Comparison of Clinical Outcome and Costs with CC + Gonadotropins and GnRHa + Gonadotropins During IVF/ICSI Cycles

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Objective: To compare clinical outcome and costs of CC + gonadotropins with GnRHa + gonadotropins during IVF/ICSI cycles.

Materials and methods: Clinical outcome and expenses of 382 CC + gonadotropin and 964 GnRHa + gonadotropin cycles were compared. Medication costs were calculated on the basis of the mean number of ampoules and the proportion of various gonadotropins. Costs per clinical pregnancy were calculated on the basis of expenses and clinical pregnancy rates.

Results: Women in the CC + gonadotropin group were younger, and had fewer follicles, oocytes, embryos, and embryos transferred. Clinical pregnancy rates were higher in the GnRHa group (35.9 % vs 26.2%, $p < 0.001$). More ampoules of gonadotropins were used in the GnRHa group (24.0 ± 0.3 vs 20.0 ± 0.5 , $p < 0.001$). Medication costs *per cycle* were higher in the GnRHa group (US\$ 357 vs 248). Expenses *per pregnancy* however were lower in the GnRHa group (US\$ 4197 vs 5335 with IVF; US\$ 5590 vs 7244 with ICSI). When different age subgroups with similar baseline characteristics and stimulation parameters were compared, pregnancy rates were significantly higher in the GnRHa groups. Medication cost *per cycle* was higher in the GnRHa subgroups, and the expense *per pregnancy* was lower with GnRHa protocol.

Conclusions: Cost per cycle is higher with GnRHa + gonadotropin. However, because of the better performance of the GnRHa + gonadotropin stimulation, the cumulative costs are reduced by the time a clinical pregnancy is achieved.

KEY WORDS: Clomiphene citrate; cost; gonadotropin-releasing hormone; in vitro fertilization; pregnancy rate.

INTRODUCTION

The first successful in vitro fertilization (IVF) treatment was reported 25 years ago. Since then assisted reproductive technology (ART) has undergone major improvements. In the early years, oocyte retrieval in the woman's menstrual cycle was carried out without any additional stimulation (1,2). Controlled ovarian hyperstimulation was later introduced to increase

the oocyte yield in order to increase the efficacy of IVF. Various preparations are used to stimulate multiple follicular growth. Clomiphene citrate (CC) is a selective estrogen receptor modulator that induces follicle growth via hypothalamic and pituitary effects (3). Human menopausal gonadotropins (HMG), recombinant follicle stimulating hormone (rFSH), and recombinant luteinizing hormone (rLH) act directly at the level of ovary. The incorporation of these drugs into treatment protocols not only increased efficacy and pregnancy rates, but costs as well. In addition to medication costs, in many countries treatment costs also need to be covered by the couple. These additional expenses, especially when repeated

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cycles are needed, can put a financial burden on some patients.

In most countries, IVF treatment is covered by insurance, and even the medication expenses are covered to some degree. In Hungary, an infertile couple is covered for five IVF cycles (100% of treatment costs); in addition, 50% of medication costs are reimbursed. Several recent reports suggested that insurance coverage has an impact on IVF practices (4,5). If the patient does not have to pay for the treatment, there is less "pressure" on both the physician and the couple undergoing treatment. Therefore, less "aggressive" stimulation with the incorporation of cheaper drugs can be utilized.

In our retrospective study, we evaluated outcome and costs with two stimulation protocols. The combination of CC and HMG requires the use of fewer ampoules of gonadotropins and therefore is associated with lower medication costs. With the gonadotropin releasing hormone agonist (GnRHa) ultrashort protocol, gonadotropins are administered every day and costs are thereby higher. We determined pregnancy rates with the two treatments and calculated medication-only and medication plus treatment costs as well. Further more, we analyzed if any of these treatment combinations were more cost-effective.

MATERIALS AND METHODS

All IVF/ ICSI cycles that were performed at our center from January 1, 2002, until September 1, 2002, were considered for the analysis ($N = 1382$). During the study period, several stimulation protocols were in use, but in the majority of the cycles ($N = 1346$) one of two methods were utilized. In 964 cycles, GnRHa ultrashort stimulation was used (see below), whereas in 382 CC in combination with gonadotropins. IVF treatment was performed for the usual indications (male factor infertility, unexplained infertility, tubal factor infertility, uterine factor infertility, endometriosis). The exact stimulation protocol was chosen by the primary physician according to physician and/ or patient preference. The decision was influenced by patients' baseline characteristics and response during earlier cycles, when available. For the ultrashort protocol, an oral contraceptive pill (OCP) (Marvelon, Organon) was given from the 2nd day of the menstrual cycle for 3 weeks. Five days after the last pill, buserelin (Suprefact, Avensis) 0.5 mg subcutaneously was started and was administered for 4 days. On the 2nd day of buserelin, gonadotropins (HMG, rFSH, or

a combination of both) were started and were administered daily up to the day of human chorionic gonadotropin (HCG) (Profasi, Serono) injection. Similarly to the ultrashort stimulation, OCP was administered for 3 weeks in the CC group as well. Five days after the last birth control pill, CC was started at 100 mg daily for 5 days. Gonadotropins (HMG or the combination of rFSH and HMG) were given on days 1, 3, 5, and 7 and then daily if necessary. The following two gonadotropin preparations were in use during the study period: rFSH (Gonal-F, Serono Italy) (cost, US\$ 19.7/ampoule), and HMG (Merional, IBSA, Switzerland) (cost, US\$ 4.6/ampoule). The dose and type of gonadotropin was determined by the treating physician on the basis of age, baseline FSH level, response to previous stimulation, as well as the patients' financial resources. Follicle growth was followed by transvaginal ultrasonographic examination. When at least two follicles reached 17 mm in diameter, 10,000 IU HCG was given intramuscularly. Transvaginal oocyte retrieval followed 35 h after the HCG injection. Laboratory and transfer procedures followed general laboratory protocols, and were similar in all cycles. The oocytes were fertilized on the day of retrieval and cleaving stage embryos were transferred on day 2 or 3 following the retrieval. Embryos were qualified on the basis of blastomere number and fragmentation (6). Data were collected for patient characteristics (age, baseline hormones, indication, order of treatment cycle [first vs repeat]), for stimulation characteristics (number of follicles >13 mm, number of oocytes retrieved, number of mature [MII] oocytes, number of fertilized oocytes, number and quality of embryos, number of embryos transferred), and cycle outcome (pregnant [positive serum β HCG] vs. not pregnant). Pregnancies were further categorized as normal, ongoing pregnancy, or pathologic pregnancy. Any pregnancy (singleton, twins, etc.) where a heart-beat was seen on ultrasound prior to discharge to the referring obstetrician (around 8–10 weeks' gestation) was considered an ongoing pregnancy. Any pregnancy that resulted in a loss (spontaneous abortion, missed abortion, ectopic pregnancy, etc.) was considered an abnormal pregnancy. We know how many ampoules of gonadotropin a patient is using during her treatment but we do not routinely collect information about the type of gonadotropin they are using. Because there is a significant price difference between urinary and recombinant products, to evaluate expenses, 50 charts were randomly chosen from both groups to assess the proportion of various gonadotropins (rFSH and HMG) used. Medication

cost was calculated on the basis of this proportion and the actual number of ampoules of gonadotropins the patient was using. The cost of IVF treatment alone is US\$ 1150; ICSI is an extra US\$ 500. These figures were used to evaluate medication plus treatment costs. In addition to medication-only and medication plus treatment cost *per cycle*, expenses *per pregnancy* were calculated as well on the basis of pregnancy rates and costs.

Statistical analysis: The Mann–Whitney *U* test was used to compare continuous variables between cycles that resulted in pregnancy and those that did not. Categorical variables were compared using the chi square test. A multiple logistic regression was used to further evaluate the association between cycle outcome and those factors that potentially influence outcome. The independent factors studied were number of MII oocytes, number of oocytes fertilized, embryo quality, number of embryos transferred, baseline FSH, age, and type of protocol. The model of logistic regression was gained by a stepwise procedure, and specific interactions between parameters of interest were also investigated. Models were compared by the likelihood ratio test. A *p* value <0.05 was considered significant.

RESULTS

A total of 1382 IVF/ICSI cycles was performed at our center during the study period of which 964 GnRHa + gonadotropin cycles (66%) and 382 CC + gonadotropin cycles (26%) were identified. Cancellation rates were similar with the two protocols (66/964 [6.8%] vs 29/382 [7.6%]). Treatment outcome (pregnancy outcome) was available for over 90% of these cycles (874/964 in the GnRHa group and 354/382 in the CC group).

Women in the GnRHa group were older (33.0 ± 0.15 SEM vs 32.0 ± 0.26 SEM; $p < 0.01$) and the index treatment was more likely to be repeat treatment (70.6% vs 43.3%, $p < 0.01$). Women in the GnRHa group required significantly more ampoules of gonadotropins (24.0 ± 0.31 SEM vs 20.0 ± 0.47 SEM; $p < 0.001$). Stimulation parameters (number of follicles, mature oocytes, quality of embryos, and number of embryos transferred) were significantly better in the GnRHa group. The quality of the best embryo transferred and endometrial thickness were similar (Table I).

The overall pregnancy rate was 33.1% (407/1228). Clinical pregnancy rate was 35.9% (314/874) in the

Table I. Baseline Characteristics and Cycle Outcome with the Two Stimulation Protocols

	GnRH ultrashort protocol (<i>n</i> = 964)	CC + HMG protocol (<i>n</i> = 382)
Age (yrs)*	33.1 ± 0.1	32.0 ± 0.2
Baseline FSH (IU/l)	7.9 ± 0.1	8.1 ± 0.1
Ampoules of medication used*	24.0 ± 0.3	20.0 ± 0.5
Number of follicles >13 mm*	8.6 ± 0.1	7.2 ± 0.2
Number of oocytes*	7.5 ± 0.1	5.7 ± 0.2
Number of mature (MII) oocytes*	6.1 ± 0.1	4.7 ± 0.1
Embryo score*	40.0 ± 0.7	36.8 ± 1.1
Number of embryos transferred*	2.7 ± 0.03	2.4 ± 0.04

Note. Values are shown as value $\pm$ SEM.

* $p < 0.05$.

GnRHa + gonadotropin group and 26.2% (93/354) in the CC + gonadotropin cycles ($p < 0.001$). First-trimester outcome was known for 365 pregnancies; 323/365 (88.5%) pregnancies were normal, ongoing pregnancies.

The average medication costs calculated on the basis of the proportion of various preparations used and based on the mean number of ampoules of medication used was higher in the GnRHa group (US\$ 357.4 ± 4.6 SEM vs US\$ 248.2 ± 8.0 SEM, $p < 0.001$), a 43% difference. When the total cost *per cycle* was analyzed (treatment + medication), it was 7.8% higher with IVF (US\$ 1507 vs 1398) and 5.7% (US\$ 2007 vs 1898) higher with ICSI in the GnRHa group. Because there were significant differences in pregnancy rates and treatment costs differed as well, we estimated the costs *per pregnancy* on the basis of pregnancy rates and of medication-only/medication plus treatment costs. The medication cost *per pregnancy* was still somewhat higher with the use of the GnRHa ultrashort protocol (US\$ 994 vs 946, 5.0% difference). However, when the cost of treatment was included as well, the expenses per pregnancy were lower with the GnRHa ultrashort stimulation (US\$ 4197 vs 5335 with IVF [27.1% difference], and US\$ 5590 vs 7244 with ICSI [29.5% difference]).

In the logistic regression model, age, embryo score, number of embryos transferred and the type of stimulation protocol were significantly associated with pregnancy outcome. The chance of pregnancy significantly improved when the GnRH ultrashort protocol was used (OR = 1.56; 95%CI = 1.2–2.1, $p = 0.003$). Age was negatively associated

Table II. Results of the Final Logistic Regression Model

Variable	Logistic regression coefficients (<i>B</i>)	<i>p</i> *	Adjusted odds ratio (95% CI)**
Age	-0.0354	0.0155	0.9612 (0.9343–0.9889)
Embryo score (ESC)	0.0147	0.0001	1.0150 (1.0075–1.0226)
Number of embryos transferred			
2 embryos compared to 1	1.2288	0.0023	3.5372 (1.6105–7.7688)
3 embryos compared to 1	1.3471	0.0007	3.8984 (1.7915–8.4834)
4 embryos compared to 1	0.9965	0.0238	2.7190 (1.1484–6.4379)
GnRH vs CC protocol	0.4442	0.0032	1.5593 (1.1602–2.0957)

*Wald statistic test. A $p < 0.05$ is considered significant.

**Odds ratios (OR) are adjusted for the other variables in the equation.

with pregnancy outcome, whereas embryo quality and the number of embryos transferred were positively associated with pregnancy outcome (Table II).

Treatment outcome was compared between the two stimulation protocols in subgroups created on the basis of age (≤ 35 years, 36–39 years, ≥ 40 years). Within these groups, baseline FSH was similar between the two stimulation groups. The number of embryos transferred and the mean embryo score were comparable as well. Within all three age subgroups, medication costs per cycle were significantly higher with the GnRHa ultrashort stimulation. Pregnancy rates were also significantly higher in the two younger age groups when the GnRHa ultrashort stimulation was used (Table III). Total cost (medication plus treatment) per pregnancy was compared within the subgroups with the two stimulation protocols. IVF and ICSI cycles were analyzed separately. Within all three groups cost per pregnancy was higher with the CC protocol (Table IV).

We noted that 88.5% of the pregnancies were ongoing pregnancies. The rate of pathologic pregnancies was similar in the GnRHa + gonadotropin group when compared to the CC + gonadotropin group (11.1% vs 7.5%, $p = \text{NS}$).

DISCUSSION

Controlled ovarian hyperstimulation is now an integral part of IVF cycles. Several different preparations are available that can be used for stimulation. In addition to different gonadotropin preparations, the availability of several treatment protocols allows us to tailor treatment to the individual patient's needs. In the early years unstimulated cycles were used (1,2). This was followed by the use of CC alone (7). Later HMG was used in various combinations with CC (8,9). The next major step in the evolution of stimulation protocols was the combination of GnRHa into COH (10,11). GnRHa is used to prevent premature LH surges, and therefore lower cancellation rates and improved oocyte yields, can be achieved. These days, with the availability of GnRH antagonists, premature ovulation can be prevented as well (12). Because GnRH antagonists effectively prevent LH surges once administered, their availability resulted in a renewed interest in the CC + HMG protocol, as premature ovulation can now be prevented (13,14).

IVF cycles can be evaluated by several ways. Stimulation parameters, embryology outcome, treatment outcome, and cost are compared most frequently. We compared cycle outcome and costs with two

Table III. Treatment Outcome and Medication Cost in Subgroups Created Based on Age

Age subgroups	Stimulation protocol	FSH (IU/l)	Number of embryos transferred (mean $\pm$ SEM)	Mean embryo score (mean $\pm$ SEM)	Mean medication cost per cycle in US\$ (mean $\pm$ SEM)	Pregnancy rate (number of pregnancies per number of cycles)
≤ 35 yrs	GnRHa	7.5 $\pm$ 0.1	2.7 $\pm$ 0.03	40.4 $\pm$ 0.7	331.5 $\pm$ 5.1*	242/617 (39.2%)*
≤ 35 yrs	CC	7.6 $\pm$ 0.1	2.5 $\pm$ 0.05	37.3 $\pm$ 1.1	233.6 $\pm$ 9.2*	82/284 (28.9%)*
36–39 yrs	GnRHa	8.9 $\pm$ 0.2	2.7 $\pm$ 0.08	41.2 $\pm$ 1.8	401.7 $\pm$ 11.3*	49/157 (31.3%)*
36–39 yrs	CC	9.1 $\pm$ 0.7	2.6 $\pm$ 0.1	35.7 $\pm$ 2.9	275.1 $\pm$ 18.9*	7/37 (18.9%)*
≥ 40 yrs	GnRHa	9.2 $\pm$ 0.3	2.6 $\pm$ 0.1	35.8 $\pm$ 2.0	446.7 $\pm$ 12.4*	23/100 (23%)*
≥ 40 yrs	CC	10.9 $\pm$ 0.9	2.2 $\pm$ 0.2	33.0 $\pm$ 5.1	337.0 $\pm$ 22.1*	4/33 (12.1%)*

* $p < 0.05$.

Table IV. Medication plus Treatment Cost *Per Pregnancy* (USD) with the Two Stimulation Protocols in the Three Age Groups

Age	Stimulation protocol	IVF vs ICSI	Medication plus treatment cost per pregnancy (US\$)
≤35 yrs	GnRHa	IVF	3797 ^a
		ICSI	5079 ^b
	CC	IVF	4768 ^a
		ICSI	6493 ^b
36–39 yrs	GnRHa	IVF	5003 ^c
		ICSI	6616 ^d
	CC	IVF	7500 ^c
		ICSI	10131 ^d
≥40 yrs	GnRHa	IVF	6939 ^e
		ICSI	9113 ^f
	CC	IVF	12391 ^e
		ICSI	16558 ^f

Note. IVF and ICSI are calculated separately. CC: clomiphene citrate. GnRHa: gonadotropin releasing hormone agonist.

^a 25.5% difference.

^b 27.8% difference.

^c 49.9% difference.

^d 53.1% difference.

^e 78.5% difference.

^f 81.7% difference.

stimulation protocols that are commonly used in our center. Cycle parameters are collected prospectively in our IVF database. Costs are not routinely evaluated; therefore we calculated average costs based on representative samples of patients from both groups.

We found that all stimulation parameters and pregnancy rates were significantly higher in the GnRHa group among patients with similar baseline (age, FSH) characteristics. We also noted that patients in the GnRHa group required significantly more ampoules of medication for oocyte retrieval. This resulted in increased medications and medication plus treatment costs *per cycle*. However, when we evaluated cumulative expenses by the time a successful pregnancy was achieved, medication plus treatment costs were lower with the GnRHa stimulation. Indeed, the cost difference was the cost of an IVF treatment! So although the patient saves money in the short term, she will end up spending more by the time she successfully conceives.

The combination of GnRH antagonist into the CC + HMG protocol could improve the performance of this protocol as it prevents premature luteinization and reduces cancellation rates. The use of GnRH antagonist would, however, significantly increase the costs as well (patient cost of one ampoule of 0.25 mg Cetrotide is US\$ 39.5). Mansour *et al.* showed that the combination of GnRH antagonist into the CC + HMG stimulation was not as cost-effective as the use

of the standard GnRHa long protocol among infertile couples undergoing ICSI treatment (15).

Our findings suggest that GnRHa-based protocols should be used as a first line of stimulation in IVF programs. They are associated with superior clinical performance and reduced costs.

REFERENCES

1. Lopata A, Johnston IW, Hoult IJ, Speirs AI: Pregnancy following intrauterine implantation of an embryo obtained by in vitro fertilization of a preovulatory egg. *Fertil Steril* 1980;33:117–120
2. Edwards RG, Steptoe PC, Purdy JM: Establishing full-term human pregnancies using cleaving embryos grown in vitro. *Br J Obstet Gynaecol* 1980;87:737–756
3. Adashi EY: Clomiphene citrate: Mechanism(s) and site(s) of action—a hypothesis revisited. *Fertil Steril* 1984;42:331–343
4. Reynolds AM, Schieve LA, Jeng G, Peterson HB: Does insurance coverage decrease the risk for multiple births associated with assisted reproductive technology? *Fertil Steril* 2003;80:16–23
5. Jain T, Harlow BL, Hornstein MD: Insurance coverage and outcomes of in vitro fertilization. *N Engl J Med* 2002;347:661–666
6. Steer CV, Mills CL, Tan SL, Campbell S, Edwards RG: The cumulative embryo score: A predictive embryo scoring technique to select the optimal number of embryos to transfer in an in-vitro fertilization and embryo transfer programme. *Hum Reprod* 1992;7:117–119
7. Trounson AO, Leeton JF, Wood C, Webb J, Wood J: Pregnancies in humans by fertilization in vitro and embryo transfer in the controlled ovulatory cycle. *Science* 1981;212:681–682
8. Quigley MM, Schmidt CL, Beauchamp PJ, Pace-Owens S, Berkowitz AS, Wolf DP: Enhanced follicular recruitment in an in vitro fertilization program: Clomiphene alone versus a clomiphene/human menopausal gonadotropin combination. *Fertil Steril* 1984;42:25–33
9. Kemeter P, Feichtinger W: Experience with a new fixed-stimulation protocol without hormone determinations for programmed oocyte retrieval for in-vitro fertilization. *Hum Reprod* 1989;4(8 Suppl):53–58
10. Wildt L, Diedrich K, van der Ven H, al Hasani S, Hubner H, Klases R: Ovarian hyperstimulation for in-vitro fertilization controlled by GnRH agonist administered in combination with human menopausal gonadotrophins. *Hum Reprod* 1986;1:15–19
11. Neveu S, Hedon B, Bringer J, Chinchole JM, Arnal F, Humeau C, Cristol P, Viala JL: Ovarian stimulation by a combination of gonadotropin-releasing hormone agonist and gonadotrophins for in vitro fertilization. *Fertil Steril* 1987;47:639–643
12. Diedrich K, Diedrich C, Santos E, Zoll C, al-Hasani S, Reissmann T, Krebs D, Klingmuller D: Suppression of endogenous luteinizing hormone surge by the gonadotrophin-releasing hormone antagonist Cetrorelix during ovarian stimulation. *Hum Reprod* 1994;9:788–791
13. Engel JB, Ludwig M, Felderbaum R, Albano C, Devroey P, Diedrich K: Use of cetrorelix in combination with clomiphene citrate and gonadotrophins: A suitable approach to “friendly” IVF? *Hum Reprod* 2002;17:2022–2026

14. Williams SC, Gibbons WE, Muasher SJ, Oehninger S: Minimal ovarian hyperstimulation for in vitro fertilization using sequential clomiphene citrate and gonadotropin with or without the addition of gonadotropin-releasing hormone antagonist. *Fertil Steril* 2002;78:1068–1072
15. Mansour RT, Aboulghar MA, Serour GI, Al-Inany HG, Fahmy I, Amin Y: The use of clomiphene citrate/human menopausal gonadotrophins in conjunction with GnRH antagonist in an IVF/ICSI program is not a cost effective protocol. *Acta Obstet Gynecol Scand* 2003;82:48–52