Ovarian stimulation in PCOS
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Questions
Why is PCOS different?
Why does this happen?
How to overcome the problems?

Why is PCOS different?
Greater sensitivity to gonadotrophin stimulation
therefore:
Multiple (“explosive”) follicular development
Why does this happen?

x6 the density of pre-antral follicles compared with normal ovary. (Webber et al, 2003)

Large cohort of small follicles arrest in development but capable of responding to exogenous FSH.

Follicle size distribution per ovary

Human Follicle Growth

Primordial follicle 1 layer flat granulosa cells (36 µm, × 570)

Primary follicle 1 layer cuboidal GCs (46 µm, × 570)

Secondary follicle 2 layers of GCs (77 µm, × 480)

Pre-antral follicle class 1 (theca cells & arterioles) (120 µm, × 350)

Early antral follicle class 2 (180-250 µm, × 170)

Small antral follicle class 4 (2 mm, × 25)
Androgens & follicular development

- Androgens increase the number of pre-antral and small antral follicles before they are sensitive to gonadotrophins.
  
  Hillier et al, 1997

- Androgens have a stimulatory role in early follicular growth by augmenting follicular FSH receptor expression and therefore amplifying FSH effects.

  Hillier & Tetsuka, 1997; Weil et al, 1999

Problems – IVF for PCOS

- Excessive ovarian response
- Low fertilization rates
- High number of immature oocytes
- Reduced cleavage rates
- Low implantation rates
- High miscarriage rates
Overcoming the problems

- Importance of making the diagnosis
- Avoid IVF by treating well beforehand

Multiple Choice

- Weight loss
- Clomiphene citrate (CC)
- Aromatase inhibitors (AI’s)
- Insulin lowering medications
- Low dose FSH
- Laparoscopic ovarian drilling

Figure 3: Cumulative pregnancy rate resulting in singleton live birth of a consecutive series of 240 normogonadotropic anovulatory infertile women undergoing classical ovulation induction (CC as first-line, followed by FSH as second-line therapy) (Bijleveld et al., 2003, with
Prevalence of PCOS in IVF programs

33-50% of IVF patients have PCO by US criteria at basal scan

Jacobs HS 1987; Balen et al., 1993; MacDougall et al., 1994

PCOS patients in IVF

• Failure to conceive in ovulatory cycles

• Additional infertility factors

• Combination of the above

IVF: PCOS vs controls

PCOS – more oocytes, lower fertilization rate

Similar pregnancy and live birth rates per cycle
Why the difference in fertilization rates?

- ? Immaturity of oocytes
  
  **MII oocytes / total oocytes (%)**
  
  PCOS – 53.5% Controls – 62% (NS)

  **Fertilized oocytes / MII oocytes (%)**
  
  PCOS – 62% Controls – 56% (NS)

  ? Problem of cytoplasmic maturity

  Ludwig et al, 1999

Oocyte quality

Wood et al, 2007

- Oocyte DNA – microarray & PCR
- Oocyte expressed genes – PCOS vs controls
- 374 genes different in PCOS - Subset of these associated with chromosomal alignment and segregation during mitosis/meiosis

Defects in meiosis or early embryonic development may contribute to reduced developmental competency

Lack of association between PCOS and embryonic aneuploidy

Weghofer et al, 2007

- n=74 PCOS vs 100 controls, IVF

- PGD for chromosomes X, Y, 13, 15,16,17,18,21,22
- Stratified for age and egg numbers

- No difference in euploidy rates
**Oocyte quality**

- Fertilization rates/oocytes recovered reduced. (If not immaturity then why?)
- Once fertilized, pregnancy rates not different.
- Miscarriage rates increased. (Probably not due to chromosomal abnormalities, maybe due to defects in meiosis or early embryonic development).

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**Prevalence of miscarriage in PCOS - IVF**

<table>
<thead>
<tr>
<th>Study</th>
<th>PCOS</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homburg et al, 1993</td>
<td>37%</td>
<td>25%</td>
</tr>
<tr>
<td>Balen et al, 1993</td>
<td>36%</td>
<td>24%</td>
</tr>
<tr>
<td>Ludwig et al, 1999</td>
<td>41%</td>
<td>21%</td>
</tr>
<tr>
<td>Winter et al, 2002</td>
<td>26%</td>
<td>15%</td>
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<tr>
<td>Wang et al, 2002</td>
<td>25%</td>
<td>18%</td>
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</tbody>
</table>

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**Why higher rate of EPL in PCOS?**

- Obesity
- High PAI-1
- Hyperinsulinemia
- High LH
- Poor egg quality
- Poor endometrial receptivity
Overcoming the problems

Mild stimulation
Oral contraceptive pre-treatment
Agonist vs antagonist
GnRH agonist to trigger ovulation
Metformin
Freeze embryos
IVM

Dual suppression
OC’s + GnRH agonist
Damario et al, 1997

• Rationale:
  GnRHa long protocol not sufficient to normalize entirely the unfavourable hormonal milieu which may interfere with normal folliculogenesis in PCOS.

• OC’s for 25 days
• Agonist from day 21 of pills
• From d3 of menstruation – ½ dose agonist + 150 IU FSH or hMG usually reduced to 75 IU/day up to hCG
### Dual suppression
**OC’s + GnRH agonist**

**Damario et al, 1997**  
*n=99 cycles, 73 patients*

- 13 cycles cancelled (13.1%)
- Clinical pregnancy rate
  - 46.3% / started cycle
  - 51.7% / OPU
  - 59% / ET
- Ongoing pregnancy rate – 51.3% / ET
- OHSS – 8 (mild/moderate)

### Dual suppression
**OC’s + GnRH agonist**

vs GnRH agonist alone:

- Lower A’s, E2, LH
- Higher rates of fertilization
  - Implantation
  - Pregnancy
- Lower cancellation rates

**Damario et al, 1997**

### GnRH antagonists in IVF

- Do not activate the GnRH receptor
- Produce rapid suppression of gonadotropin suppression within hours
- Shorter and simpler treatment as compared to the long protocol
Prospective multicenter study with historical controls

87 patients on a long mid-luteal GnRH agonist protocol

• High risk for OHSS
• Many cancelled (49 - 56.5%) because of high risk for OHSS
• Many developed mod-severe OHSS (24 – 27.6%)

• GnRH antagonist protocol
• Identical dose of gonadotropin as in the long protocol

Ragni et al., Hum Reprod 2005

Figure 1. Comparison of stopped cycles, oocyte retrieval, embryo transfer and incidence of OHSS between the two treatment cycles (filled bars, GnRH agonist; empty bars, GnRH antagonist). Values are expressed in percentages; differences were statistically significant for stopped cycles and oocyte retrieval (both P < 0.001), embryo transfer (P = 0.003) and OHSS (P < 0.006).
CONCLUSIONS:

.... limitations owing to the use of historical controls, 

.... a favorable effect of GnRH antagonists in reducing 
the incidence of OHSS and the number of 
assisted fertilization cycles cancelled because of the 
risk of OHSS in high responder patients.

Ragni et al., Hum Reprod 2005

| IVF cycles in PCOS | 
|-------------------|-------------------|
| GnRH agonist vs GnRH antagonist | 
| **Agnostist** | **Antagonist** |
| Number of cycles | 50 | 102 |
| Patient age (yrs) | 30±3.9 | 30.9±4.6 | ns |
| BMI (kg/m2) | 27.4±4.9 | 27.5±5.3 | ns |
| Length of stimulation (d) | 11.1±2.9 | 10.2±2.4 | p=0.05 |
| # of Gnr amp. used | 35.0±16.8 | 28.6±15.3 | p<0.03 |
| Peak E2 (pg/ml) | 1800±772 | 1738±1048 | ns |
| P (ng/ml) | 0.6±0.3 | 0.7±0.6 | ns |
| # of OPU | 11.9±7.2 | 11.7±8.7 | ns |
| FR (%) | 55±54 | 58±61 | ns |
| # of ET | 2.2±0.6 | 2.2±0.7 | ns |
| Pregnancy rate | 36.0% | 19.6% | p<0.04 |
| (18/50) | (20/102) |

Orvieto, Homburg et al, 2008

Incidence and prediction of ovarian hyperstimulation syndrome in women undergoing gonadotropin-releasing hormone antagonist in vitro fertilization cycles

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Effeeta T. Kolihaizad, M.D., Ph.D., Michel Coma, M.D., Rosem Tsohm, M.D., Ph.D.,
Heman M. Fath, M.D., André Vae Tseurpoun, M.D., Ph.D., and Paul Dunne, M.D., Ph.D.
Center for Reproductive Medicine, University Hospital, Duffüsseldorf Research Fair, University, Remu, Belgium

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**Conclusions:**

- Clinically significant OHSS still remains a limitation of multifollicular ovarian stimulation for IVF even with the use of GnRH antagonist protocols.

_Papanikolaou et al., Fertil Steril 2006_

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**Conclusions:**

- The number of follicles can discriminate the patients who are at risk for developing OHSS, whereas E2 concentrations are less reliable for the purpose of prediction.

_Papanikolaou et al., Fertil Steril 2006_
Conclusions:

- There is more than ever an urgent need for alternative final oocyte maturation–triggering medication.

*Papamikolaou et al., Fertil Steril 2006*

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**GnRH agonist for triggering final oocyte maturation in the GnRH antagonist ovarian hyperstimulation protocol: a systematic review and meta-analysis**

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1Department of Obstetrics and Gynecology, University of Athens School of Medicine, Greece; Leibniz, Germany; and 3Center of Reproductive Medicine, Catholic University, Brussels, Belgium.

Conclusions: the likelihood of an ongoing clinical pregnancy after GnRH agonist triggering is significantly lower as compared to standard HCG treatment.

*Griesinger et al., Fertil Steril 2007*

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**Triggering of final oocyte maturation with GnRH-a or HCG: Live birth after frozen-thawed embryo replacement cycles**

![Graph showing LBR/ET and Cum LBR for GnRH and hCG]

P = 0.02

*Griesinger et al., Fertil Steril 2007*
GnRH agonist vs hCG in high risk IVF patients

RCT, n=66 with PCO’s
  - Antag + GnRH trigger
  - vs
  - Agonist + hCG trigger

OHSS – 0% vs 31%
Ongoing pregnancy rates – 53% vs 48%
Adequate E2, P supplementation in luteal phase

Engmann et al, 2008

Metformin for IVF

- n=73 PCOS for IVF/ICSI
  - metformin (2G/d)
  - placebo for 16 weeks

- No difference in any stimulation, IVF or clinical criteria.
- BUT in group with BMI < 28, pregnancy rates double on metformin.

Kjotrod et al, 2004

Metformin in IVF

Tang, Bart & Balen, 2005

- Single centre, double-blind RCT

- 94 patients, PCOS, BMI 27.8
  - 101 IVF/ICSI cycles, long agonist protocol

- Metformin (850mg bd)
  - or placebo from start of agonist to OPU
**Metformin in IVF**

- No difference:
  - Total dose FSH
  - No. of oocytes
  - Fertilisation rates

  Tang, Barth & Balen, 2005

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**Metformin for IVF in PCOS**

![Bar chart showing CPR/Cycle and CPR/Transfer comparison between placebo and metformin.](chart.png)

- CPR/Cycle: Placebo vs. Metformin
- CPR/Transfer: Placebo vs. Metformin

  P = 0.02

  Tang et al., Hum Reprod 2005

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**Metformin in IVF**

- Short term co-treatment with metformin for PCOS in IVF/ICSI:
  - Does not improve response to stimulation
  - Improves pregnancy rates
  - Reduces the risk of OHSS

  Tang, Bart & Balen, 2005
40 PCOS patients undergoing IVF-ICSI

Stimulated with rFSH 150IU + GnRH antagonist

Group A: Pretreatment with metformin 1.5 g/day
Group B: rFSH + GnRH antagonist only

Doldi et al., Gynecol Endocrinol 2006
Endometrial dysfunction

- Low luteal phase serum glycodelin and IGFBP-1 (Jacubowicz et al, 2001)
- Plasma endothelin-1 levels high in PCOS (Diamantis-Kandarakis et al, 2005)
- Inadequate endometrial blood flow (Orio et al, 2005)

All induced by hyperinsulinemia and improved by metformin.

In-vitro maturation in PCOS

Rationale: PCOS women have many antral follicles

Good ‘harvest’ possible    \   \ Avoids OHSS

IVM: Clinical Protocol

- Prime with FSH for 2-3 days
- Prime with hCG 36 hours before retrieval
- Retrieval when diameter 8-12 mm
- Aspirate under lower vacuum (55mmHg)
- Prime endometrium with 6-10mg E2 and P4 600mg/day per day from oocyte retrieval
- Continue support for 12 weeks
Clinical Outcomes from IVM

<table>
<thead>
<tr>
<th>Centre</th>
<th>Cycles (n)</th>
<th>Implantation (n%)</th>
<th>Clinical pregnancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGill Reproductive Centre, Montreal, Canada</td>
<td>254</td>
<td>11.2</td>
<td>24.0 (5)</td>
</tr>
<tr>
<td>Seoul National Hospital, Seoul, Korea</td>
<td>152</td>
<td>33.6</td>
<td>32.7 (17)</td>
</tr>
<tr>
<td>Beijing Women's Hospital, Beijing, China</td>
<td>152</td>
<td>37.2</td>
<td>15.0 (45)</td>
</tr>
<tr>
<td>COH General Hospital, Seoul, Korea</td>
<td>94</td>
<td>3.9</td>
<td>27.5 (25)</td>
</tr>
<tr>
<td>Shin Kong Yu Ho Gu National Hospital, Taipei, Taiwan</td>
<td>68</td>
<td>38.2</td>
<td>23.8 (23)</td>
</tr>
<tr>
<td>Hospital Antoine Béclère, Chartres, France</td>
<td>45</td>
<td>38.9</td>
<td>28.0 (9)</td>
</tr>
</tbody>
</table>

Papanikolaou et al, 2005 RBM Online 10:587

IVM from unstimulated PCO

N=118 women, PCOS. 152 cycles
OPU day 9-14
ET – 140 cycles
Clinical pregnancy rate – 40% / transfer
56 livebirths and another 10 ongoing.

Zhao et al, F&S, 2008

Summary and conclusions:
The GnRH antagonist protocol appears to be an attractive option for PCOS patients undergoing IVF.

It offers greater safety in terms of OHSS risk:

- Severe OHSS is significantly reduced
- Interventions to prevent OHSS are significantly reduced
- The goal of “soft stimulation” can be easily achieved
- Ovulation triggering with GnRH-a may be a better option than cycle cancellation or prolonged coasting
Summary and conclusions:

• The addition of metformin to the treatment protocol may be beneficial
• Pretreatment with an OCP may be beneficial
• Favorable pregnancy rates can be expected with fresh and frozen cycles
• Specifically designed RCTs’ should be conducted