GnRHa trigger State of the ART
Peter Humaidan
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Aarhus University, Denmark
The Ugly Duckling
Overview

• Luteal phase rescue after GnRHa trigger
• Reproductive outcome and OHSS incidence
• New concept of “tailored” luteal phase support
• GnRHa trigger – for whom and how?
GnRHa or hCG for triggering of final oocyte maturation - Why GnRHa?

- Significant decrease/elimination in the incidence of OHSS
  - $T_{1/2}$ of endogenous LH shorter than $T_{1/2}$ of hCG (20 min versus 33 hours)

- More MII oocytes harvested in IVF
  (Imoedemhe et al., 1999; Humaidan et al., 2005; Humaidan et al., 2010; 2011; Oktay et al., 2010)

- Higher patient convenience
  (Cerillo et al., 2009; Hernandez et al., 2009)

- Negative impact of hCG on endometrial receptivity and oocyte quality
  (Forman et al., 1988; Fanchin et al., 2001; Fatemi et al., 2010; Valbuena et al., 2001)

- More physiological
  - Luteal phase steroid level closer to the physiological range
  - Endogenous FSH and LH surge
GnRHa trigger – development of protocol

• First trials low clinical pregnancy rate – high early pregnancy loss
  (Humaidan et al., 2005; Kolibianakis et al., 2005)

Additional studies in:

• Follicular fluid
  (Yding Andersen et al., Hum Reprod 2006)

• FER live birth after GnRHa versus hCG triggering
  (Griesinger et al., Fertil Steril 2007)

• Amphiregulin levels in follicular fluid after GnRHa triggering, hCG triggering and in natural cycle
  (Humaidan et al., Fertil Steril 2011)

Luteal phase insufficiency caused by low LH?
The role of LH in the luteal phase

LH plays a crucial role in the luteal phase

• Totally responsible for steroidogenic activity of the corpus luteum
  (Casper and Yen, 1979)

• Upregulation of growth factors, VEGFA, FGF2
  (Sugino et al., 2004; Wang et al., 2002)

• Upregulation of cytokines (LIF) involved in implantation
  (Licht et al., 2001)

• Stimulation of LH receptors in endometrium
  (Rao, 2001; Tesarik et al., 2003)
Correlation between LH and P4 during midluteal phase

Figure 5. Plasma concentrations of LH (○) and P (●) during 24 h of blood sampling at 10-min intervals in volunteer D, who was studied in the MLP (LH mid cycle surge + 8 d). The mean LH, E₂, and P concentrations on the day of the study are shown in the upper right hand corner. Asterisks indicate significant LH pulsations. The cross-correlation between LH and P in this subject is significant (P < 0.05) at +30–40 min.
Luteal phase physiology after COS

- Supraphysiological steroid level (estradiol and progesterone) in early-mid luteal phase exert a negative feed-back on the hypothalamic-pituitary axis reducing LH secretion in early luteal phase.
  
  (Tavaniotou and Devroey, 2006; Tavaniotou et al., 2001)

- GnRHa triggering leads to significantly reduced total amounts of gonadotropins (LH and FSH) released by the pituitary due to profile and duration of surge

  (Gonen et al., 1990; Itskovitz et al., 1991)
Mid-luteal LH levels

- 6.0 IU/l in natural cycle (Tavaniotou and Devroey 2003)
- 1.5 IU/l in GnRHa group (Humaidan et al, 2005)
- 0.2 IU/l in hCG group (Humaidan et al, 2005)
Early Luteal Phase After HCG Triggering

Damewood et al., 1989; Bonduelle et al., 1988
Early Luteal Phase After GnRHa Triggering

28-32 hours

LH activity deficiency period

Damewood et al., 1989; Bonduelle et al., 1988; Gonen et al., 1990; Itskovitz et al., 1991
OVULATION INDUCTION

1,500 IU human chorionic gonadotropin administered at oocyte retrieval rescues the luteal phase when gonadotropin-releasing hormone agonist is used for ovulation induction: a prospective, randomized, controlled study

Peter Humaidan, M.D., a Helle Ejdrup Bredkjaer, M.D., Ph.D., b Lars Grabow Westergaard, M.D., D.M.Sc., c and Claus Yding Andersen, D.M.Sc. d

a The Fertility Clinic, Skive Regional Hospital, Skive, Denmark; b The Fertility Clinic, Holbæk Hospital, Holbæk, Denmark; c The Fertility Clinic, Department of Obstetrics and Gynecology, University Hospital of Odense, Odense, Denmark; and d Laboratory of Reproductive Biology, University Hospital of Copenhagen, Copenhagen, Denmark

Humaidan et al., 2010
Early Luteal Phase After GnRHa Triggering

GnRHa → OPU → hCG → Day 8 → LH activity deficiency period

28-32 hours

Damewood et al., 1989; Bonduelle et al., 1988; Gonen et al., 1990; Itskovitz et al., 1991
# Reproductive Outcome

<table>
<thead>
<tr>
<th></th>
<th>GnRHa/hCG</th>
<th>hCG</th>
<th>P-value</th>
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<tbody>
<tr>
<td><strong>Patients, n</strong></td>
<td>152</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td><strong>Rate of transfer, n (%)</strong></td>
<td>130/152 (86)</td>
<td>138/150 (92)</td>
<td>0.054</td>
</tr>
<tr>
<td><strong>Pos. hCG per ET, n (%)</strong></td>
<td>63/130 (48)</td>
<td>66/138 (48)</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Ongoing PR per patient (%)</strong></td>
<td>40/152 (26)</td>
<td>49/150 (33)</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>Delivery rate/patient</strong></td>
<td>36/152 (24)</td>
<td>47/150 (31)</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Early pregnancy loss, n (%) of pos</strong></td>
<td>13/63 (21)</td>
<td>11/66 (17)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

*) Fishers exact test

Humaidan et al., Fertil Steril, 2010
## Reproductive Outcome

<table>
<thead>
<tr>
<th></th>
<th>GnRHa (2005)</th>
<th>GnRHa + hCG 1500</th>
<th>hCG 1500</th>
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<tbody>
<tr>
<td>Patients, n</td>
<td>55</td>
<td>152</td>
<td>150</td>
</tr>
<tr>
<td>Rate of ET, n (%)</td>
<td>48/55 (87)</td>
<td>130/152 (86)</td>
<td>138/150 (92)</td>
</tr>
<tr>
<td>Pos. hCG/ET, n (%)</td>
<td>14/48 (29)</td>
<td>63/130 (48)</td>
<td>66/138 (48)</td>
</tr>
<tr>
<td>Ongoing PR per pat (%)</td>
<td>3/55 (6)</td>
<td>40/152 (26)</td>
<td>49/150 (33)</td>
</tr>
<tr>
<td>Delivery rate per pat (%)</td>
<td>3/55 (6)</td>
<td>36/152 (24)</td>
<td>47/150 (31)</td>
</tr>
<tr>
<td>Early PL, n (%)</td>
<td>11/14 (79)</td>
<td>13/63 (21)</td>
<td>11/66 (17)</td>
</tr>
</tbody>
</table>
OHSS reduction?

hCG triggering:

3/150: 2% (1 severe/2 moderate)

GnRHa triggering:

0/152

Humaidan et al., Fertil Steril, 2010; 93:847-54
GnRHa trigger in OHSS high-risk patients
Retrospective observational study

- 71 patients ≥ 14 follicles ≥ 12 mm
- GnRHa trigger plus 1.500 IU hCG
- SET
- Luteal phase support until 8 weeks (Crinone + E2 4mg)
- Clinical pregnancy rate 52% (37/71)
- 1 OHSS case (1/71)

Radesic and Tremellen, Hum Reprod, 2011
Consistent high clinical pregnancy rates and low ovarian hyperstimulation syndrome rates in high-risk patients after GnRH agonist triggering and modified luteal support: a retrospective multicentre study

Stamatina Iliodromiti1,*, Christophe Blockeel2, Kelton P. Tremellen3, Richard Fleming1, Herman Tournaye2, Peter Humaidan4†, and Scott M. Nelson1,†

1Maternal and Reproductive Medicine, School of Medicine, University of Glasgow, 3rd Floor McGregor Building, Glasgow, UK, 2University Hospital of the Free University of Brussels, Laarbeeklaan 101-1090, Brussel, 3Repromed Adelaide, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, Australia and 4The Fertility Clinic, Skive Regional Hospital, Denmark and Aarhus University, Faculty of Health, Aarhus, Denmark.

Iliodromiti et al., 2013
Multicenter retrospective study

<table>
<thead>
<tr>
<th></th>
<th>Centre 1 (UK)</th>
<th>Centre 2 (Belgium)</th>
<th>Centre 3 (Australia)</th>
<th>Comparison of three centres</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combined (n=275)</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Number of oocytes collected</td>
<td>17.8 ± 8.4</td>
<td>12.2 ± 6.1</td>
<td>19.1 ± 9.7</td>
<td>p&lt;0.001</td>
<td></td>
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<tr>
<td>Number of embryos produced</td>
<td>10.2 ± 5.6</td>
<td>6.9± 4.5</td>
<td>11.1±6.2</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Number of embryos transferred</td>
<td>1 (1-2)</td>
<td>2 (1-2)</td>
<td>1 (1-2)</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Number of embryos cryopreserved</td>
<td>3 (1-5)</td>
<td>4 (2-5.75)</td>
<td>2 (0-5.25)</td>
<td>p=0.006</td>
<td></td>
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<tr>
<td>No blastocyst formation (%)</td>
<td>2.9%</td>
<td>2/68 (2.9%)</td>
<td>3/94 (3.2%)</td>
<td>p=1.0</td>
<td></td>
</tr>
<tr>
<td>Biochemical pregnancy rate</td>
<td>55.3%</td>
<td>39/68 (57.4%)</td>
<td>52/94 (55.3%)</td>
<td>p=0.91</td>
<td></td>
</tr>
<tr>
<td>Clinical pregnancy</td>
<td>41.8%</td>
<td>27/68 (39.7%)</td>
<td>41/94 (43.6%)</td>
<td>p=0.88</td>
<td></td>
</tr>
<tr>
<td>Miscarriages</td>
<td>6.55%</td>
<td>3/68 (4.4%)</td>
<td>5/94 (5.3%)</td>
<td>p=0.52</td>
<td></td>
</tr>
<tr>
<td>OHSS (severe)</td>
<td>0.72% (severe)</td>
<td>1/68</td>
<td>0/94</td>
<td>p=0.072 (MNS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 severe</td>
<td>1 severe</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>3 mild</td>
<td>2 mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 moderate</td>
<td></td>
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Normally distributed variables are expressed as mean ± SD. Variables that are not normally distributed are expressed as median (25th-75th percentile). Outcome data are presented per cycle started.
A clinical pregnancy was defined as the presence of at least one viable fetal heart on a 8 week ultrasound scan, while a biochemical pregnancy was an embryo transfer resulting in a positive serum hCG.
Miscarriages are defined as occurring after a clinical pregnancy was established.
GnRHa trigger and individualized luteal phase hCG support according to ovarian response to stimulation: two prospective randomized controlled multi-centre studies in IVF patients

P. Humaidan¹,²,* , N.P. Polyzos³, B. Alsbjerg¹, K. Erb⁴, A.L. Mikkelsen⁵, H.O. Elbaek⁶, E.G. Papanikolaou⁷, and C.Y. Andersen⁸

¹The Fertility Clinic, Skive Regional Hospital, Skive, Denmark ²Faculty of Health, Aarhus University, Aarhus, Denmark ³Centre for Reproductive Medicine, Dutch Speaking University Brussels, Brussels, Belgium ⁴The Fertility Clinic, Odense University Hospital, Odense Denmark ⁵The Fertility Clinic, Holbaek Hospital, Holbaek, Denmark ⁶The Fertility Clinic, Braedstrup Hospital, Braedstrup, Denmark ⁷Aristotle University, Thessaloniki, Greece ⁸Laboratory of Reproductive Biology, Section 5712, University Hospital of Copenhagen, Copenhagen, Denmark

*Correspondence address. The Fertility Clinic, Skive Regional Hospital, Reservej 25, 7800 Skive, Denmark. Tel: 45-78-44-57-68; E-mail: peter.humaidan@vborg.m.dk, peter.s.humaidan@gmail.com

Humaidan et al., 2013
GnRHa trigger and tailored luteal support Multicenter RCT - new data 384 patients

Tailored luteal phase support:

- Normo-responder patient (≤ 14 follicles ≥ 12 mm)
  - Repeat bolus of hCG (1500 IU, OPU + OPU+5) + E2/P4 until 7 weeks

- OHSS risk patient (>14 follicles ≥ 12 mm)
  - One bolus of hCG (1500 IU, OPU) + E2/P4 until week 7

OHSS risk patients > 25 follicles excluded from study

Humaidan et al. Hum Reprod 2013
Tailored luteal phase support

OHSS low risk patients with ≤ 14 follicles ≥ 12 mm on day of trigger
GnRHa + 1500 IU hCG x 2  versus 5000 IU hCG

<table>
<thead>
<tr>
<th></th>
<th>GnRHa/hCG</th>
<th>hCG</th>
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<tbody>
<tr>
<td>Patients, n</td>
<td>125</td>
<td>141</td>
</tr>
<tr>
<td>Rate of transfer, n (%)</td>
<td>110/125 (88)</td>
<td>116/141 (82)</td>
</tr>
<tr>
<td>Embryos transferred, mean</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>IR</td>
<td>49/158 (36)</td>
<td>43/145 (30)</td>
</tr>
<tr>
<td>Pos hCG per ET, n (%)</td>
<td>47/110 (43)</td>
<td>41/116 (35)</td>
</tr>
<tr>
<td>Clinical pregnancy per patient, n (%)</td>
<td>43/125 (34)</td>
<td>40/141 (28)</td>
</tr>
<tr>
<td>Ongoing pregnancy per patient, n (%)</td>
<td>37/125 (30)</td>
<td>36/141 (26)</td>
</tr>
</tbody>
</table>

Humaidan et al., Hum Reprod 2013
### Tailored luteal phase support

OHSS risk patients with >14 follicles ≥ 12 mm on day of trigger
GnRHa + 1500 IU hCG x 1  versus 5000 IU hCG

<table>
<thead>
<tr>
<th></th>
<th>GnRHa/hCG</th>
<th>hCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>60</td>
<td>58</td>
</tr>
<tr>
<td>Rate of transfer, n (%)</td>
<td>52/60 (87)</td>
<td>57/58 (98)</td>
</tr>
<tr>
<td>Embryos transferred, mean</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>IR</td>
<td>22/62 (35)</td>
<td>20/68 (29)</td>
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<tr>
<td>Pos hCG per ET, n (%)</td>
<td>25/52 (48)</td>
<td>21/57 (37)</td>
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<td>Clinical pregnancy per patient</td>
<td>21/60 (35)</td>
<td>17/58 (29)</td>
</tr>
<tr>
<td>Ongoing pregnancy per patient</td>
<td>17/60 (28)</td>
<td>15/58 (26)</td>
</tr>
</tbody>
</table>

Humaidan et al., Hum Reprod 2013
OHSS reduction?

- HCG triggering
  - 2/58: 3% (2 moderate)

- GnRHa triggering
  - 0/60

Humaidan et al., Hum Reprod 2013
Intensive luteal phase support after GnRHa trigger

- Babayof et al. (N: 15): ↓ IR and CPR
- Engmann et al. (N: 30): → IR and CPR
- Imbar et al. (N: 70): → IR and CPR
- Orvieto (N: 67): ↓ IR and CPR
- Iliomidriti et al. (N:363) → IR and CPR

Babayof R et al., Hum Reprod, 2006
Engmann L et al., Fertil Steril, 2008
Imbar T et al., Hum Reprod, 2012
Orvieto R, RBM Online, 2012
Iliodromiti et al., J Ovarian Research, 2014
Which patient is suitable for GnRHa trigger?

Apart from the hypogonadotrophic/hypogonadal patient:

All patients co-treated with a GnRH antagonist can be triggered with a bolus of GnRHa, followed by a modified luteal phase support or a total freeze.
How to Use GnRHa Trigger

• No difference regarding the duration of the surge of gonadotropins between different GnRHa types and administration forms (Parneix, et al. 1996)

  – Most commonly used GnRHa triggering doses:
    • Buserelin 0.5 mg s.c.
    • Buserelin 0.2 mg i.n.
    • Triptorelin 0.2 mg s.c.
    • Leuprolide 1.0 mg s.c.

  – Timing of bolus:
    • Same as for hCG triggering (34-36 hours)
GnRHa Trigger and tailored luteal support in Practice 2014

Day of oocyte pick-up (OPU):

≤ 14 follicles

• 1500 IU hCG at OPU & 1000 OPU+5 + Standard Luteal Phase support

15 – 25 follicles

• 1500 IU hCG at OPU + Standard Luteal Phase support

25 – 30 follicles

• Freeze all

  (750 - 1000 IU hCG at OPU + Standard Luteal Phase support)

> 30 follicles

• Freeze all

Humaidan unpublished
Conclusions GnRHa versus hCG trigger

GnRHa trigger

• Decreases significantly early and late onset OHSS
• More MII oocytes
• Higher patient convenience
• The option to perform a total freeze in cases with an excessive response to stimulation with minimal risk of OHSS in the patient
• Less abandoned cycles
• The protocol of choice in oocyte donors

Humaidan et al  Hum Reprod Update 2011; 17:510-24
GnRHa trigger - the future trigger concept for all patients

Golden opportunity for:

Paradigm shift in ovulation triggering and introducing the tailored luteal support concept in ART

On our way to the “OHSS free” clinic

Thank You for Your attention
peter.humaidan@midt.rm.dk
Reviews about GnRHa triggering

Humaidan et al., Hum Reprod, 2009, **24**:2389-2394

Humaidan et al., Hum Reprod Update, 2011, **17**:510-524

Humaidan et al., RBM Online, 2012, **24**:134-41

Kol and Humaidan, RBM Online, 2013, **26**:226-30
Fresh transfer – why?

• Optimal freezing program ??

• Pregnancy rates after FER ↓

Pinborg, 2012

• Pregnancy loss rate ↑

Tomas et al., 2012

• Epigenetic changes – OR: 1.6 for LGA after FER versus fresh IVF and natural conception

Henningsen et al., 2011; Pinborg, 2012, Pinborg et al., 2014
Fresh transfer – why?

- Malformation rate after ICSI FER vs IVF FER 2 fold higher
  Belva et al., 2008

- Patient expectation – psychological stress

- Long term follow-up studies absent

- ”Wild stimulation”
Severe ovarian hyperstimulation syndrome after gonadotropin-releasing hormone (GnRH) agonist trigger and “freeze-all” approach in GnRH antagonist protocol

Human Mousavi Fatemi, M.D., Ph.D., a Biljana Popovic-Todorovic, M.D., Ph.D., b Peter Humaidan, M.D., D.M.Sc., c Shahar Kol, M.D., Ph.D., d Manish Banker, M.D., e Paul Devroey, M.D., Ph.D., a and Juan Antonio García-Velasco, M.D., Ph.D. f

a Center for Reproductive Medicine, Dutch-Speaking Free University Brussels, Brussels, Belgium; b Special Gynecology Hospital “Ivanovic,” Belgrade, Serbia; c Fertility Clinic, Skive Regional Hospital and Faculty of Health, Aarhus University, Aarhus, Denmark; d Department of Obstetrics and Gynecology, IVF Unit, Rambam Medical Center, Haifa, Israel; e NOVAIVI, Ahmadabad, India; and f Instituto Valenciano de Infertilitat-MADRID, Madrid, Spain

Fatemi et al., 2014

Two cases – 30 oocytes each
Future scenario

- GnRHa trigger for all patients

- Normo-responder (< 14 follicles): The exogenous progesterone free luteal phase – relying on endogenous progesterone sources only

- High responder (14-30) follicles: Fresh transfer and modified luteal phase support

- > 30 follicles: Freeze all
Happy not to have been in the freezer…