Circulating progesterone levels and ongoing pregnancy rates in controlled ovarian stimulation cycles for in vitro fertilization: analysis of over 4000 cycles

Hum Reprod 2010 Aug;25(8):2092-100

Presented by R4 蔡幸君

2010.08.17

background

- IVF / ICSI – ET
- controlled ovarian stimulation (COS):
  - hCG → to induce final oocyte maturation
- premature LH surge
  - caused by E2 (induced by gonadotropin) → premature luteinization and cancellation of cycles
  - GnRHa or GnRH antagonist → suppress endogenous gonadotropin → prevent premature LH surge

- Progesterone ↑ rapidly after hCG
- Subtle ↑ progesterone have been observed at the end of follicular phase in COS cycles
  - Frequency varies
  - Incidence:
    - 35% (5-35%) of stimulated cycles with GnRH agonist
    - 38% (20-38%) with GnRH antagonist

- Pre-hCG progesterone ↑ referred to as "premature luteinization"
  - Occur in the presence of GnRH analogues **(X)** → ***low LH***
  - No relationship exists between LH and P at late follicular phase

Bosch et al., 2003

  - Excess follicle number, with each one producing a normal amount of P in late follicular phase
  - Speculation: ↑ progesterone reflect mature granulosa cell response to high FSH exposure

Whether the presence of ↑ progesterone on the day of hCG administration are associated with the ongoing pregnancy rate ?

- **Much debate**
  - No association
  - Inversely associated

- Meta-analysis: ↑ progesterone does not correlate with pregnancy rate

Venetis et al., 2007

However …

- different GnRH analogue and different P cut-off level defined as “high”
  - Most study use threshold value of 0.9 ng/ml without performing a trend analysis
- Methodological assay
  - Identify small P rise
  - Valid, show great consistency at appropriate range of P

The mechanism between ↑ progesterone and pregnancy rate is unclear.

- Impair endometrial receptivity rather than oocyte quality

Aim

- Investigate the relationship between serum progesterone level on the day of hCG administration and probability of ongoing pregnancy

Materials and Method

Study population and design

- non-interventional, retrospective, observational cohort study
- no inclusion / exclusion criteria: to reflect broad range pts
- single center at Instituto Valenciano de infertilidad
- Jan 2003 to Dec 2007

Controlled ovarian stimulation

GnRH agonist long protocol (n=1177)	GnRH antagonist (n=2855)

1. rFSH alone (Gonal-F®, Puregon®)
2. rFSH + rLH
3. highly purified human menopausal gonadotrophin (HP-hMG)
4. rFSH + HP-hMG.

Choice of protocol and dose adjustment: case-by-case, according to patient characteristics and clinician preference

Progesterone measurement

- on the day of hCG administration
  - ≧3 follicles ≧18 mm
- Microparticle exzyme immunoassay Axsym System:
  - Sensitivity: 0.2 ng/ml
  - Intraobserver and interobserver variation coefficients: 9.6 & 3.9%
  - Internal quality control daily by lab
  - External quality control monthly at *Spanish Society of Clinical Biochemistry and molecular Pathology*

ongoing pregnancy rate

- the presence of at least one viable fetus beyond 20 weeks on ultrasound

- 1 ° objective:
  - to determine the relationship between serum progesterone on the day of hCG administration and ongoing pregnancy rate

- 2 ° objective
  - identify a progesterone threshold to define detrimental circulating progesterone levels for cycle outcomes
  - examine factors related to progesterone elevation

Statistical analysis

- Pts divided to 6 groups according to P
  - ≦1.00, 1.01-1.25, 1.26-1.50, 1.51-1.75, 1.76-2.00, ＞2.00 ng/ml
- trend analysis – Mantel-Haenszel test
- Odds ratio (OR) and 95% CI
- Stratification (to control confounding factors)
  - age, BMI, overweight, gonadotropin consumption and E2 level
- Factors related to P elevation:
  - multivariate analysis

Results

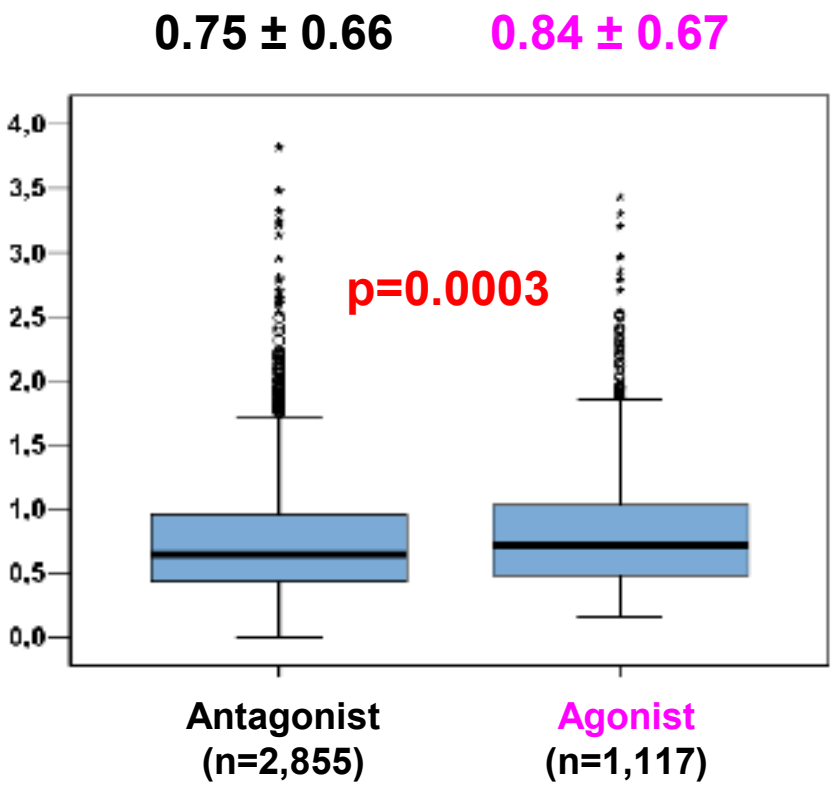
Table I Baseline characteristics of the IVF/ICSI–ET population.

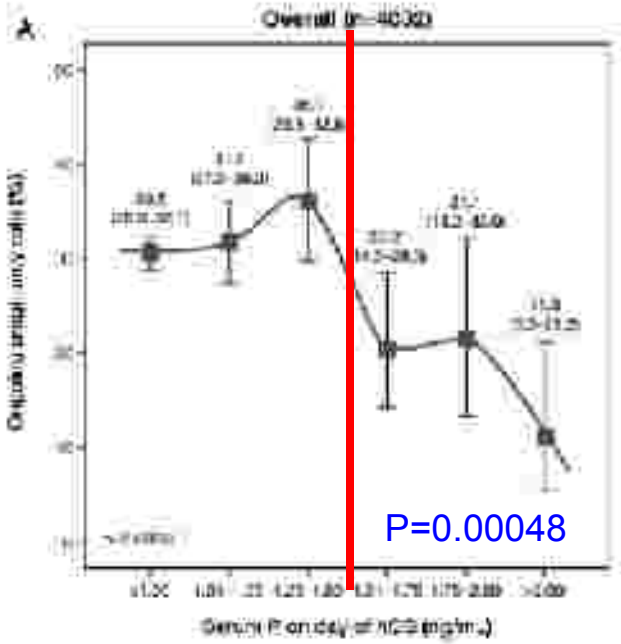
Parameter	$n = 4032$
Age (years)	35.3 ± 4.1
Body mass index (kg/m^2)	23.4 ± 5.4
Primary infertility cause [*n* (%)]	
Male factor	1237 (30.7)
Female age	713 (17.7)
Previous low response	433 (10.7)
Endometriosis	390 (9.7)
Tubal factor	312 (7.7)
Polycystic ovary	275 (6.8)
Recurrent pregnancy loss	138 (3.4)
Genetic	85 (2.1)
Unknown	449 (11.1)
Procedure [*n* (%)]	
ICSI	3447 (85.5)
IVF/ICSI	468 (11.6)
IVF	117 (2.9)

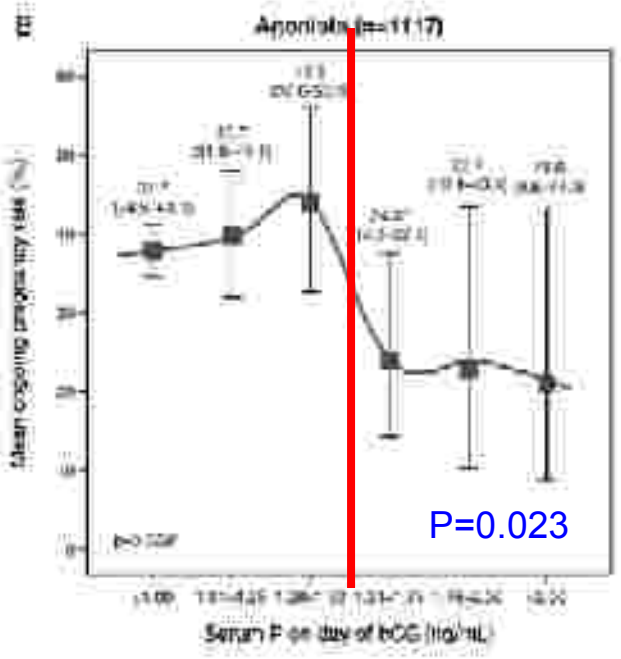
IVF, in vitro fertilization; ICSI–ET, intracytoplasmic sperm injection–embryo transfer.

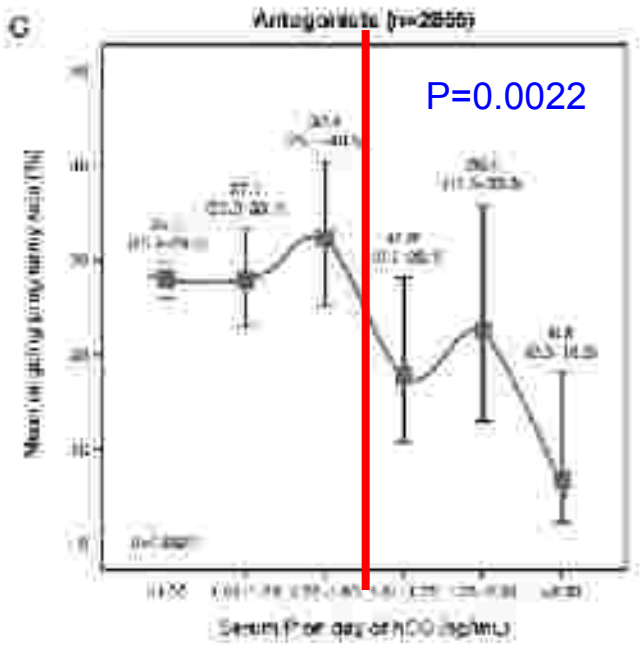
Results

- Serum progesterone: 0.77± 0.66 ng/ml
  - ✓ incidence of high P very similar during each year



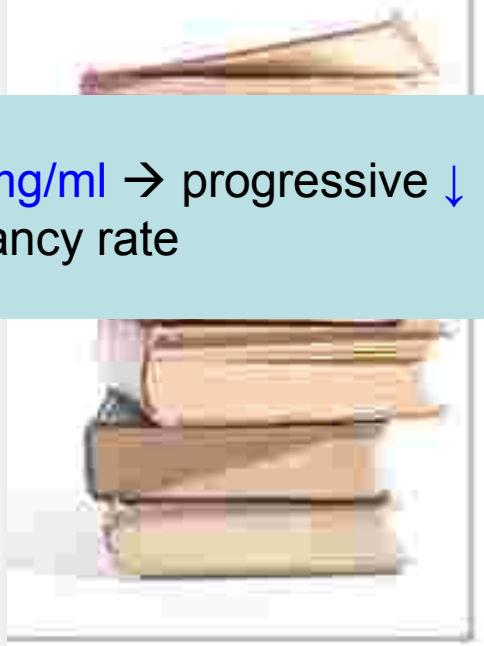


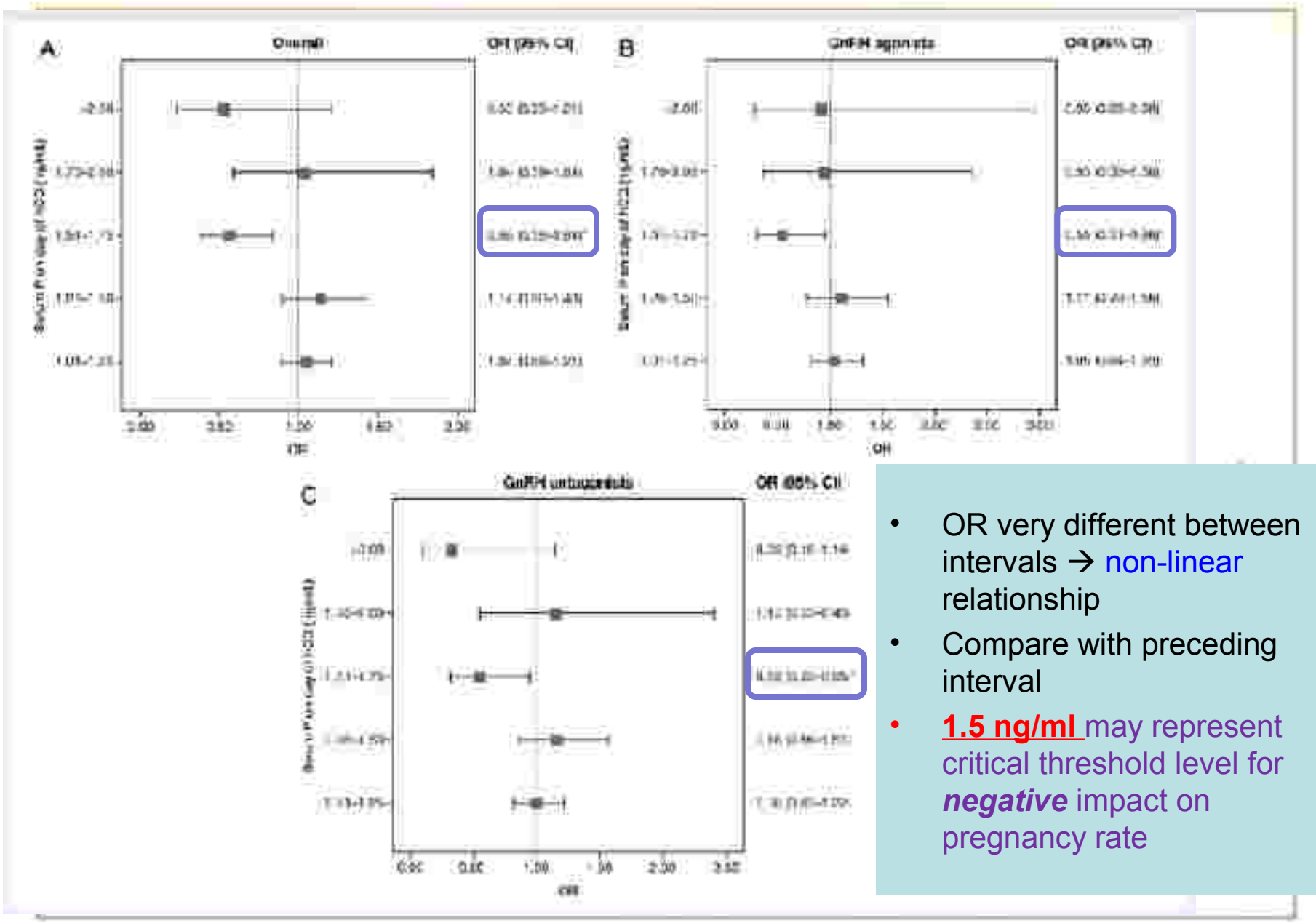




Trend analysis

- P > 1.5 mg/ml → progressive ↓ in pregnancy rate





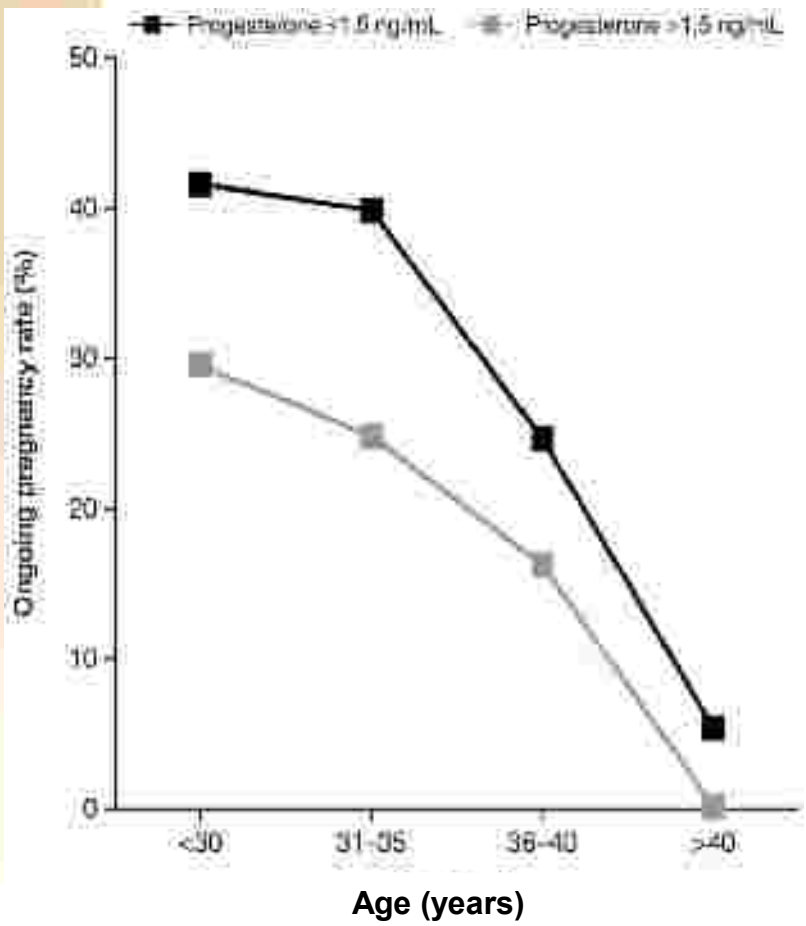
- OR very different between intervals → non-linear relationship
- Compare with preceding interval
- **1.5 ng/ml** may represent critical threshold level for ***negative*** impact on pregnancy rate

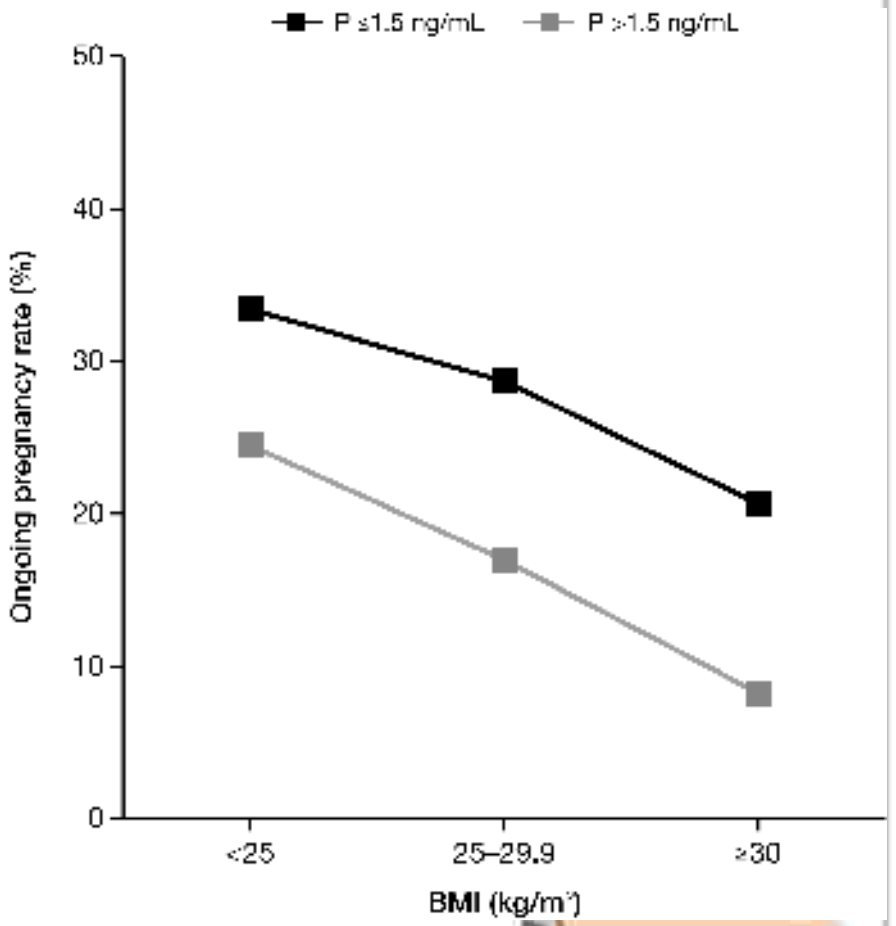
P ≦ 1.5 ng/ml → better outcome

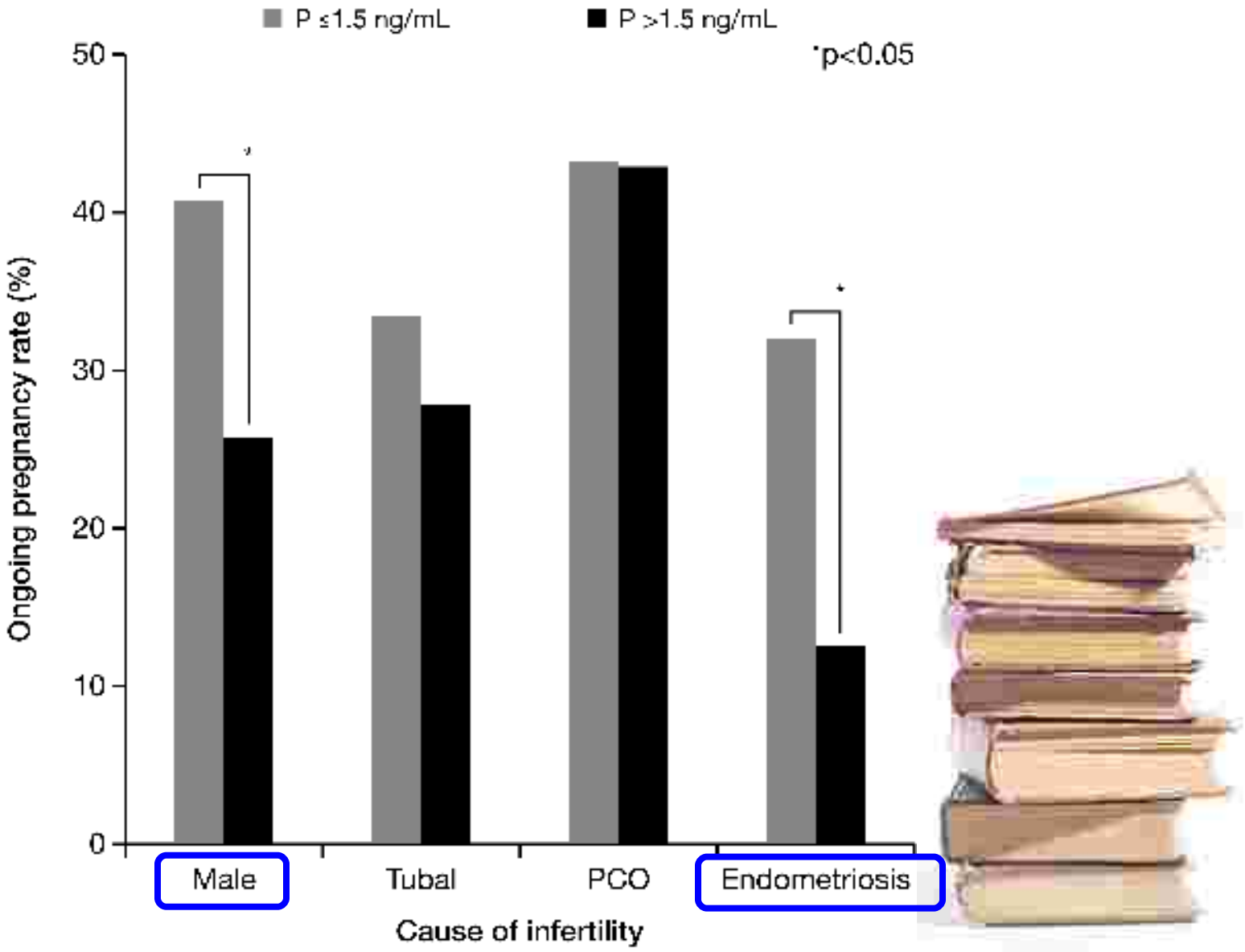
Table II Ongoing pregnancy rates for participants with serum progesterone levels ≤1.5 or >1.5 ng/ml.

Serum progesterone level (ng/ml)	All (n = 4032)	GnRH agonist (n = 1177)	GnRH antagonist (n = 2855)
≤1.5	31.0 (29.5–32.5)	38.4 (35.4–41.5)	28.1 (26.4–29.9)
>1.5	19.1 (14.4–24.4)	24.2 (15.8–34.3)	16.1 (11.0–22.8)
Difference in ongoing pregnancy rate	0.53 (0.36–0.72)*	0.51 (0.31–0.84)†	0.50 (0.33–0.76)‡

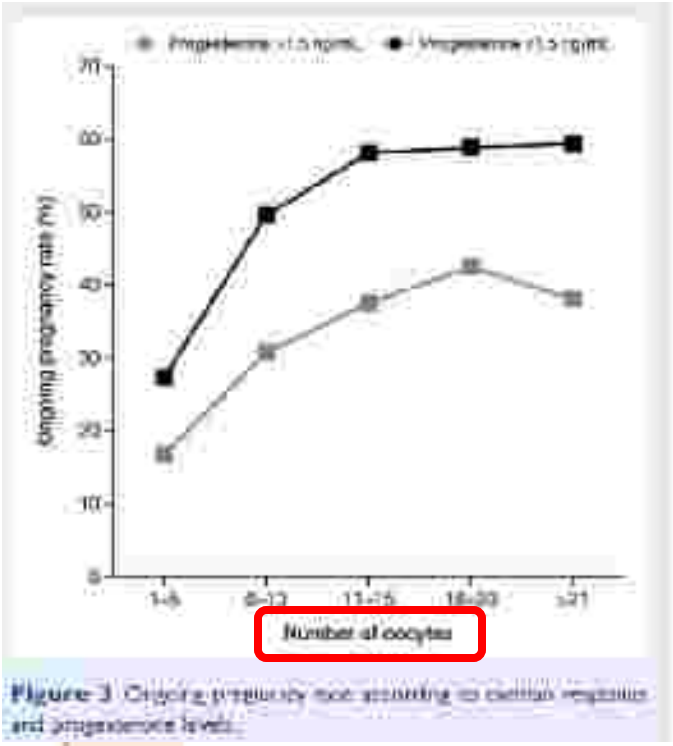
*P = 0.0006; †P = 0.007; ‡P = 0.0009; data are expressed as percentage (range) or OR (95% CI). GnRH, gonadotropin-releasing hormone.

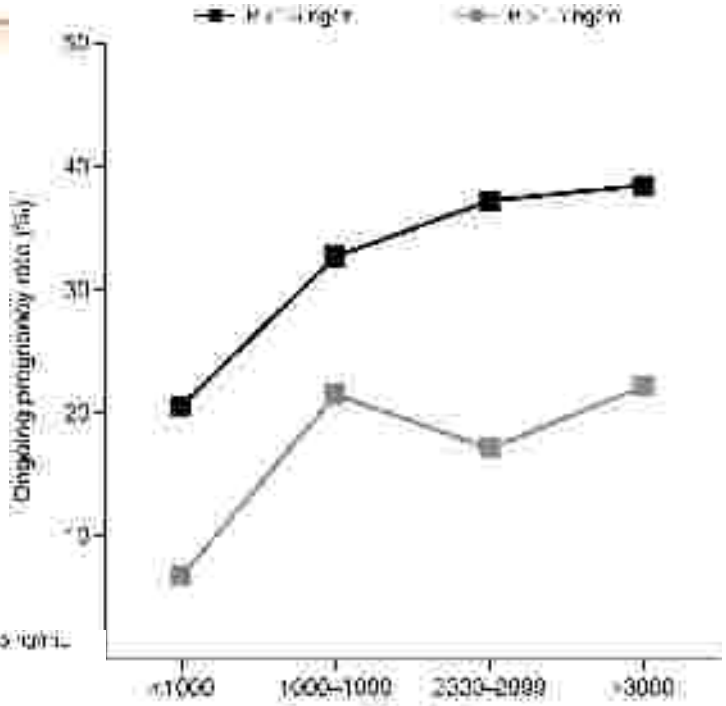

Progesterone ≤1.5 ng/mL
Progesterone >1.5 ng/mL
Ongoing pregnancy rate (%)
50
40
30
20
10
0
<30
31–35
36–40
>40
Age (years)


P ≤1.5 ng/mL
P >1.5 ng/mL
Ongoing pregnancy rate (%)
50
40
30
20
10
0
<25
25–29.9
>30
BMI (kg/m²)


P ≤1.5 ng/mL
P >1.5 ng/mL
*p<0.05
Ongoing pregnancy rate (%)
50
40
30
20
10
0
Male
Tubal
PCO
Endometriosis
Cause of infertility

Ovarian response





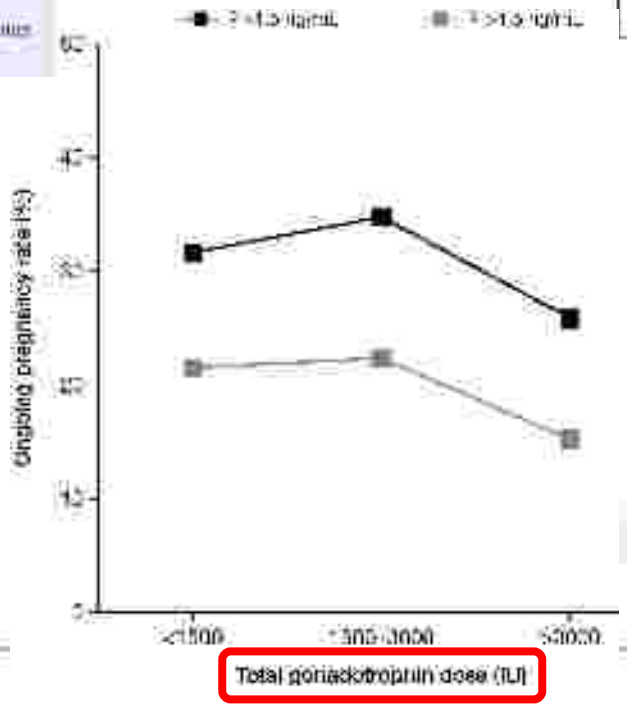
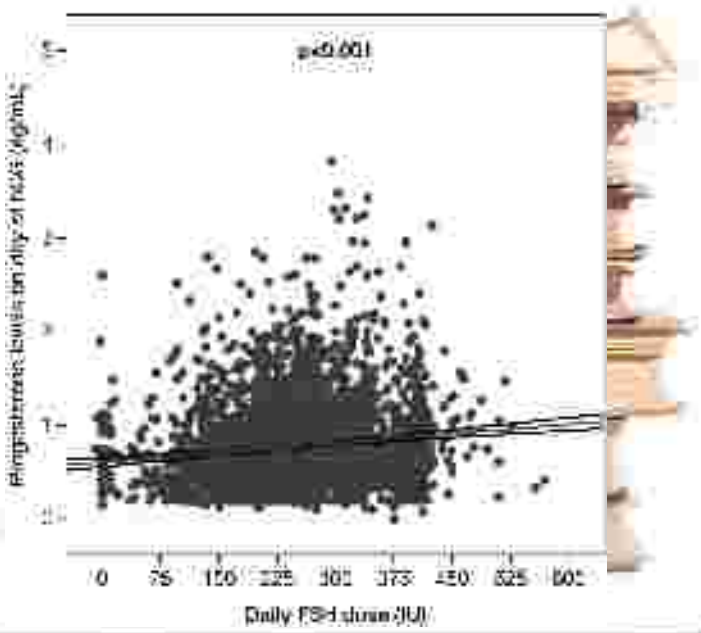


Table III Multivariate analysis of factors related to progesterone elevation.

Factor	OR (95% CI)	*P*-value
Daily FSH	1.44 (1.28–1.63)*	<0.0001
Number of oocytes	1.063 (1.041–1.085)	<0.0001
E_2 on day of hCG administration	1.0004 (1.0002–1.0010)	<0.0001

Incidence of OHSS		
P ≦ 1.5 ng/ml		P > 1.5 ng/ml
4.6%	P<0.0001	13.7%



Stimulation protocol – bias ??

	GnRH agonist long protocol (n=1177)		GnRH antagonist (n=2855)	
	rFSH (n=138)	protocol with LH activity (n=979)	rFSH (n=261)	protocol with LH activity (n=2594)
P > 1.5 ng/ml	8.7%	8.1%	11.5%	5.2%

Discussion

- ↑ circulating progesterone levels at the end of COS related to poorer ongoing pregnancy rates, irrespective of GnRH analogue use
- Serum progesterone of 1.5 ng/ml on hCG day → appropriate threshold to define detrimental level for outcome

Human Reproduction Update, Vol.13, No.4 pp. 343–355, 2007
Advance Access publication April 2, 2007

Is progesterone elevation on the day of human chorionic gonadotrophin administration associated with the probability of pregnancy in *in vitro* fertilization? A systematic review and meta-analysis

- No correlation
- Heterogeneity of studies included
- Different assay
- Different threshold level

- A smaller study: ROC analysis to assess progesterone level of < 1 or ≧ 1 ng/ml on pregnancy outcome → NOT predictive
  - ROC not suitable test

Saleh et al., 2009

- Approach to classify
  - discrete and regular interval
  - large sample size expected to compensate misclassified

- progesterone threshold of 1.5 ng/ml can be applied to ***all ovarian responses***
- a modifying effect of ovarian response on progesterone elevation and pregnancy outcome
  - cut-off value of P
  - criteria for ovarian response

Fanchin et al., 1997b

➔ appropriate methodological approach

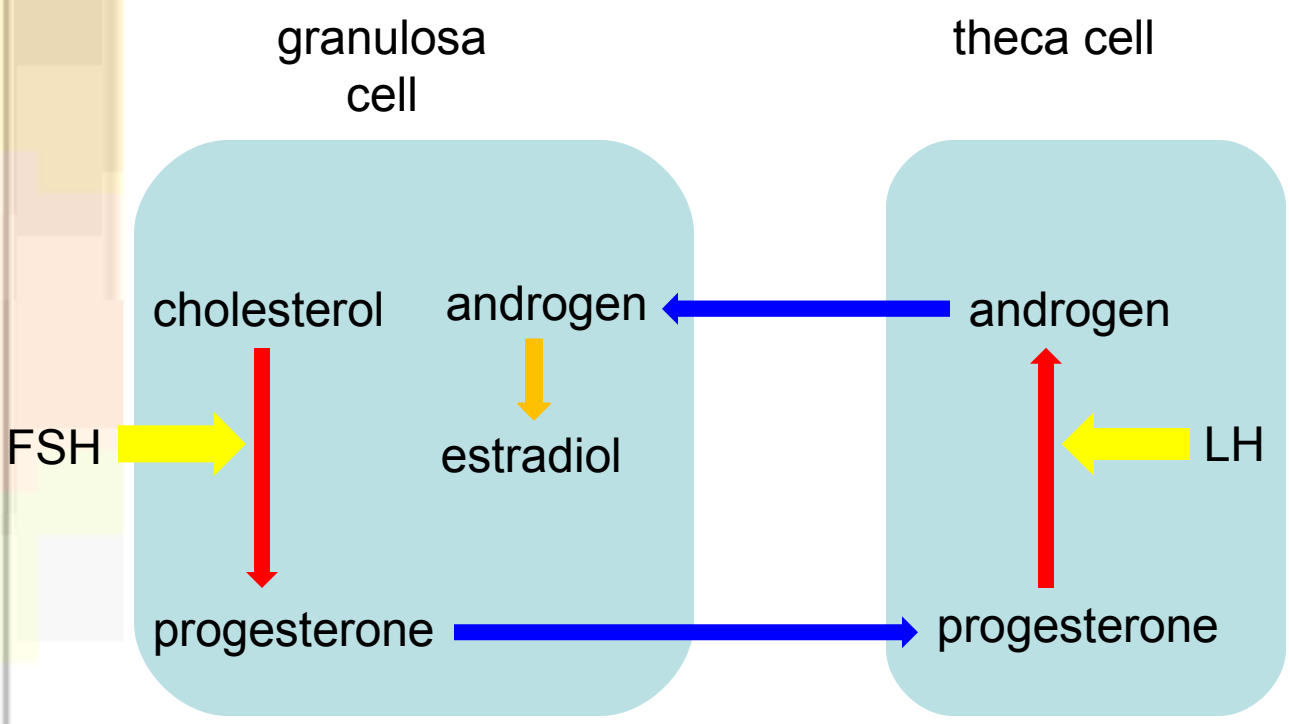
- Progesterone assay:
  - consistency and limited variability across control
  - Internal & external quality control
- Further studies required → whether threshold **1.5 ng/ml** applies to different assays ?

Why progesterone level rise?

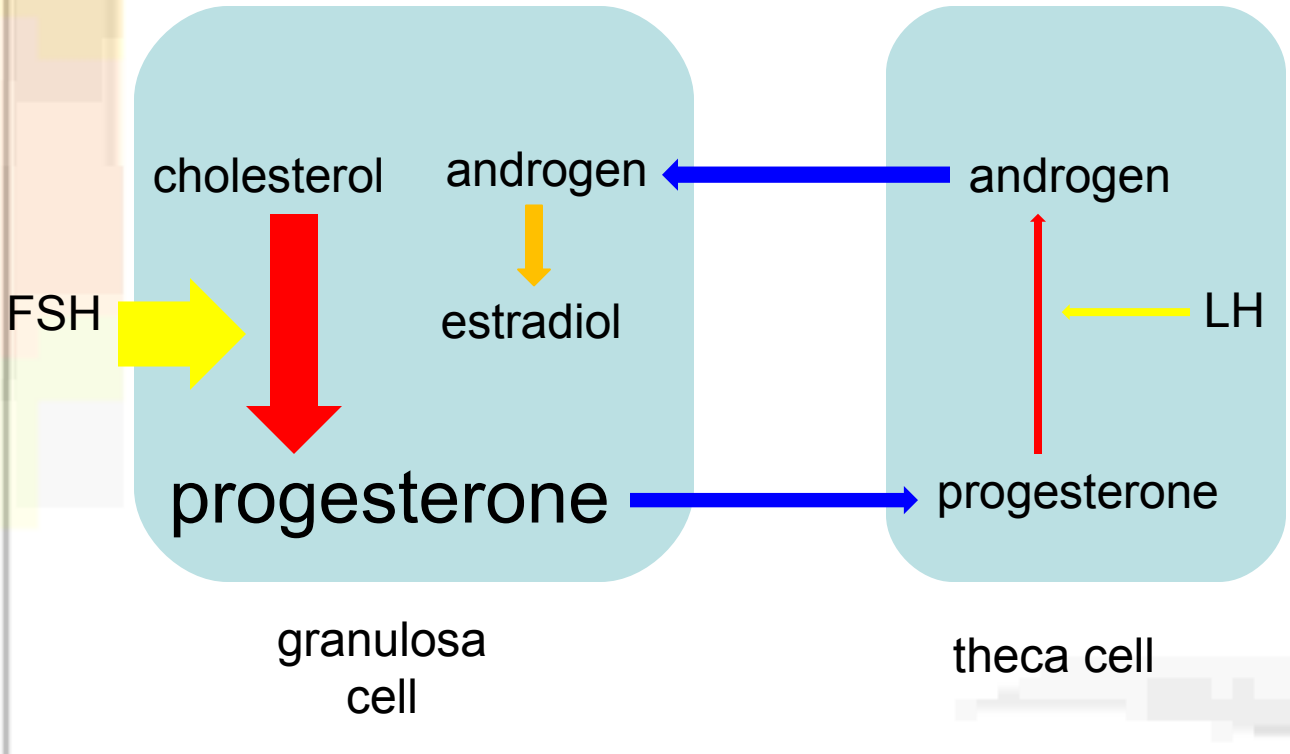
- Not luteinization of granulosa cell
- Higher daily FSH dose, E2 on hCG day and # of oocyte collated → significant association with P elevation
- Initial intense FSH stimulation → ↑ granulosa cell steroidogenic activity
  - Positive correlation between follicular phase P level with administered FSH dose and circulating FSH conc.

Filicori et al., 2002, Adonakis et al., 1998

2-cell, 2-gonadotropin



In COS cycle …


cholesterol
androgen
androgen
FSH
estradiol
LH
progesterone
progesterone
granulosa cell
theca cell

- Progesterone ↑ → influence endometrium, not the oocyte and embryo quality
  - Asynchrony between embryo and endometrium dating → reduced implantation
  - **MERiT**: ↑ oocyte production → implantation rate was **lower** when P > 4 nmol/l on hCG day
    - = 1.26 ng/ml
    - Incidence of higher P at the end of stimulation: rFSH > HP-hMG (24.1 vs 11.8%)

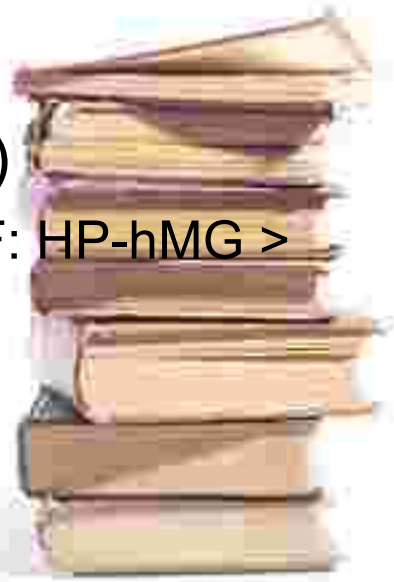
    → balanced LH activity
  - Oocyte donation: pregnancy rates of recipients not influenced by P level of donor at the end of stimulation *Melo et al., 2006*

require further investigation

Threshold value Optimize treatment

- continue to ET or cryopreserve the embryos and transfer in frozen-thawed cycle ?
- administrating hCG at an earlier timepoint in the follicular phase, prior to P elevation → beneficial ??
- gonadotropin choice (rFSH, HP-hMG)
  - Meta-analysis: pregnancy outcome in IVF: HP-hMG > rFSH

Al-Inany et al., 2009



Conclusion

- ↑ progesterone on hCG day is associated with reduced ongoing pregnancy rates.
- directly related to **total FSH dose** during COS and # of oocyte obtained
- **>1.5 ng/ml** associated with lower ongoing pregnancy rates following IVF/ICSI cycles irrespective of the GnRH analogue used for pituitary down-regulation

THE END