Is the clomifene citrate/human menopausal gonadotropin protocol cost effective in IVF/ICSI treatment?

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Abstract

Objective: The objective of this trial was to evaluate the cost/effectiveness of Clomifene Citrate/Human Menopausal Gonadotropin in comparison to GnRH agonist long protocol/ HMG-HCG in treatment of IVF cycles in infertile couples.
Materials & Methods: This study prospective, controlled trial comprised a total of 88 couples undergoing IVF/ICSI treatment. Patients were divided into 2 groups: 37 couples who could not afford the cost of medications for the long protocol were recruited in group A and stimulated by the CC/HMG protocol. 51 women were recruited in group to receive the GnRH agonist long protocol. The primary outcome measure was clinical pregnancy rate per woman. The secondary outcomes were the total amount of gonadotropins, number of oocytes retrieved, and cycle cancellation rate.

Results: Seventy three women (82%) had reached embryo transfer. Only seventeen women out of the eighty eight women (19%) ended with clinical pregnancy. A total of fifteen cycles were cancelled. The cost of the cycle in the GnRHa/HMG group was significantly higher than cost of the cycle in the clomifene/HMG by 1460 EP (95% CI 1300-1600, p=0.01). The cost of pregnancy in the GnRHa/HMG group was significantly higher than the cost per pregnancy in the clomifene/HMG by 17496 EP (95% CI 16600-18400, p=0.01).

Conclusions: Clomifene/HMG protocol was associated with significantly lower pregnancy and higher cycle cancellation rate compared to the conventional long agonist protocol.
Key words: clomifene citrate, human menopausal gonadotropin, cost effective, IVF/ICSI

Introduction

Clomifene citrate was the first drug to be used for ovarian stimulation in preparation for IVF (1). It was used initially alone (1), then with gonadotropins (2,3). The high rates of cycle cancellation, due to premature LH surges, as well as the deleterious antioestrogenic effect of clomifene on the endometrium were the two main disadvantages of clomifene citrate stimulated IVF protocols (4,5). Later on, the use of clomifene citrate in IVF has been widely disfavoured after the introduction of gonadotropin releasing hormones (GnRH) agonist in IVF practices (6). However, the use of clomifene citrate in IVF was revived again following calls for milder stimulation protocols in IVF (7).

It has been estimated that the cost of medications in IVF represents approximately 50% of the total cost of IVF cycle (8). In countries where IVF treatment is only self-funded, the high cost of the long agonist protocol may hamper some patients from utilizing IVF service (9). The absence of pituitary suppressing drugs as well as the significant reduction in the number of gonadotropins ampoules in the clomiphene citrate (CC)/human menopausal gonadotropin (HMG) protocol, as reported in almost all relevant randomized trials (10-12), may point to some potential economic benefits from that protocol. Hence, we decided to investigate the genuine cost effectiveness of the CC/HMG protocol versus a long-acting GnRH agonist/HMG protocol.

Materials & methods

From December 2006 to December 2010, infertile couples who attended Mansoura Fertility Care Unit (MFCU), seeking ICSI treatment, were approached and asked to participate into the study. Our inclusion criteria included women < 39 years old undergoing their first ICSI cycle. Women with history of previous IVF/ICSI attempt(s) or with azospermic partner were excluded from the study. A total of 88 couples were included. All patients signed an informed written consent. The study was approved by the University Ethics Committee.

Women were assigned to either one of two groups. Thirty seven couples who could not afford the cost of medications for the long protocol were recruited in group A. Those women were stimulated by the CC/HMG protocol; they received CC (Clomid; Merrell Dow SA, Neuilly sur-Seine, France) 100mg daily for 5 days from day 2 of the cycle. From days 7, 150 IU/day of HMG (Merional; IBSA, Geneva, Switzerland) was administered intramuscularly (I.M). From day 7 onwards, daily vaginal ultrasound (using a 7-MHz

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2012
Running title: CC/hMG cost effectiveness in IVF/ICSI

transducer; Medison 5220; Seol, South Korea) and twice daily urinary LH monitoring (Clearplan; Unipath Limited, Bedford, United Kingdom) were performed. Ten thousand units of human chorionic gonadotropin (HCG) (Pregnyl; NY Organon, Oss, The Netherlands) were given I.M. when two or more follicles reached 18mm in mean diameter.

Fifty one women were recruited in group B in whom they received the GnRH agonist long protocol which is the standard controlled ovarian hyperstimulation (COH) protocol in our unit. In brief, Decapeptyl 0.1mg/day was started on day 20 of the cycle until the day of HCG injection. After down regulation was confirmed (by serum E2 and transvaginal ultrasound), 150-225 IU of HMG/day was started for 7days, then the dose was adjusted according to the response.. From day 7, the dose was adjusted according to the follicular response. HCG (Pregnyl1; NY Organon, Oss, The Netherlands), 10 000 IU, was given when at least two follicles had reached 18 mm. Oocyte retrieval was performed 34–36 h after HCG injection, under ultrasound guidance transvaginally using single lumen needle (Labotect Labor-Technik-Göttingen GmbH, Germany). ICSI was performed by the standard technique. Embryo transfer was performed on two or three days following egg retrieval. All patients received luteal phase support with 200 mg of micronized progesterone (Utrogestan; Piette, Brussels, Belgium) daily per vaginum starting from the day of oocyte retrieval. Clinical pregnancy was defined as a visible fetal heart beat on ultrasonography. The primary outcome measure was clinical pregnancy rate per woman. The secondary outcomes were the total amount of gonadotropins used for stimulation, number of oocytes retrieved, multiple pregnancy rate, and cycle cancellation rate and severe ovarian hyperstimulation (OHSS) rate. Clinical pregnancy was confirmed when at least one fetal pole with a detectable cardiac beat could be identified in a gestational sac five weeks after embryo transfer. All cycles ended without embryo transfer, prior to oocyte retrieval for poor response or after retrieval for fertilization failure, were counted within the cancelled cycles. Calculation of the drug costs for HMG were based on the price of the HMG (Merional, IBSA, Switzerland), HCG (Pregnyl, Organon, The Netherlands), Clomifene (Clomid) in Egypt obtained from the Egyptian Ministry of Health (i.e. retail cost). Besides, a fixed fees of 2000 Egyptian Pounds paid by the couples to the Mansoura University Hospitals, Egypt.

Statistical analysis:

All statistical analysis was performed using Statistical Package for Social Science programme version 16 (SPSS). Univariate analysis was conducted to compare variables between the two groups; women on the clomifene/HMG and women on the GnRHa/HMG. Multivariate analysis was conducted to evaluate the association between the outcome (clinical pregnancy) and those factors that potentially influence the outcome. Parametric and non-parametric tests were used to compare groups depending on data whether normally distributed or not. The student "t" test, Mann-Whitney test and Chi-square tests were used whenever appropriate. All tests were two tailed with the statistical significance described at 5% significance level. Mean and standard deviation were used to describe continuous normally distributed data while the median with the range were used to describe the data when non-parametric tests were used. Numbers and percentages were used to describe nominal data. To evaluate the direction and magnitude of differences for continuous outcome measures, we deployed the correlation analysis using the Pearson or Spearman correlation coefficient, for normally distributed and skewed data, respectively. The logistic regression analysis, the forward stepwise conditional method, was deployed to calculate the odds ratio for clinical pregnancy for women on the clomifene/HMG compared to women on the GnRHa/HMG long protocol, before and after adjusting for other significant variables.

Results

A total of 88 women were recruited in this study. Seventy three women 73/88 (82%) reached embryo transfer step. Seventeen women out of the eighty eight women (19%) ended with clinical pregnancy. A total of fifteen cycles were cancelled; 5 prior to oocyte retrieval for poor follicular development and 8 for absence of embryos for transfer due to fertilization failure or cleavage arrest. Thirty seven women were stimulated by the CC/HMG protocol while fifty one women were stimulated by the long GnRH agonist/HMG protocol. The demographic and stimulation characteristics of patients in the two groups are shown in Table I. There were no differences in age, body weight causes of infertility or serum baseline FSH levels between the two groups. Data regarding the outcomes are shown in table 2. The total dose of gonadotropins used (in international units (IU), the number of oocytes retrieved, the number of embryos available, the number of embryos transferred, clinical pregnancy and cancellation rates were significantly different between the two protocols (table 2 and table 3).

Correlation Analyses demonstrated that the number of oocytes retrieved positively correlated with the number of gonadotropins ampoules used ($r=0.322$, $P<0.001$). There was a significant negative correlation between the number of oocytes retrieved and body mass index (BMI) ($r=-0.159$, $P<0.04$) as well as the duration of subfertility ($r=-0.226$, $P=0.003$). Logistic regression was deployed to calculate the odds of clinical pregnancy using the long agonist protocol compared to the CC/HMG protocol. The clinical pregnancy rate was significantly higher with long GnRHa/HMG protocol than with the Clomifene/HMG protocol (unadjusted Odds Ratio (OR) = 4.28, 95%CI 1.13-16.23). however, the pregnancy rate was found not to be significantly different between the two groups after adjustment for the total dose of gonadotropins used and the number of embryos transferred (OR =1.62; 95% CI= 0.31-8.36).

The mean cost of the cycle (Mean±SD) in the clomifene/HMG group was 2600±200 Egyptian Pounds (EP) while it was 4100±400 EP in the GnRHa/HMG group. The cost of the cycle in the GnRHa/HMG group was significantly higher than cost of the cycle in the clomifene/HMG by 1460 EP (95% CI 1300-1600, $p=0.01$). The mean cost per pregnancy in the clomifene/HMG group was 32400±2600 EP while it was 14900±1600 EP in the GnRHa/HMG group. The cost of pregnancy in the GnRHa/HMG group was significantly higher than the cost per pregnancy in the clomifene/HMG by 17496 EP (95% CI 16600-18400, $p=0.01$).

Discussion

This prospective non-randomized trial showed a significant reduction in clinical pregnancy rate in the clomifene/HMG stimulated IVF patients compared to GnRHa/HMG long agonist stimulated patients. Two randomised studies have shown the same results (10,11). Our results are in discordance with the results from some other randomised studies that showed no differences in pregnancy rates (13-18).

Our results have also demonstrated a significant increase in cycle cancellation rate within the clomifene/HMG group compared the long agonist group. These findings were in agreement with similar findings from four randomized studies (10,12,13,16). This is contrary to reports of comparable cancellation rates between the two protocols in few other randomized trials (14,17,18). There is no general consensus on when to cancel an IVF cycle prior to retrieval. Some clinicians relied on the number of 16 or 18 mm size follicles while others might rely on biochemical measures, as serum E2 level or LH level, either independently or twined to ultrasonographic criteria. This lack of consensus on the pre-retrieval criteria for cancellation may explain the inconsistency of these reports.

In agreement with almost all randomized and non-randomized trials in the literature (10,11,13,14,17). There were significant increase in the number of oocytes and embryos available for transfer with the GnRHa/HMG protocol compared to the clomifene/HMG protocol. It had been suggested that this increase in the availability of embryos, despite of the policy of small number of embryos transferred, may provide good chance for selection of embryos for transfer and cryopreservation of the surplus ones (10). The added benefit of cryopreserved embryos on the cumulative live birth rate in the long agonist protocol, compared to the CC/HMG protocol, has never been investigated.

In this study, there was a significant difference between the numbers of embryos transferred in each group. Logistic regression showed that the difference in pregnancy rates has no longer been significant after control for the number of embryos transferred. Similarly, Tummon et al. (1992) found pregnancy rate not to differ between the two protocols after controlling for the number of embryo transferred (16). The limited availability of embryos for transfer and cryopreservation after the clomifene/HMG protocol compared to the long agonist protocol had been reported by many other authors (11,12,19).

The implantation rate was not statistically different between the two protocols in our study which came in agreement with other relevant studies (12,18,20). Embryo implantation depends mainly on embryo quality and endometrial receptivity. Clomifene citrate may yield better quality embryos (21). However, clomifene citrate may also have a deleterious antioestrogenic effect of on the whole reproductive system, including the endometrium receptivity (22-25). It is not clear yet which one of these opposing factors could dominate the other and under which circumstances. This controversy and uncertainty may point to the importance of using live birth as the most important outcome in infertility studies (26). Based on the charges collected by our unit from infertile couples and costs paid by the couples for the medications in the Egyptian market, our study showed that the mean cost of a cycle with the clomifene/HMG protocol was significantly lesser than the mean cost per cycle with the long agonist protocol, however, the cost per pregnancy was three times higher than that with the standard long agonist protocol. We acknowledge the fact that a proper cost analysis should be based on calculating direct, indirect and downstream costs (27).

We are aware of the limitations in our study as our study was not a randomized study. Well-designed randomized trials are meant to provide the highest grade of evidence in absence of a systematic review and meta-analysis of randomized trials. Moreover, our study was underpowered. The small sample size of the population may make it prone to a type one (alpha) statistical error where a significant result would be detected while it is not genuinely existed.

To conclude, the clomifene/HMG protocol was associated with significantly lower pregnancy and higher cycle cancellation rate compared to the conventional long agonist protocol. The limited availability of embryos with this protocol might be responsible for the difference in pregnancy rates between the two protocols. Although the cost of per cycle was significantly reduced with the cc/HMG compared to the long protocol, the total cost per pregnancy with the former was significantly higher than with the later. More studies are warranted to measure more precisely the differences between the two protocols.

Disclosure

There is nothing to disclose for any of the authors

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Legend to tables:

Table (1): Demographic characteristics for all recruited women

Variable		(N=88)
Mean age (years) ±SD		30.9 ± 3.3
Mean BMI ±SD		26.7 ± 2.2
Mean duration of sub-fertility (months) ±SD		72.7 ± 24.6
Mean basal FSH (IU/ml) ±SD		7.6 ± 1.3
Type of sub-fertility Number of primary infertility (%)		74/88 (84%)
Number of secondary infertility (%)		14/88 (16%)
Aetiology of sub-fertility Number (%)	**Male**	23/88 (26%)
	Tubal	25/88 (28%)
	Unexplained	22/88 (25%)
	Endometriosis	10/88 (11%)
	PCOS (%)	8/88 (10%)

Table (2): Comparison between CC/HMG and GnRH agonist/HMG protocols as regard cycle outcomes

	CC+HMG (N=37)	Long agonist N (51)	P value
Clinical Pregnancy Rate	3/37 (8%)	14/51(27%)	0.04*
Multiple pregnancy rate	0/3(0%)	4/14(28%)	0.57
Severe OHSS rate	0/37(0%)	2/51(4%)	0.52
Cancellation rate	11/37(29.7%)	4/51(7.8%)	0.01*
Implantation rate	3/44(7%)	18/139(13%)	0.07
Median number of oocytes retrieved [IQR]	4[2-5]	8[5-10]	< 001*
Median number of embryos available [IQR]	2[0-2]	3[2-6]	< 001*
Median number of embryos transferred [IQR]	1[1-2]	3[2-3]	< 001*

Table (3): Comparison between CC/HMG and GnRH agonist/ HMG protocols as regard patient characteristics and stimulation characteristics

Parameter		CC+HMG (N=37)	Long agonist N (51)	P value
Mean age (years) ±SD		30 .7±3.2	31±3.4	0.62
Mean BMI ±SD		26.7 ±2	26.6 ±2.3	0.83
Mean duration of sub-fertility (years) ±SD		6.6 ±2.3	7.2 ±2.7	0.10
Mean basal FSH (IU/ml) ±SD		7.8 ±1.2	7.4±1.4	0.23
Type of sub-fertility {Number (%)}		Primary 33 (89%)	41(80%)	0.62
		Secondary4 (11%)	10(20%)	
Aetiology of sub-fertility Number (%)	Male	11(30%)	12(23%)	0.37
	Tubal	11(30%)	14(28%)	
	Unexplained	9 (24%)	13(25%)	
	Endometriosis	2(5%)	8(16%)	
	PCOS	4(10%)	4(8%)	
Mean duration of stimulation (days) ±SD		10.2± 0.9	10.5±1.1	0.18
Median amount of gonadotropins used in IU [IQR]		900 [750-1200]	2250 [1575-3750]	< 001*