42/74, respectively, with a total of 596 cases as indicated.

---

Economic impact of Evaluating and Treating PCOS-Related Infertility

- Approximately 33-75% of PCOS women report having infertility
- An estimated 50% of PCOS women actively seen infertility services during their reproductive years
- Using standard treatment algorithms in the United States, the cost per live pregnancy in 1997 varies from $5,600 - $9,600
- Average cost per pregnancy in 2005, adjusted for inflation, was approximately $8000
- **Average annual cost of infertility care for PCOS**
  ~ $533 Million not including increased risk of pregnancy complications (GDM, PET, PIH, SAB)

Azziz et al., JCEM 90(8): 4650-4658
LIFESTYLE MODIFICATION: Preconceptional Counseling

- Preconceptional counseling and lifestyle modification should take precedence
- Identify risk factors
  - Folate supplementation
  - Insulin resistance and diabetes
  - Blood pressure
  - Genetic screening
  - Vitamin D levels
  - Alcohol intake
  - Tobacco use
- Opportunity for patient optimization: the goal of counseling is to identify and ideally correct risk factors prior to starting treatment
LIFESTYLE MODIFICATION: Weight Loss in Obese PCOS Patients

- Approximately 50% of PCOS women are overweight to obese
- Obese women demonstrate greater PCOS severity:
  - Worsened ovulatory dysfunction
  - Greater severity of hirsutism, insulin resistance
  - Lower rates of spontaneous or unassisted pregnancy
  - Greater risk of pregnancy complications
- Weight loss is considered first-line treatment in obese PCOS women seeking pregnancy
- Multifaceted approach: behavioral counseling, diet, exercise, sometimes medical and surgical
Lifestyle Modification: Weight Loss

- Loss of as little as 5% initial body weight results in improved metabolic parameters:
  - Reduced total cholesterol and triglyceride levels
  - Reduced LDL cholesterol
  - Reduced fasting and post-load insulin levels after 2-hr OGTT
  - Increased SHBG
  - Decreased testosterone levels
  - Improved menstrual regularity
  - Increased ovulatory cycles

Hoeger K, Best Pract Res Clin Endocrinol Metab. 2006; 20:293.
OVULATION INDUCTION IN PCOS: Diet

- Case series of 33 anovulatory overweight patients with PCOS enrolled in 1200 kcal/d diet
- >5% reduction in initial body weight resulted in:
  - Significant reduction in WHR, BMI
  - Reduction in ovarian volume and #microfollicles
  - 67% had resumption of regular cycles
  - 56% had spontaneous ovulation
  - 10 spontaneous pregnancies occurred (30%)

*Crosignani et al., Hum Reprod 2003;18:1928.*
Case series of 14 obese PCOS patients treated for approximately 8-mo with hypocaloric diet

>5% reduction in initial body weight resulted in:
- 35% decrease in plasma testosterone levels
- Significant improvement in AN and hirsutism
- 40% had significant improvement in menstrual regularity
- Four pregnancies occurred

Pasquali et al., JCEM 1989;68:173.
OVULATION INDUCTION IN PCOS:
Diet

• RCT of 35 obese PCOS patients studied
• Short term effects of two energy-restricted diets:
  – High protein (30% protein, 40% carbs, 30% fat)
  – High carb (15% protein, 55% carbs, 30% fat)
• Of 26 women completing study:
  – No difference between the two diets in mean weight loss, androgen levels, glucose metabolism, and leptin levels
  – High prevalence of menstrual bleeding during diet (54%)

OVULATION INDUCTION IN PCOS: Diet

• Disagreement on optimal diet for PCOS women
• Recommended diet for obese PCOS women is to one that patient can follow to achieve ≥ 5% weight loss
• Goal is hypocaloric (with ~500 kcal/day deficit)
• Recent data suggests hypocaloric diet with reduced glycemic load improves androgen levels, metabolic changes, cardiovascular risk factors markers

Mehrabani et al., 2012; Marsh et al., Am J Clin Nutr 2010
OVULATION INDUCTION IN PCOS: Exercise

- Exercise reduces insulin resistance and visceral fat
- May increase muscle cell metabolism and insulin sensitivity
- Shown to improve menstrual irregularity and restore ovulation in obese PCOS patients
- Duration of type of exercise not important: just do it!

Panidis et al., Endocrine 2013. 44:583-590
Exercise can restore menstrual regularity in 60%; ovulation in 50%; and pregnancy in 35% of PCOS patients with irregular ovulation!

- No guidelines for type, frequency, intensity or duration.
- Greatest metabolic improvement seen in obese PCOS women seen after at least 30 min daily for at least 5 days per week; in combination with diet.

Panidis et al., Endocrine 2013. 44:583-590
MEDICAL OVULATION INDUCTION: Clomiphene citrate

- First line for ovulation induction in PCOS
- Nonsteroidal E-R agonist-antagonist
- Prolonged binding and depletion of E-R in hypothalamus
- Increases GnRH pulse amplitude
- Increases FSH, LH secretion
MEDICAL OVULATION INDUCTION:
Clomiphene citrate

- Available as 50-mg tablets
- Empirically administered starting at 50mg x 5d starting days 2-5 after spontaneous or induced menses
- Increase dose by 50-mg until ovulation
- FDA-approved for up to 150-mg QD x 5d, for up to 3 cycles
- 7-10% multiple gestation rate
MEDICAL OVULATION INDUCTION: Clomiphene citrate

- Majority of women with anovulatory infertility ovulate in response to clomiphene
- Approximately 70% ovulate in response clomiphene; of responders ~70% respond to 50 – 100 mg doses
- Up to 30% remain anovulatory
- Only 50% of ovulatory responders conceive

Predictors of Poor Response to Clomiphene

- Obesity and higher body mass index (BMI)
- Higher androgen/ testosterone levels
- Increased ovarian volume (measured by ultrasound)
- Severity of menstrual abnormality
- Severity of insulin abnormality
- Older age
- Higher AMH levels
INSULIN RESISTANCE & PCOS

• Hyperinsulinemic insulin resistance appears to affect 25-70% of women with PCOS

• PCOS is associated with a profound form of insulin resistance that is intrinsic to the syndrome, independent of obesity

• Hyperinsulinemic insulin resistance occurs in obese and nonobese women with PCOS

• Appears related to a post-receptor defect

  Dunaif et al., Diabetes 1989; 38:1165.
  Ciaraldi et al., JCEM 1992; 75:577.
Diabetes and IGT in PCOS

Fig. 1. Combined prevalence of glucose intolerance by WHO criteria in 254 PCOS women. NGT, Normal glucose tolerance; Type 2 DM, type 2 diabetes mellitus.

Legro et al., JCEM 1999: 84; 165.
MEDICAL OVULATION INDUCTION

Insulin Sensitizer: Metformin

• Gastrointestinal
  – Diarrhea (53%), nausea, vomiting (26%), flatulence, indigestion, abdominal discomfort

• Rare cases lactic acidosis
  – Check chem panel pre-Rx: r/o hepatic disease
  – Intravascular iodinated contrast may change renal function and increase r/o lactic acidosis

• Cimetidine competes for renal clearance

• Vit B12 malabsorption in 10-30%
  – Anemia rare, but check B12 levels annually
Details regarding individual studies are summarized in Lord, et al. (27)
Clomiphene, Metformin or Both:
Cooperative Multicenter Reproductive Medicine Network:

- Multicenter, randomized trial of 626 subjects
- PCOS diagnosed by older, strict criteria
  - Oligomenorrhea (<8 spontaneous menses/year)
  - Hyperandrogenemia by local lab standards
  - Exclusion of hyperPRL, CAH, thyroid disease, POF
- Three arms followed for up to 6 cycles
  - Glucophage XR 2000 mg daily / matching placebo
  - Clomiphene 50 mg tablets daily / matching placebo
  - Both

Clomiphene, Metformin or Both: Cooperative Multicenter Reproductive Medicine Network:

- Baseline characteristics similar in age, BMI, degree of hirsutism, race, fertility history and prior conception.
- No significant difference in ultrasound findings
  - %PCO morphology
  - Ovarian volume
- Metabolic parameters similar
  - Insulin levels
  - SHBG
  - Testosterone levels

Clomiphene, Metformin or Both:

A

Rate of Live Birth vs. Days from Randomization to Live Birth

- Combined
- Clomiphene
- Metformin

P < 0.001

B

Rate of Live Birth vs. Days from Randomization to Live Birth

- BMI < 30
- BMI 30–34
- BMI ≥ 35

P < 0.001
Clomiphene vs. Metformin
Pregnancy Loss

- Single center randomized, double blinded controlled trial
  - Total of 92 subjects studied over 426 cycles in 6 months
  - Randomized to Metformin 850 BID + placebo or to placebo + Clomid 150 mg x 5 days
- Followed ovulation, pregnancy, LB and SAB rates
- Metformin associated with significantly lower spontaneous abortion rate compared with clomid (9.7% vs 37.5%, p=0.045)

Palombo et al., JCEM 2005;90:4068.
Metformin and Fetal Malformation

• Meta-analysis of 13 studies from 1966-2004
  – Control: disease matched women without metformin exposures
  – Disease: women exposed to metformin during the first trimester

• OR for major malformation in women exposed to metformin was 0.50 (95% CI 0.15-1.60)

• Mean malformation rate in the metformin group was 1.7% vs 7.2% in the untreated group

• Subanalysis to separate diabetic vs PCOS subjects showed no increase malformation after metformin

### Table 1. Baseline Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clomiphene Group (N=376)</th>
<th>Letrozole Group (N=374)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age — yr</strong></td>
<td>28.8±4.0</td>
<td>28.9±4.5</td>
</tr>
<tr>
<td><strong>Body-mass index†</strong></td>
<td>35.1±9.0</td>
<td>35.2±9.5</td>
</tr>
<tr>
<td><strong>Ferriman–Gallwey hirsutism score‡</strong></td>
<td>16.9±8.5</td>
<td>17.0±8.6</td>
</tr>
<tr>
<td><strong>Race or ethnic group — no. (%)§</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>302 (80.3)</td>
<td>288 (77.0)</td>
</tr>
<tr>
<td>Black</td>
<td>44 (11.7)</td>
<td>56 (15.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>12 (3.2)</td>
<td>12 (3.2)</td>
</tr>
<tr>
<td>Mixed race</td>
<td>12 (3.2)</td>
<td>15 (4.0)</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>68 (18.1)</td>
<td>60 (16.0)</td>
</tr>
<tr>
<td><strong>Fertility history</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of time attempting to conceive — mo</td>
<td>42.5±37.6</td>
<td>40.9±38.0</td>
</tr>
<tr>
<td>Previous live birth — no. (%)</td>
<td>73 (19.4)</td>
<td>75 (20.1)</td>
</tr>
<tr>
<td><strong>Ultrasonographic findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antral follicle count in both ovaries</td>
<td>46.5±28.5</td>
<td>47.4±27.4</td>
</tr>
<tr>
<td>Polycystic ovaries according to modified Rotterdam criteria — no./total no. (%)¶</td>
<td>349/374 (93.3)</td>
<td>354/369 (95.9)</td>
</tr>
<tr>
<td>Endometrial thickness in sagittal plane — mm</td>
<td>6.7±2.9</td>
<td>6.8±3.0</td>
</tr>
<tr>
<td><strong>Fasting serum biochemical values</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total testosterone — ng/dl</td>
<td>56.3±30.1</td>
<td>53.8±27.4</td>
</tr>
<tr>
<td>Sex hormone–binding globulin — nmol/liter</td>
<td>33.2±23.7</td>
<td>34.5±22.4</td>
</tr>
<tr>
<td>Free androgen index</td>
<td>8.2±6.2</td>
<td>7.4±5.6</td>
</tr>
<tr>
<td>Estradiol — pg/ml</td>
<td>55.7±40.5</td>
<td>54.6±32.6</td>
</tr>
<tr>
<td>Progesterone — ng/ml</td>
<td>1.5±2.9</td>
<td>1.5±3.3</td>
</tr>
<tr>
<td>Antimüllerian hormone — ng/ml</td>
<td>8.1±6.9</td>
<td>8.0±7.1</td>
</tr>
</tbody>
</table>

---

OVULATION INDUCTION IN PCOS:
Aromatase Inhibitors Letrozole

OVULATION INDUCTION IN PCOS: Glucocorticoids in Clomiphene Resistant Patients

OVULATION INDUCTION IN PCOS: Glucocorticoids in Clomiphene Resistant Patients

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3.1 Pregnancy rate (per woman)</td>
<td>Daly 1984</td>
<td>17</td>
<td>32</td>
<td>8</td>
<td>32</td>
<td>48.2%</td>
<td>3.40 [1.18, 9.81]</td>
</tr>
<tr>
<td></td>
<td>Elnashar 2006b</td>
<td>16</td>
<td>40</td>
<td>2</td>
<td>40</td>
<td>15.4%</td>
<td>12.67 [2.67, 60.05]</td>
</tr>
<tr>
<td></td>
<td>Parsanezhad 2002a</td>
<td>46</td>
<td>111</td>
<td>5</td>
<td>119</td>
<td>36.3%</td>
<td>16.14 [6.11, 42.65]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>183</td>
<td>191</td>
<td>100.0%</td>
<td></td>
<td>9.46 [5.05, 17.70]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>79</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 4.88, df = 2 (P = 0.09); I² = 59%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 7.03 (P &lt; 0.000001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.3.2 Ovulation rate (per woman)</td>
<td>Daly 1984</td>
<td>23</td>
<td>32</td>
<td>14</td>
<td>32</td>
<td>48.3%</td>
<td>3.29 [1.16, 9.30]</td>
</tr>
<tr>
<td></td>
<td>Elnashar 2006b</td>
<td>30</td>
<td>40</td>
<td>6</td>
<td>40</td>
<td>18.4%</td>
<td>17.00 [5.52, 52.36]</td>
</tr>
<tr>
<td></td>
<td>Parsanezhad 2002a</td>
<td>98</td>
<td>111</td>
<td>24</td>
<td>119</td>
<td>33.3%</td>
<td>29.84 [14.36, 62.02]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>183</td>
<td>191</td>
<td>100.0%</td>
<td></td>
<td>14.65 [8.76, 24.49]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>151</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 11.64, df = 2 (P = 0.003); I² = 83%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 10.24 (P &lt; 0.000001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.3.3 Multiple pregnancy (per woman)</td>
<td>Daly 1984</td>
<td>3</td>
<td>32</td>
<td>0</td>
<td>32</td>
<td>100.0%</td>
<td>7.71 [0.38, 155.64]</td>
</tr>
<tr>
<td></td>
<td>Elnashar 2006b</td>
<td>0</td>
<td>40</td>
<td>0</td>
<td>40</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>72</td>
<td>72</td>
<td>100.0%</td>
<td></td>
<td>7.71 [0.38, 155.64]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>3</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.33 (P = 0.18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 7. Forest plot of comparison: 3 Anti-oestrogen plus medical adjunct versus anti-oestrogen alone, outcome: 3.3 Clomiphene plus dexamethasone versus clomiphene.

Ovulation Induction in PCOS
Injectable Hormones aka Gonadotropins

- Synthetic or urinary hormones secreted by pituitary
- Injected into subcutaneous fat or muscle
- Requires careful monitoring due to potential for multiple eggs to develop and multiple gestation
- May require several weeks to develop mature egg follicle
- Higher risk of ovarian hyperstimulation syndrome (OHSS)
### Table 2  Treatment outcomes.

<table>
<thead>
<tr>
<th></th>
<th>CoQ\textsubscript{10}-clomiphene citrate (n = 51)</th>
<th>Clomiphene citrate (n = 50)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of follicles &gt;14 mm</td>
<td>1.94 ± 0.25</td>
<td>0.13 ± 0.29</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>No. of follicles ≥18 mm</td>
<td>1.85 ± 0.27</td>
<td>1.30 ± 0.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endometrial thickness on day of HCG (mm)</td>
<td>8.82 ± 1.49</td>
<td>7.03 ± 0.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum oestradiol on the day of HCG (pg/ml)</td>
<td>168.93 ± 75.01</td>
<td>138.32 ± 70.24</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Midluteal progesterone (pg/ml)</td>
<td>10.2 ± 1.03</td>
<td>8.9 ± 0.91</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ovulation per cycle</td>
<td>54/82 (65.9)</td>
<td>11/71 (15.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical pregnancy per patient</td>
<td>19 (37.3)</td>
<td>3 (6.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%).
Ovulation Induction in PCOS: The Role of Supplements

- D-chiro-Inositol
- Myo-Inositol
- Proposed mechanisms of action
- No randomized controlled trial examining the potential fertility benefits
- Not routinely recommended by physicians
- Recommend discontinuation upon positive pregnancy test
SURGICAL OVULATION INDUCTION
Laparoscopic ovarian drilling (LOD)

- Decreased adhesion formation compared with laparotomy
- Laparoscopy routine part of infertility evaluation
- No increase in risk of OHSS
- Lower risk of multiple gestation compared with gonadotropins
- Single procedure results in multiple ovulatory cycles
SURGICAL OVULATION INDUCTION
Laparoscopic ovarian drilling (LOD)

- Ovarian biopsy
- Electrocautery
  - Unipolar needlepoint
- Laser
  - Carbon dioxide
  - KTP
  - Nd-YAG
### Study or sub-category

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Ovarian drilling n/N</th>
<th>Gonadotrophins n/N</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>01 Six months follow-up after ovarian drilling versus 3 cycles of FSH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farquhar 2002</td>
<td>4/29</td>
<td>4/21</td>
<td>17.53</td>
<td>0.69</td>
<td>[0.15, 3.10]</td>
<td>A</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>29</td>
<td>21</td>
<td>17.53</td>
<td>0.69</td>
<td>[0.15, 3.10]</td>
<td>A</td>
</tr>
<tr>
<td><strong>02 Twelve months follow-up after ovarian drilling+/- medical ovulation versus six cycles of gonadotrophins only</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayram 2004</td>
<td>52/83</td>
<td>51/85</td>
<td>82.47</td>
<td>1.12</td>
<td>[0.60, 2.08]</td>
<td>A</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>83</td>
<td>85</td>
<td>82.47</td>
<td>1.12</td>
<td>[0.60, 2.08]</td>
<td>A</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>112</td>
<td>106</td>
<td>100.00</td>
<td>1.04</td>
<td>[0.59, 1.85]</td>
<td></td>
</tr>
</tbody>
</table>

Footnotes: Test for heterogeneity: Chi²=0.35, df=1 (p=0.55), I²=0%
Test for overall effect: Z=0.14 (p=0.89)

### Study or sub-category (b)

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Ovarian drilling n/N</th>
<th>Gonadotrophins n/N</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayram 2004</td>
<td>1/56</td>
<td>9/57</td>
<td>58.28</td>
<td>0.10</td>
<td>[0.01, 0.79]</td>
<td>A</td>
</tr>
<tr>
<td>Farquhar 2002</td>
<td>0/5</td>
<td>0/5</td>
<td>15.44</td>
<td>0.14</td>
<td>[0.01, 3.63]</td>
<td>A</td>
</tr>
<tr>
<td>Kaya 2006</td>
<td>0/6</td>
<td>2/6</td>
<td>19.29</td>
<td>0.10</td>
<td>[0.00, 2.44]</td>
<td>B</td>
</tr>
<tr>
<td>Lazovitz 1998</td>
<td>0/14</td>
<td>2/9</td>
<td>6.98</td>
<td>0.43</td>
<td>[0.01, 14.08]</td>
<td>B</td>
</tr>
<tr>
<td>Vegetti 1996</td>
<td>0/3</td>
<td>1/5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>84</td>
<td>82</td>
<td>100.00</td>
<td>0.13</td>
<td>[0.03, 0.52]</td>
<td></td>
</tr>
</tbody>
</table>

Footnotes: Test for heterogeneity: Chi²=0.35, df=3 (p=0.91), I²=0%
Test for overall effect: Z=2.89 (p=0.91)
SURGICAL OVULATION INDUCTION
Laparoscopic ovarian drilling (LOD)

• Cochrane analysis of 6 RCT LOD vs. Gn
  – Similar cumulative ongoing PR after 6 -12 months after LOD vs. 3-6 cycles Gn
  – LOD advantage: monofollicular ovulation and reduction in multiple PR

• Multicenter study comparing LOD vs. Gn
  – 12-month PR in 168 CC-resistant PCOS patients
  – PR similar in LOD vs. Gn groups
  • 3-6 months Gn
  • 12 months LOD, LOD + CC, + Gn; multiple pregnancy rates lower
IN VITRO FERTILIZATION (IVF): SUMMARY

A. Ovaries are examined at baseline;
B. Patient takes injectable hormones (FSH & HMG) to stimulate ovaries;
C. Oocytes are retrieved under ultrasound guidance;
D. Oocyte is recovered from follicular fluid and is inseminated (E) or injected with sperm via ICSI (F);
G-H. Embryos are frozen and subsequently transferred at the cleavage or blastocyst stage.

Van Voorhis 356 (4): 379, Figure 1
January 25, 2007
IVF OUTCOMES:  
PCOS versus Non-PCOS

- Significantly increased chance of cycle cancellation in PCOS (12.8% versus 4.1%)
- Higher number of oocytes retrieved in PCOS
- Lower fertilization rate in PCOS
- No difference in clinical pregnancy rates per started cycle (37.4% versus 32.3%)
- No difference in live birth rates per cycle

*Heijnen et al., Hum Reprod Update 2006 12(1):13-21*
Thank you for your time and attention!