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Research Article

To compare the effectiveness of recombinant gonadotropin versus the combination of recombinant follicle stimulating hormone and highly purified human menopausal gonadotropin versus urinary human menopausal gonadotropin alone for ovarian stimulation in women undergoing in vitro fertilisation or intracytoplasmic sperm injection treatment cycles

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ABSTRACT

Background: The question of the dominance of recombinant FSH(r FSH) for controlled ovarian stimulation (COS) in in-vitro fertilization (IVF) is not yet defined. Cheaper and equally efficient drugs for COS are valuable for the poor infertile couple.

Methods: This retrospective study includes total of 371 fresh, non-donor, IVF cycles with COS excluding PCOS, endometriosis and poor ovarian reserve patients. To minimize the bias, only the first cycle for each patient below 40 years old, in one year period (Jan 2014 to Dec 2014) was analyzed. This selection comprised of respondents in 3 groups i.e. rFSH n= 132, HP-HMG +rFSH, n=141 and uHMG, n=98. The primary outcome studied as the result of COS are the mean number of retrieved oocytes and mature oocytes, fertilization rate, mean number of good quality embryos, and -cryopreserved embryos. The secondary outcome was the clinical pregnancy rates and the delivery rates.

Results: The current studies do not demonstrate significant differences in duration and dosage of gonadotropins required and clinical outcome of treatment in patients in all 3 groups. We found significant higher E2 levels & better quality oocytes an embryo in patients treated with uHMG and combination groups & significantly increased number of cryopreserved embryos in uHMG group. Lower cancellation rates in rFSH group and HMG group. OHSS rates were similar in all 3 groups.

Conclusions: Treatment with uHMG or with combination could achieve the same results and reduce the whole cost of stimulation in comparison with rFSH

Keywords: Maternal death, Mortality Related to Pregnancy, Pregnancy, Mortality

INTRODUCTION

In the last decade the number of gonadotropins available for ovulation induction and controlled ovarian stimulation (COS) has rapidly expanded. In addition to the introduction of various types of recombinant (r) preparations such as r FSH (a and b), r LH and r CG, better human-derived gonadotropins have also entered the

market. Highly purified (HP) hMG is the latest addition to this family of infertility drugs. The purification process of HP hMG allows its administration through the subcutaneous route with an incidence of local cutaneous reactions comparable with recombinant products. A recent large multicentre trial comparing HP hMG with rFSHa in 727 treatment cycles has shown that these two drugs appear to be equally effective when employed in

assisted reproductive technology programmes.¹ The question of the dominance of recombinant FSH for COS in IVF, as most new medications over other forms of gonadotropins is available, is not yet defined. Studies give advantage to one preparation over the others. A cheaper and equally efficient drug for COS is necessary for the poor infertile couple, prevalent in a developing country like India.

METHODS

This retrospective study is done at Institute of Reproductive Medicine and Women's health, Madras Medical Mission, Chennai, India. This study includes total of 371 fresh, non-donor, IVF/ICSI cycles with controlled ovarian stimulation (COS) excluding PCOS, endometriosis and poor ovarian reserve patients as these conditions could affect the oocyte and embryo quality. To minimize the bias, only the first cycle for each patient below 40 years old, in a year period i.e. Jan 2014 to Dec 2014, was analysed. This selection comprised of respondents in 3 groups i.e. rFSH, n = 132, HP-HMG +rFSH, n=141 and uHMG, n=98. All patients had antagonist protocol. From day 2 of the period, Gonadotropins (Gonal F, Recagon, Menopure, IVF M) according to the group was started and antagonist (Cetrorelix) was added after 5 days of gonadotropins till the day of hCG trigger. E2 level was measured on the day of trigger. Oocyte retrieval was done under USG guidance and under intravenous sedation. After oocytes screening i.e. GV, MI or M II and oocytes abnormality (giant oocytes, large perivitelline space, fragments in perivitelline space, large or too small first polar body and fragmented polar body, presence of refractile body, large or small vacuole and smooth endoplasmic reticulum (SER) in the cytoplasm, all M II oocytes were injected (ICSI) with good morphology sperms. Developmental status of embryos were checked at fertilization i.e. 2 PN stage and at 4 cell stage. Number of embryos having cleavage arrest or rapid cleavage were noted and embryos

had been graded according to morphological criteria i.e. degree of fragmentation and symmetry of blastomeres. According to the developmental status of the embryos they were transferred on day 2, day 3 or blastocyst stage. Fresh embryo transfer using after loading technique was done with endometrial thickness between 8-12 mm with good sub endothelial blood flow. Average 3 embryos were transferred in all 3 groups. In few patients with recurrent implantation failure 4 embryos were transferred. Surplus embryos were cryopreserved and elective cryopreservation of embryos in patients with high estradiol level to prevent ovarian hyperstimulation syndrome. After embryo transfer luteal support was given in form of, vaginal and injectable progesterone preparation. In patients with recurrent implantation failure or with impaired thrombophilia profile Low molecular weight heparin 40 mg subcutaneously and oral aspirin 75 mg was added. Pregnancy test with serum β hCG was done 16 days after the embryo transfer. The primary outcome studied as the result of COS are the mean number of retrieved oocytes and mature oocytes, fertilization rate (FR), number of embryos with cleavage arrest, mean number of good quality embryos, and cryopreserved embryos. The secondary outcome was the cancellation rate, clinical pregnancy rates (CPR), implantation rate (IR), on-going pregnancy report (OPR) and the live birth rate (LBR). Implantation rate was determined by number of embryos transferred and number of gestational sacs on transvaginal sonography (TVS). Clinical pregnancy was documented by transvaginal sonography near 6 weeks of gestation with cardiac activity. On-going pregnancy rates were documented with fetus with good cardiac activity at 12 weeks of gestation.

Data was analysed using Chi square test and Student's t test

RESULTS

Table 1: Clinical parameters in all 3 groups.

Parameters	Recombinant FSH (n=132)	HMG + recombinant FSH (n=141)	Urinary HMG (98)	Sig (P value)	Sig (P value)	Sig (P value)
	Mean	SD	Mean	SD	Mean	SD
Age (yrs)	26	4	27	5	26	2
BMI (kg/m ²)	24.5	2.4	25	2	24.6	2.6
Type of infertility	102/30		109/32		75/23	
Partner's S/A (X 106)	20	4	19.5	3.5	22	3.2
FSH (IU/L)	7	0.4	7.1	0.6	7	0.5
LH (IU/L)	4.5	0.5	4.6	0.4	4.5	0.8
PRL(ng/ml)	16.5	2.4	17	1.9	16.7	2
E2 (pg/ml)	46	2	45.6	2.4	45.3	2.5

Table 2: Amount of gonadotropins and oocyte maturity in all 3 groups.

Parameters	Recombinant FSH (n=132)	HMG + recombinant FSH (n=141)	Urinary HMG (98)	Sig	Sig	Sig
	Mean	SD	Mean	SD	Mean	SD
Average no. of days of gonadotropin administration	10	1	9.8	2	9.7	2.1
Average dose of gonadotropin	2250	100	2275	125	2220	200
E2 on trigger	1700	75	2127	90	2250	80
No of oocytes retrieved	8.3	2.1	7.7	3	7.8	2.4
GV	1	0.11	0.85	0.985	1	0.2
M1	0.6	0.1	0.63	0.2	0.39	0.2
M2	6.7	0.23	6.65	0.3	6.68	0.25

Table 3: Comparison of oocyte quality in all 3 groups.

Parameters	Recombinant FSH (n=132)	HMG + recombinant FSH (n=141)	Urinary HMG (98)	Sig	Sig	Sig
	Mean	SD	Mean	SD	Mean	SD
Central granularity	0.76	0.2	0.42	0.1	0.62	0.3
Multiple vacuole	0.66	0.1	0.08	0.001	0.08	0.02
Empty zona/thick zona	0.27	0.1	0.28	0.12	0.26	0.01
Thick zona/no zona	0.09	0.01	0.007	0.001	0	0
Large PV space	0.53	0.01	0.03	0.02	0.07	0.02
Large/fragmented polar body	0.1	0.01	0.101	0.01	0	0
Giant oocyte	0.0075	0.001	0	0	0	0
SER	0.16	0.01	0	0	0.04	0.2
No of abnormal oocyte (%)	30.9		11.4		13.1	
Total no. of embryos	6.7	0.2	6.68	0.196	6.66	0.3
Grade A	5.08	0.3	5.3	0.2	4.5	0.2
Grade B	1.5	0.1	0.6	0.1	1.3	0.1
Grade C	0.09	0.01	0.02	0.01	0.04	0.1

Table 4: Comparison of clinical outcome in all 3 groups.

Parameters	Recombinant FSH (n=132)	HMG + recombinant FSH (n=141)	Urinary HMG (98)	Sig	Sig	Sig
	Mean	SD	Mean	SD	Mean	SD
OHSS (mild/mod/severe) Rate (%)	24/3/1 (28.0%)		23/5/1 (29.0%)		24/6/2 (32%)	
Cancellation rate (%)	15.9	0.1	29.4	0.4	18.3	0.2
Fertilization rate (%)	79.7	3	79.4	3.1	80	2.9
No. of cleavage arrest or rapid cleavage (%)	16.9	2.5	16.4	2.8	16.7	2.6
Average no. of embryos transferred	3.4	0.2	3.42	0.19	3.4	0.21
D2/D3 transfer/blastocyst	38/68/5		52/48/0		37/43/0	
No. of embryos cryopreserved	2.7	0.1	2.66	0.1	2.7	0.11
Implantation rate	46.8	5.2	47.1	4.8	45.9	5.4
CPR (%)	36.3	2.4	35.9	2.6	35.6	2.45
OPR (%)	30.3	4.2	29.9	3.8	30.5	4.1
LBR (%)	22	2.1	22.4	2.8	21.8	2.2
Pregnancy rate per embryo transfer (%)	43.2	6.4	42.8	5.4	42.4	6
Twin	12		9		6	
Miscarriage rate (%)	6	1.4	6.1	1.38	5.9	1.42

The current study does not demonstrate significant differences in duration and dosage of gonadotropins required. We found significant higher E2 levels in patients treated with uHMG (2127±90) and combination groups (2250±80). There was no significant difference in clinical outcome of treatment in patients in all 3 groups i.e. Fertilization rate (FR), Implantation rate (IR), Clinical pregnancy rate (CPR), On-going pregnancy rate (OPR) and Live birth rate (LBR) Significantly increased number of cryopreserved embryos (2.7±0.11) in uHMG group were present quality of embryos (Grade A: 5.3±0.2 and 4.5±0.02, Grade B: 0.6±0.1 and 1.3±0.1, Grade C: 0.02±0.01 and 0.04±0.1) were significantly better in combination group and in u HMG group and oocytes abnormalities were less in combination group (11.4%) and uHMG group (13.1%). Lower cancellation rates (15.9%±0.1) in rFSH group and HMG group (18.3±0.2). OHSS rates were similar in all 3 groups.

Table 5: Comparison of cost of different drugs used.

Generic name	Unit	Cost (Rs.)
Menotropin urinary HMG	150	850
HP menotropin	150	1900
Recombinant FSH	150	3140 (850X3.6 & 1900X1.6)

DISCUSSION

Although follicular growth can be induced by FSH alone, it needs the LH threshold for proper development.^{2,3} Current study do not demonstrate significant differences in duration and dosage of gonadotropins required. Most previous studies comparing FSH-only gonadotropin preparations with menotropins (providing both FSH and LH activity) failed to uncover significant differences in treatment duration or gonadotropin dose requirements.^{2,4} We found significant higher E2 levels in patients treated with uHMG and in the combination group. The finding of significantly higher E2 levels in patients treated with HP hMG and combination group seems to confirm indirectly that this preparation contains greater amounts of LH activity. However, the increment in serum E2 could be due to: (i) an increase in the androgen substrate produced by LH activity-stimulated theca cells (which nevertheless could not be detected through peripheral serum measurements of testosterone; (ii) to the direct actions of LH activity on the granulosa cell aromatase system of larger follicles that became responsive to LH through the acquisition of specific receptors (iii) better stimulation of the aromatase system by the increased immunoreactive FSH concentrations found in the HP hMG group; or through a combination of these factors.^{5,6} We observed significantly increased number of cryopreserved embryos in uHMG group and hence increased cumulative pregnancy rates, similar to previous studies.⁶ Quality of embryos were significantly better in combination group and oocyte abnormalities were less in combination and in uHMG groups unlike with the previous studies.⁷ Lower

cancellation rates (15.9%) were seen in rFSH group. OHSS rates were similar in all 3 groups but other studies found more in HMG group. When we analysed the specific features of the ICSI procedure, we could not identify any significant difference in clinical outcome of treatment in patients in all 3 groups i.e. fertilization rate, implantation rate, clinical pregnancy rate, on-going pregnancy rate and live birth rate. These results again confirm the findings of the only previous investigation.^{2,4}

Clinical relevance

Treatment with uHMG or with combination could achieve the comparable clinical results with better oocyte and embryo quality. As addition of HMG in combination protocol and u HMG alone reduces the whole cost of stimulation, which is fruitful for poor infertile couples in developing countries like India where resources are limited.

CONCLUSION

This study found that the uses of HP hMG alone or in combination with rFSH are valuable, comparable and cheaper options for COS. But in future it may be difficult to have urinary HMG as it is manufactured from urine of menopausal women.

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