Managing Anovulatory Infertility
Patience, controversy, options, and surveillance

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I have no conflicts of interest to disclose

Off-label use of drugs will be specified as such
As Shakespeare said, "What's in a name?"

I have one bias to make clear:

I don’t like the name …

PolyCYSTic Ovarian Syndrome

Munch, *The Scream*, 1893
PCOS
What’s in a name??

Poly
Cystic
Ovarian
Syndrome
PCOS
What’s in a name??

P atience
C ontroversy
O ptions
S urveillance

Learning Objectives

• Compare and contrast treatment options for ovulation induction
• Review considerations for both pre- and post-treatment surveillance/monitoring
• Understand the risks and prognosis associated with ovulation induction
• Develop a strategy for approaching the challenging anovulatory infertility patient
Approaching the Patient

• Explain, in simple terms, what PCOS is (and why it matters)

  Educate - Plant the seed re: long-term implications

• Determine the goal: Cycle control or pregnancy achievement

  Educate - Plant the seed re: long-term implications

• Make a plan for pretreatment evaluation
Pretreatment Evaluation

• Rule-out uncommon causes of chronic anovulation

• Determine if additional endometrial evaluation is indicated

• Counsel regarding obesity

• Consider AMH testing

• Consider other causes of infertility
Pretreatment Evaluation
Rule-out uncommon causes of chronic anovulation

- Thyroid disease
  - Excess or deficiency
  - Serum TSH level suffices

- Hyperprolactinemia
  - Standard ovulation induction approach would be ineffective
  - Serum prolactin level (and brain MRI if elevated)

- Nonclassic congenital adrenal hyperplasia
  - Not necessary for every patient
  - Early follicular phase 17-OH-progesterone (add a progesterone level if elevated)

- Clinically significant androgen excess
  - Primary indication for testing: Ruling-out androgen-secreting tumor
  - Key tests: Total testosterone and DHEA-S (no indication for free testosterone)

- Chronic anovulation with estrogen absent (i.e. hypogonadotrophic hypogonadism)
  - History and exam will typically help to differentiate
  - Serum estradiol and gonadotropins
Pretreatment Evaluation
Determine if additional endometrial evaluation is indicated

Cheung AP, Green Journal, 2001
- 56 consecutive women with PCOS underwent ultrasound and EMB
- 20 (36%) had endometrial hyperplasia (25% of cases featured atypia)
- Both endometrial thickness and intermenstrual interval were significant predictors
  - Endometrial thickness >7mm
  - Intermenstrual interval >3 months

Key Points
- Understudied, but significance is unquestioned
- Incidence 30-50% in other studies
- Immediate and ongoing concern for these patients
- Predictive values of the above thresholds still far from ideal
- Provides some framework for decision-making

Have a low threshold for EMB
Pretreatment Evaluation
Acknowledge the implications of obesity

Obesity and reproduction: a committee opinion

Practice Committee of the American Society for Reproductive Medicine
American Society for Reproductive Medicine, Birmingham, Alabama

November 2015

• Weight loss improves success rates in those seeking pregnancy
• The impact of obesity on maternal/fetal obstetric morbidity is dose-dependent

What does ASRM say?

Obese women wishing to conceive should consider a weight management program that focuses on preconception weight loss (to a BMI less than 35 kg/m²)
Does Pretreatment Weight Loss Improve Response to Ovulation Induction?

J Clin Endocrinol Metab, November 2015, 100(11):4048–4058

**Randomized Controlled Trial of Preconception Interventions in Infertile Women With Polycystic Ovary Syndrome**

Richard S. Legro, William C. Dodson, Penny M. Kris-Etherton, Allen R. Kunselman, Christy M. Stetter, Nancy I. Williams, Carol L. Gnatuk, Stephanie J. Estes, Jennifer Fleming, Kelly C. Allison, David B. Sarwer, Christos Coutifaris, and Anuja Dokras

**The OWL-PCOS Trial**

- 149 women randomly assigned to pre-clomid OCP, lifestyle modification, or combo
- BMI 27 - 42
- Lifestyle intervention: 16 weeks, caloric restriction + exercise + anti-obesity Rx
- Ovulation induction: Clomid (50 - 150mg) for up to 4 cycles
- Intercourse every 2-3 days (no OPKs, IUI, or sono monitoring)
The OWL-PCOS Trial

How much weight did they lose?

6.5% of pre-intervention weight (goal 7%)

2-3 BMI units

Legro et al, JCEM, 2016
What About Pretreatment Weight Loss vs. Immediate Treatment?

- Post hoc analysis comparing outcomes in the lifestyle group in previous study to those in a RCT which included a clomid arm (the PPCOS II trial)
- N=142 for the former and 187 for the latter
- Intentionally identical treatment/monitoring protocols and enrollment criteria
- Age- and BMI-matched

Benefit of Delayed Fertility Therapy With Preconception Weight Loss Over Immediate Therapy in Obese Women With PCOS

## What About Pretreatment Weight Loss vs. Immediate Treatment?

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<th>OWL - PCOS</th>
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<td>Weight Loss Prior to</td>
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<td><strong>Ovulation</strong></td>
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<td>Cumulative Ovulation</td>
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<td>62%</td>
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<td>Cumulative Live Birth</td>
<td>10.2%</td>
<td>25%</td>
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Legro, NEJM, 2007

Legro, JCEM, 2016
**Pretreatment Evaluation**

**Consider AMH testing**

**Rationale**
- Women with very high AMH levels more likely to be clomid resistant
- Pretreatment measurement/detection may aid in counseling re: potential for success
- May help to determine optimal starting dose of clomid

**ROC Curve Analysis (AUC 0.87)**
- Cut-off of 3.4 ng/mL
- Sensitivity 73% and specificity 78% in predicting anovulation

*Figure 1. Pregnancy and ovulation rates per cycle (A) and per patient (B) in PCOS women with high vs low AMH using a cutoff value of 3.4 ng/mL. A χ² test was used for comparison. ***, P < .001; *, P < .05.*

*Mahran A, JCEM, 2013*
Pretreatment Evaluation
Consider other causes of infertility

• Make sure to check a semen analysis
  - The incidence of a coexisting male factor is significant
  - If normal, intrauterine insemination (IUI) is not indicated

• Consider HSG
  - Not necessary for everyone
  - Indications:
    - Age >35
    - Other risk factors for tubal disease
Treatment Options

Ovulation Induction With Oral Agents

IVF

Ovulation Induction With Gonadotropins

Weight loss

Metformin
Standard Ovulation Induction (Clomid)
Choosing the dose

- Responsiveness correlates with body weight (but predictive value is suboptimal)
- In general, start at 50mg (1 tablet) for 5 days (50% of women will respond)
- **Disclaimer:** I tend to start at 100mg in obese patients

- Reviewing records (if available) is helpful
- Increase in 50mg increments until ovulation induction achieved
- Overall, response is consistent, but don’t be alarmed by intermittent anovulatory cycles

- Most providers will not exceed 150mg (and few require it)
- Some will be exquisitely responsive (doses of 12.5 or 25mg may be sufficient)

**Goal:** Monofollicular Ovulation

Doses in excess of 100mg are not FDA approved
Standard Ovulation Induction (Clomid) Prognosis

- Approximately 80% of women will achieve regular ovulation
- Cumulative pregnancy rate 55-73%

Don’t be in a hurry to recommend more aggressive treatment

IVF is expensive and complex
Gonadotropin-based ovulation induction is risky

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<th>50mg</th>
<th>100mg</th>
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<tr>
<td>3 cycles</td>
<td>50%</td>
<td>45%</td>
<td>33%</td>
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<tr>
<td>6 cycles</td>
<td>62%</td>
<td>66%</td>
<td>38%</td>
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Cumulative Pregnancy Rates
Imani B, JCEM, 84, 1999

ASRM: Therapy beyond 6 months is generally not recommended
Standard Ovulation Induction (Clomid) 
Side Effects and Risks

-Mood swings are the most common side effect (64-78%)
-Vasomotor symptoms occur in only 10%
-Visual disturbances are rare (<2%) and transient: Consider alternative options
  -Blurred vision and diplopia
  -Scotomata
  -Light sensitivity
-Less specific: Breast tenderness, pelvic discomfort, nausea (2-5%)

By far, the most significant risk to discuss is multiple pregnancy

-Baseline risk of twins: 1%
-Incidence of twins in pregnancies following clomid use: 8-10%
-Note: A good time to educate re: relative vs. absolute risk
-Higher-order: 0.08-1.1%
Standard Ovulation Induction (Clomid) Complications

**Miscarriage**
- Early studies suggested an increase in risk following clomid
- The totality of recent data is entirely reassuring

**Ovarian Hyperstimulation Syndrome**
- Definition varies
- Classic/severe OHSS almost unheard of with *standard dosing regimens*

**Ovarian Cancer**
- 2 studies in the early 90’s found an increased risk in a heterogeneous group of subjects
- A more recent pooled analysis of 8 case-control studies found no risk with:
  - Any fertility drug use
  - Use for more than 12 months

-Silva Idos et al, Br J Cancer, 2009

ASRM Practice Committee, 2013
Standard Ovulation Induction (Clomid)  
Practical Tips: Sonographic Monitoring

ASRM: Provides insight, but is costly, logistically demanding, and best reserved for those in whom less complicated methods fail to provide “the necessary information”

What is the necessary information?
- Is it OK to start?
- Does she respond?
- What is the pace of her cycle?
- Are ovulation predictor kits (OPKs) providing reliable guidance?
- Does she over-respond?
- Does the dose need to be adjusted?
- Is it time to cancel the cycle?

Disclaimer: I like answers to all the above, and routinely utilize it
- At least initially (I care about cost-efficiency, too)
- If response is relatively predictable and OPKs are reliable, it may be tailored/limited
- At a minimum: Baseline clearance and mid-follicular scan to rule-out over-response
Ovulation Predictor Kits

- They can be used effectively in most women
- False positivity may be a problem: Can be recognized early with a basal serum LH level
- BID use can be helpful when the pretest probability of a (+) result is greater
- Once positive: Daily IC x 2-3 days, or IUI the next day

hCG Trigger Injections

- Costly and simply not necessary for most patients
- A meta-analysis (>1000 subjects) reported lower odds of pregnancy when utilized
- Best reserved for those in whom IUI is planned and OPKs are unreliable
- If using, pregnancy rates are highest when the leading follicle is >23mm in diameter

ASRM Practice Committee, 2013
More Tips

Is IUI beneficial?
- Not if partner’s SA is normal and the indication is anovulatory infertility
- Unexplained infertility is a different scenario
- Reasonable to consider after 3-4 failed cycles, especially if IVF isn’t an option
- As before, hCG trigger isn’t an automatic indication in this setting

Starting a cycle or transitioning to a new one
- Ovulation/pregnancy rates are similar regardless of day of cycle start (2, 3, 4, or 5)
- May start at any time if at anovulatory baseline
  - Estradiol, progesterone, and hCG levels may be helpful
  - Pay attention to endometrial thickness

- Progestin withdrawal not always necessary
  - Live birth rate higher when a progestogen was NOT used
- Diamond et al, Green Journal, 2012

My Practice:
Start immediately if at anovulatory baseline and endometrium <8mm
Does Metformin Improve Outcomes When Combined with Clomiphene?

The PPCOS Trial

- 626 women assigned to clomid (up to 150mg), metformin (ER, 1g BID), or combo
- Intercourse every 2-3 days (no OPKs, IUI or sono monitoring)
- Treated for up to 6 cycles, or 30 weeks
The PPCOS Trial

• CC vs combination therapy: P=0.31
• Metformin vs. both CC and combination: P<0.001

Legro et al, NEJM, 2007
Take-Home Points from PPCOS

• Clomid significantly more likely to lead to live birth than metformin

• Addition of metformin did not increase the likelihood of achieving pregnancy with clomid
  - Equal fecundity per ovulated patient (~30%)
  - Equal fecundity per ovulated cycle (~10%)

• Incidence of clomid resistance: 25% (never ovulated during the study)

• Approximately 75% of women taking clomid did not have a baby
  - **Note:** Mean BMI in all groups ~35
  - **Note:** The protocol

Legro et al, NEJM, 2007
Metformin Pretreatment for Obese Women?

- Multicenter European RCT: 320 women
- Randomized to 3 months of metformin (1000mg BID) pretreatment or placebo
- Followed by 4-6 cycles of clomid, if indicated

Morin-Papunen et al, JCEM, 2012
ADA Recommendations

- PCOS is an *additional risk factor* that should prompt screening for T2DM in *asymptomatic overweight* (BMI ≥ 25) adults

- Hemoglobin A1c is considered an appropriate screening test


- Prediabetes: A1c 5.7 – 6.4%
- Diabetes: A1c ≥ 6.5%

- Consider metformin for T2DM risk reduction in those with prediabetes, especially if:
  - BMI ≥ 35
  - Age < 60yo
  - History of GDM

**So …**

- PCOS is not an automatic indication for metformin for T2DM risk reduction
- PCOS is an indication for T2DM screening
- Metformin may be considered if A1c > 5.7% and BMI ≥ 35

ADA Standards of Medical Care in Diabetes - 2016
What About Letrozole?

Rationale
- It (along with anastrozole) is a 3rd generation, reversible aromatase inhibitor
- Potent: Reduces estrogen levels by $\geq 97\%$
- Half-life 45hr, cleared by the liver

Mechanism of Action
- Prevents estrogen’s exertion of negative feedback at the hypothalamus/pituitary
  • Augments FSH release
- Leads to temporary accumulation of intraovarian androgens
  • Augments follicular FSH-receptor expression
  • Stimulates IGF-I expression (augments FSH action)
- May have favorable endometrial effects
  • Blockade of estrogen synthesis leads to upregulation of estrogen-receptor expression
  • Favors robust endometrial development once estrogen secretion is restored

Casper and Mitwally, JCEM, 2006
Does it work differently than clomiphene?

**Key Differences**

- Letrozole has a much shorter half-life
- Letrozole does not deplete hypothalamic/pituitary estrogen receptors

**Theoretical Benefits (for letrozole)**

- Higher rates of monofollicular ovulation (less risk of multiple pregnancy)
- Less risk of early pregnancy and cumulative exposure
- More favorable endometrial development (can be problematic with clomid)

_Casper and Mitwally, JCEM, 2006_
Is Letrozole Better than Clomiphene?

The PPCOS II Trial

- 750 women assigned to clomid (up to 150mg) or letrozole (up to 7.5mg) [CD3 start]
- Intercourse every 2-3 days (no OPKs, IUI, or sono monitoring)
- Treated for up to 5 cycles
PPCOS II Trial

Rate ratio for live birth (LTZ vs. CC)
1.44; 95% CI 1.10 - 1.87

Legro et al, NEJM, 2014
What About Letrozole?

More take-home points from PPCOS II
-Ovulation rates per cycle superior to clomid
-Improved fecundity with letrozole per subject who ovulated
-Significantly more hot flashes with clomid (33% vs. 20% with letrozole)

Letrozole vs. Clomid: Meta-Analysis
-Franik et al, Cochrane Database, 2014
-9 RCTs
-n=1783
-Superior live birth rate with letrozole
-OR 1.63; 95% CI 1.31 – 2.03
Letrozole: Why the controversy?

Two Primary Reasons
• It is not FDA-approved for ovulation induction
• Ill-informed concern re: risk of fetal anomalies

FDA-Approval: Safety + Efficacy
• Off-label use of drugs is common
• I doubt that FDA-approval will ever be sought

We now have Level I evidence that letrozole is not only efficacious, but also likely superior to clomiphene

What about safety?
Letrozole: Safety Concerns?

November 29, 2005

- Manufacturer warned that letrozole should not be used for ovulation induction

[Letrozole] “should not be used in women who may become pregnant, during pregnancy and/or while breast-feeding, because there is a potential risk of harm to the mother and the fetus, including risk of fetal malformations”

- Based on a single abstract presented at the 2005 ASRM annual meeting

Biljan MM et al, ASRM O-231
- Retrospective “cohort” study
- 150 births resulting from letrozole
- Compared with 36,050 “mostly low risk babies” not born after maternal letrozole use

- Overall anomaly rate was not increased
- Significant increase in locomotor and cardiac anomalies in letrozole-related births

This work was never published
The FDA never took any action
Letrozole: Safety Concerns?

A Few Thought/Comments
- The reaction to the abstract was much like the media response to the first WHI paper
- Small number of exposed cases and wide confidence intervals
- Can’t specifically comment, but unaddressed bias is highly likely

• One that is certain: The unexposed group did not consist of infertile women
• The work did not survive peer review

A better (published) study (soon after controversy arose):
- Tulandi et al, 2006
- 911 live births from women who conceived following clomiphene or letrozole
- Overall anomaly rate: Equal
- Significantly fewer cardiac anomalies in the letrozole group

No difference in anomaly rates (CC vs. letrozole) in the two largest RCTs

No peer-reviewed data have ever demonstrated a higher anomaly rate after conception preceded by letrozole use

Just consider: Time of use and half-life
Approaching the Difficult Patient
Not Getting Pregnant

• Be patient, but expand evaluation/surveillance after 3 cycles
• Complete the fertility evaluation (i.e. HSG and SA if not already performed)
• Implement monitoring
  - Impaired endometrial development in up to 30% of CC users
  - Confirm that ovulation is being induced
• No need to increase dose if ovulation is occurring
• Consider IUI
• Refer to REI if pregnancy not achieved after 4-6 ovulatory cycles
Approaching the Difficult Patient
Clomiphene Resistance

Easy on the dose, beware progesterone levels, and implement monitoring

**Treatment Options**
- Extend treatment duration (7-8 days)
- Consider metformin pretreatment in obese patients
- Add dexamethasone (0.5-2mg beginning on day of CC start)
  - Use for up to 10 days
  - May be best in those with elevated DHEA-S levels
  - Promptly discontinue if not successful
- Switch to letrozole (will be successful in about half)
- Consider sequential therapy with gonadotropins
  - Begin low dose (37.5 – 75 IU daily) immediately following letrozole or clomid
  - Requires diligent monitoring
- **Be careful:** The goal is monofollicular ovulation
Summary

☑ Develop a routine plan for pretreatment patient evaluation and counseling

☑ Emphasize the long-term health implications of PCOS

☑ Encourage weight loss prior to initiation of ovulation induction (minimum 5%)

☑ Explain per-cycle and cumulative prognosis: Prepare to be patient

☑ Metformin is best reserved for obese patients with prediabetes

☑ While not, yet, endorsed as first-line therapy, letrozole appears superior to clomiphene

☑ Be prepared to provide proper counseling and obtain consent if Rx letrozole

☑ Refer if response (ovulation) is concerning, unclear, or after 4-6 cycles
Thank You


