Controlled Ovarian Hyperstimulation vs. personalized preparation of the ovaries for egg collection

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Wolfson Medical Center, Holon
Sackler Faculty of Medicine,
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No conflict of interest
Induction of ovulation for in-vitro fertilization using Buserelin and gonadotropins

RN Porter, W Smith, IL Craft, NA Abdulwahid, HS Jacobs

The Lancet (1984)

LHRH Analogue HOE 766

FSH or hMG

Ultrasound Scans

Menses

hCG

EC

ET

0 14 30 32 34 36 Days
The use of GnRH agonists in IVF practice:
• Lower cancellation rates
• An increased number of oocytes retrieved
• Higher pregnancy and live birth rates

The introduction of GnRH antagonists:
• Allowed for less aggressive and more individualized protocols
• Increased safety
• Avoided the initial flare up and subsequent estrogen deprivation symptoms

Hughes EG et al., Fertil Steril 1992
Frydman R et al., Fertil Steril 1991
Diedrich K et al., Hum Reprod 1994
Key players in successful implantation

- The embryo
- The endometrium
- The maternal immune system

All affected by the way we stimulate the ovaries
Success of IVF is clearly dependent on the size and quality of the oocyte cohort.

- Type of gonadotropins given
- Dose of gonadotropins given
- Regimen of pituitary suppression used
- Type of ovulatory trigger
- Administration of adjuvant agents
Types of stimulated cycles in IVF

- Fresh IVF cycle
- Segmented IVF cycle
Success of IVF is clearly dependent on the size and quality of the oocyte cohort

- Type of gonadotropins given
- Doses of gonadotropins given
- Regimen of pituitary suppression used
- Type of ovulatory trigger
- Administration of adjuvant agents
Ovarian stimulation for IVF: what is optimal?

- Poor response: 1-5
- Optimal: 8-15
- Disturbed risk/benefit balance: >15

Oocyte number
Association between the number of eggs and live birth in IVF treatment: an analysis of 400,135 treatment cycles
Oocyte number as a predictor for ovarian hyperstimulation syndrome and live birth: an analysis of 256,381 in vitro fertilization cycles
Success of IVF is clearly dependent on the size and quality of the oocyte cohort.

Does the size of the cohort affect oocyte quality?
Success of IVF is clearly dependent on the size and quality of the oocyte cohort

- Oocyte – largest cell in the female body
- Cytoplasmic maturation and quality
- Sufficient to support normal chromosome segregation
- Not necessarily successful implantation
- Limited access to study oocyte quality
Natural versus Stimulated Folliculogenesis and Embryonic Aneuploidy

- **Prospective observational**
- **Historic Control**
- **Ages 21-49 years**
- **Follicular diameter at retrieval ~ 21 mm**
- **hCG induced follicular maturation**

Hong ASRM 2014
Aneuploidy vs. No. Oocytes Retrieved

<table>
<thead>
<tr>
<th>Number of oocytes retrieved</th>
<th>&lt;38 years old</th>
<th>≥38 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 oocytes</td>
<td>51.5%</td>
<td>65.2%</td>
</tr>
<tr>
<td>5-9 oocytes</td>
<td>29.9%</td>
<td>64.2%</td>
</tr>
<tr>
<td>10-14 oocytes</td>
<td>28.7%</td>
<td>59.1%</td>
</tr>
<tr>
<td>15-20 oocytes</td>
<td>30.4%</td>
<td>56.4%</td>
</tr>
<tr>
<td>&gt;20 oocytes</td>
<td>28.4%</td>
<td>53.9%</td>
</tr>
</tbody>
</table>

Source: RMANJ, 1st CCS cycle per patient 2010-2012

4,674 embryos from 780 patients
1,792 embryos from 497 patients
Embryonic aneuploidy in natural and stimulated cycles

Embryonic aneuploidy rates do not differ:
• In natural cycles
• Following mild stimulation
• Following intense stimulation

These data do not support a causative role for gonadotropin stimulation in embryonic aneuploidy

~50% of euploid blastocysts do not implant...
Success of IVF is clearly dependent on the **size** and **quality** of the oocyte cohort

- Type of gonadotropins given
- Doses of gonadotropins given
- Regimen of pituitary suppression used
- Type of ovulatory trigger
- Administration of adjuvant agents
A synergic and synchronized action of FSH and LH at the follicular level is crucial to achieve an adequate steroidogenesis for proper oocyte maturation and endometrial development.

In the ovarian stimulation for IVF context:
- FSH is related to ovarian response in terms of oocyte yield
- LH modulates follicular steroidogenesis

LH action induces androgen synthesis for their aromatization into estrogens.
Type of gonadotropin used

- The physiologic role of LH during the follicular phase of a natural cycle is unquestionable.

- Its impact during a COS cycle remains controversial.

- To date there seems to be no clear benefit obtained by combining LH and FSH in unselected normogonadotrophic patients.

Kolibianakis et al., Hum Reprod Update 2006
Mochtar et al., Cochrane Database Syst Rev 2007
Implantation rate

- p=0.84
  OR: 1.03 (0.73-1.47)

- p=0.03
  OR: 1.56 (1.04-2.33)

Ongoing Pregnancy rate per Randomized patient (ITT analysis)

- OR: 1.0 (0.65-1.57); p=1.0
- OR: 1.49 (0.93-2.38); p=0.09

Bosch et al (2011) Fertil Steril 95; 1031-6
ASRM 2008 General Program Price Paper Award
Rec h-LH in patients with advanced reproductive age: a meta-analysis

Forest plot of embryo implantation

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size (embryos)</th>
<th>Measure (CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrs 2004</td>
<td>262</td>
<td>1.43 (0.75; 2.69)</td>
<td>14.11%</td>
</tr>
<tr>
<td>Humaidan 2004</td>
<td>63</td>
<td>3.71 (1.04; 13.22)</td>
<td>2.3%</td>
</tr>
<tr>
<td>Fabregues 2005</td>
<td>320</td>
<td>0.96 (0.55; 1.67)</td>
<td>22.21%</td>
</tr>
<tr>
<td>NyboeAndersen 2008</td>
<td>170</td>
<td>0.82 (0.4; 1.67)</td>
<td>14.48%</td>
</tr>
<tr>
<td>Barrenetxea 2008</td>
<td>184</td>
<td>1.21 (0.38; 3.74)</td>
<td>4.72%</td>
</tr>
<tr>
<td>Mattoros 2009</td>
<td>285</td>
<td>1.72 (0.98; 3.37)</td>
<td>11.41%</td>
</tr>
<tr>
<td>Bosch 2011</td>
<td>526</td>
<td>1.58 (1.04; 2.4)</td>
<td>30.78%</td>
</tr>
<tr>
<td>Synthesis</td>
<td>1810</td>
<td>1.36 (1.05; 1.78)</td>
<td>100%</td>
</tr>
</tbody>
</table>

Forest plot of clinical pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size (patients)</th>
<th>Measure (CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrs 2004</td>
<td>88</td>
<td>2.91 (1.14; 7.42)</td>
<td>6.73%</td>
</tr>
<tr>
<td>Humaidan 2004</td>
<td>39</td>
<td>1.75 (0.42; 7.35)</td>
<td>3.64%</td>
</tr>
<tr>
<td>Fabregues 2005</td>
<td>120</td>
<td>0.93 (0.45; 1.83)</td>
<td>18.99%</td>
</tr>
<tr>
<td>NyboeAndersen 2008</td>
<td>100</td>
<td>0.59 (0.25; 1.42)</td>
<td>16.87%</td>
</tr>
<tr>
<td>Barrenetxea 2008</td>
<td>84</td>
<td>1.15 (0.41; 2.19)</td>
<td>8.68%</td>
</tr>
<tr>
<td>Mattoros 2009</td>
<td>131</td>
<td>2.14 (0.9; 5.12)</td>
<td>8.89%</td>
</tr>
<tr>
<td>Bosch 2011</td>
<td>340</td>
<td>1.49 (0.93; 2.38)</td>
<td>36.19%</td>
</tr>
<tr>
<td>Synthesis</td>
<td>902</td>
<td>1.37 (1.03; 1.83)</td>
<td>100%</td>
</tr>
</tbody>
</table>

Conclusion: type of gonadotropin used

The addition of LH activity to FSH induces variations in follicular steroidogenesis that may benefit older patients (>35 years) through a higher synthesis of androgens, which are diminished in older women.

Apart from the arbitrary criteria of age, there is a lack of an appropriate biomarker to determine the need of LH in a COS cycle in a given patient.
Success of IVF is clearly dependent on the **size** and **quality** of the oocyte cohort

- Type of gonadotropins given
- Doses of gonadotropins given
- Regimen of pituitary suppression used
- Type of ovulatory trigger
- Administration of adjuvant agents
## Long Agonists vs. GnRH Antagonists: meta-analysis of RCTs:

<table>
<thead>
<tr>
<th></th>
<th>No. of RCTs</th>
<th>Ongoing pregnancy/Live birth rate</th>
<th>Severe OHSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Inany et al. Cochrane Colab. 2011</td>
<td>45</td>
<td>OR= 0.86, 95% CI 0.69-1.08</td>
<td>OR= 0.43, 95% CI 0.33-0.57</td>
</tr>
</tbody>
</table>

**Agonist** VS. **Antagonist**
(a) Synchronized follicular development after FSH administration in a long GnRH agonist regimen and (b) Follicular development in a fixed day 6 GnRH antagonist regimen without OC pre-treatment

Conclusion: regimen of pituitary suppression used

GnRH antagonist cycles offer similar live birth rates with improved safety compared with the GnRH-a long protocol.

Nevertheless, patients with endometriosis, or those with accelerated folliculogenesis, could benefit from a GnRH-a long protocol, owing to the better control of endogenous gonadotropins and follicular growth.

There is a lack of an appropriate biomarker to determine a-priori which patients would benefit from a GnRH-a protocol.
Success of IVF is clearly dependent on the **size** and **quality** of the oocyte cohort

• Type of gonadotropins given

• Doses of gonadotropins given

• Regimen of pituitary suppression used

• Type of ovulatory trigger

• Administration of adjuvant agents
Types of ovulatory triggers currently in use

• hCG

• GnRH agonist trigger

• Dual trigger

→ Individualized luteal support regimen
GnRH agonist trigger

→ Individualized luteal support regimen

• Intensive luteal support
• Adjuvant low dose hCG
  o Dual trigger with hCG (range 1,000 - 2500IU)
  o Adjuvant hCG at time of oocyte retrieval
  o Very low hCG dose
• Recombinant LH
• Freeze all
Combination gonadotropin-releasing hormone agonist, a novel approach to avoid ovarian hyperstimulation syndrome and enable fresh-embryo transfer in high responders

- 46 patients at risk for OHSS
- GnRH-a trigger
- Nafarein (Synarel) 200 μg*2 daily from the evening of OPU
- No other form of luteal support

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oocytes retrieved</td>
<td>23 (8–67)</td>
</tr>
<tr>
<td>Single-embryo transfer</td>
<td>38 (82.6)</td>
</tr>
<tr>
<td>Midluteal P level (nmol/L)</td>
<td>190 (2.3–600)$^a$</td>
</tr>
<tr>
<td>Midluteal E$_2$ level (pmol/L)</td>
<td>5,381 (224–18,155)</td>
</tr>
<tr>
<td>P level at first positive pregnancy test (nmol/L)</td>
<td>190 (1.9–1,750)</td>
</tr>
<tr>
<td>E$_2$ level at first positive pregnancy test (pmol/L)</td>
<td>5,407 (89–16,089)</td>
</tr>
<tr>
<td>Clinical ongoing pregnancies</td>
<td>24 (52.1)</td>
</tr>
</tbody>
</table>
Gonadotropin-releasing hormone analogue as sole luteal support in antagonist-based assisted reproductive technology cycles

Itai Bar Hava, M.D.,a Moran Blushtein, Ph.D.,b Hadas Ganer Herman, M.D.,a Yeela Omer, M.D.,a
and Gila Ben David, M.D.a

TABLE 1

Baseline characteristics and primary results for the GnRH agonist (GnRH-a) and the P supplementation groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>GnRH-a (n = 1,436)</th>
<th>P (n = 1,093)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive β-hCG, n (%)</td>
<td>401 (27.9)</td>
<td>217 (19.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chemical pregnancy</td>
<td>51/401 (12.7)</td>
<td>32/217 (14.7)</td>
<td>.48</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>74/401 (18.4)</td>
<td>65/217 (29.9)</td>
<td>.001</td>
</tr>
<tr>
<td>Live birth</td>
<td>254/401 (63.3)</td>
<td>108/217 (49.7)</td>
<td>.001</td>
</tr>
<tr>
<td>Midluteal P (mmol/L)</td>
<td>194.3 ± 146.0</td>
<td>134.0 ± 113.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Midluteal E2 (mmol/L)</td>
<td>3,453.7 ± 2,826.8</td>
<td>1,810.1 ± 2,314.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pregnancy with P (mmol/L)</td>
<td>222.1 ± 155.0</td>
<td>144.9 ± 82.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pregnancy with E2 (mmol/L)</td>
<td>6,921.3 ± 4,476.7</td>
<td>3,407.5 ± 2,970.0</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Note: Data presented as mean ± SD, unless stated otherwise. BMI = body mass index.
Dual trigger

Potential **biological role** for the FSH surge at the time of final oocyte maturation:

- FSH stimulates plasminogen activator activity within granulosa cell cultures
- Involved in dissociating the oocyte from the follicular wall and weakening the wall to facilitate rupture
- Improved oocyte recovery with higher follicular fluid FSH levels
- FSH promotes formation of LH receptors in luteinizing granulosa cells
- Keep gap junctions open between the oocyte and cumulus cells
- Promote nuclear maturation and cumulus expansion

Strickland et al., J Biol Chem 1976  
Morioka et al., Prog Clin Biol Res 1989  
Rosen et al., Reprod Biol Endocrinol 2009  
Atef et al., Mol Reprod Dev 2005  
Zelinski-Wooten et al., Hum Reprod 1998  
Yding Andersen et al., Mol Hum Reprod 1999
Dual trigger
GnRH-agonist and a standard dosage of hCG

Significantly higher proportion of mature oocytes in patients with a previous history of >25% immature oocytes

Griffin et al., Fertil Steril 2014

In normal responders GnRH-antagonist IVF cycles:
• More oocytes MII oocytes
• Significantly improved implantation, CPR and LBR
• Improved endometrial receptivity?

Lin et al., Fertil Steril 2013
Key players in the successful implantation

- The embryo
- The endometrium
- The maternal immune system
Impact of high serum progesterone during the late follicular phase on IVF outcome

Charlotte Sonigo *, Géraldine Dray, Clémence Roche, Isabelle Cédrin-Durnerin, Jean-Noel Hugues

• Serum P may increase during the last few days of ovarian stimulation
• P increase does not reflect ‘premature luteinization’
• The risk of endogenous LH surge is controlled by simultaneous administration of GnRH analogues
• Primarily related to the intensity of the ovarian response to FSH [No. of follicles; No. of oocytes; Serum E2 levels]
• Also dependent on the studied population
ORs for pregnancy achievement in women with PE when compared with those without PE

Advanced Access publication on July 4, 2013 doi:10.1093/humupd/dmt014

C.A. Venetis*, E.M. Kolibianakis, J.K. Bosdou, and B.C. Tarlatzis

Progesterone elevation and probability of pregnancy after IVF: a systematic review and meta-analysis of over 60,000 cycles
Odds ratios for achievement of pregnancy in women undergoing (a) FET and (b) oocyte donation after a fresh cycle with or without progesterone elevation.

No effect for progesterone elevation in frozen-thawed ET cycles and in cycles with donated oocytes.
A distinct difference in endometrial gene expression profile between patients with P concentration above and below 1.5 ng/ml on the day of HCG administration.

Impairment of endometrial receptivity, which is reflected as lower PRs.

Differential gene expression between groups of P4 concentration.

Results in moderately altered receptivity in 86%.

Strongly altered receptivity in 14%.

140 genes significantly dysregulated (64 up- and 76 down-regulated) regardless of GnRH analogue used. These genes are required for cell adhesion, developmental processes & immune system functioning.

Haouz et al HR 2009
Labarta et al HR 2011
Van Vaerenbergh et al RBM Online 2011
Serum progesterone threshold and type of GnRH analogue

Serum progesterone at the time of HCG triggering is significantly higher in women treated with GnRH agonist as compared with GnRH antagonist.

Stronger ovarian response to FSH as attested by the average difference of about two oocytes in favor of GnRH agonist.

Bosch et al., 2010;
Hugues et al., 2011;
Papanikolaou et al., 2012

Higher endogenous LH concentration is observed during the last few days of stimulation in women treated with GnRH agonist as compared with those who received GnRH antagonist.

Hugues et al., 2011
The duration of pre-ovulatory serum progesterone elevation before hCG administration affects the outcome of IVF/ICSI cycles

Huang et al.

- Retrospective, single-centre cohort study
- 1784 IVF and/or ICSI-ET cycles
Progesterone elevation does not compromise pregnancy rates in high responders

- Retrospective analysis from 6 clinical trials
- rFSH/GnRH antagonist protocol

Ongoing pregnancy rate per embryo transfer and associated 95% confidence interval by number of oocytes retrieved and serum P level on the day of hCG.

Griesinger et al. Fertil Steril 2013
Late elevations in follicular blood P:
[1] Increased P production per follicle - High PFI - detrimental
[2] the recruitment of additional follicles, with no change in the P secreted from each one of them - Low PFI – benign

The PFI enables clinicians to differentiate these conditions

- Retrospective study
- 8,649 IVF cycles in normal responders

PFI = Progesterone (nmol)
# follicles ≥ 14 mm

Shufaro et al. Fertil Steril 2015
Progesterone elevation > 1.5 ng/mL and the ratio of total exogenous LH to-FSH dosing in stimulation

- 10280 first long agonist and antagonist cycles
The optimal ratio of exogenous LH-to-FSH to prevent a premature increase in P according to response group

- High response group - 37%
- Normal response group - 22%
- Low response group - 11%

\[ P < 0.001 \]
Clinical practice: Preventing premature progesterone rise

• Progesterone elevation is strongly correlated to the intensity of stimulation

• Measurement of serum P is required before ovulation triggering

• P threshold should be individually defined in each center

• The starting FSH dose should be individually adjusted so as to not surpass the objective of getting 8–12 oocytes

• GnRH antagonist protocol should be preferred

• FSH should not be increased during ovarian stimulation because granulosa cells become highly sensitive to FSH

• Use of LH activity products - controversial

Sonigo et al, RBM Online 2014
Clinical practice: Which strategy in case of P elevation?

• In the case of gradual increase in serum P during ovarian stimulation, consider triggering ovulation earlier

  Kyrou et al., Fertil Steril 2011

• Administration of dexamethasone during ovarian stimulation may reduce the adrenal contribution to P secretion

  Fanchin et al., Fertil Steril 1997

• Cancellation of oocyte retrieval is not recommended

• P elevation does not have any impact on oocyte quality

• Embryo transfer should be deferred

• Freezing the whole cohort of oocytes or embryos

Sonigo et al., RBM Online 2014
Why iCOS?

- Huge diversity in the population of infertile patients
- Individualization of a therapeutic strategy
- Prediction of extremes of ovarian response
- Correct selection of GnRH analogue
- Fine tuning of the gonadotropin dose
- Reduced risks and dropouts
- Reduced treatment burden
<table>
<thead>
<tr>
<th>Characteristics for a Good Marker</th>
<th>Age</th>
<th>AMH</th>
<th>FSH</th>
<th>AFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediction of poor response</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Prediction of hyper response</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Low inter-cycle variability</td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Low intra-cycle variability</td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Applicable to all patients</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Economic</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

-, not appropriate; +, not very appropriate; ++, very appropriate. AFC, antral follicle count; AMH, anti-Mullerian Hormone.
Question:
If you had to choose one of the factors listed below, which would serve you best in assigning the starting gonadotropin dose?

- Age
- FSH
- AFC
- AMH
- Total

796 units
593,200 cycles
Strategic modelling of controlled ovarian stimulation on the basis of ovarian reserve markers

La Marca and Sunkara Hum. Reprod. Update 2014;20:124-140
The future: increased IVF success through the development and implementation of iCOS

AMH and AFC are currently the best biomarkers to predict ovarian response to iCOS

iCOS guided by such biomarkers is aimed to maximize the beneficial effects of treatment while minimizing complications and risks

iCOS should result in a better cycle final outcome and a more cost-effective approach

iCOS is still at its infancy.....

Needs to be validated in independent and prospective studies...
iCOS – Current recommendations

- Flexible GnRH antagonist protocol
- OCP or luteal estradiol with accelerated folliculogenesis
- 75-450 IU starting dose
- Use history, age, AMH, AFC, FSH, BMI for dosing
- Aim at 8-12 oocytes
- FSH:LH 2:1
- hCG/GnRH-trigger/dual trigger
- Segment the cycle if:
  - Progesterone elevation/OHSS risk/no plan for fresh ET
- **Good luck!**
Thank You