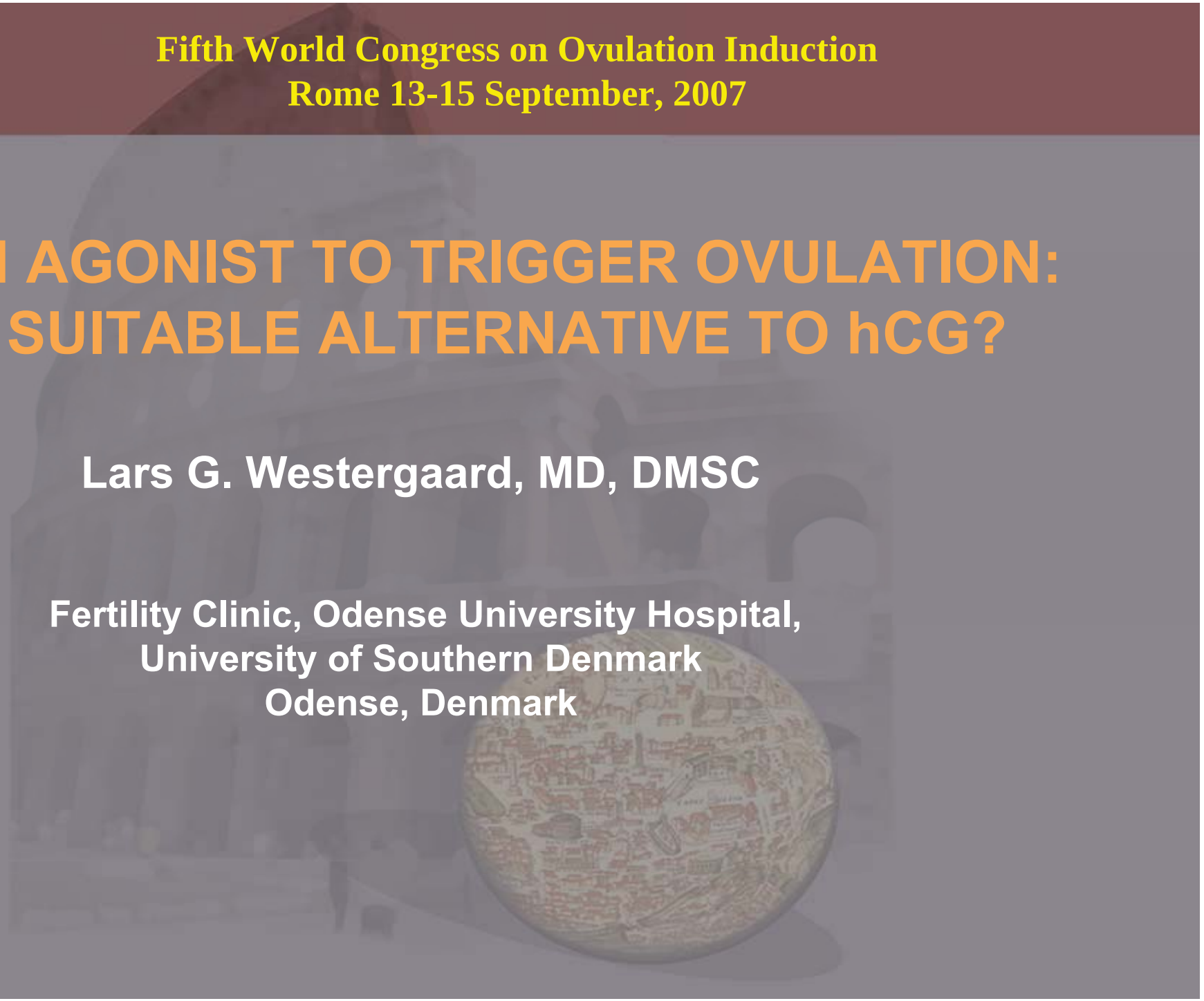
Fifth World Congress on Ovulation Induction
Rome 13-15 September, 2007

GnRH AGONIST TO TRIGGER OVULATION: A SUITABLE ALTERNATIVE TO hCG?

Lars G. Westergaard, MD, DMSC

Fertility Clinic, Odense University Hospital,
University of Southern Denmark
Odense, Denmark



hCG is the classical trigger of ovulation in ART

- An injection of 5000 – 10.000 IU hCG induces final follicle and oocyte maturation (MII)
- Allows optimal timing oocyte pick-up, i.e. 36-38 h after injection, and has formed the basis of successful human ART since its start in the early 1980's.
- Why then replace it with GnRH agonist as ovulation trigger?

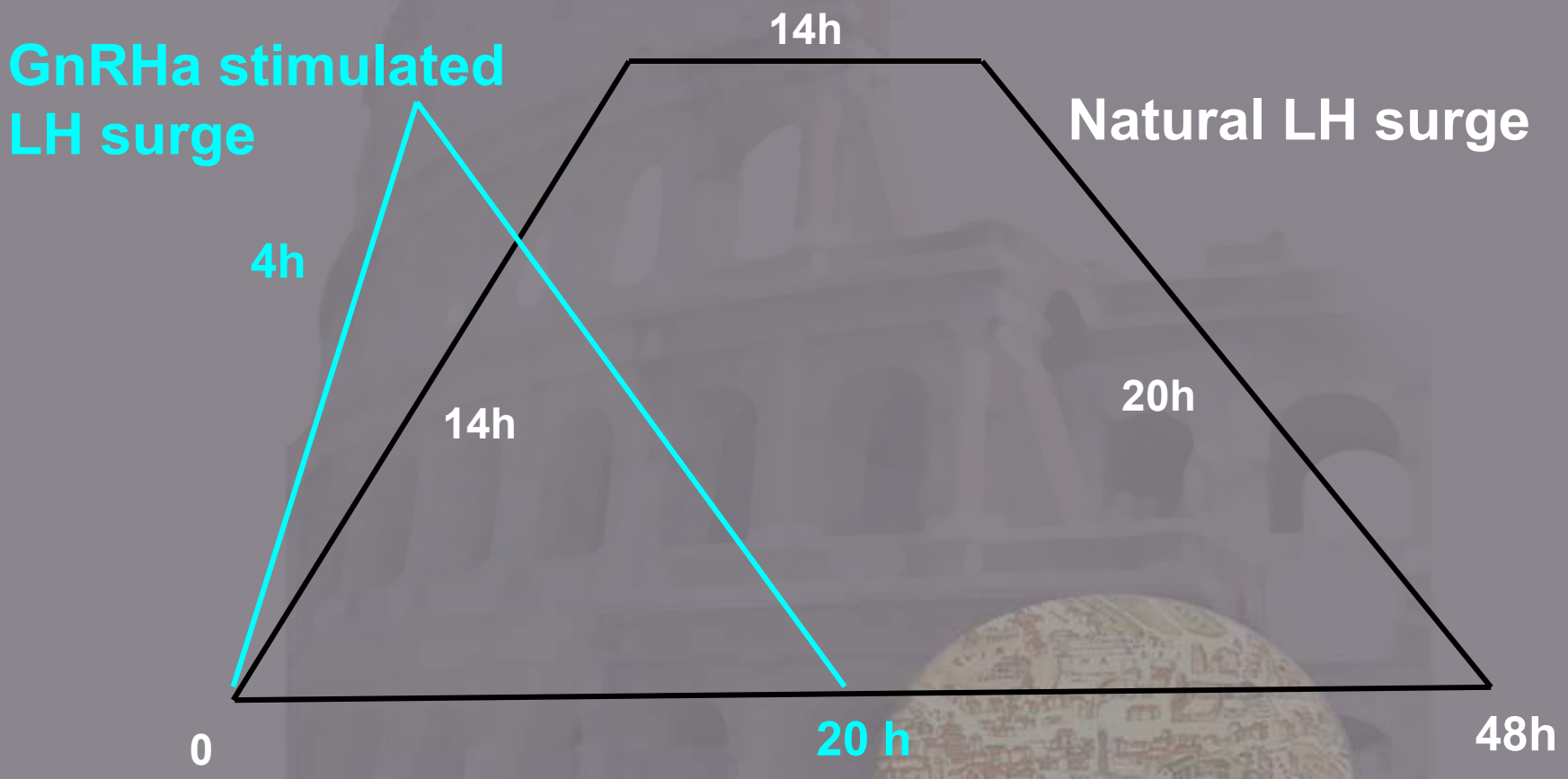
hCG is the classical trigger of ovulation in ART

Why replace hCG with GnRH agonist?

Reduction of OHSS risk in high responder patients

- Due to its long half-life (days) hCG may trigger early onset OHSS in high responder patients.
- Due to the short half-life of LH (hours) early onset OHSS does not occur after ovulation triggered by the normal LH surge.
- *GnRH agonist triggers* final follicle and oocyte maturation (MII) by stimulation of pituitary release of LH and FSH:
  More physiological ?

The LH surge triggered by GnRH agonist is of shorter duration and lower amplitude than the natural surge



Hoff et al., 1983 Itskovits et al., 1991

GnRH agonist as ovulation trigger

Studies in the early 1990's (the pre-antagonist era) documented:

that bolus administration of various GnRH agonists in various doses effectively trigger final oocyte maturation and ovulation with the same timing (36-38h) as hCG injection

- *'Buserelin sc (200-500 µg):*
  (Itskovits et al. 1991; Imoedemhe et al., 1991; Yding Andersen et al., 1993)
- *Leuprolide acetate sc (500 µg):*
  (Gonen et al., 1990; Segal & Casper, 1992)
- *Nafarelin intranasal (600-800 µg):*
  (Emperaire 1993; Schmidt-Sarosi et al., 1995)

Most studies noted decreased progesterone and oestradiol levels during the luteal phase, indicating that the shorter LH surge triggered by GnRH agonist is *insufficient to support normal CL function*

but

- Due to the success of the long protocol GnRH agonist pituitary down-regulation further exploration of GnRH agonist as ovulation trigger was put on halt for the next decade

GnRH Agonist as Ovulation Trigger

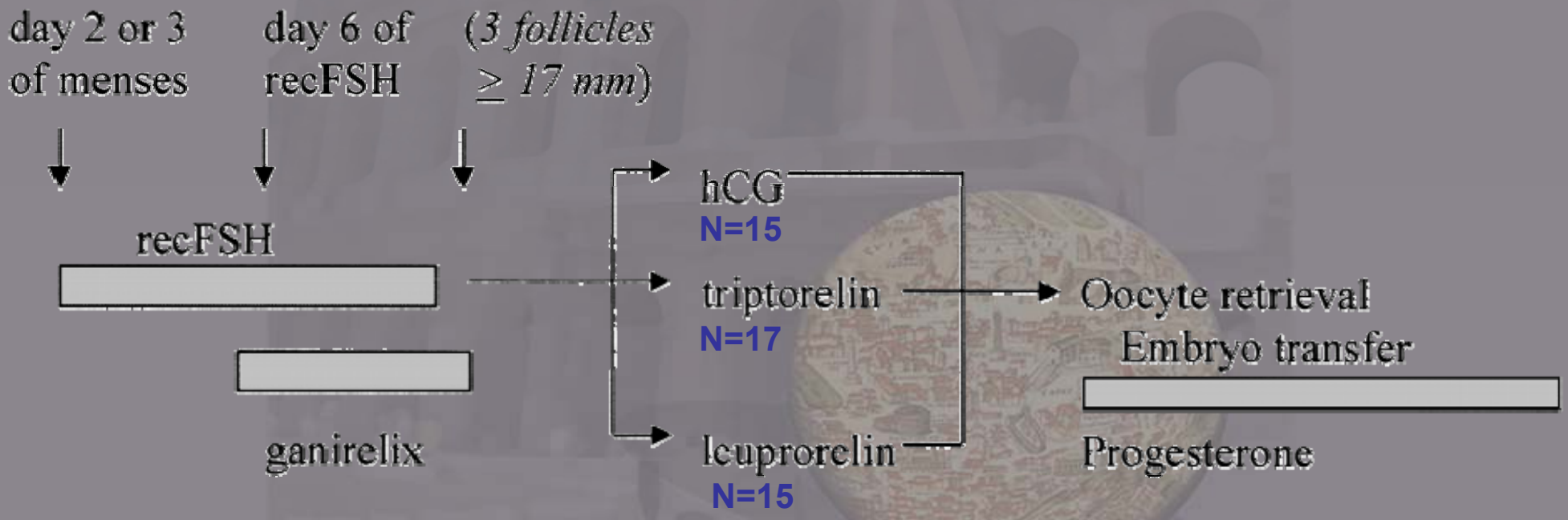
The antagonist era (2002 -

- Introduction of GnRH antagonist in ovarian stimulation protocols for ART revived the interest for using GnRH agonist as ovulation trigger.

Fauser, B. C. et al. J Clin Endocrinol Metab 2002;87:709-715

Ovarian stimulation for IVF using recombinant FSH and ganirelix followed by the triggering of final oocyte maturation by a single dose of two GnRH agonists (triptorelin or leuprorelin) or hCG.

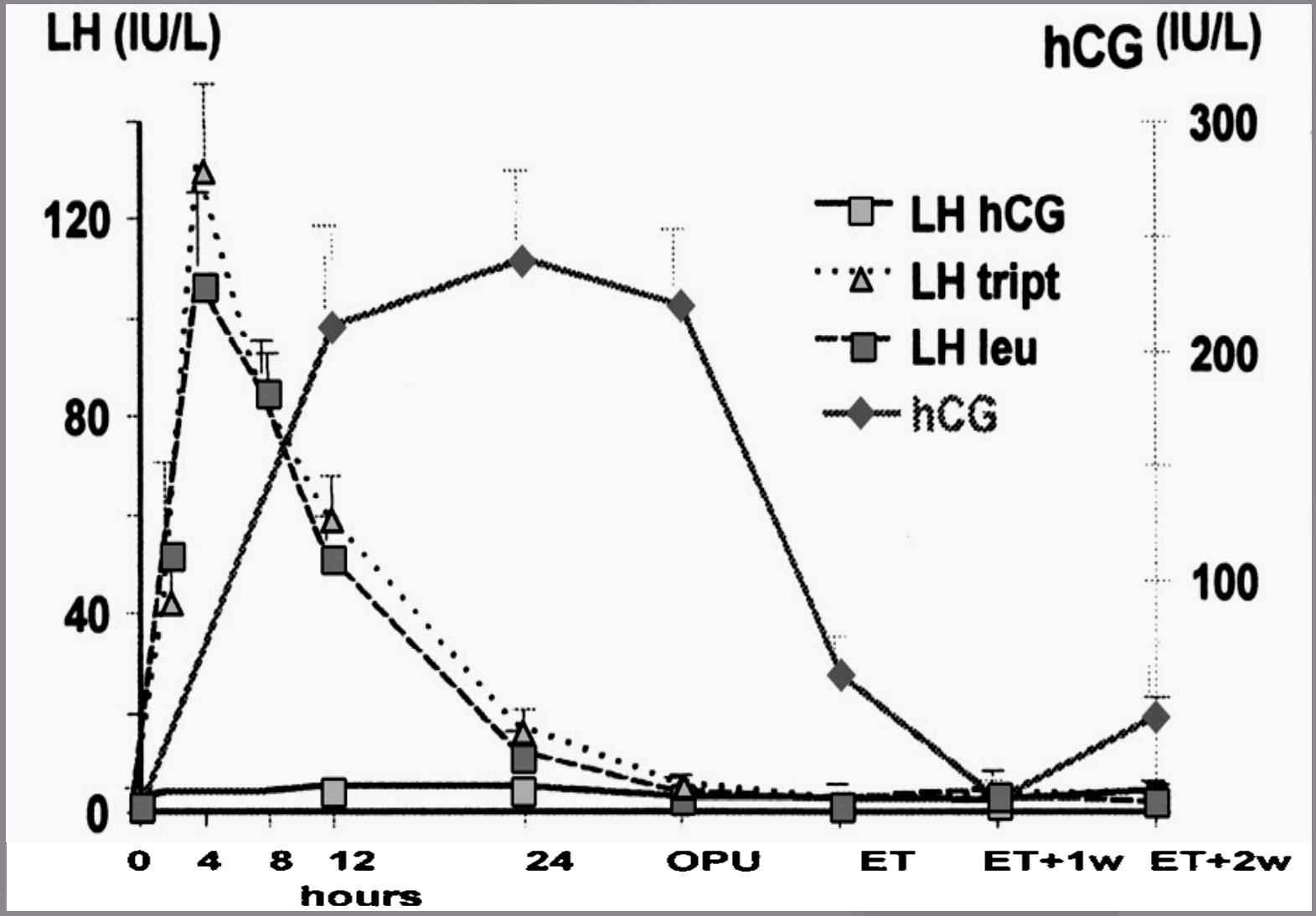
DESIGN:



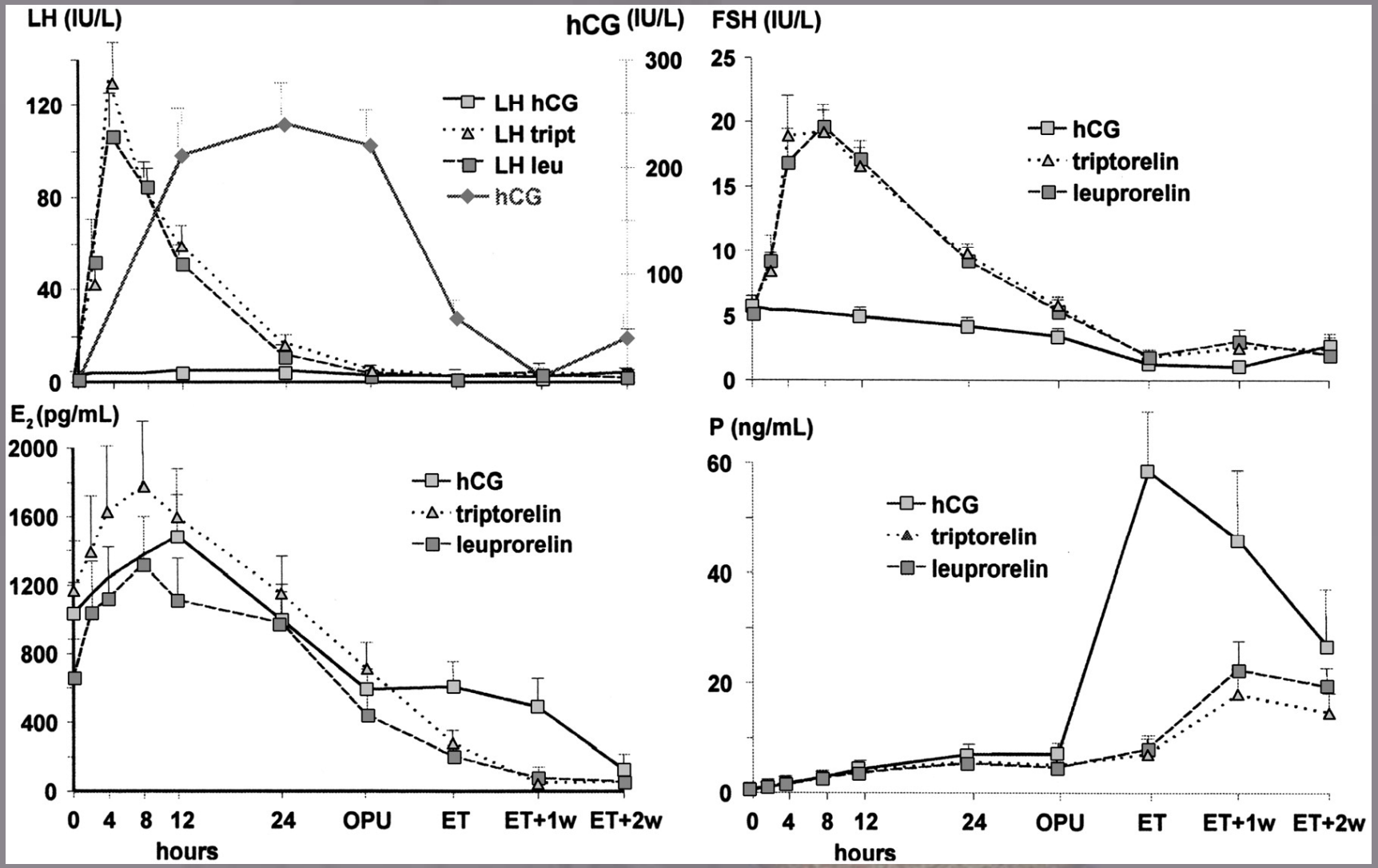
Fauser, B. C. et al. J Clin Endocrinol Metab 2002;87:709-715

Endocrine profile during the peri-ovulatory and luteal phases

Se-LH activity (LH and hCG) profile



Endocrine profiles during the peri-ovulatory and luteal phases



Fauser, B. C. et al. J Clin Endocrinol Metab 2002;87:709-715

Later and larger RCT's comparing GnRH agonist and hCG as ovulation trigger in FSH/GnRH antagonist stimulated ART cycles:

Humaidan P. et al. Hum Reprod 20:1213-, 2005

- Danish two-centre trial, included 122 normogonadotropic women for IVF/ICSI
- Ovulation triggers : sc Buserelin 0.5 mg (N=55) or sc hCG 10.000 IU (N=67)
- Luteal support: vag. progesterone (Crinone) 90 mg/day + oral E2 4 mg/day

Kolibianakis EM et al. Hum Reprod 20: 2887 -, 2005

- Belgian/German two-centre trial, included 106 normogonadotropic women for IVF/ICSI
- Ovulation triggers: sc Triptorelin 0.2mg (N=52) or sc hCG 10.000 IU (N=54)
- Luteal support: vag. progesterone (Utrogestan) 600 mg/day + oral E2 4 mg/day

Both trials were stopped prematurely due to poor reproductive outcome in the agonist groups

Meta-analysis of RCTs comparing GnRH agonist and hCG as ovulation triggers

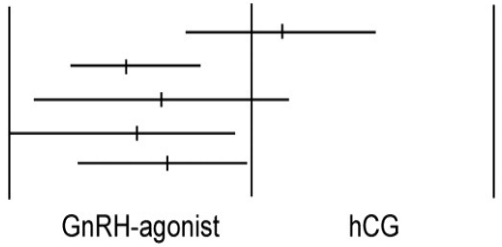
Griesinger, G. et al. Hum Reprod Update 2006 12:159-168

Inclusion criteria: a) prospective randomized trial; b) short FSH/antagonist protocol for COH c) GnRH-a used as ovulation trigger; d) control group with hCG as ovulation trigger

Only 3 of 23 published studies satisfied these inclusion criteria

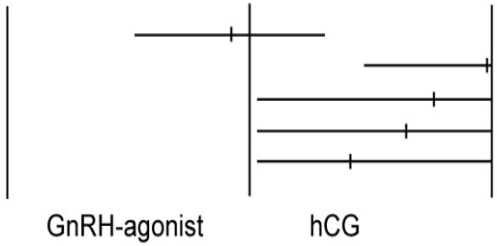
Pregnancy rate per randomised patient : ***Significantly decreased in the agonist group***

Citation	EffectName	GnRH-agonist	hCG	NTotal	Effect	Lower	Upper	PValue
Fauser, 2002	PR	6 / 32	2 / 15	47	1,500	,265	8,489	,645
Humaidan, 2005	PR	3 / 55	24 / 67	122	,103	,029	,367	,000
Kolibianakis, 2005	PR (centre 2)	1 / 34	5 / 30	64	,152	,017	1,380	,060
Kolibianakis, 2005	PR (centre 1)	1 / 18	10 / 24	42	,082	,009	,724	,008
Combined (4)		11 / 139	41 / 136	275	,214	,055	,840	,027



Pregnancy loss ***Significantly increased in the agonist group***

Citation	EffectName	GnRH-agonist	hCG	NTotal	Effect	Lower	Upper	PValue
Fauser, 2002	Preg. loss	5 / 11	3 / 5	16	,556	,065	4,755	,590
Humaidan, 2005	Preg. loss	11 / 14	1 / 25	39	88,000	8,201	944,219	,000
Kolibianakis, 2005	Preg. loss (centre 2)	5 / 6	1 / 6	12	25,000	1,200	520,734	,021
Kolibianakis, 2005	Preg. loss (centre 1)	2 / 3	1 / 11	14	20,000	,848	471,576	,031
Combined (4)		23 / 34	6 / 47	81	11,515	,954	138,988	,054



Nota bene: Standard luteal support with progesterone and oestradiol in all studies

Why such a poor reproductive outcome in the group receiving GnRHa for ovulation induction?

- Poor maturation of the follicle enclosed oocyte?

  and/or

- Luteal phase deficiency ?

Possible reasons for the poor reproductive outcome using GnRH agonist as ovulation trigger

Poor maturation of the follicle enclosed oocyte?

Not likely!

- **Number of retrieved oocytes, fertilization and embryo development rates similar between GnRH-a and hCG groups in all previous studies**
  (Griesinger et al., meta-analysis, Hum Reprod Update 12: 159-, 2006)
- **Significantly increased rate of MII oocytes in ICSI cycles in one study (FSH effect?).**
  (Humaidan et al., Hum Reprod 20: 1213-, 2005)
- **Follicular fluid hormonal profile in GnRH-a triggered cycles in agreement with normal preovulatory follicular maturation.**
  (Yding Andersen et al., Hum Reprod 21: 2116, 2006)
- **Oocytes from donors triggered with GnRH-a or hCG result in similar ongoing pregnancy and implantation rates in recipients**
  (***Acevedo et al., Fertil Steril 86: 1682-, 2006)***

Possible reasons for the poor reproductive outcome using GnRH agonist as ovulation trigger

Luteal phase deficiency ?

Most likely!

- All previous studies have shown significantly shorter luteal phase and lower se-progesterone and se-E2 in the luteal phase in GnRH-a versus hCG triggered cycles.
- Reason: The luteotropic signal resulting from the agonist triggered LH surge is not strong enough to support a normal CL function.
- Standard luteal support with vag. progesterone and oral E2 is not sufficient when GnRH-a is used to trigger final oocyte maturation.

How do we rescue the luteal phase in GnRH-a triggered cycles?

How do we rescue the luteal phase in GnRH-a triggered cycles?

Periovulatory hCG (1500 IU) supplementation. A pilot study

(Humaidan et al., RBM Online, 13:173-, 2006)

- Normogonadotropic women subjected to rFSH/antagonist COH for IVF/ICSI (PCOS ptt excluded)
- Randomisation to ovulation trigger in one of three groups:

1. N=15: hCG 10.000 IU (N=15)
1. N=17: GnRH agonist (buserelin 0.5 mg) + *hCG 1500 IU 12 h later*
1. N=13: GnRH agonist (buserelin 0.5 mg) + *hCG 1500 IU 35 h later (i.e. at OPU)*

GnRHa triggered ovulation and the effect of periovulatory hCG 1500 IU on mid-luteal progesterone and pregnancy outcome

Humaidan et al., RBM, Vol 13,No. 2, 2006

Results

	No cycles	OPU + 7 Se-progesterone, mean (nmol/l)	CPR/Cycle (%)
hCG (10.000)	15	248 ±125[c]	8/15 (53)[a]
GnRH-a+ hCG (1500) *12 hrs*	17	60 ±33[d]	2/17 (12)[b]
GnRH-a + hCG (1500) *35 hrs*	13	103 ±70[e]	6/13 (46)[a]

[c,d,e] $p<0.05$ [a,b] $p<0.02$

Periovulatory hCG (1500 IU) supplementation.A pilot study.

CONCLUSIONS

- *Supplementation with hCG (1500 IU) at **12 h*** after ovulation trigger with GnRH agonist:

  No positive effect on luteal function (se-P4) or reproductive outcome

- *Supplementation with hCG (1500 IU) at **35 h*** after ovulation trigger with GnRH agonist:

  A positive effect on luteal function (se-P4) and a reproductive outcome comparable to that in the group with hCG 10.000 IU for ovulation trigger.

To be confirmed in a larger RCT!

RCT comparing GnRH-a + hCG (1500 IU) after 35 h and hCG (10.000 IU) as ovulation triggers - a Danish three-centre study.

Humaidan, Ejdrup Bredkjær, Westergaard & Yding Andersen
PRELIMINARY RESULTS : ESHRE, LYON, 2007. O-203

- **Inclusion criteria:**
  Normogonadotropic women, aged 25-40 y, regular cycles (25-34 d) BMI: 18-30.

- **COH:**
  rec. FSH (150-200 IU/day) fixed from CD 2-6. Antagonist (ganirelix) 0.25 mg/day when leading foll. ≥ 14 mm

- **Randomization** to ovulation trigger when foll. diam. ≥ 17 mm, ≥ 2 foll.

1. GnRH-a (Buserelin 0.5 mg sc) + hCG 1500 IU sc 35 h later
2. hCG (Pregnyl) 10.000 IU sc

- **Luteal Phase Support:**
  Micronized vag progestrone (Crinone) 90 mg/day and oral estradiol 4 mg/day from day of OPU+1 until OPU + 14

.

RCT comparing GnRH-a + hCG (1500 IU) after 35 h and hCG (10.000 IU) as ovulation triggers - a Danish three-centre study.

305 patients/cycles randomized

GnRH-a/hCG -group	hCG-group
N= 153	N= 152

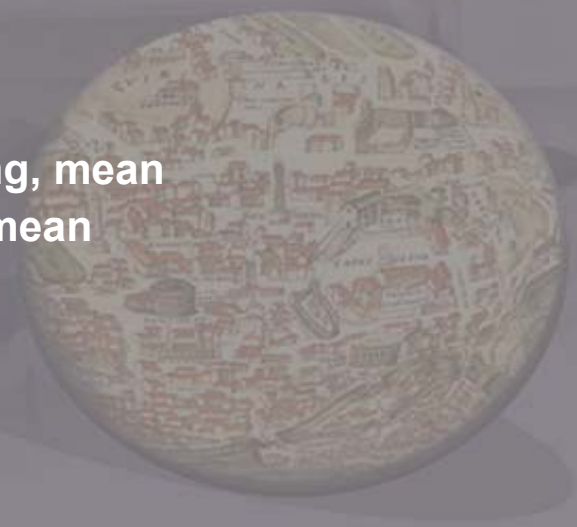
NO SIGNIFICANT DIFFERENCES BETWEEN GROUPS REGARDING:

Demographic data:

- Age, BMI, base-line se-FSH and-LH
- Infertility diagnosis
- Previous IVF/ICSI attempts

Ovarian stimulation outcome:

- Total dose FSH IU, mean
- Total dose GnRH antagonist, mg, mean
- Duration of stimulation, days, mean



.

RCT comparing GnRH-a + hCG (1500 IU) after 35 h and hCG (10.000 IU) as ovulation triggers - a Danish three-centre study.

Results

Oocyte maturation, fertilization and cleavage in GnRHa/hCG vs. hCG-group

	GnRHa/hCG	hCG	P –value *
Patients	153	152	
Oocytes (Mean)	1361 (8.9)	1420 (9.3)	NS
M II (%), only ICSI	85 % (465/546)	81 % (468/574)	P= 0.06
2 PN oocytes total	58% (790/1361)	55% (780/1420)	NS
Good available embryos	30 %	30 %	NS

*) Fishers exact test

RCT comparing GnRH-a + hCG (1500 IU) after 35 h and hCG (10.000 IU) as ovulation triggers - a Danish three-centre study.

Reproductive Outcomes

	GnRHa/hCG	hCG	P-value *
Patients, n	153	152	
Rate of transfer, n (%)	132 (86%)	138 (91%)	NS
Pos. hCG per ET, n (%)	67(51%)	72 (52%)	NS
CP/ET, W7, n (%)	50 (38%)	55 (40%)	NS
IR, n (%)	60/211 (28%)	71/235 (30%)	NS
Early pregnancy loss, n (%)	18/67 (27%)	14/72 (19%)	NS

*) Fishers exact test

RCT comparing GnRH-a + hCG (1500 IU) after 35 h and hCG (10.000 IU) as ovulation triggers - a Danish three-centre study.

REDUCTION OF OHSS RISK?

Combining GnRH-a and hCG for ovulation triggering.

Is it safe?

OHSS: Actual study

hCG-group: Three cases: 2% (3/152)
(1 severe / 2 moderate)

GnRHa/hCG-group : 0 cases: 0% (0/153)

Larger studies in high risk patients needed to prove safety

CONCLUSION

GnRH-a + hCG (1500 IU) after 35 h compared to hCG (10000 IU) as ovulation triggers

GnRH agonist used as ovulation trigger:

- Confirm the tendency towards more MII oocytes (effect of the concomittant FSH surge?)

Supplemented with 1500 IU hCG 35 hours post ovulation:

- Secures a sufficient corpus luteum function

This regimen provides a suitable alternative to hCG induced ovulation in normogonadotropic women

GnRH AGONIST AS OVULATION TRIGGER: A suitable alternative to hCG to reduce risk of OHSS?

Future investigations are needed to prove this:

- RCT comparing risk of OHSS in high risk patients (PCOS/high responders) using GnRH agonist + hCG(1500) or hCG (10.000) as ovulation trigger
- Alternative to hCG to save the CL function after GnRH agonist ovulation trigger:

  Continued intranasal GnRH agonist (buserelin 100µg x 3/day) as luteal support (Pirard et al., HR 21: 1894-, 2006; Loumaye et al., ESHRE, Lyon, 2007; O-206)
- RCTs comparing these two regimens in OHSS high-risk patients