Role of luteinizing hormone supplementation in the follicular phase and pregnancy, during controlled ovarian hyperstimulation in in vitro fertilization

Systematic review by:

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## Outline of the presentation

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## Introduction

- Luteinizing hormone (LH) has been well known as a contaminator of Follicle stimulating hormone (FSH) during the process of controlled ovarian hyperstimulation (COH) in In vitro fertilization (IVF)
- HMG has been purified to produce the highly purified FSH
- With the Chinese hamster recombinant model, recombinant FSH and recombinant LH had been developed
- AND SINCE THEN, the role of LH in the induction protocols had been restudied again

### Background Normal menstruation

 FSH AND LH act synergistically to promote follicular development and estradiol synthesis and to determine follicular rupture and ovulation (the two cell theory):

1. FSH induces a cohort of follicles, stimulates aromatase enzyme in granulosa cells & induces LH receptors on the granulosa cells

2. LH induces androgen synthesis in the theca cells, which acts as a growth factor to the follicle as well together with LH, may share in the granulosa cell apoptosis and follicular atresia (i.e. modulation of folliculogenesis)

# Background LH supplementation and dose

- Experimental and clinical evidence seems unequivocal, ovarian follicles have development-related requirements for stimulation by luteinizing hormone
- Many studies suggest that LH supplementation improves pregnancy rate and it is beneficial to be added to ovulation induction protocols [Ferraretti et al; Filicori et al (a); Filicori et al (c); Gordon et al]
- While other studies show that it decreases pregnancy rate [Sills et al; Daya et al; De Placido et al; De Placido et al (b)]

# Objective

 The objective of this systematic review is to detect the effect of LH supplementation to FSH during the follicular phase of controlled ovarian hyper stimulation in in vitro fertilization on the pregnancy rate and also to detect if there is a relation between FSH and LH ratios on the pregnancy rate

## Inclusion Criteria: Criteria for considering studies for this review

- Types of studies
  Randomised controlled trials (RCTs)
- Types of participants

Women undergoing pituitary desensitization with GNRH analogue

### Types of interventions

They undergo controlled ovarian hyperstimulation with FSH in one group and FSH and LH in the other group followed by In vitro fertilization and embryo transfer (IVF-ET)

#### Types of outcome measures

-Primary outcome measure: number of pregnancies (Chemical pregnancy) in each group

-Secondary outcome measures: number of fertilization in each group as well as number of pregnancies between >1 FSH:LH ratio group and ≤1 FSH:LH ratio group

# Methodology

Search strategy for identification of studies

- Different computer data bases: the PubMed, the Cochrane library, the Reproductive health library & Google search

- *keywords* : LH supplementation, controlled ovarian hyperstimulation, In vitro fertilization

Methods of the review (online & hand searching)

- WHO library

- Library of the Faculty of medicine, University of GENEVA

#### Description of studies

14 RCTs had been found, where 3 had been excluded due to insufficient information

[The oldest trial was on September 1993]

[The most recent was on February 2005]

# Methodology

### Methodological quality of included studies

All the trials have the inclusion criteria. They represent the results in the form of **number of pregnancies** in all of them (Allocation concealment A)

Some of the studies present also <u>fertilization rate</u>, <u>implantation rate</u>. very few of these present the <u>multiple pregnancy rate</u>, <u>abortion rate and live birth rate</u>. One study of <u>DePlacido et al 2005</u> described <u>cancellation</u> of IVF-ET due to OHSS risk, other three studies stated that there were no OHSS

### Statistical Analysis

It was done by the **<u>Review Manager software(4.2.7)</u>** of the Cochrane Collaboration

### Results: Primary outcome

Review: Role of luteinizing hormone supplementation in the follicular phase and pregnancy during COH in IVF

Comparison: 01 pregnancy rate in the (FSH+LH) / (FSH only)

Outcome: 01 number of pregnancies

Study FSH+LH FSH only RR (fixed) Weight RR (fixed) or sub-category πN πN 95% CI % 95% CI Year Duijkers et al 22/110 2/10 2.14 1.00 [0.27, 3.65] 1993 Daya et al 14/117 22/115 12.98 0.63 [0.34, 1.16] 1995 Sills et al 5/145.81 0.55 [0.25, 1.21] 11/171999 Filicori et al (a) 6/25 5/25 2.92 1.20 [0.42, 3.43] 2001 Gordon et al 19/59 15/69 8.09 1.48 [0.83, 2.65] 2001 Ngetal 5/20 2.34 1.25 [0.39, 3.99] 2001 4/20Filicori et al (b) 18/90 6/30 5.26 1.00 [0.44, 2.29] 2002 Filicori et al (c) 7/25 2.34 4/25 1.75 [0.58, 5.24] 2003 De Placido et al 16/46 22/46 12.87 0.73 [0.44, 1.20] 2004 Ferraretti et al 24/76 13.83 28/104 1.17 [0.74, 1.85] 2004 De Placido et al (b) 39/115 53/112 31.41 0.72 [0.52, 0.99] 2005 Total (95% CI) 573 697 100.00 0.89 [0.75, 1.07] Total events: 175 (FSH+LH), 172 (FSH only) Test for heterogeneity: Chi<sup>2</sup> = 11.62, df = 10 (P = 0.31), l<sup>2</sup> = 14.0% Test for overall effect: Z = 1.22 (P = 0.22) 10 0.1 0.2 0.5 2 5 Favours FSH Favours FSH+LH

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### Results: secondary outcomes

Review: Role of luteinizing hormone supplementation in the follicular phase and pregnancy during COH in IVF

Comparison: 02 Fertilization rate in the FSH+LH/FSH only

Outcome: 01 Fertilization rate in FSH+LH / FSH only

Study or sub-category	FSH+LH n/N	FSH n/N		RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl	Year
Duijkers et al	6/10	5/10			1.91	1.20 [0.54, 2.67]	1993
Daya et al	91/109	97/105		•	37.72	0.90 [0.82, 1.00]	1995
Sills et al	10/14	13/17		-	4.48	0.93 [0.61, 1.43]	1999
Ng et al	14/20	11/20		<b>+</b> •	4.20	1.27 [0.78, 2.08]	2001
Ferraretti et al	47/76	62/104		<b>_</b>	19.98	1.04 [0.82, 1.31]	2004
De Placido et al (b)	81/115	82/112		+	31.71	0.96 [0.82, 1.13]	2005
Total (95% CI)	344	368		•	100.00	0.97 [0.89, 1.06]	
Total events: 249 (FSH+LH), 2	270 (FSH)						
Test for heterogeneity: Chi <sup>2</sup> =	$3.79, df = 5 (P = 0.58), l^2 = 0\%$	)					
Test for overall effect: Z = 0.6	65 (P = 0.51)						
			0.1 0.2	0.5 1 2	5 10		
			Fav	vours FSH Favours	FSH+LH		
1/3/2005		WHO	GEME			111111	11

### Results: secondary outcomes

Review: Role of luteinizing hormone supplementation in the follicular phase and pregnancy during COH in IVF Comparison: 03 FSH:LH ratio

Outcome: 01 pregnancy rate in >1 FSH+LH/1 FSH:LH

Study or sub-category	>1FSH:LH n∕N	1FSH:LH nN	RR (fixed) 95% Cl	Weight %	RR (fixed) 95% Cl	Year
Gordon et al	8/30	11/29	-+-	42.98	0.70 [0.33, 1.49]	2001
Filicori et al (b)	9/60	9/30	<b>_</b>	46.10	0.50 (0.22, 1.13)	2002
Ferraretti et al	22/54	2/22		→ 10.92	4.48 [1.15, 17.46]	2004
Total (95% CI)	144	81	•	100.00	1.02 [0.63, 1.66]	
Total events: 39 (>1FSH	(LH), 22 (1FSH:LH)					
Test for heterogeneity:	Chi <sup>2</sup> = 8.45, df = 2 (P = 0.01), l <sup>2</sup> = 76.3	%				
Test for overall effect: 2	Z = 0.09 (P = 0.93)					
			0.1 0.2 0.5 1 2 :	<del></del> 5 10		
			Favours 1FSH:LH Favours >1F	SH:LH		
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### Results: summary

	Number studied	FSH+LH/FSH 95% CI Relative risk	P-value
Pregnancy	1270	0.89(0.75-1.07)	0.22
Fertilization	712	0.97(0.89-1.06)	0.5

 It was found that >1FSH:LH ratio supplementation on pregnancy as compared to 1 or less FSH:LH ratio (only 3 studies); it has 95% confidence interval relative risk of 1.02 (0.63-1.66) and a P-value of 0.93 (non-significant)

## Discussion

- According to the pooled analysis, there was no evidence that one treatment is better than the other
- It seems that LH supplementation reduces pregnancy and fertilization rates slightly but these differences are not statistically significant
- It seems that while comparing different FSH:LH dose ratios, FSH must be more but still not statistically significant
- The results of fertilization and the different drug ratios backs up the primary outcome results

## Discussion: Possible cause of Bias

Small sample size (1270 cases)
 The pregnancy rate per total (implantation)
 No cancellation rate (10 out of 11)
 No incidence of OHSS (EXCEPT one study)

## Conclusions

Implications for practice

LH should not be supplemented during the follicular phase in COH; more research is needed to prove its advantage as well the optimum dose to be used

### Implications for research

Advantages of LH supplementation during the follicular phase as on multiple pregnancy rate and OHSS risk and incidence, has to be addressed and, if this is proved positively, the optimum LH dose during the follicular phase supplementation had to be determined

## **Potential conflict of interest**

As LH supplementation to FSH is no better than FSH alone, are we going to stop using LH with FSH or are we going to use it with FSH, better as HMG, because of low cost?

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