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:

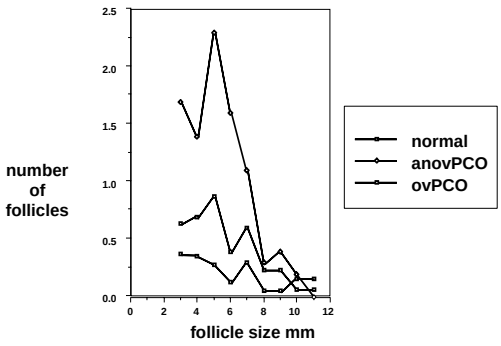
Multiple (“explosive”) follicular development

Why does this happen?

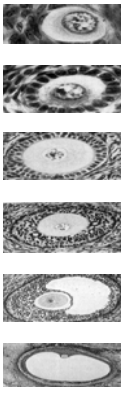
x6 the density of pre-antral follicles compared with normal ovary.
(Webber et al, 2003)

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 (36µm, × 570)

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

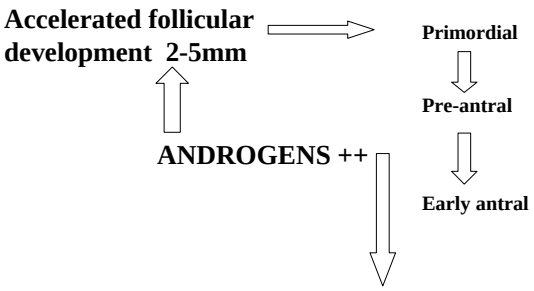
Secondary follicle
2 layers of GCs (77 µm, ×480)

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)

(Gougeon, Endocr Rev 1996)



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**

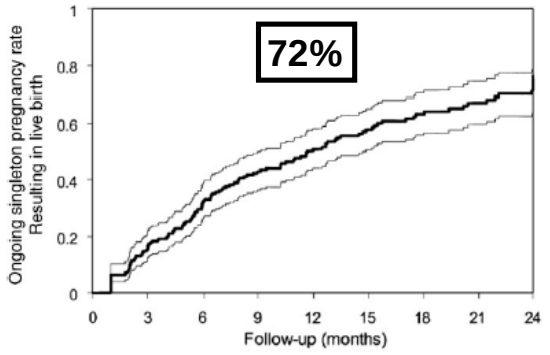


Figure 3: Cumulative pregnancy rate resulting in singleton live birth of a consecutive series of 240 normogonadotrophic anovulatory infertile women undergoing classical ovulation induction (CC as first-line, followed by FSH as second-line therapy) (Eijkemans *et al.*, 2003, with

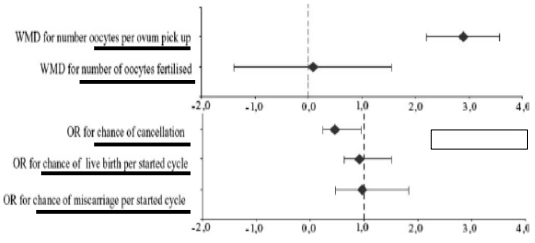
Prevalence of PCOS in IVF programs

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



Main findings of clinical IVF outcomes in women with PCOS compared with matched controls (Heijnen *et al.*, 2006).

IVF: PCOS vs controls

PCOS – more oocytes, lower fertilization rate

Similar preganacy 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).**

Prevalence of miscarriage in PCOS - IVF

	PCOS	Controls
• Homburg et al, 1993	37%	25%
• Balen et al, 1993	36%	24%
• Ludwig et al, 1999	41%	21%
• Winter et al, 2002	26%	15%
• Wang et al, 2002	25%	18%

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.

Dual suppression
OC's + GnRH agonist

Damario et al, 1997

- **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

Human Reproduction Vol.20, No.9 pp. 2421–2425, 2005 doi:10.1093/humrep/d
Advance Access publication May 12, 2005

Comparison of GnRH agonists and antagonists in assisted reproduction cycles of patients at high risk of ovarian hyperstimulation syndrome

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- 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

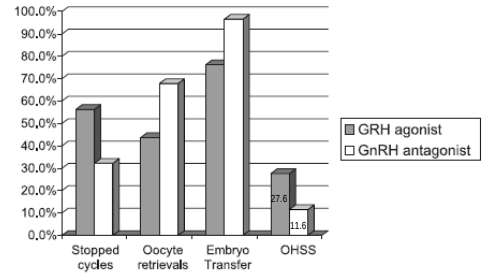

Figure 1. Comparison of stopped cycles, oocyte retrieval, embryo transfer and incidence of OHSS between the two treatment cycles (filled bars, GnRH agonist; empty bars, GnRH antagonist). Values are expressed in percentages; differences were statistically significant for stopped cycles and oocyte retrieval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

	Agonist	Antagonist	
Number of cycles	50	102	
Patient age (yrs)	30±3.9	30.9±4.6	ns
BMI (kg/m2)	27.4±4.9	27.9±5.3	ns
Length of stimulation (d)	11.1±2.9	10.2 ±2.4	p=0.05
# of Gn amp. used	35.0±16.8	28.8±15.3	p<0.03
Peak E2 (pg/ml)	1800±872	1738±1048	ns
P (ng/ml)	0.6±0.3	0.7±0.6	ns
# of OPU	11.8±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% (18/50)	19.6% (20/102)	p<0.04

Orvieto, Homburg et al, 2008

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

Evangelos G. Papanikolaou, M.D., Ph.D., Cristina Pozzobon, M.D., Efstratios M. Kolibianakis, M.D., Ph.D., Michel Camus, M.D., Herman Tournaye, M.D., Ph.D., Human M. Fatemi, M.D., Andre Van Steirteghem, M.D., Ph.D., and Paul Devroey, M.D., Ph.D.

Centre for Reproductive Medicine, University Hospital, Dutch-Speaking Brussels Free University, Brussels, Belgium

Fertility and Sterility® Vol. 85, No. 1, January 2006

•rFSH+GnRH antagonist protocol
1801 patients; 2524 IVF-ICSI cycles (2002-2003)
65.2% had PCOS

•53 patients (2.1%) hospitalized with mod-severe OHSS
•Early OHSS in 31 patients (1.2%)
•Late OHSS in 22 patients (0.9%)
•Late OHSS more often severe (72.7% vs. 42%; p<0.05)

Papanikolaou et al., Fertil Steril 2006

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

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.

Papanikolaou et al., Fertil Steril 2006

Human Reproduction Update, Vol.12, No.2 pp. 159–168, 2006 doi:10.1093/humupd/dmi045
Advance Access publication October 27, 2005

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

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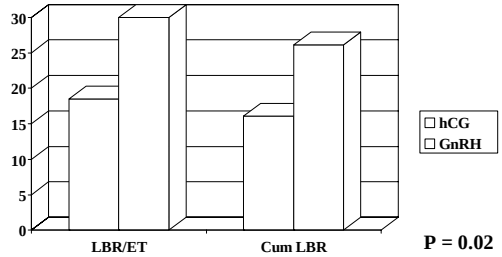
Conclusions:
the likelihood of an ongoing clinical pregnancy after GnRH agonist triggering is significantly lower as compared to standard HCG treatment.

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



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

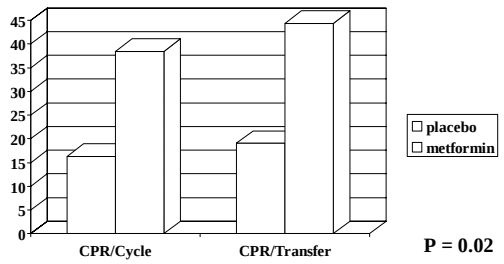
- **Single centre, double-blind RCT**
- **94 patients, PCOS, BMI 27.8**
  101 IVF/ICSI cycles, long agonist protocol
- **Metformin (850mg bd)**
  or placebo from start of agonist to OPU

Metformin in IVF

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

Tang, Barth & Balen, 2005

Metformin for IVF in PCOS



P = 0.02

Tang et al., Hum Reprod 2005

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

Gynecological Endocrinology, May 2006; 22(5): 235–238

Taylor & Francis

ASSISTED REPRODUCTIVE TECHNOLOGY

Gonadotropin-releasing hormone antagonist and metformin for treatment of polycystic ovary syndrome patients undergoing *in vitro* fertilization–embryo transfer

NICOLA DOLDI, PAOLA PERSICO, FRANCESCA DI SEBASTIANO, ELENA MARSIGLIO, & AUGUSTO FERRARI

IVF Unit, Ob-Gyn Department, Vita-Salute University, Milan, Italy

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

Table I. Comparison of ovulation induction in the two groups of patients.

	metformin		*p* Value
	Group A	Group B	(A vs. B)
n	20	20	
Duration of stimulation (days)	9.9 ± 2.1	9.8 ± 1.9	NS
No. of rFSH ampoules	18 ± 6	24 ± 8	<0.05*
Serum E_2 on hCG day (pg/ml)	2400 ± 600	3370 ± 900	<0.05*
No. of follicles ≥14 mm diameter	18 ± 1.2	19 ± 1.7	NS

Group A, standard short gonadotropin-releasing hormone (GnRH) antagonist protocol for ovarian stimulation with metformin pretreatment; Group B, standard short GnRH antagonist protocol for ovarian stimulation without metformin pretreatment; rFSH, recombinant follicle-stimulating hormone; E_2, estradiol; hCG, human chorionic gondadotropin; NS, not significant; data are expressed as mean ± standard deviation; *statistically significant difference.

Doldi et al., Gynecol Endocrinol 2006

Table II. Comparison of *in vitro* fertilization–embryo transfer outcomes in the two groups of patients.

	metformin Group A	Group B	*p* Value (A vs. B)
No. of oocytes retrieved	13 ± 4.4	14 ± 5.1	NS
No. of mature oocytes	8.4 ± 1.5	5.0 ± 1.5	<0.05*
No. of grade A embryos	2.5 ± 0.5	2.2 ± 0.3	NS
No. of cancelled cycles	1 (5)	3 (15)	<0.05*
OHSS incidence	1 (5)	2 (15)	<0.05*

Group A, standard short gonadotropin-releasing hormone (GnRH) antagonist protocol for ovarian stimulation with metformin pretreatment; Group B, standard short GnRH antagonist protocol for ovarian stimulation without metformin pretreatment; OHSS, ovarian hyperstimulation syndrome; NS, not significant; data are expressed as mean ± standard deviation or *n* (%); *statistically significant difference.

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.

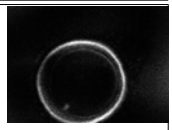
In-vitro maturation in PCOS

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 2. Pregnancy outcomes from four reproductive centres practising IVM in PCO patients (modified by Chian, 2004).

	Cycles (n)	*Implantation rate* (%)	*Clinical pregnancies* % (n)
McGill Reproductive Centre, Montreal, Canada	254	11.1	24.0 (61)
Maria Infertility Hospital, Seoul, Korea			
Day 3 transfer	419	11.6	32.7 (137)
Day 5 transfer	80	27.2	53.8 (43)
Infertility Medical Centre, CHA General Hospital[1] Seoul Korea	94	6.9	27.1 (23)
Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan	68	10.5	33.8 (23)
Hospital Antoine Béclère[2], Clamart, France	45	10.9	20.0 (9)

[1]Cha *et al.*, 2000.
[2]Le Du *et al.*, 2005.

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