A prospective comparison of in vitro fertilization (IVF) outcome following controlled ovarian hyperstimulation (COH) regimens using follitropin alpha exclusively or with the addition of low dose human chorionic gonadotropin (hCG) and ganirelix

J.H. Check, E. Davies, D. Brasile, J.K. Choe, J. Amui

The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology & Infertility, Camden, NJ (USA)

Summary

Purpose: To determine if the addition of luteinizing hormone (LH) activity to a controlled ovarian hyperstimulation regimen for purposes of in vitro fertilization adds any additional benefit to the exclusive use of recombinant (r) FSH in antagonist protocols. *Methods:* Women with normal endogenous gonadotropin levels were randomly assigned to receive either follitropin alpha exclusively or have the addition of 25 IU human chorionic gonadotropin (hCG) daily. Ganirelix was used when a 14 mm follicle was attained. The data would be analyzed after 70 women were selected for the study and divided into two groups. *Results:* There were 22 women in each group who proceeded with embryo transfer (some purposely cryopreserved all embryos because of risk of ovarian hyperstimulation syndrome). There were no trends for differences in clinical or delivered pregnancy rates or implantation rates. *Conclusions:* There does not appear to be any clinical advantage of adding exogenous LH activity to the drug regimen for stimulation of multiple follicles for purposes of in vitro fertilization when using follitropin alpha in an antagonist protocol.

Key words: Gonadotropin releasing hormone antagonist; In vitro fertilization; Luteinizing hormone; Follitropin alpha.

Introduction

Two separate meta-analyses comparing urinary follicle stimulating hormone (FSH) and human menopausal gonadotropin (hMG) found that uFSH yielded better results when used alone but observed similar outcomes in women pretreated with a gonadotropin releasing hormone (GnRH) agonist [1, 2]. However a carefully controlled randomized clinical trial comparing recombinant (r) FSH and hMG after down regulation with an agonist observed no difference in pregnancy rates [3]. Nevertheless a meta-analysis of five clinical trials found a higher clinical pregnancy rate in hMG-treated women when using an agonist protocol [3].

Most authors agree that there are so many opposite conclusions about the superiority of regimens that involve exclusive FSH or the addition of some hMG that they are probably equally effective [4, 5].

Most of the studies comparing FSH only to FSH with LH used GnRH agonist protocols. The present study compared the outcomes using a GnRH antagonist protocol.

Materials and Methods

Women were randomly assigned by random numbers table to receive either 300 IU daily of follitropin alpha only (group 1) or the same regimen with 25 IU hCG added (group 2). Ganirelix 250 IU day was added once a 14 mm dominant follicle was obtained.

Oocyte retrieval was 35 hours from hCG injection. Embryo transfer was performed on day 3. Oocytes were inseminated by conventional means or by intracytoplasmic sperm injection. Only women having ≥ 2 embryos transferred were compared.

Women with hypogonadotropic amenorrhea or those with diminished egg reserve were excluded from the study. The plan was to analyze the data after there were 35 women in each group registered. If there appeared to be a trend for a difference in pregnancy rates between the groups in either direction we would perform a power analysis to determine how many more couples to recruit. If there did not appear to be a difference at this stage the study would be stopped.

Results

There were 35 women assigned to each treatment regimen. One woman assigned to group 1, and two in the group with hCG added (Group 2), conceived naturally and were eliminated from the study; one group 2 woman was stimlating poorly and dropped out of the study. Fresh embryo transfers were deferred and all embryos were frozen in 12 women taking FSH exclusively and in 12 adding low dose hCG to the COH regimen for risk of ovarian hyperstimulation. Thus fresh embryo transfers occurred in 22 group 1 women and 20 group 2 women.

Revised manuscript accepted for publication September 22, 2008

Table 1. — *Pregnancy and implantation rates following IVF-ET in women using an antagonist controlled ovarian hyperstimulation regimen according to whether daily low dose hCG was added or not.*

	Total	Follitropin and hCG (Group 2)	Follitropin Only (Group 1)
# retrievals	66	32	34
# transfers	42	20	22
# transfers ≥ 2 embryos	40	20	20
Average age	34.3	35.1	33.6
# follicles	1296	564	732
Avg. # follicles/retrieval	19.6	17.6	21.5
# eggs retrieved	969	413	556
Avg. # eggs retrieved	14.7	12.9	16.4
# metaphase II eggs retrieved	763	343	420
% metaphase II eggs retrieved	78.7	83.1	75.5
# inseminated	819	376	443
# fertilized	505	210	295
% fertilized	61.7	55.9	66.6
# pregnancies	17	7	10
% pregnant/transfer	42.5	35.0	50.0
# clinical	14	7	7
% clinical preg./transfer	35.0	35.0	35.0
# chemical	3	0	3
# ectopic	0	0	0
# delivered	12	6	6
% delivered/transfer	30.0	30.0	30.0
# miscarried	3	2	1
% miscarried	21.4	28.6	14.3
# embryos transferred	120	60	60
Average # embryos transferred	3.0	3.0	3.0
# cryopreserved	330	130	200
# sac implanted	19	10	9
Implantation rate (%)	15.8	16.7	15.0
# twins	3	1	2
% twins/clin. preg.	21.4	14.3	28.6
# triplets	1	1	0
% triplets/clin. preg.	7.1	14.3	0.0

The fertilization rate was 66.6% for the group receiving follitropin alpha only and 55.9% for group 2 receiving additional low dose hCG (p = NS). The clinical pregnancy rate per transfer (2 embryos or more) was 35% (7/20) in each group and the ongoing/delivered pregnancy rate was 30% (6/20) in each group. The respective implantation rates were 15% (9/60) for group 1 and 16.7% (10/60) for group 2. The average age for group 1 was 33.6 years vs 35.1 years for group 2. These results and other important data are provided in Table 1.

Conclusions

Only about 1% of LH receptors need to be occupied to support normal follicular maturation [6]. GnRH agonists usually result in low levels of LH by down regulation but the levels are usually sufficient to allow follicular maturation [7]. There are probably however a minority of women where the GnRH agonist suppressed the LH below the level necessary to allow normal follicular development [8]. There are data suggesting that fertilization, implantation and pregnancy rates may be adversely affected when LH levels are extremely low [9].

Theoretically if one used a GnRH antagonist protocol there should not be suppression of LH at all in menstruating women for most of the follicular phase. Besides using hMG, LH activity can be provided by the use of recombinant LH or low-dose hCG [10]. The present study prospectively evaluated whether the addition of LH activity by adding low- dose hCG provided any improvement in pregnancy rates over the exclusive use of rFSH alone in women using a GnRH antagonist protocol. The hypothesis was that without the marked LH suppression that could sometimes be seen with GnRH agonist protocols, the addition of LH activity would probably not improve the pregnancy rates.

The data did in fact support the aforementioned hypothesis. Thus the decision was made to conclude the study since no clinical differences were found in the data after 40 transfers of ≥ 2 embryos.

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Address reprint requests to:
J.H. CHECK, M.D., Ph.D.
7447 Old York Road
Melrose Park, PA 19027 (USA)
e-mail: laurie@ccivf.com