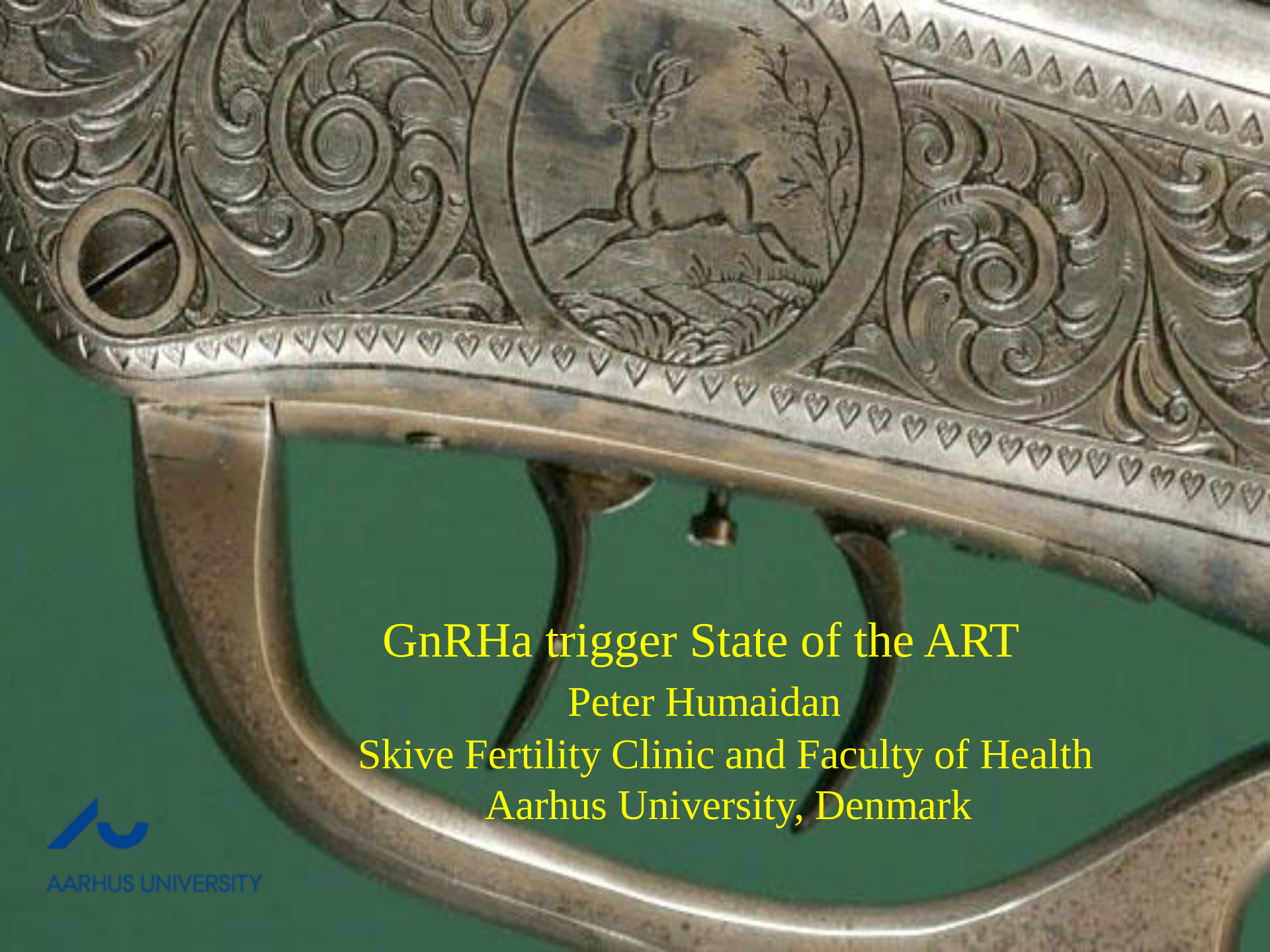

GnRHa trigger State of the ART

Peter Humaidan
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AARHUS UNIVERSITY


The Ugly Duckling
www.hiren.info

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 insufficency 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

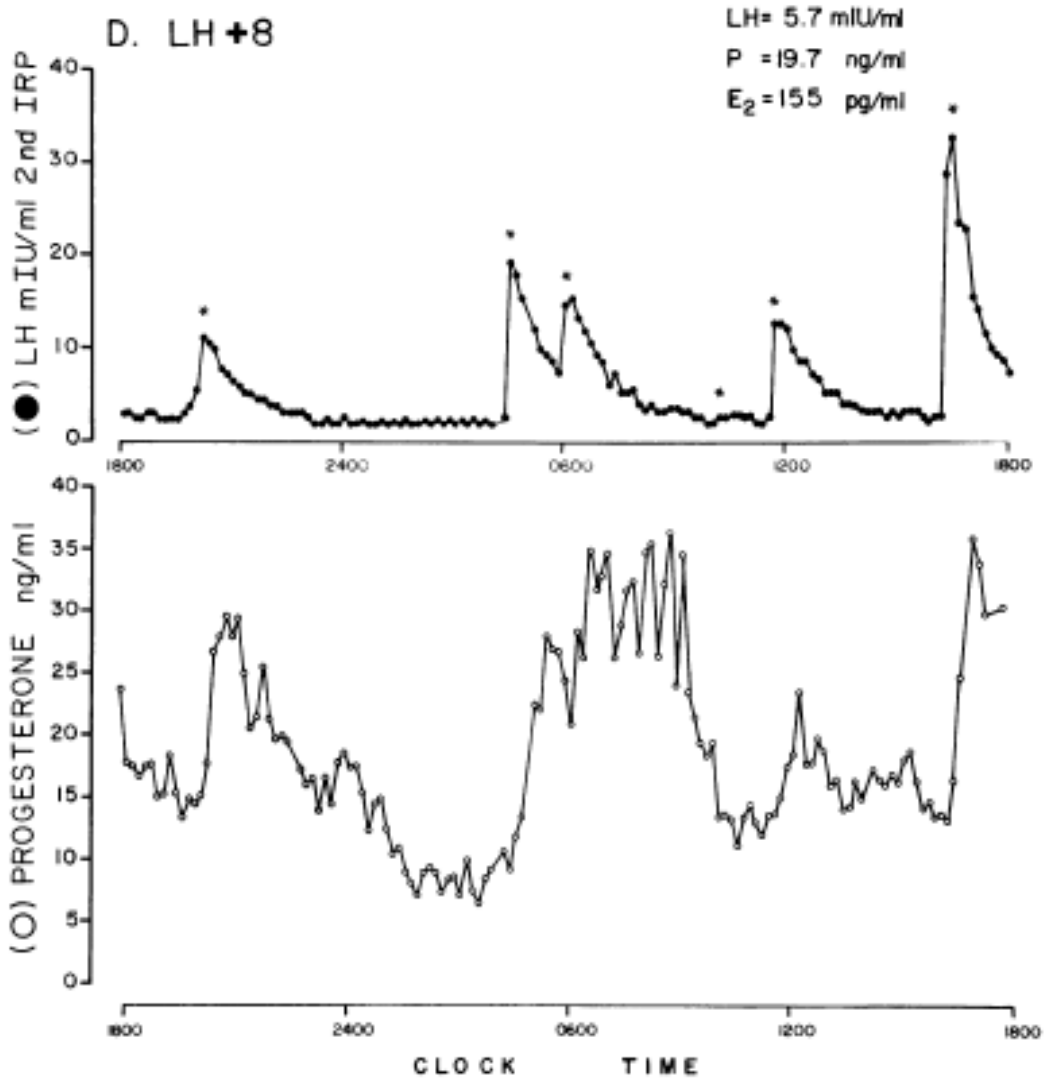


Figure 5. Plasma concentrations of LH (●) and P (○) during 24 h of blood sampling at 10-min intervals in volunteer D, who was studied in the MLP (LH mid cycle surge + 8 d). The mean LH, E_2, and P concentrations on the day of the study are shown in the upper right hand corner. Asterisks indicate significant LH pulsations. The cross-correlation between LH and P in this subject is significant ($P < 0.05$) at +30–40 min.

Filicori et al., 1984

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)

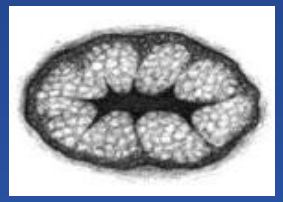
- GnRHa triggering leads to significantly reduced total amounts of gonadotropins (LH and FSH) released by the pituitary due to profile and duration of surge

  (Gonen et al., 1990; Itskovitz et al., 1991)

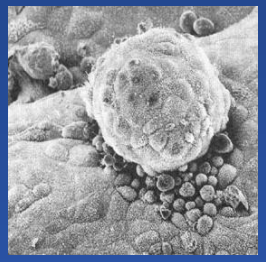
Mid-luteal LH levels

- 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



hCG



hCG OPU

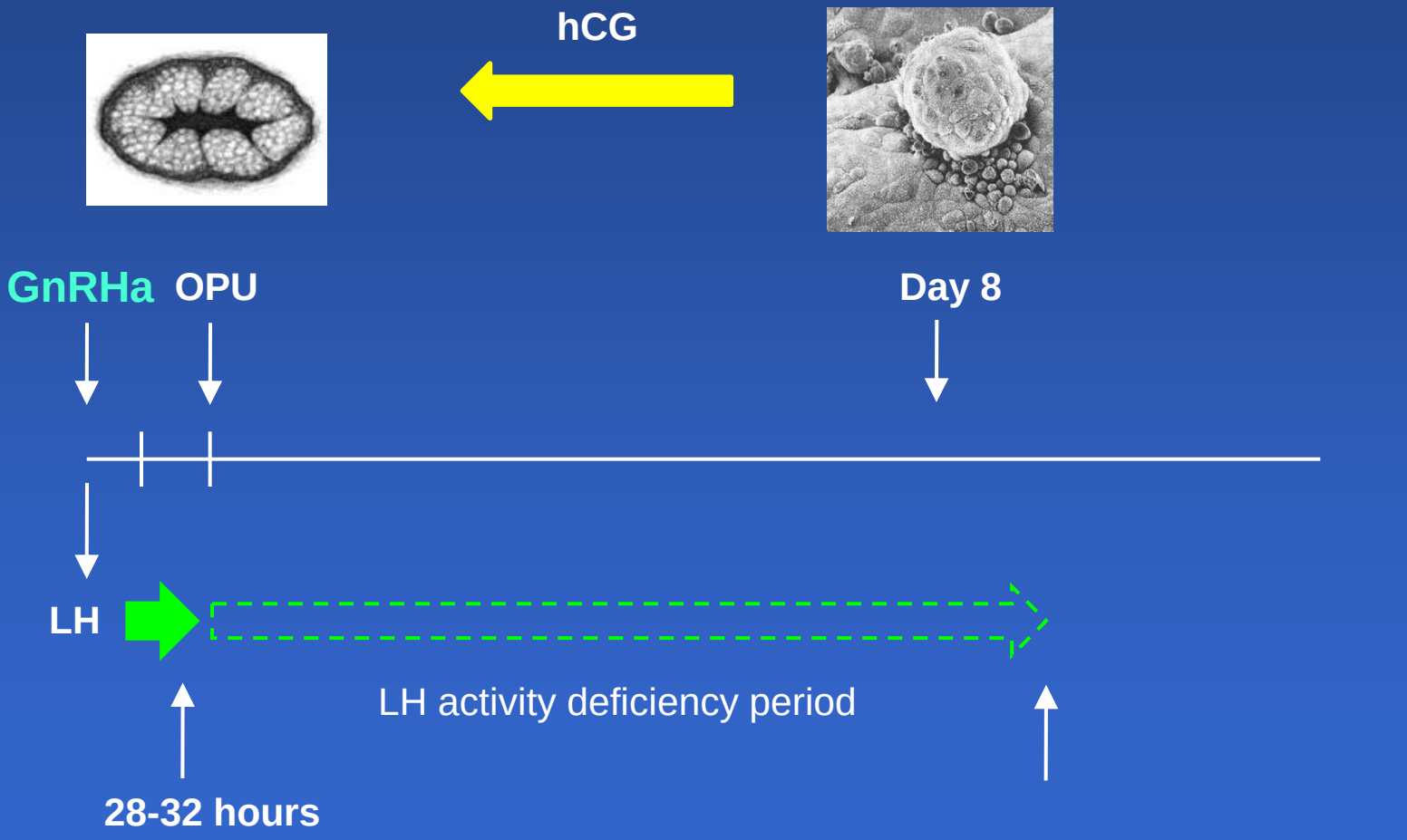
Day 8

hCG

Day 9-10

Damewood et al., 1989; Bonduelle et al., 1988

Early Luteal Phase After GnRHa Triggering



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 Bredkjær, M.D., Ph.D.,*[b] *Lars Grabow Westergaard, M.D., D.M.Sc.,*[c] *and Claus Yding Andersen, D.M.Sc.*[d]

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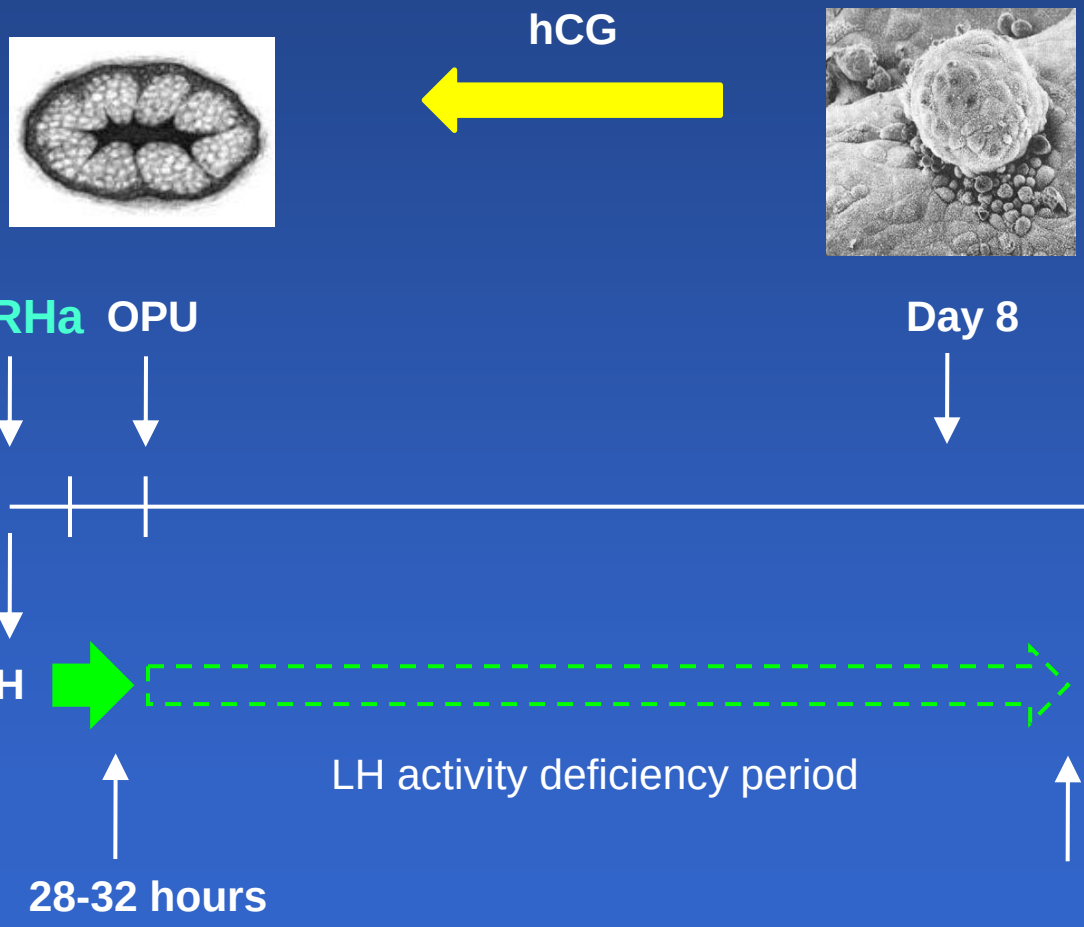
Humaidan et al., 2010

Early Luteal Phase After GnRHa Triggering



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

Reproductive Outcome

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

*) Fishers exact test

Humaidan et al., Fertil Steril, 2010

Reproductive Outcome

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

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

Human Reproduction, Vol.28, No.9 pp. 2529–2536, 2013
Advanced Access publication on July 19, 2013 doi:10.1093/humrep/det304

human reproduction

ORIGINAL ARTICLE *Reproductive endocrinology*

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 Iliodromiti[1,*], Christophe Blockeel[2], Kelton P. Tremellen[3], Richard Fleming[1], Herman Tournaye[2], Peter Humaidan[4,†], and Scott M. Nelson[1,†]

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

Iliodromiti et al., 2013

Multicenter retrospective study

Table 2. ART treatment outcomes in each centre

	Combined (n=275)	Centre 1 (UK) (n=68)	Centre 2 (Belgium) (n=94)	Centre 3 (Australia) (n=113)	Comparison of three centres p
Number of oocytes collected	17.8 ± 8.4	12.2 ± 6.1	19.1± 9.7	19.9±6.7	p<0.001
Number of embryos produced	10.2 ± 5.6	6.9± 4.5	11.1±6.2	11.3±4.7	p<0.001
Number of embryos transferred	1 (1-2)	2 (1-2)	1 (1-2)	1(1-1)	p<0.001
Number of embryos cryopreserved	3 (1-6)	4 (2-5.75)	2 (0-5.25)	4 (2-7)	p=0.006
No blastocyst formation (%)	2.9%	2/68 (2.9%)	3/94 (3.2%)	3/113 (2.7%)	p=1.0
Biochemical pregnancy rate	55.3%	39/68 (57.4%)	52/94 (55.3%)	61/113 (54%)	p=0.91
Clinical pregnancy	41.8%	27/68 (39.7%)	41/94 (43.6%)	47/113 (41.6%)	p=0.88
Miscarriages	6.55%	3/68 (4.4%)	5/94 (5.3%)	10/113 (8.8%)	p=0.52
OHSS (severe)	0.72% (severe)	1/68 1 severe 3 mild	0/94 1 mild	1/113 1 severe 2 mild 5 moderate	p=0.72

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 βhCG.
Miscarriages are defined as occurring after a clinical pregnancy was established

Iliodromiti et al., 2013

Hum. Reprod. Advance Access published June 9, 2013

Human Reproduction, Vol.0, No.0 pp. 1–11, 2013

doi:10.1093/humrep/det249

human reproduction

ORIGINAL ARTICLE *Reproductive endocrinology*

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. Humaidan[1,2,*], N.P. Polyzos[3], B. Alsbjerg[1], K. Erb[4], A.L. Mikkelsen[5], H.O. Elbaek[6], E.G. Papanikolaou[7], and C.Y. Andersen[8]

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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

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

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

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

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 hypogonadotropic/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 taylored 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

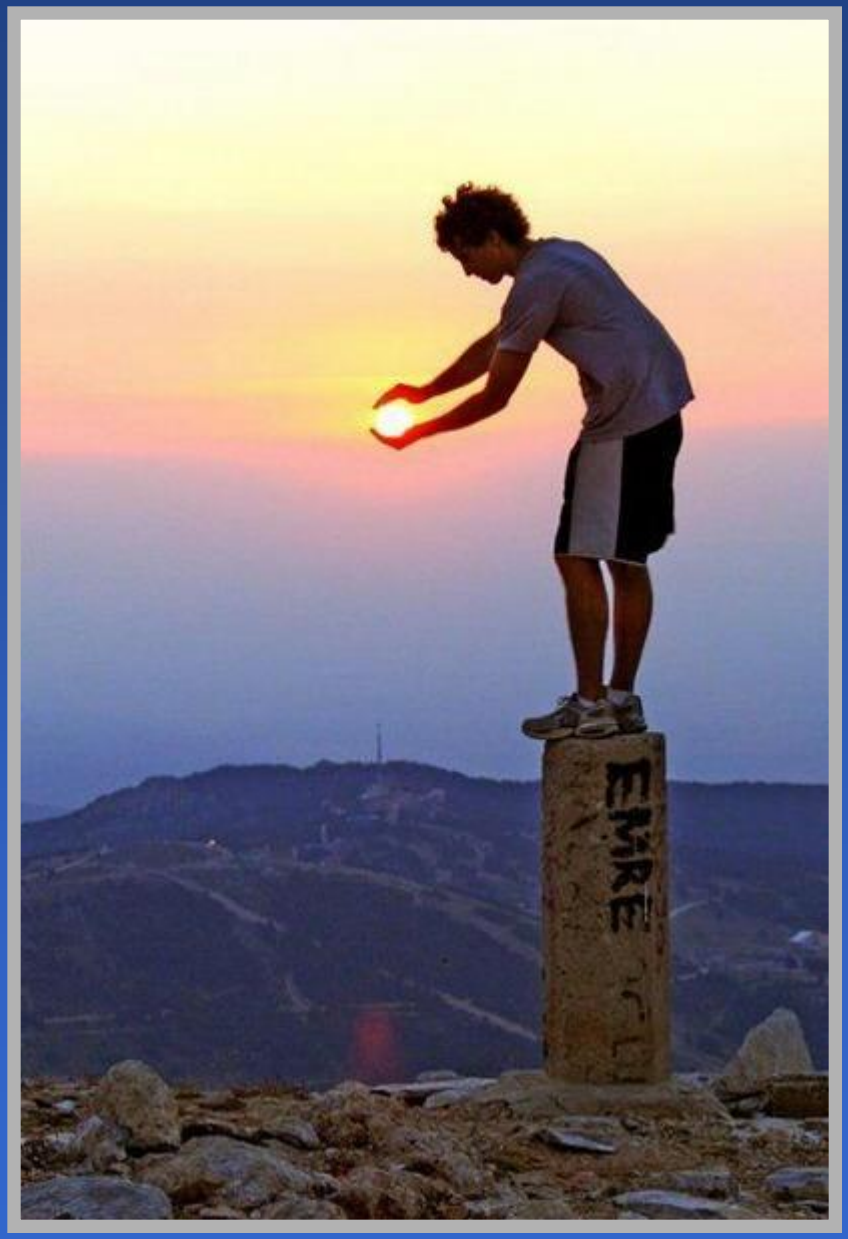
Golden opportunity for:

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?

- Malfornation 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”

Two cases – 30 oocytes each

ARTICLE IN PRESS

ORIGINAL ARTICLE: ASSISTED REPRODUCTION

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

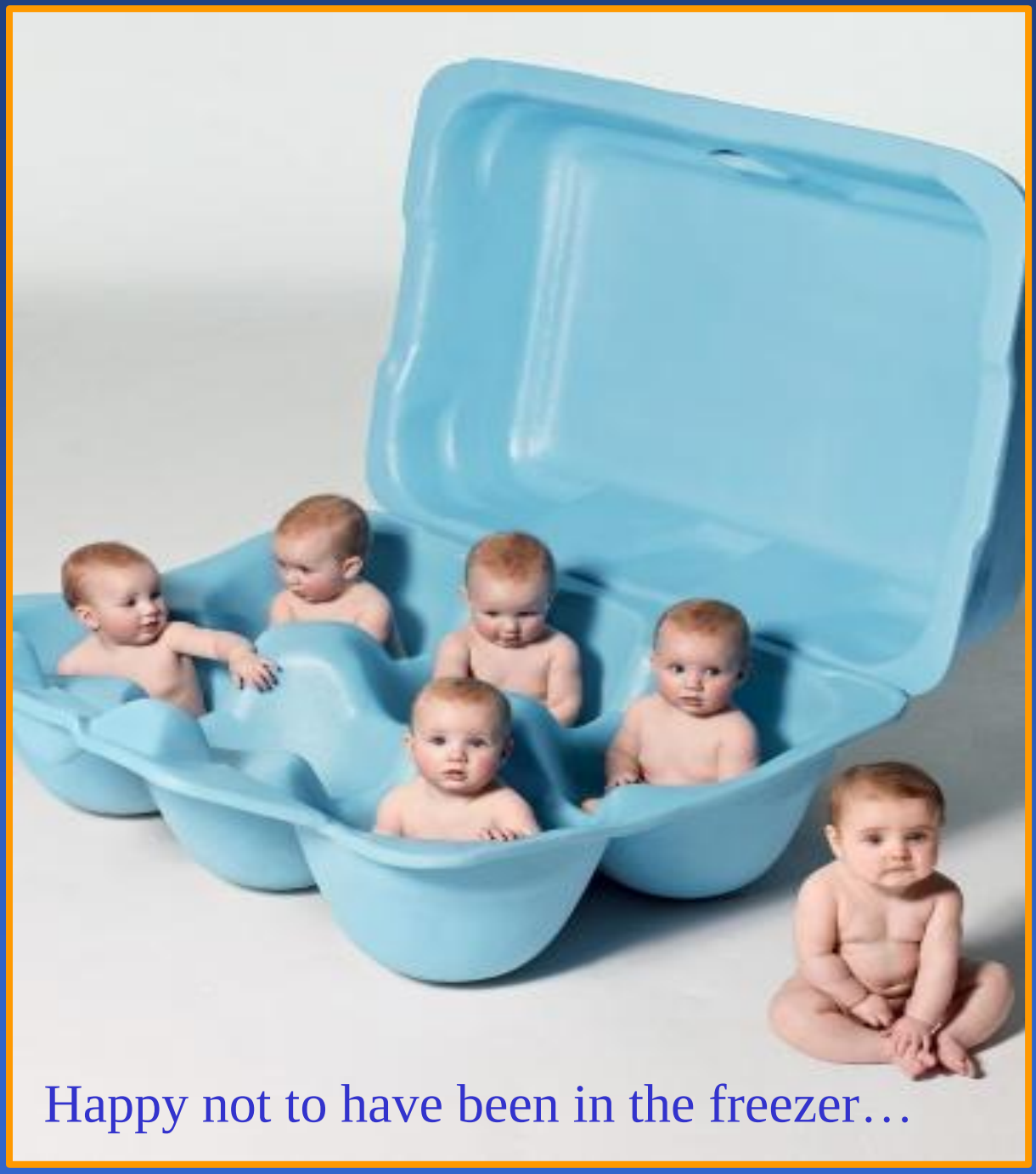
Human Mousavi Fatemi, M.D., Ph.D.,[a] Biljana Popovic-Todorovic, M.D., Ph.D.,[b] Peter Humaidan, M.D., D.M.Sc.,[c] Shahar Kol, M.D., Ph.D.,[d] Manish Banker, M.D.,[e] Paul Devroey, M.D., Ph.D.,[a] and Juan Antonio García-Velasco, M.D., Ph.D.[f]

[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 Infertilidad-MADRID, Madrid, Spain

Fatemi et al., 2014

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…