INTRODUCTION

- The endocrine control of ovarian function through gonadotropins - Follicular growth and differentiation

- ART- Folliculogenesis, ovulation and luteal phase support


Loutradis et al, J Steroid Biochem Mol Biol 2008 Nov;112(1-3):1-4
INTRODUCTION

- Specific modification of the endocrine environment by the pharmacologic agents used in ART cycles

- The use of hormonal assessments in order to control the ovarian hyperstimulation and predict the cycle outcome
INTRODUCTION

- Assessment of the required supply of exogenous FSH and LH in ART cycles
- Steroid output - Implantation and paracrine/autocrine effects on the cumulus-oocyte unit
FOLLICULOSIS

60 days

14 days

14 days

1mm. -> 4-6 mm. -> 20 mm.

Gougeon, 1982
PRIMORDIAL GERM CELL

mitosis ↓ 5-20. week

OOGONIUM

1. meiosis ↓ MSF

PRIMARY OOCYTE

(46, XX)

LH SURGE

OVULATION

SECONDARY OOCYTE

(23, X)

FERTILIZATION

HAPLOID OVUM

7.000.000

2.000.000

400.000
PRIMORDIAL FOLLICLE

DEVELOPING FOLLICLES

RECRUITMENT
(1-4. day)

FOLLICLES DESTINED TO OVULATE

SELECTION
(5-7.day)

DOMINANT FOLLICLE (8-12. day)

OVULATION (13-15. day)

atresia

atresia

atresia
inactive → inactive → atresia → Developing follicle → OVULATION → atresia
GnRH

HYPOPHYSIS

Hipotalamus

FSH

LH

OVARY

Testosterone

Estrogen

Progesterone
FSH

GnRH

OVARY

activin

inhibin

+ 

E₂

FSH

ovary

activin

inhibin

E₂
TWO CELL-TWO GONADOTROPIN THEORY
Dorrington and Armstrong, 1979

Hillier SG, Hol Hum Reprod 2009

Vegetti et al, RBM Online 2006
reproduction

- **FSH**
- **LH**

**HORMONE FREE PHASE**

**GRANULOSA LAYER**

**THECA**

**GRANULOSA LAYER**

**LUTEINISED GRANULOZOA CELLS**

- **PRIMARY FOLLICLE**
- **SECONDARY FOLLICLE**
- **TERTIARY FOLLICLE**
- **CORPUS LUTEUM**

**KÜBİK GRANÜLOZA HÜCRELERİ**

**oocyte**

**GRANULOSA LAYER**

**CUMULUS OOPHORUS**

**recruitment**

**selection**

**dominance**
Review

Significance of inhibin in reproductive pathophysiology and current clinical applications

Kumanov P, Reprod Biomed Online 2005
Figure 1
Diagram of the events occurring in the ovary and reproductive tract during the initial three weeks of the fertile menstrual cycle leading to natural reproduction in primates.
Overriding follicle selection in controlled ovarian stimulation protocols: Quality vs quantity
Richard L. Stouffer* and Mary B Zelinski-Wooten

Controlled Ovarian Stimulation Cycles IVF/ET

Figure 2
Diagram of events occurring in the ovary and in vitro during controlled ovarian stimulation cycles leading to assisted reproduction in primates. This chapter will discuss the methods and their limitations for increasing circulating levels of gonadotropins (FSH, LH, CG) to override the typical selection and maturation of a single "dominant" follicle in the natural menstrual cycle, thereby stimulating the development and maturation of multiple large follicles whose oocytes can be collected for in vitro manipulation (e.g., in vitro fertilization, IVF) prior to return to the reproductive tract (embryo transfer, ET) for pregnancy initiation.
FOLLICLE STIMULATING HORMONE (FSH)

- FSH - Folliculogenesis, recruitment, selection and dominance phases and follicular differentiation

- Trophic effect on granulosa cells, recruitment of the cohort at the early follicular phase

FSH TRESHOLD-FSH WINDOW

- **FSH TRESHOLD**: A certain amount of FSH is required to induce the follicular growth

- **FSH WINDOW**: Follicular growth is maintained as long as FSH is above the follicle’s threshold

- FSH is the crucial therapeutic agent to control the folliculogenesis in ART cycles (except hypohypo)

Atresia

Atresia

FSH EŞİK / PENCERE KAVRAMI

Ovulation

FSH
LH
Threshold value

FSH window

MONOOVULATION

MULTIPLE OVULATION

Baird DT, J Steroid Biochem 1987;27:15-23
GnRH

SPONTANEOUS

CC

GONADOTROPINS

LH

FSH

E2
Article
FSH and folliculogenesis: from physiology to ovarian stimulation

Vegetti et al, RBM Online 2006
The Science behind 25 Years of Ovarian Stimulation for *in Vitro* Fertilization

Nick S. Macklon, Richard L. Stouffer, Linda C. Giudice, and Bart C. J. M. Fauser

Department of Reproductive Medicine and Gynecology (N.S.M., B.C.J.M.F.), University Medical Center Utrecht, 3508 GA Utrecht, The Netherlands; Division of Reproductive Sciences (R.L.S.), Oregon National Primate Research Center, Oregon Health & Science University, Portland, Oregon 97229-3058; and Department of Obstetrics and Gynecology (L.C.G.), Stanford University School of Medicine, Stanford, California 94305
The impact of ovarian stimulation for IVF on the developing embryo

Margarida Avo Santos, Ewart W Kuijk and Nick S Macklon
Ovarian antral folliculogenesis during the human menstrual cycle: a review

Angela R. Baerwald, Gregg P. Adams, and Roger A. Pierson

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**Figure 4** Schematic representation of the FSH threshold (window) concept and follicle growth dynamics (recruitment, selection and dominance) during the follicular phase of the menstrual cycle. [Reproduced with permission from Elsevier, Fauser and Van Heusden, 1997, Endocrine Reviews, 18(1): 71–105; Originally adapted from Baird et al., 1987, J Steroid Biochem, 71(1): 15–23].

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Reproductive biology and IVF: ovarian stimulation and luteal phase consequences

Bart C.J.M. Fauser and Paul Devroey

1Center for Reproductive Medicine, Erasmus Medical Center, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands
2Center for Reproductive Medicine, University Hospital, Dutch-speaking Free University of Brussels (Vrije Universiteit), Brussels, Belgium

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Fig. 2. Abnormal corpus luteum function following ovarian stimulation for in vitro fertilization. Abnormally raised progesterone levels during the early luteal phase coincide with premature luteolysis. Adapted, with permission, from [48].
FOLLICLE STIMULATING HORMONE (FSH)

- FSH levels is not suitable to evaluate the adequacy of exogenous FSH supply

- Plasma FSH-not contributive enough to tailor a gonadotropin regimen in a proper manner

LUTEINISING HORMONE (LH)

- LH directly acts on granulosa cells as soon as cell differentiation is FSH-induced.

- LH ensures the synthesis of androgens through LH receptors located on Theca cells (Two cell-two gonadotropin theory).

- Pivotal role of LH on steroidogenesis in hypo-hypo patients.
LUTEINISING HORMONE (LH)

- Addition of LH increases estradiol thus preparing the endometrium for implantation
- CL – luteal phase support
- Minimal amount of LH is required for pregnancy (LH TRESHOLD)

LUTEINISING HORMONE (LH)

- High endogenous LH levels are associated with increased incidence of miscarriages and infertility (Endometrium/oocyte)

- Beyond a certain ceiling level, LH seems to have an inhibitory effect on cell growth and the granulosa proliferation initiating atresia of less mature follicles

Current concepts and novel applications of LH activity in ovarian stimulation

Marco Filicori, Graciela E. Cognigni, Patrizia Pocognoli, Walter Ciampaglia and Silvia Bernardi

Reproductive Endocrinology Center, University of Bologna, Via Massarenti 13, 40138 Bologna, Italy

Fig. 2. Correlation between the number of small preovulatory follicles (<10 mm diameter) and the total amounts of (a) follicle-stimulating hormone (FSH) and (b) luteinizing hormone (LH) activity administered to each patient. Reproduced, with permission, from [89].
LUTEINISING HORMONE (LH)

- Within the interval of LH threshold and ceiling, LH support is adequate for androgen and subsequent estradiol secretion thus participating in follicular growth
LUTEINISING HORMONE (LH)

- Determining plasma LH levels is not very informative to evaluate the actual consequences of LH preparations.
- During stimulated cycles plasma LH level determination is restricted to detection of endogenous LH surge.

The use of LH activity to drive folliculogenesis: exploring uncharted territories in ovulation induction

Marco Filicori¹,², Graciela E.Cognigni¹, Arafat Samara¹, Silvia Melappioni¹, Tiziana Perri¹, Barbara Cantelli¹, Lodovico Parmegiani¹, Giuseppe Pelusi² and Domenico DeAloysio²

Figure 1. Serum gonadotropin and gonadal steroid levels in two groups of 25 patients, each treated with either HP FSH or hMG for controlled ovarian stimulation. All patients had been suppressed with a long GnRH agonist regimen. E2 = estradiol; P = progesterone; T = testosterone. Reproduced with permission The Endocrine Society; Filicori, M., Cognigni, G.E., Taraborelli, S., Spettoli, D., Ciampaglia, W., Tabarelli De Fatis, C., Pocognoli, P., Cantelli, B. and Boschi, S. (2001) Luteinizing hormone activity in menotropins optimizes folliculogenesis and treatment in controlled ovarian stimulation. J. Clin. Endocrinol. Metab., 86, 337–343. Copyright owner, The Endocrine Society.
Benefits of luteinizing hormone activity in ovarian stimulation for IVF

Coomarasamy et al, 2008

<table>
<thead>
<tr>
<th>Study</th>
<th>HMG Events Total</th>
<th>rFSH Events Total</th>
<th>Rate difference M-H, Fixed, 95% CI</th>
<th>Rate difference M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen et al., (2006)</td>
<td>93 363</td>
<td>82 368</td>
<td>0.03 [-0.03, 0.10]</td>
<td>-0.07 [-0.28, 0.15]</td>
</tr>
<tr>
<td>Balasch et al., (2003)</td>
<td>6 30</td>
<td>8 30</td>
<td>0.03 [-0.03, 0.08]</td>
<td></td>
</tr>
<tr>
<td>EISG (2002)</td>
<td>80 365</td>
<td>67 386</td>
<td>0.03 [-0.13, 0.29]</td>
<td></td>
</tr>
<tr>
<td>Gordon et al., (2001)</td>
<td>9 29</td>
<td>9 39</td>
<td>0.02 [-0.14, 0.18]</td>
<td></td>
</tr>
<tr>
<td>Klini et al., (2003)</td>
<td>12 50</td>
<td>11 50</td>
<td>0.00 [-0.25, 0.25]</td>
<td></td>
</tr>
<tr>
<td>Ng et al., (2001)</td>
<td>4 20</td>
<td>4 20</td>
<td>0.08 [-0.02, 0.17]</td>
<td></td>
</tr>
<tr>
<td>Westergaard et al., (2001)</td>
<td>67 189</td>
<td>53 190</td>
<td>0.04 [0.004, 0.075]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 271/1076 234/1083
Heterogeneity: P = 0.93

Figure 1. Rate difference in live births between patients stimulated with human menopausal gonadotrophin (HMG) and patients stimulated with recombinant FSH (rFSH) using a long gonadotrophin-releasing hormone agonist protocol (based on data from Coomarasamy et al., 2008, by permission of Oxford University Press, published on behalf of the European Society of Human Reproduction and Embryology). CI = confidence interval; EISG = European and Israeli Study Group on highly purified menotropin versus recombinant follicle-stimulating hormone.

Tarlatzis et al, RBM Online 2009
Benefits of luteinizing hormone activity in ovarian stimulation for IVF

<table>
<thead>
<tr>
<th>Study</th>
<th>HMG Events</th>
<th>HMG Total</th>
<th>rFSH Events</th>
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<th>Rate difference M-H, Fixed, 95% CI</th>
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</thead>
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<tr>
<td>Andersen et al. (2006)</td>
<td>96</td>
<td>363</td>
<td>82</td>
<td>368</td>
<td>0.04 [-0.02, 0.10]</td>
</tr>
<tr>
<td>Balasch et al. (2003)</td>
<td>6</td>
<td>30</td>
<td>8</td>
<td>30</td>
<td>-0.07 [-0.28, 0.15]</td>
</tr>
<tr>
<td>ESIG (2002)</td>
<td>80</td>
<td>395</td>
<td>67</td>
<td>386</td>
<td>0.03 [-0.03, 0.08]</td>
</tr>
<tr>
<td>Gordon et al. (2001)</td>
<td>9</td>
<td>29</td>
<td>9</td>
<td>39</td>
<td>0.08 [-0.13, 0.29]</td>
</tr>
<tr>
<td>Hompes et al. (2006)</td>
<td>79</td>
<td>312</td>
<td>75</td>
<td>317</td>
<td>0.02 [-0.05, 0.08]</td>
</tr>
<tr>
<td>Kilani et al. (2003)</td>
<td>12</td>
<td>50</td>
<td>11</td>
<td>50</td>
<td>0.02 [-0.14, 0.18]</td>
</tr>
<tr>
<td>Ng et al. (2001)</td>
<td>4</td>
<td>20</td>
<td>4</td>
<td>20</td>
<td>0.00 [-0.25, 0.25]</td>
</tr>
<tr>
<td>Rashidi et al. (2005)</td>
<td>4</td>
<td>30</td>
<td>3</td>
<td>30</td>
<td>0.03 [-0.13, 0.20]</td>
</tr>
<tr>
<td>Westergaard et al. (2001)</td>
<td>67</td>
<td>189</td>
<td>53</td>
<td>190</td>
<td>0.08 [-0.02, 0.17]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>357/1418</strong></td>
<td><strong>312/1430</strong></td>
<td><strong>Rate difference M-H, Fixed, 95% CI</strong></td>
<td><strong>0.034 [0.003, 0.065]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Rate difference in live births between patients stimulated with human menopausal gonadotrophin (HMG) and patients stimulated with recombinant FSH (rFSH) using a long gonadotrophin-releasing hormone agonist protocol (based on data from Al-Inany et al., 2008). CI = confidence interval; EISG = European and Israeli Study Group on highly purified menotropin versus recombinant follicle-stimulating hormone.

Tarlatzis et al, RBM Online 2009
Benefits of luteinizing hormone activity in ovarian stimulation for IVF

Figure 3. Rate difference in live births between patients stimulated with FSH+LH and patients stimulated with FSH only (based on data from Kolibianakis et al., 2007, by permission of Oxford University Press, published on behalf of the European Society of Human Reproduction and Embryology). CI = confidence interval.
Role of the endocrine profile for the achievement of pregnancy with IVF

Table 2. Association of endogenous LH concentrations and the probability of ongoing pregnancy above 12 weeks in normo-ovulatory or World Health Organization II patients undergoing IVF using gonadotrophin-releasing hormone analogues for inhibition of premature LH surge.

<table>
<thead>
<tr>
<th>Study</th>
<th>Endogenous LH concentrations (IU/l)</th>
<th>Ongoing pregnancy (20 weeks) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 8 of stimulation</td>
<td></td>
</tr>
<tr>
<td>Westergaard et al., 2000</td>
<td>&lt;0.5</td>
<td>98 (32.9, 24-40)</td>
</tr>
<tr>
<td></td>
<td>≥0.5</td>
<td>102 (32.2, 24-39)</td>
</tr>
<tr>
<td></td>
<td>15 (15.3)</td>
<td>27 (26.5)</td>
</tr>
<tr>
<td></td>
<td>Day 7 of stimulation</td>
<td></td>
</tr>
<tr>
<td>Balasch et al., 2001*</td>
<td>144 (34.0, 23-42)</td>
<td>58 (40.3)</td>
</tr>
<tr>
<td></td>
<td>Average of 4–5 assessments starting from day 5 of stimulation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;3</td>
<td>32 (34.4)</td>
</tr>
<tr>
<td></td>
<td>116 (34.4)</td>
<td>50 (34.3)</td>
</tr>
<tr>
<td></td>
<td>40 (34.5)</td>
<td>16 (32.0)</td>
</tr>
<tr>
<td></td>
<td>Day 8 of stimulation</td>
<td></td>
</tr>
<tr>
<td>Humaidan et al., 2002</td>
<td>&lt;0.5</td>
<td>24 (31.4 ± 0.6)</td>
</tr>
<tr>
<td></td>
<td>≥0.5</td>
<td>108 (30.9 ± 0.4)</td>
</tr>
<tr>
<td></td>
<td>8 (33.3)</td>
<td>48 (44.4)</td>
</tr>
<tr>
<td></td>
<td>Ongoing pregnancy (12 weeks) (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;0.5</td>
<td>14 (12.6)</td>
</tr>
<tr>
<td></td>
<td>≥0.5</td>
<td>17 (14.3)</td>
</tr>
<tr>
<td></td>
<td>119 (33.7 ± 9)</td>
<td>151 (33.6 ± 4.7)</td>
</tr>
<tr>
<td></td>
<td>Day of HCG</td>
<td></td>
</tr>
<tr>
<td>Merviel et al., 2004</td>
<td>&lt;0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>119 (33.7 ± 9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17 (14.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 8 of stimulation</td>
<td></td>
</tr>
<tr>
<td>Kolibianakis et al., 2004</td>
<td>&lt;0.5</td>
<td>29 (31.8 ± 0.6)</td>
</tr>
<tr>
<td></td>
<td>≥0.5</td>
<td>62 (32.1 ± 0.4)</td>
</tr>
<tr>
<td></td>
<td>14 (56.0)</td>
<td>25 (40.3)</td>
</tr>
</tbody>
</table>

Differences between groups are not significant with the exception of Kolibianakis et al. 2004b (modified from Kolibianakis et al. 2006, by permission of Oxford University Press, published on behalf of the European Society for Human Reproduction and Embryology). HCG = human chorionic gonadotrophin. Receiver operating characteristic curve analysis found no correlation between LH concentration and conception.

Humaidan and Kolibianakis → LH is associated with ongoing pregnancy rates

Kolibianakis et al, Reprod Biomed Online 2009
STEROID PROFILES THROUGH ART CYCLES

ESTRADIOL

- Cervical mucus production, endometrial proliferation and the induction of midcycle LH surge
  

- A good indicator of granulosa cell differentiation and used as an index of follicular maturity
  

- Ovarian response prediction
  
  Loutradis et al, J Steroid Biochem Mol Biol 2008 Nov;112(1-3):1-4
STEROID PROFILES THROUGH ART CYCLES

 Estradiol

- To calibrate the gonadotropin doses in conjunction with USG data in stimulated cycles

- Monitorization of the ART cycle in order to detect the risk of OHSS and decide for cycle or transfer cancellation
ESTRADIOL-GnRHa-GNRH ANTAGONISTS

- To assess the effectiveness of the hypophyseal desensitization (<50pg/mL)

- The plasma estradiol pattern of GnRH antagonist treatment is not similar with that of GnRH-a (LOWER PREGNANCY RATES)
## Table 1. Characteristics of the studies that evaluated the association between oestradiol and pregnancy achievement (modified from Kosmas et al. 2004, by permission of Oxford University Press, published on behalf of the European Society of Human Reproduction and Embryology).

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Sample size (patients/ cycles)</th>
<th>Type of down-regulation</th>
<th>Gonadotrophin regimen</th>
<th>Method of oestradiol assessment</th>
<th>Primary outcome</th>
<th>Type of association between oestradiol concentrations on the day of HCG administration and pregnancy achievement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mettler and Tavmergen, 1989</td>
<td>94/94</td>
<td>Decapeptyl long protocol</td>
<td>HMG</td>
<td>Radioimmunoassays—monoclonal-antibody technique (oestradiol Biermann, Bad Nauheim) Radioimmunoassays (Tandem, Hybritech, San Diego, CA, USA)</td>
<td>Pregnancy rate$^{*}$ per oocyte retrieval</td>
<td>Negative</td>
</tr>
<tr>
<td>Chenette et al., 1990</td>
<td>141/141</td>
<td>Leuprolide acetate long protocol</td>
<td>HMG</td>
<td>Radioimmunoassays (Diagnostic Products Corp., Los Angeles, CA, USA)</td>
<td>Clinical pregnancy per oocyte retrieval</td>
<td>Positive</td>
</tr>
<tr>
<td>Dor et al., 1992</td>
<td>9/216</td>
<td>Decapeptyl long protocol</td>
<td>HMG</td>
<td>Radioimmunoassays (Pantex, Santa Monica, CA, USA)</td>
<td>Clinical pregnancy rate per oocyte retrieval</td>
<td>No association</td>
</tr>
<tr>
<td>Gelety and Buyalos, 1995</td>
<td>50/50</td>
<td>Leuprolide acetate long protocol</td>
<td>HMG</td>
<td>Radioimmunoassays (Pantex, Santa Monica, CA, USA)</td>
<td>Clinical pregnancy rate per embryo transfer</td>
<td>Negative</td>
</tr>
<tr>
<td>Simon et al., 1995</td>
<td>164/177</td>
<td>Leuprolide acetate long protocol</td>
<td>FSH + HMG</td>
<td>Immuno-enzymatic assay (MEIA, Imm. Abbott Scientific SA)</td>
<td>Pregnancy rate per cycle started</td>
<td>No association</td>
</tr>
<tr>
<td>Sharara and McClamrock, 1999</td>
<td>106/106</td>
<td>Leuprolide acetate long/short protocol</td>
<td>FSH + HMG</td>
<td>Radioimmunoassays (Coat-a-Count Diagnostic Products Corporation, Los Angeles, CA, USA)</td>
<td>Clinical pregnancy per oocyte retrieval</td>
<td>No association</td>
</tr>
<tr>
<td>Yu Ng et al., 2000</td>
<td>1122/1122</td>
<td>Buserelin long protocol</td>
<td>HMG</td>
<td>Not mentioned (Diagnostic Products Corp., Los Angeles, CA, USA)</td>
<td>Clinical pregnancy rate per embryo transfer</td>
<td>Negative</td>
</tr>
<tr>
<td>Papageorgiou et al., 2002</td>
<td>762/905</td>
<td>Decapeptyl short protocol</td>
<td>iFSH ( follitropin $\omega/\beta$)</td>
<td>Immuno-enzymatic assay (Bayer, Germany)</td>
<td>Pregnancy rate$^{*}$</td>
<td></td>
</tr>
<tr>
<td>Chen et al., 2003</td>
<td>697/697</td>
<td>Leuprolide acetate long protocol</td>
<td>FSH</td>
<td>Not mentioned</td>
<td>Clinical pregnancy per embryo transfer</td>
<td>No association</td>
</tr>
</tbody>
</table>
STEROID PROFILES THROUGH ART CYCLES

PROGESTERONE

- To detect the hypophyseal desensitization to make sure that the corpus luteum is not still active

- Plasma P levels in early and late follicular phases are recently assessed to predict the cycle outcome
STEROID PROFILES THROUGH ART CYCLES

- Adverse effect on folliculogenesis, oocyte quality and pregnancy outcome (early follicular phase)

- Despite suppression by GnRH-a, a small increment in P has been reported in 20% of the stimulated cycles (late follicular phase, endometrium)

- Premature endogenous LH surges related with subsequent luteinization of granulosa cells
Current concepts and novel applications of LH activity in ovarian stimulation

Marco Filicori, Graciela E. Cognigni, Patrizia Pocognoli, Walter Ciampaglia and Silvia Bernardi

Reproductive Endocrinology Center, University of Bologna, Via Massarenti 13, 40126 Bologna, Italy

**Fig. 1.** Correlation between serum progesterone (P) levels during ovulation induction and the total amounts of (a) follicle-stimulating hormone (FSH) activity and (b) luteinizing hormone (LH) activity administered to each patient. P levels were determined daily throughout gonadotropin administration in each patient and expressed as area under the curve. Reproduced, with permission, from [89].
PROGESTERONE RISE IN FOLLICULAR PHASE

- P450 side-chain cleavage enzyme is required for de novo P synthesis

CL, THECA INTERNA CELLS OF THE FOLLICLE, ADRENAL GLAND

Residual activity of CL, developing follicle, adrenal gland activity, indirect sign of ovarian aging, different FSH isoforms

Al-Azemi et al, Reprod Biomed Online 2012 Apr;24(4):381-8
STEROID PROFILES THROUGH ART CYCLES

PROGESTERONE

- EXPOSURE TO LARGE DOSES OF EXOGENOUS FSH

- Potential adverse effect and plasma P cut off values for a decision making for the cycle outcome

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

C.A.Venetis¹, E.M.Kolibianakis¹, E.Papanikolaou¹, J.Bontis¹, P.Devroey² and B.C.Tarlatzis¹

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Table 3: Pregnancy outcomes examined in the studies included in the systematic review

<table>
<thead>
<tr>
<th>Study number</th>
<th>Authors and year</th>
<th>Pregnancy outcome examined*a</th>
<th>Definition</th>
<th>OR (CIs)</th>
<th>Association of progesterone elevation with pregnancy outcome examined</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Edelstein <em>et al.</em> (1990)</td>
<td>Clinical pregnancy per hCG</td>
<td>Not reported</td>
<td>1.09 (0.43–2.79)</td>
<td>No association</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ongoing pregnancy per hCG</td>
<td>Not reported</td>
<td>1.03 (0.38–2.83)</td>
<td>No association</td>
</tr>
<tr>
<td>2</td>
<td>Silverberg <em>et al.</em> (1991)</td>
<td>Clinical pregnancy per hCG</td>
<td>Fisher's hCG by USS at 7 wks of gestation</td>
<td>0.16 (0.01–2.86)</td>
<td>No association</td>
</tr>
<tr>
<td>3</td>
<td>Check <em>et al.</em> (1993a)</td>
<td>Live birth per oocyte retrieval</td>
<td>Live birth</td>
<td>0.18 (0.06–0.51)</td>
<td>Negative association</td>
</tr>
<tr>
<td>4</td>
<td>Check <em>et al.</em> (1994)</td>
<td>Live birth per oocyte retrieval</td>
<td>Viable infant at delivery</td>
<td>0.46 (0.15–1.43)</td>
<td>No association</td>
</tr>
<tr>
<td>5</td>
<td>Shechter <em>et al.</em> (1994)</td>
<td>Clinical pregnancy per ET</td>
<td>Sac at USS</td>
<td>1.22 (0.47–3.16)</td>
<td>No association</td>
</tr>
<tr>
<td>6</td>
<td>Hofmann <em>et al.</em> (1996)</td>
<td>Ongoing pregnancy per ET</td>
<td>&gt; 20 wks/delivered</td>
<td>1.48 (0.69–3.19)</td>
<td>No association</td>
</tr>
<tr>
<td>7</td>
<td>Miller <em>et al.</em> (1996) (Group A)</td>
<td>Clinical pregnancy per ET</td>
<td>Fisher's hCG by USS at 7 wks of gestation</td>
<td>0.44 (0.16–1.18)</td>
<td>No association</td>
</tr>
<tr>
<td></td>
<td>Miller <em>et al.</em> (1996) (Group B)</td>
<td>Clinical pregnancy per ET</td>
<td>Fisher's hCG by USS at 7 wks of gestation</td>
<td>1.03 (0.53–2.00)</td>
<td>No association</td>
</tr>
<tr>
<td>8</td>
<td>Ubaldi <em>et al.</em> (1996b)</td>
<td>Clinical pregnancy per hCG</td>
<td>Fisher's hCG by USS at 7 wks of gestation</td>
<td>1.87 (0.24–14.65)</td>
<td>No association</td>
</tr>
<tr>
<td>9</td>
<td>Moffitt <em>et al.</em> 1997</td>
<td>Clinical pregnancy per ET</td>
<td>Not reported</td>
<td>1.16 (0.59–2.28)</td>
<td>No association</td>
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<tr>
<td>10</td>
<td>Urman <em>et al.</em> (1999)</td>
<td>Ongoing pregnancy per ET</td>
<td>&gt; 20 wks</td>
<td>1.65 (0.84–3.25)</td>
<td>No association</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical pregnancy per ET</td>
<td>Fisher's hCG by USS at 6 wks of gestation</td>
<td>1.42 (1.07–1.88)</td>
<td>No association</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ongoing pregnancy per ET</td>
<td>&gt; 12 wks</td>
<td>1.27 (0.94–1.72)</td>
<td>No association</td>
</tr>
<tr>
<td>11</td>
<td>Bosch <em>et al.</em> (2003)</td>
<td>Clinical pregnancy per hCG</td>
<td>Fisher's hCG by USS at 6–7 wks of gestation</td>
<td>0.27 (0.10–0.72)</td>
<td>Negative association</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ongoing pregnancy per hCG</td>
<td>&gt; 20 wks</td>
<td>0.29 (0.11–0.79)</td>
<td>Negative association</td>
</tr>
<tr>
<td>12</td>
<td>Martinez <em>et al.</em> (2004)</td>
<td>Clinical pregnancy per hCG</td>
<td>Sac at USS at 6 wks of gestation</td>
<td>0.89 (0.58–1.35)</td>
<td>No association</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delivery per hCG</td>
<td>Delivery</td>
<td>0.98 (0.62–1.55)</td>
<td>No association</td>
</tr>
</tbody>
</table>
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

C.A. Venetis¹, E.M. Kolibianakis¹,³, E. Papanikolaou¹, J. Bontis¹, P. Devroey² and B.C. Tarlatzis¹

<table>
<thead>
<tr>
<th>Study</th>
<th>Progesterone elevation n/N</th>
<th>No progesterone elevation n/N</th>
<th>OR 95% CI</th>
<th>Effect</th>
<th>Lower</th>
<th>Upper</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edelstein et al. (1990)</td>
<td>9/29</td>
<td>21/72</td>
<td>1.09</td>
<td>1.09</td>
<td>0.43</td>
<td>2.79</td>
<td>0.85</td>
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<tr>
<td>Silverberg et al. (1991)</td>
<td>0/14</td>
<td>17/99</td>
<td>0.16</td>
<td>0.16</td>
<td>0.10</td>
<td>2.86</td>
<td>0.16</td>
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<tr>
<td>Ubaldi et al. (1996b)</td>
<td>2/5</td>
<td>5/19</td>
<td>1.87</td>
<td>1.87</td>
<td>0.24</td>
<td>14.65</td>
<td>0.55</td>
</tr>
<tr>
<td>Bosch et al. (2003)</td>
<td>8/34</td>
<td>27/51</td>
<td>0.27</td>
<td>0.27</td>
<td>0.10</td>
<td>0.72</td>
<td>0.01</td>
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<tr>
<td>Martinez et al. (2004)</td>
<td>70/197</td>
<td>69/180</td>
<td>0.89</td>
<td>0.89</td>
<td>0.58</td>
<td>1.35</td>
<td>0.57</td>
</tr>
<tr>
<td>Combined (fixed effects model)</td>
<td>89/279</td>
<td>139/421</td>
<td>0.75</td>
<td>0.75</td>
<td>0.53</td>
<td>1.06</td>
<td>0.10</td>
</tr>
<tr>
<td>(heterogeneity: P = 0.12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2:** OR of clinical pregnancy rate per patient reaching hCG administration for final oocyte maturation
Role of the endocrine profile for the achievement of pregnancy with IVF

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>P Elevation Events</th>
<th>Total Events</th>
<th>No P Elevation Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M–H, Fixed, 95% CI</th>
<th>Risk Ratio M–H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosch 2003</td>
<td>8</td>
<td>34</td>
<td>27</td>
<td>51</td>
<td>19.2%</td>
<td>0.44 [0.23, 0.86]</td>
<td></td>
</tr>
<tr>
<td>Edelstein 1990</td>
<td>9</td>
<td>29</td>
<td>21</td>
<td>72</td>
<td>10.7%</td>
<td>1.06 [0.55, 2.04]</td>
<td></td>
</tr>
<tr>
<td>Martinez 2004</td>
<td>70</td>
<td>197</td>
<td>69</td>
<td>180</td>
<td>64.1%</td>
<td>0.93 [0.71, 1.21]</td>
<td></td>
</tr>
<tr>
<td>Silverberg 1991</td>
<td>0</td>
<td>14</td>
<td>17</td>
<td>99</td>
<td>4.1%</td>
<td>0.19 [0.01, 3.00]</td>
<td></td>
</tr>
<tr>
<td>Ubaldi 1996</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>19</td>
<td>19%</td>
<td>1.52 [0.41, 5.64]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>279</td>
<td>421</td>
<td>100%</td>
<td></td>
<td>0.83</td>
<td>[0.66, 1.04]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 89, 139

Heterogeneity: Chi² = 6.60, df = 4 (P = 0.16); I² = 39%
Test for overall effect: Z = 1.62 (P = 0.11)

Figure 1. Relative risk for clinical pregnancy per patient reaching human chorionic gonadotrophin administration for final oocyte maturation according to the presence of progesterone (P) elevation. CI = confidence interval.
ANDROGENS

- A stimulatory effect on granulosa cell proliferation, follicular recruitment
  

- Flare-up effect may be related with increased androgen production in ART cycles

- No significant evidence that the oocyte quality is reduced

The role of androgens in follicle maturation and ovulation induction: friend or foe of infertility treatment?

Norbert Gleicher1,2,3*, Andrea Weghofer1,4 and David H Barad1,2,5

Figure 1 Synergism between androgen and FSH. The figure depicts the potential synergism of androgens and follicle stimulating hormone (FSH) during early folliculogenesis. Here in detail depicted only on pre-antral and early antral follicles, the figure is meant to demonstrate the high concentration of androgen receptor (AR) at pre-antral to antral stages, declining thereafter [10,15-17]. High concentrations of AR at these stages are strongly suggestive of peak androgen effects at these stages of folliculogenesis. Androgens primarily affect granulosa cells [21] through transcriptional regulation via AR but do so also via non-genomic ways, with ligand-activated AR modulating FSH activity in granulosa cells. The box in the right lower quadrant schematically demonstrates the synergism between androgens and FSH, based on Lenie and Smits [10], practically creating a feed back loop. Synergism between androgens and FSH suggests the possibility of new pharmacologic approaches to ovulation induction, utilizing this synergism in early folliculogenesis to improve oocyte number and quality. For further detail, see text.
ANDROGENS

- Determination of plasma androgens is not required to be routinely included in monitorization of ART cycles, may be worthwhile in clinical research.


INHIBIN A AND B

- Heterodimers secreted from granulosa cells following FSH stimulation and regulate FSH secretion by negative feedback.

- Small antral follicles potentially secrete Inhibin B whereas preovulatory follicles may secrete Inhibin A.

- Serum Inhibin B in the early follicular phase is a valuable tool to evaluate the size of the follicular cohort.

*Kumanov et al, Reprod Biomed Online 2005 Jun;10(6):786-812*
Review

Significance of inhibin in reproductive pathophysiology and current clinical applications

Kumanov et al, 2005
INHIBIN A AND B

- Inhibin B (4-6. day of FSH stimulation)- Early indicator of the number of recruited follicles destined to form mature oocytes
  

- Decision making regarding cycle cancellation or modulating gonadotropin dose
  
  Eldar-Geva et al, Hum Reprod 2002 Sep;17(9):2331-7
ANTİMÜLLERIAN HORMONE

- A member of transforming growth factor beta family produced by granulosa cells of secondary, preantral, small antral follicles up to 6 mm

- Serum AMH levels are correlated with antral follicle numbers and cycle day independent

  *Broer SL et al, Fertil Steril 2008*

  *La Marca et al, Hum Reprod 2006 Dec;21(12):3103-7*

- A good predictor of ovarian reserve both for poor and hyperresponders

  *La Marca et al, Hum Reprod 2007 Mar;22(3):766-71*
ANTİMÜLLERIAN HORMONE

- Its performance to predict nonpregnancy is poor since it represents only the size of the FSH-sensitive follicles
  - Muttukrishna et al, BJOG 2005,112:1384
  - Kwee et al, Fertil Steril 2007

- The association with oocyte or embryo quality is much less clear

- Plasma AMH measurement during stimulated cycles is not actually recommended
CONCLUSIONS

- The endocrine characteristics of ART cycles are mainly related with the therapeutic agents used for COH.

- Although it is clear that FSH is required for every stimulation, plasma FSH levels are not predictive enough for the adequacy of exogenous FSH supply.

- Plasma LH levels determination is restricted to hypophyseal desensitization.
CONCLUSIONS

- There is no evidence that detection of LH levels could be useful for patients who require some addition of LH during ART cycles.

- Plasma estradiol level determination is used in conjunction to USG to assess the follicular growth.

- Determination of P levels may be restricted to hypophyseal desensitization.
CONCLUSIONS

- Plasma androgens are not routinely determined except for research purposes.
- Serum Inhibin B in the early follicular phase is a valuable tool to evaluate the size of the follicular cohort.
- AMH is a good predictor of ovarian reserve both for poor and hyperresponders.