Does PCOS Compromise the oocyte and embryo quality or the endometrium?

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Yes PCOS (or our iatrogenic practices) lead to lesser oocyte and endometrial quality in women with PCOS

It may not matter!
SART Data: PCOS with Better IVF Outcomes than Tubal Factor

<table>
<thead>
<tr>
<th>Category</th>
<th>PCOS</th>
<th>Tubal</th>
<th>PCOS vs Tubal OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean # Oocytes</td>
<td>16.4</td>
<td>12.8</td>
<td>1.27, (1.25-1.29)</td>
</tr>
<tr>
<td>Clinical Pregnancy Rate</td>
<td>43%</td>
<td>36%</td>
<td>1.32, (1.27-1.38)</td>
</tr>
<tr>
<td>Live Birth Rate</td>
<td>35%</td>
<td>29%</td>
<td>1.30, (1.24-1.35)</td>
</tr>
</tbody>
</table>
Equivalent Live Birth Rates for each year after Age 40 in Women with PCOS vs Tubal Factor
All Infertility Trials should report on Live Births and this is the preferable primary outcome.

Improving the Reporting of Clinical Trials of Infertility Treatments (IMPRINT): modifying the CONSORT statement

The Harbin Consensus Conference Workshop Group
Conference Chairs: Richard S. Legro (USA), Xiaoke Wu (China)
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ASRM PAGES

All adverse events in mother and fetus should be collected and reported through live birth.
What iatrogenic practices in women with PCOS may adversely affect pregnancy rates?

Superovulation during IVF
## Preventing OHSS in PCOS

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Likelihood in PCOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Youth</td>
<td>Yes</td>
</tr>
<tr>
<td>Thin</td>
<td>No</td>
</tr>
<tr>
<td>High Antral Folicle Count/AMH level</td>
<td>Yes</td>
</tr>
<tr>
<td>Excess Dose of Gonadotropin</td>
<td>Possible</td>
</tr>
</tbody>
</table>
FSH only preparations significantly lower the risk for OHSS compared to hMG preparations: (OR 0.20, 95% CI 0.08-0.46)
The concomitant use of a GnRHa with gonadotropin therapy increases the risk for OHSS (OR 3.15, 95% CI 1.46-6.70)

Hypothesis: Elective “Freeze-all” Embryos in Women with PCOS will lower Iatrogenic OHSS rates and improve Live Birth Rates over Elective Fresh Embryo Transfer
Fresh versus Frozen Embryos for Infertility in the Polycystic Ovary Syndrome

Chen ZJ et al, NEJM, 2016

1900 Women provided consent

392 Were excluded

1508 Underwent randomization

1508 Randomized

762 Were assigned to undergo fresh-embryo transfer

746 Were assigned to undergo frozen-embryo transfer

82 Discontinued participation or had protocol violation
14 Did not complete embryo transfer
8 Received fresh-blastocyst transfer
57 Received frozen-embryo transfer
34 Received frozen-blastocyst transfer
23 Received day 3 frozen-embryo transfer
3 Did not fulfill eligibility criteria

680 Complied with protocol

1 Was lost to follow-up

320 Delivered live-born infants

88 Discontinued participation or had protocol violation
20 Did not complete embryo transfer
23 Received frozen-blastocyst transfer
44 Received fresh-embryo transfer
4 Received fresh-blastocyst transfer
40 Received day 3 fresh-embryo transfer
1 Did not fulfill eligibility criteria

658 Complied with protocol

4 Were lost to follow-up

368 Delivered live-born infants

About 15% Crossover/ Dropout
Improved Live Birth Rates with elective FET in PCOS

- Increased rate ratio of Live birth with initial eFET: 1.17 (95% confidence interval, 1.05 to 1.31, *P = 0.004).

- Similar cumulative pregnancy rates after 12 months follow-up from initial transfer

FET is effective!!

Chen et al, NEJM 2016
Elective FET in women with PCOS may improve live birth rates largely through decreased pregnancy loss.

Mixed risk/benefit ratio.
### Mixed Risk/Benefit of Frozen vs Fresh Embryo Transfer

**FET Risk**

- Higher rate of preeclampsia (4.4% vs. 1.4%)
  - Rate ratio of 3.12 (95% CI, 1.26 to 7.73); \( P = 0.009 \)
- All stillbirths (N = 2) and neonatal deaths (N = 5) were in the FET group

**FET Benefit**

- Lower rate of pregnancy loss (22.0% vs 32.7%)
  - Rate ratio of 0.67 (95% CI, 0.54 to 0.83; \( P < 0.001 \))
- Marked reduction in OHSS (1.3% vs. 7.1%)
  - Rate ratio of 0.19 (95% CI, 0.10 to 0.37); \( P < 0.001 \)
- Increased Birth Weight
  - 162 gm increase (95% CI 56 to 267 gms, \( P < .005 \))
Spectrum of Implantation for an Euploid Embryo

Failed

Poor

Successful

Excessive

More likely after Fresh Transfer

More likely after Frozen Transfer

No Pregnancy

Conception but pregnancy loss

Live birth

Pre-eclampsia
Why is an FET better than a fresh transfer?

Because it avoids superphysiologic hormone exposure during the cycle, and allows for an optimal endometrium.
Why is Letrozole better than Clomiphene for ovulation induction in PCOS?

Aromatase inhibition achieves a more favorable ovulation/conception/implantation environment.

- Lower estradiol, higher progesterone after ovulation.
- Endometrium is relatively thinner with letrozole. Probably not an important predictive parameter.

Relatively Speaking: Clomiphene superovulates the endometrium and letrozole ovulates it.
## Significant Change in Key Parameters During Study

Mean (S.D.) [25%, 75% percentiles]

<table>
<thead>
<tr>
<th>Category</th>
<th>Change in Measure from Baseline to Last Midluteal Visit</th>
<th>Clomiphene</th>
<th>Letrozole</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ultrasound</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antral follicle count (both ovaries)</td>
<td>-3 (23) [-12, 8]</td>
<td>-5 (22) [-16, 5]</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td>Endometrial thickness: sagittal plane (mm)</td>
<td>3 (4) [1, 6]</td>
<td>2 (4) [0, 5]</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Serum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>53 (108) [-2, 92]</td>
<td>9 (60) [-21, 33]</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Progesterone (ng/dL)</td>
<td>11 (22) [-0.1, 15]</td>
<td>13 (21) [0.1, 18]</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Legro et al, NEJM, 2014
Fecundity per Ovulation Better with Clomiphene than Metformin

Legro et al, NEJM, 2007

* Significant compared to baseline
Fecundity per Ovulated Patient with Clomiphene by Pretreatments

P = .04 vs OCP

P = .08 vs OCP
All ovulations are not alike!!

Ovulation is a surrogate outcome for anovulatory infertility
Does pretreatment with OCP to start an IVF cycle adversely effect implantation in a fresh embryo transfer?
### Effect of Type of IVF Cycle Initiation on Live Birth Rate in PCOS (N = 1508)

<table>
<thead>
<tr>
<th>Type of Cycle Initiation</th>
<th>Fresh Transfer Live Birth Rate</th>
<th>FET Live Birth Rate</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous Menses</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Progestin-Induced</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>OCP-Induced</td>
<td>36%</td>
<td>49%</td>
<td>0.75 (0.61 to 0.92)</td>
</tr>
</tbody>
</table>

Wei et al, *Hum Reprod*, 2017
Does Iatrogenic Progestin after an Anovulatory Cycle Impair Subsequent Fecundity?

![Graph showing the percentage of live births per cycle and per ovulation across different conditions: Spontaneous Menses, Anovulatory Progestin Withdrawal, Anovulatory Alone, and No Progestin. The graph indicates a significant difference (*P < .01 vs Menses or Progestin*) between the conditions.](image)

Diamond et al, Obstet Gynecol 2012
Summary: Pretreatment with OCP prior to ovulation induction likely does not improve outcomes.

Routine withdrawal with progestin prior to ovulation induction cycles also likely does not improve outcomes.
Predictive Factors for Live Birth in PCOS

- Younger age
- Shorter Duration of attempting pregnancy
- Lower BMI
- Lower Free Androgen Index/Higher SHBG
- No Smoking

Note: No LH, LH/FSH, or AMH levels, No Endometrial Thickness or Morphology
Steering Committee of the PPCOS II Trial
OWL-PCOS: OCP vs Weight Loss for Pregnancy in Polycystic Ovary Syndrome (R01HD056510)
Funding/Collaborators

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