IMPROVING FERTILITY IN WOMEN WITH PCOS

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LEARNING OBJECTIVES

At the conclusion of this presentation, the participant should be better able to:

1) Understand how ovulatory dysfunction impacts fertility
2) Utilize appropriate diagnostic techniques in the evaluation of infertility
3) Initiate ovulation induction in infertile anovulatory women with PCOS
COMMERCIAL DISCLOSURES

- Research grant funding:
- Family Planning Council (trials related to HIV screening and care)
- AbbVie Pharmaceuticals (clinical trial support for endometriosis, uterine myomata)
(a) Hormonal regulation of changes in the ovary and uterus

(b) Changes in concentration of anterior pituitary and ovarian hormones
MICROSCOPIC FOLLICLES
ANTRAL FOLLICLE

25 mm in a mature follicle

0.1 mm
NORMAL OVARY
MATURING FOLLICLE
PREOVULATORY ENDOMETRIUM
CORPUS LUTEUM
INFERTILITY DUE TO ANOVULATION

- Polycystic ovary syndrome (hyperestrogenic)
- Hypothalamic dysfunction (hypoestrogenic)
- Ovarian failure
POLYCYSTIC OVARY SYNDROME

• Irregular menses (< 8/year)
• Clinical or biochemical evidence of elevated androgens (testosterone and similar hormones)
• Polycystic ovaries seen on ultrasound

Inappropriate regulation of follicular development in potentially functional ovaries
PCOS
String of Pearls
“YOUNG” OVARY
OVULATION INDUCTION

• In overweight women, weight loss
• Clomiphene citrate (Clomid®) 50 to 150 mgs, Letrozole (Femara®) 2.5 to 7.5 mg, for 5 or more consecutive days early in the cycle
• Metformin, 1,000 to 2,000 mgs/day (3 to 6 months)
• Gonadotropins (FSH or FSH + LH)
• Surgical treatment—Ovarian diathermy
Pregnancy in Polycystic Ovary Syndrome I

- 628 infertile women, 18-39, with PCOS
- No other infertility factors (at least one open fallopian tube, normal uterine cavity, partner’s sperm concentration of 20 M/ml)
- Randomized in equal proportions for up to 6 cycles:
  1) metformin XR, 1000mg 2x/day
  2) clomiphene citrate (CC), 50-150mg
  3) CC combined with metformin XR
# Results of PPCOS I

<table>
<thead>
<tr>
<th></th>
<th>METFORMIN (N=208)</th>
<th>CC (n=209)</th>
<th>CC + MET (n=209)</th>
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</thead>
<tbody>
<tr>
<td>Ovulated</td>
<td>55.7%</td>
<td>75.1%*</td>
<td>83.3%*</td>
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<tr>
<td>Conceived</td>
<td>12.0%</td>
<td>23.9%*</td>
<td>31.1%*</td>
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<tr>
<td>Live Birth Rate</td>
<td>7.2%</td>
<td>22.5%*</td>
<td>26.8%*</td>
</tr>
<tr>
<td>Conception Rate in Ovulatory Women</td>
<td>21.7%</td>
<td>39.5%*</td>
<td>46.0%*</td>
</tr>
</tbody>
</table>

*p < .05 compared to Metformin alone

PREGANCY IN POLYCYSTIC OVARY SYNDROME II

- 750 infertile women, 18-40, with PCOS
- No other infertility factors (at least one open fallopian tube, normal uterine cavity, partner’s sperm concentration of 14 M/ml)
- Randomized in equal proportions for up to 6 cycles to Clomiphene 50 to 150 mg or Letrozole 2.5 to 7.5 mg for 5 days
- Treated for up to 5 cycles
## RESULTS OF PPCOS II

<table>
<thead>
<tr>
<th></th>
<th>CC (N=376)</th>
<th>LET (N=374)</th>
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<tbody>
<tr>
<td>Ovulated</td>
<td>76.6%</td>
<td>88.5%*</td>
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<tr>
<td>Conceived</td>
<td>27.4%</td>
<td>41.2%*</td>
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<tr>
<td>Live Birth Rate</td>
<td>19.1%</td>
<td>27.5%*</td>
</tr>
<tr>
<td>Conception Rate</td>
<td>35.8%</td>
<td>46.5%*</td>
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<tr>
<td>in Ovulatory Women</td>
<td></td>
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<tr>
<td>Twins</td>
<td>6.9%</td>
<td>3.9%</td>
</tr>
</tbody>
</table>

*p<.05

CLOMIPHENE AND LETROZOLE

• Clomiphene vs. Letrozole, different mechanism of action, generally the same management

WHEN WOMEN TAKE THESE MEDICATIONS THEY SHOULD KNOW AT THE END OF EVERY CYCLE IF THEY OVULATED OR NOT
MANAGEMENT OF CLOMIPHENE AND LETROZOLE

Commonly:

One pill days 5-9, +/- blood progesterone level on about cycle day 21, await period; if no period and pregnancy test is negative, take a progestin (Provera®), await period, and then repeat with 2 pills; If no period, repeat, and increase to 3 pills/day
MANAGEMENT OF CLOMIPHENE AND LETROZOLE

- One pill daily for 5 days early in cycle.
- Ultrasound +/- blood tests on or about last pill +/- 5 days, repeat if necessary.
- If mature follicle on ultrasound attempt pregnancy (+/- ovulation detection kit)
- Consider progesterone level 4-8 days following likely day of ovulation
- If you ovulated repeat this regimen at the same dose
MANAGEMENT OF CLOMIPHENE AND LETROZOLE

• If the monitoring ultrasound(s) show no evidence of an emerging, mature follicle either:

  1. Take 2 pills daily for 5 days OR
  2. treat with progestin and then begin 2 pills daily for 5 days following period

• If there is no mature follicle seen at monitoring ultrasound after 2 pills/day, repeat with 3 pills/day. Longer duration of treatment can be considered
Live Birth Cycle Fecundity Rates

Cycle 1: Clomiphene and Letrozole
Cycle 2: Clomiphene and Letrozole
Cycle 3: Clomiphene and Letrozole
Cycle 4: Clomiphene and Letrozole
Cycle 5: Clomiphene and Letrozole

Legro et al, NEJM, 2014
(a) Hormonal regulation of changes in the ovary and uterus

(b) Changes in concentration of anterior pituitary and ovarian hormones
GONADOTROPIN TREATMENT

- Treat directly with FSH (+/- LH)
- Daily injections
- Monitored frequently with ultrasounds and blood levels
- High rates of ovulation and pregnancy
- High rates of ovarian hyperstimulation syndrome, twins (up to 25%), and high-order multiple gestations
GONADOTROPIN STIMULATION OF OVARIES
HYPOTHALAMIC DYSFUNCTION AND AMENORRHEA

• Absent or inadequate stimulation of the ovaries resulting in little or no activity
• PCOS: Inappropriate regulation of follicular development in potentially functional ovaries

MENSTRUAL DYSFUNCTION IS NOT ALWAYS PCOS!!
1,313 women screened for PPCOS I:

- 19.5% Normal serum androgens (No PCOS)
- 10.1% Low sperm count (≈20% if all sperm parameters had been evaluated)
- 4.2% Both tubes blocked
- 2.0% Pregnant
- 1.5% Diabetes Mellitus
- 1.1% Congenital Adrenal Hyperplasia
- 0.9% Uncontrolled thyroid disease
- 0.5% Premature menopause
- 2.1% Other conditions

Fertil Steril 2007; 87:442-4
CONCLUSIONS

1. Ensure that the patient is healthy before starting fertility treatment
2. Be sure the patient has PCOS (or at least estrogenized infertility) so you use the right medications
3. Letrozole is first drug to consider
4. Clomiphene is effective in inducing ovulation
5. Gonadotropins are effective, but risks are higher, especially for high order multiples
6. IVF may be a consideration, particularly if there are other causes of infertility present