EFFICACY AND SECURITY OF LUTEAL PHASE SUPPORT WITH LOW DOSES OF hCG IN *OHSS RISK PATIENTS* TRIGGERED WITH GnRH AGONISTS

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GnRH agonist for triggering of final oocyte maturation – time for a paradigm shift
ESHRE Campus symposium
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binding secretoglobin, family 2A, member 2 (SCGB2A2, FC x21) and the extra-cellular matrix elastin gene (ELN, FC x20).

Conclusions: The genes that are mis-regulated in P0 endometrium could play a function either at the cell level or in the general morphogenesis process necessary to prepare the uterus epithelium for implantation. Gene expression profile studies on the endometrium during the window of implantation stage could help to improve the success rate of implantation following an IVF cycle. The comparison of gene expression during natural and stimulated cycles will reveal markers associated with a positive implantation or altered by the COS protocol. Such markers will be used to assess the receptiveness of the recipient women's uterus before transfer in order to preserve viable embryos when the critical implantation conditions are not met. Careful monitoring will permit either to adjust the time of embryo transfer, or, when the receptiveness of the endometrium is seriously compromised, to report the embryo transfer to another cycle.

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O-202 Oral Efficacy and security of luteal phase support with low doses of hcg in ohss high risk patients triggered with GnRH agonists

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Introduction: The aim of this study was to determine the efficacy and security of luteal phase support using hCG in high responders patients triggered with GnRH agonists in IVF/ICSI – ET antagonists cycles.

Material and methods: Prospective observational study at a university center. 193 OHSS high risk patients; following flexible and multiple dose protocol with GnRH antagonists (cetrorelix 25 mg S.Q. commenced when the leading follicle was >14 mm in diameter), were triggered with a single dose of 1,5 mg S.Q. of GnRH agonist (leuprolide acetate) for ovulation. All patients received recombinant FSH for controlled ovarian stimulation. hCG low doses (250 – 1000 UI I.M.) every third day for three doses, starting from the next day after oocyte retrieval plus Progesterone 600 mg/day (vaginal route) were used for luteal phase support. hCG in urine 14 days after embryo transfer however, is significantly different from that of the natural cycle. Studies in GnRH antagonist IVF/ICSI cycles found a poor clinical outcome when GnRHa was used to trigger ovulation, presumably due to a corpus luteum deficiency, despite luteal phase support with progesterone and oestradiol. Although a previous study by our group confirmed this, the study also demonstrated that significantly more MII oocytes were retrieved when GnRH agonist was used to trigger ovulation. Encouraged by this positive finding we decided to conduct a pilot study, in which patients who had their ovulation triggered with GnRHa were supplemented with a small single dose of hCG after ovum pick-up (OPU). The results indicated that this modification of the protocol would normalize the corpus luteum function as well as the clinical outcome. The aims of the present study were to corroborate the preliminary results in a large prospective randomised trial including a total of 300 cycles.

Methods: Until now, 202 normogonadotrophic IVF/ICSI patients have been included. Patients were stimulated with recombinant FSH (r-FSH) 150–200 IU per day. When the leading follicle had reached a size of 13 mm, co-treatment with a GnRH antagonist (Orgalutran) 0.25 mg was initiated and continued up to and including the day of ovulation induction. On this day patients were randomised (sealed envelopes) to triggering of ovulation with either 0.5 mg buserelin s.c. (study) or 10 000 IU of hCG (control). Oocyte retrieval was performed 34 hours after triggering of ovulation. In addition, immediately after OPU (i.e. 35 h after triggering of ovulation), the study group was supplemented with a single bolus of 1500 IU hCG i.m. A maximum of two embryos was transferred 2–3 days later. Luteal support was given in the form of micronized vaginal progesterone, 90 mg a day as well as oestradiol 4 mg a day. Blood samples were taken on stimulation days 1 and 6, on the day of ovulation induction, on OPU day, and 7 and 14 days after OPU for later analysis. Moreover follicular fluids were collected for analysis.

Results: Ovulation was induced with GnRHa in 100 patients and hCG in 102 patients. A mean of 9.4 oocytes were aspirated in the GnRHa group versus 9.5 oocytes in the hCG group. A non-significant tendency for more MII oocytes retrieved in the GnRHa versus the hCG group was seen (71% versus 67%). However, in the GnRHa versus hCG group, no differences were seen regarding transfer rates (86% and 91%.), pos hCG/ET (46.5% and 45.2%), clinical PR/ET (40.6% and 41.9%), implantation rate (29.3% and 29.5%), and rate of early pregnancy loss (12.5% and 7.1%). No cases of OHSS were seen in the GnRHa

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ARTICLE

Cycles triggered with GnRH agonist: exploring low-dose HCG for luteal support

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Juan Carlos Castillo obtained his MD degree in 1998 and his speciality degree in Obstetrics and Gynaecology in 2005 at the Grau Emergency Hospital, Lima, Perú. In 2006, he received his Master's degree in Human Reproduction from the Universidad de Valencia, Spain. Since then he has been working as a consultant specialist in reproductive medicine at Hospital Clínico Universitario de Valencia, Spain. His PhD thesis at Universidad de Valencia is focused on the prevention of ovarian hyperstimulation syndrome and will be defended in late 2009.

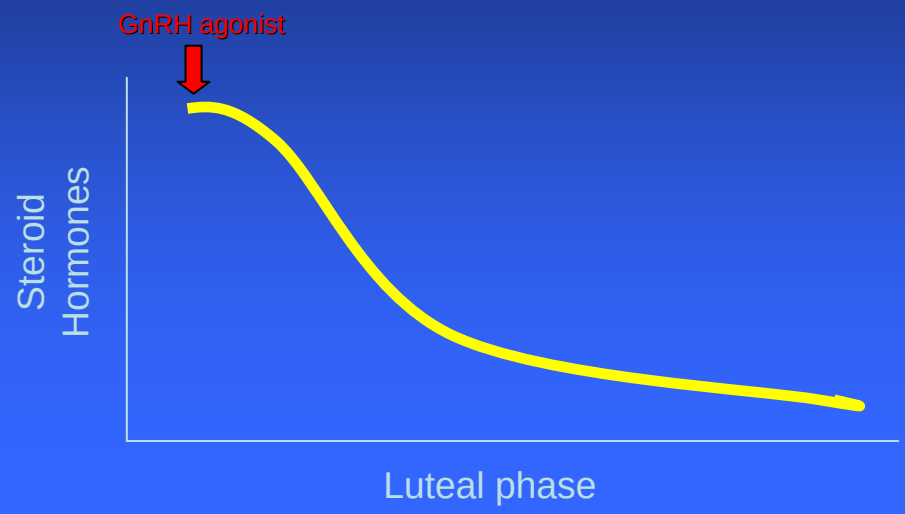
INTRODUCTION

1. Background
   - Use of GnRH antagonists
     (Reissmann *et al.* 1995)
   - Use of GnRH agonist for triggering ovulation
     (Casper 1996)
   - GnRH agonist and OHSS prevention
     (Itskovitz-Eldor *et. al.* 2000)
   - GnRH agonists and defficient luteal phase
     (Fauser *et al.* 2002)
   - Poor outcomes

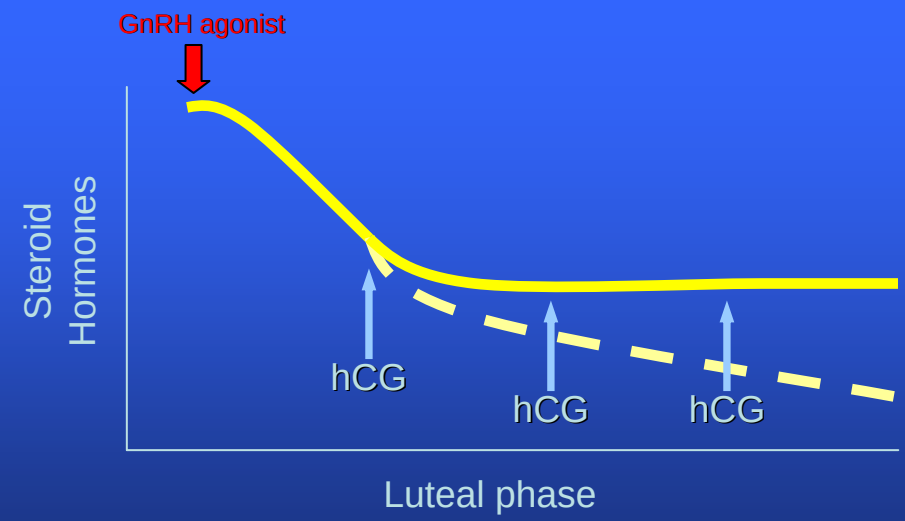
   (Griesinger *et al.* 2006)

INTRODUCTION

2. Theory
   - GnRH agonist may prevent OHSS in *risk patients*
   - Adecuate luteal phase support



3. Hypothesis
   - GnRH agonists with low doses of hCG in luteal phase may prevent OHSS and normalize outcomes in *risk patients*

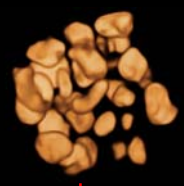


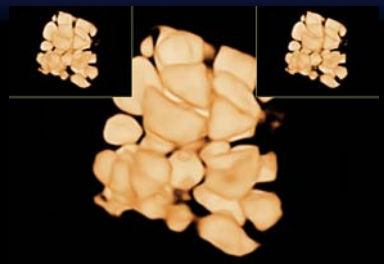
INTRODUCTION

4. Comparative Trial (2002)
   - OHSS *risk patients*
   - Triggered with GnRH agonist
     - Standard support (P4)
     - Support with hCG
   - Stopped prematurely
   - Unpublished data

ACTUAL STUDY

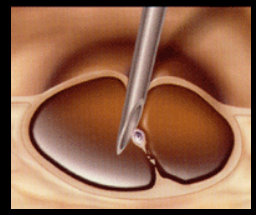
1. Observational (2002-2006)
2. Inclusion criteria
   - High responders: More than 14 follicles > 14 mm the triggering day
3. Protocol





Antagonist
0,25 mg/d

FSHr

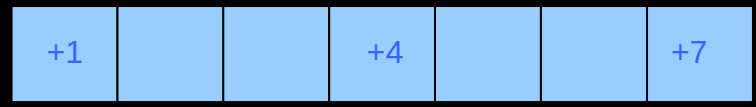


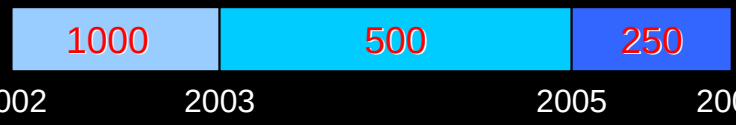
Leuprolide
Acetate 0,3 ml
(1,5 mg)

Main outcomes

Pregnancy rate

OHSS





DATA ANALYSIS

GENERAL DATA

	1000	500	250	Kruskal Wallis test	Total
n	44	115	33		192
Age	33,5	32,68	32,18	0,2	32,7
Stimulation (days)	8,5	9,3	9,4	0,06	9,1
Estradiol the triggering day (pg/mL)	2371,4	2506,6	2834	0,4	2531,3
Oocytes retrieved	15,9	13,4	17,8	*0,001*	14,8
Embryos transferred	2,6	2,1	1,9	*0,000*	2,1

PREGNANCY RATE

				Chi-square	
Pregnancy rate (%)	54,5	51,3	50	*0,911*	51,8
Clinical pregnancy (%)	47,2	42,8	40,3	NS	43,4

DATA ANALYSIS
OHSS

	1000	500	250	Chi-square test	Total
OHSS Moderate (%)	4 (9.1)	3 (2.6)	1 (2.9)	*0.172*	8 (4.1)
OHSS Severe (%)	2 (4.5)	4 (3.5)	1 (2.9)	*0.923*	7 (3.6)

		Pregnancy test	
		Negative	Positive
hcg in luteal phase	1000	0	2
	500	0	4
	250	1	0
Total		1	6
%		14,3	85,7

Days since induction of ovulation until diagnosis (mean) : 11,8

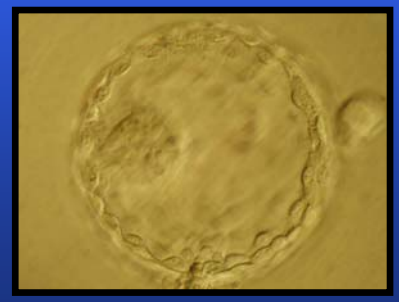
CONCLUSIONS

Despite the design of the study

1. A single dose of GnRH agonist for ovulation induction plays an importan role in the management of patients at *risk* for OHSS.
2. Luteal phase support with low doses of hCG in these cases, secure a normal pregnancy outcome, although: *The optimal dose is yet to be determined.*
3. Severe OHSS in this protocol were *late* forms of OHSS clearly related to pregnancy.
4. It is recommended to transfer a *single embryo* in this protocol.

NEXT STEPS

1. To find the *minimal effective dose* of hCG comparing 500 vs 250 IU hCG
2. To explore the impact of this protocol combined with the SBET technique over the incidence of severe forms of OHSS.



MINIMAL EFFECTIVE DOSE OF hCG AS LUTEAL PHASE SUPPORT IN *OHSS RISK PATIENTS* TRIGGERED WITH GnRH AGONISTS

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C 11- Transferencia embrionaria electiva en blastocisto en pacientes de buen pronóstico: resultados preliminares

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Unidad de Reproducción Asistida. Hospital Clínico Universitario de Valencia

Objetivo: Valorar los beneficios de la transferencia embrionaria electiva en estadio de blastocisto.

Material: Análisis de 231 ciclos de FIV-TE en pacientes de un 1º ó 2º ciclo de FIV consideradas de "buen pronóstico"; normo-respondedoras, > de 5 ovocitos fecundados y más de 3 embriones de alta calidad en día +2 ó +3. Cultivo prolongado con medios secuenciales G 1 / G 2 plus v.3 de Vitrolife. Se establecen dos grupos: grupo control: pacientes con transferencia embrionaria en día +2 ó +3 en el que alguno de los embriones sobrantes alcanzaron el estadio de blastocisto, y el grupo de estudio: pacientes con transferencia embrionaria en día +5 en estadio de blastocisto.

Resultado: Se realizaron 232 transferencias. 101

C 12- Dosis mínima eficaz de hCG como soporte lúteo en pacientes con riesgo de SHO y maduración final con agonista GnRH

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Unidad de Medicina Reproductiva. Departamento de Ginecología y Obstetricia. Hospital Clínico Universitario de Valencia. España.

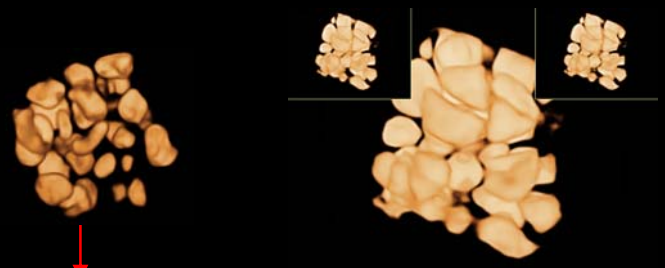
Objetivo: Evaluar resultado clínico y dosis mínima eficaz de hCG como soporte lúteo en altas respondedoras con maduración final de agonistas-GnRH en ciclos FIV/ICSI-antagonistas.

Material: 30 pacientes con riesgo de SHO, recibieron FSHr y antagonistas (cetrorelix 25mg/día). 1,5mg de agonista-GnRH (leuprorelina) fue empleado para maduración final. En la punción fueron aleatorizadas a recibir hCG-250-UI (n=15, grupo-1) o hCG-500-UI (n=15, grupo-2) i.m. cada tres días (tres dosis) y progesterona 600mg/día/vaginal como soporte lúteo. TIG 14 días post-transferencia y ultrasonido de 10 semanas verificaron gestación.

Resultado: Sin diferencias entre grupos 1 y 2 en: edad (35,4±2,7 vs 33,3±4,3años), estimulación (9,2±2,2 vs 9,8±1,6 días), antagonistas (0,8±0,3 vs

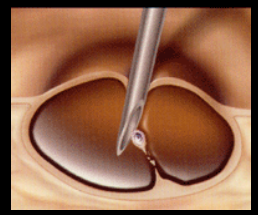
DESIGN

1. Prospective randomized comparative trial (2007)
2. Inclusion criteria
   - High responders: More than 14 follicles > 14 mm the triggering day
3. Protocol



Antagonist
0,25 mg/d

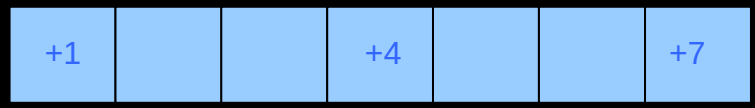
FSHr



Leuprolide
Acetate 0,3 ml
(1,5 mg)

Main outcomes

- Pregnancy rate
- OHSS
- Singleton term live birth per cycle



500 vs 250

DATA ANALYSIS

GENERAL DATA

	250	500	P-value
Nº of patients	15	15	
Age	35,4 +-2,7	33,3 +-4,3	NS
ART			
IVF (%)	5(33)	6(40)	
ICSI (%)	8(53)	7(47,7)	NS
IVF-ICSI (%)	2(13)	2(13)	
Total dose of FSH (IU)	1763,2 +- 559	2169 +- 519	0,04
Duration of FSH stimulation (days)	9,2 +- 2,2	9,8 +- 1,6	NS
Total dose of antagonist (mg)	0,8 +-0,3	1,0 +- 0,2	NS
Serum estradiol (pg/ml)			
triggering day	2870 +- 1289	2884 +- 498	NS

DATA ANALYSIS
OUTCOME

	250	500	P-value
Nº of patients	15	15	
Nº of oocytes	22,3 +-8,6	17 +- 8,8	NS
% of mature oocytes	74	68	NS
Nº of embryos	13,2 +- 6	10 +- 6,2	NS
Nº of embryos transferred	1,73 +- 0,4	1,73 +- 0,4	NS
Embryo stage per transfer (%)			
Cleavage	6/15 (40)	5/15 (33,3)	
Blastocyst	9/15 (60)	10/15 (66,7)	
Single Blastocyst Embryo Transfer (%)	4/9 (44)	4/10 (40)	
Positive hCG (%)	6/15 (40)	8/15 (53,3)	NS
Clinical pregnancy (%)	4/15 (26,7)	6/15 (40)	NS
Early pregnancy loss (%)	2/6 (33)	2/8 (25)	NS
Birth outcome (%)			
Term	3/4 (75)	5/6 (83)	NS
Pre-term	1/4 (25)	1/6 (16)	NS
Singleton term live births per cycle (%)	3/15 (20)	5/15 (33)	NS

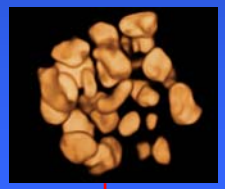
DATA ANALYSIS
OHSS

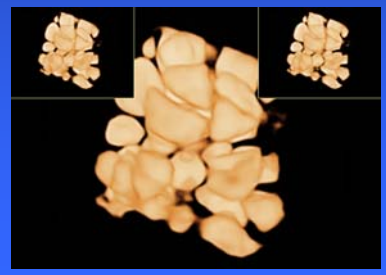
	250	500	P-value
OHSS			
Moderate (%)	1 (6,7%)	0	NS
Severe (%)	0	1 (6,7%)	NS

CONCLUSIONS II

1. Luteal phase support with low doses of hCG in *high risk patients*, secure a normal pregnancy outcome.
2. However, ongoing pregnancy rate in group 1 (250 UI) suggests that this dose might be ***insufficient***.
3. It is strongly recommended to transfer a **single blastocyst** in this protocol.

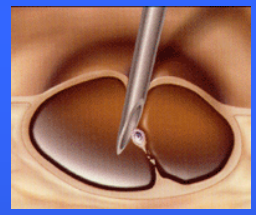
PROTOCOL SUGGESTED





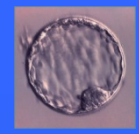
Antagonist
0,25 mg/d

FSHr



Leuprolide
Acetate 0,3 ml
(1,5 mg)

SBET



+1			+4			+7

hCG

hCG

hCG

500

FINAL CONCLUSIONS

1. A single dose of GnRH agonist for ovulation induction plays an importan role in the management of patients with ***high response*** at high ***risk*** for OHSS.
2. A subsequent luteal support with scheduled ***500 IU*** of hCG secures a normal pregnancy outcome.
3. This protocol ***always*** allows transfer in ***fresh cycles***.
4. A *single blastocyst embryo transfer* protocol is strongly recommended within this approach.

Thanks for your attention

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