

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)

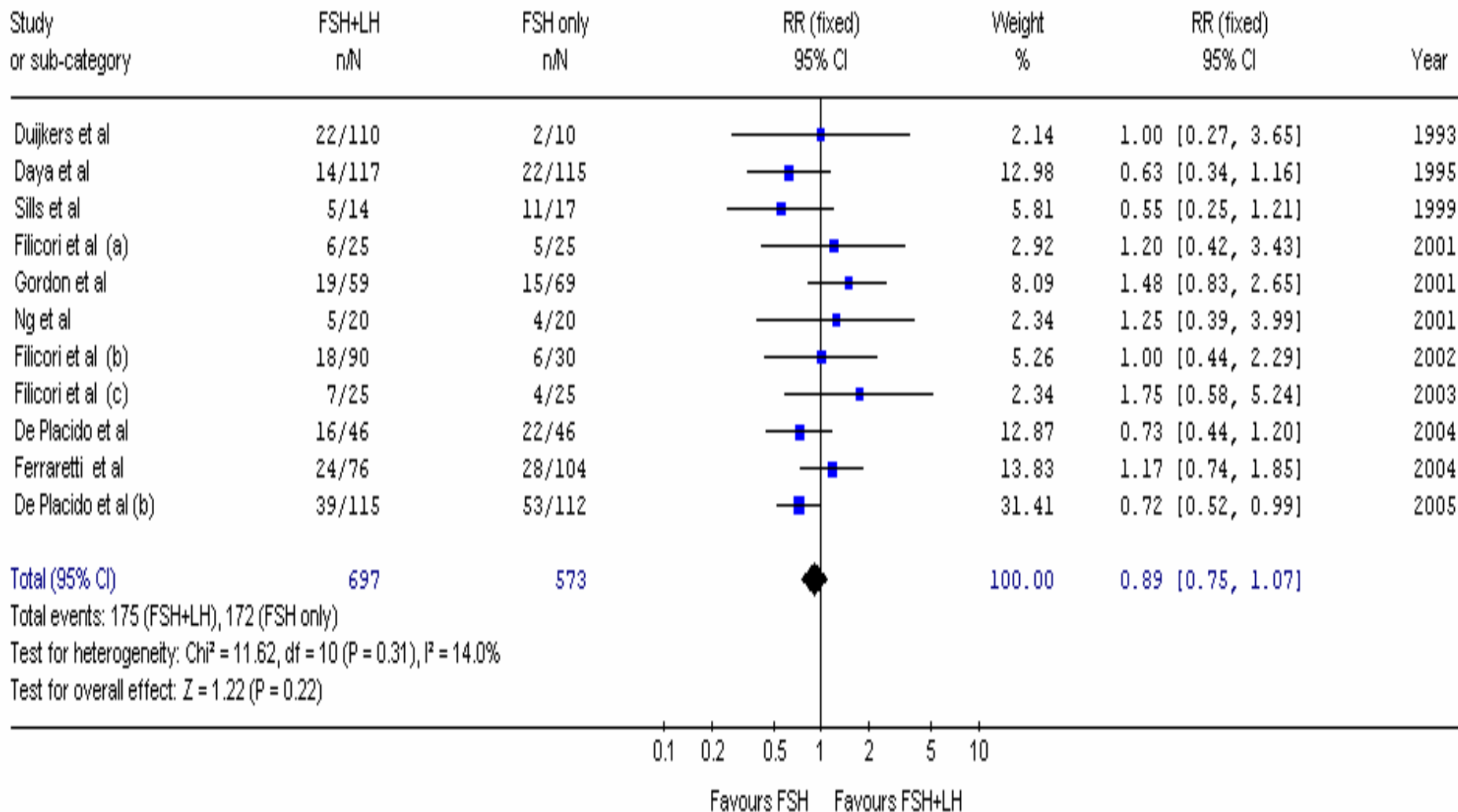
Some of the studies present also fertilization rate, implantation rate. very few of these present the multiple pregnancy rate, abortion rate and live birth rate. One study of DePlacido et al 2005 described cancellation of IVF-ET due to OHSS risk, other three studies stated that there were no OHSS

- ***Statistical Analysis***

It was done by the Review Manager software(4.2.7) 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

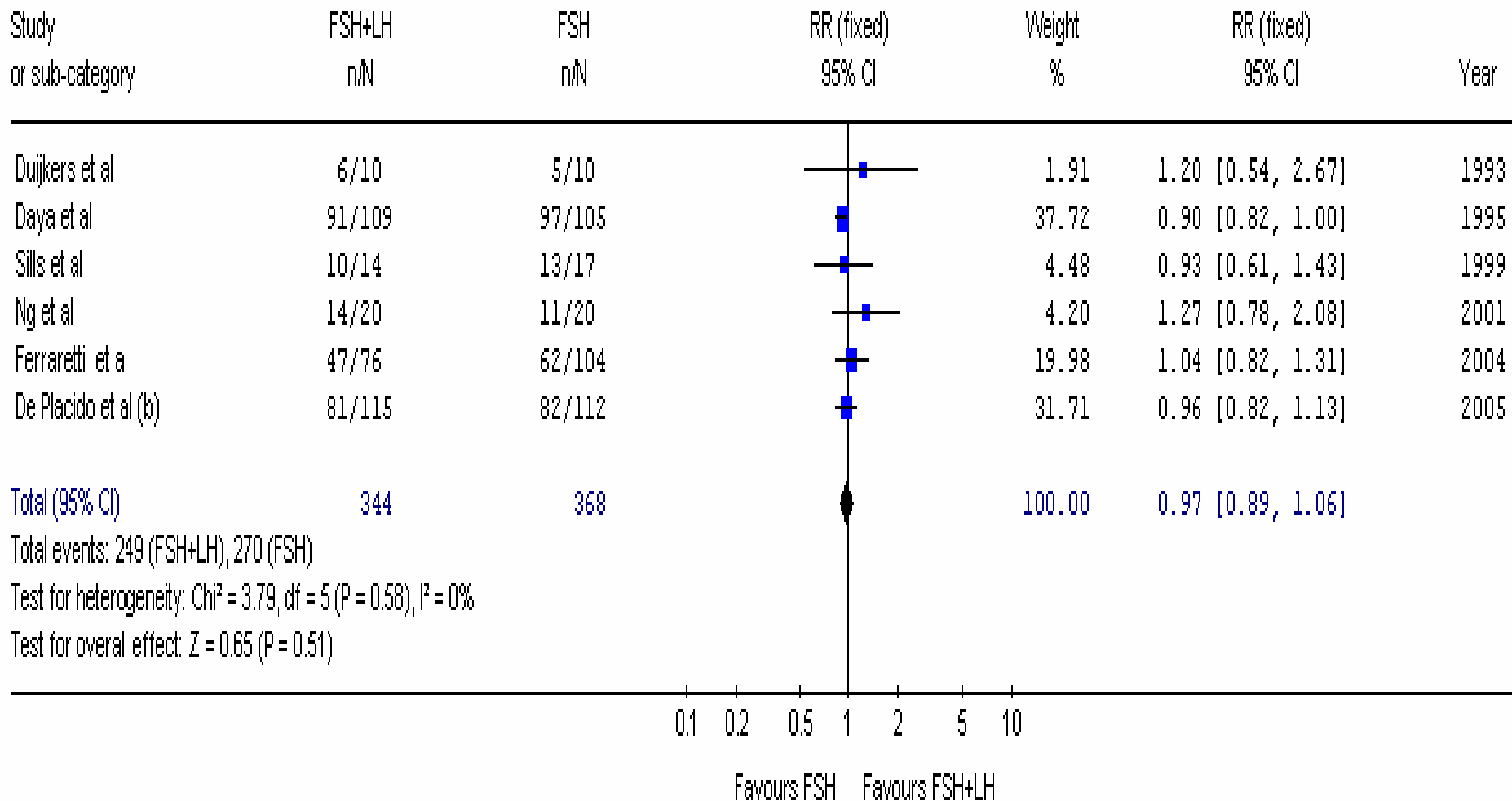


Results: *secondary outcomes*

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

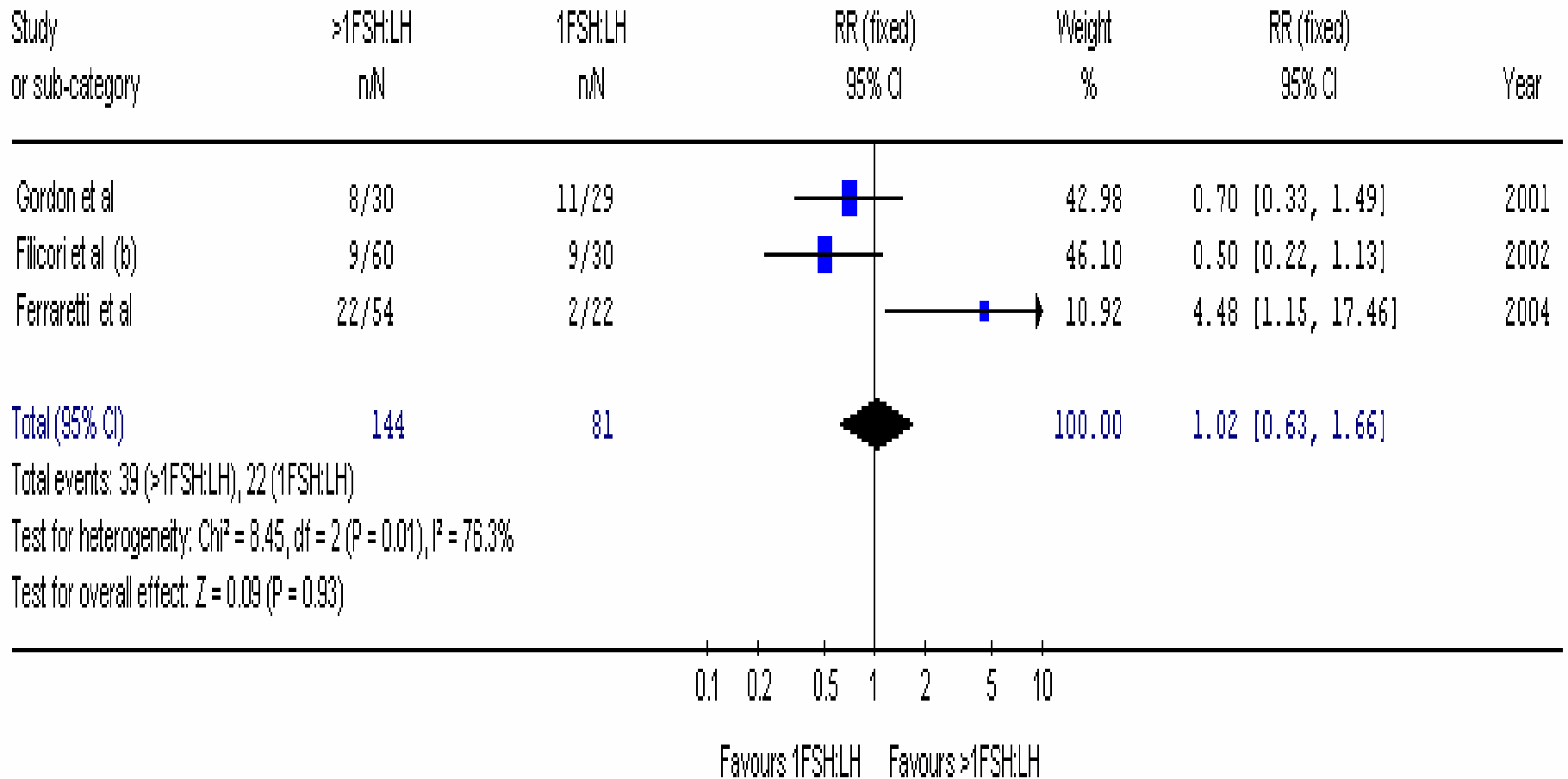


Results: *secondary outcomes*

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



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

1. Small sample size (1270 cases)
2. The pregnancy rate per total (implantation)
3. No cancellation rate (10 out of 11)
4. 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?

Acknowledgments

- I would like to thank **God** for his ever lasting help.....
- Then comes my father and mother who both of them are my guiding light
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Egypt
Thank you

