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ASSISTED REPRODUCTION

The effect of oral contraceptive pill for cycle scheduling prior to GnRH-antagonist protocol on IVF cycle parameters and pregnancy outcome

Haim Pinkas · Onit Sapir · Ori M. Avrech · Avi Ben-Haroush · Jacob Ashkenzi · Benjamin Fisch · Jacob Farhi

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Abstract

Objective To evaluate the effect of oral contraceptive pills (OCP) pretreatment on IVF cycle outcome in GnRH-antagonist protocol.

Design Retrospective cohort study.

Setting Major tertiary university-affiliated center.

Patients All patients treated with GnRH antagonist in our IVF unit during the last 3 years were included in the study. Overall 1,799 IVF cycles were performed. Of these, in 604 cycles OCP pretreatment was used prior to GnRH-antagonist for cycle scheduling. Patients were divided into two age groups—young group aged ≤35 years and older group aged ≥36 years.

Interventions The young group underwent 927 cycles, 281 cycles with OCP pretreatment and 646 cycles without. The older group underwent 872 cycles, 323 cycles with OCP pretreatment and 549 cycles without. Data was analyzed within each age group.

Main outcome measures Treatment duration and total dose of FSH IU used for stimulation, number of oocytes retrieved, implantation and pregnancy rates.

Results All OCP-pretreated cycles required significantly longer stimulation than non-pretreated cycles (young: 10.76 vs. 9.21 days; older: 10.48 vs. 8.73 days, respectively) and higher total dose of FSH IU (young: 3,210 IU vs. 2,565 IU; older: 4,973 IU vs. 3,983 IU, respectively). There were no other differences in cycle characteristics between groups. Implantation and pregnancy rates were not affected by OCP pretreatment.

Conclusions OCP pretreatment can be offered as a mode for cycle scheduling prior to GnRH-antagonist protocol, though it may be associated with longer stimulation and higher gonadotropin consumption.

Keywords IVF · GnRH antagonists · Oral contraceptive pills

Capsule OCP prior to GnRH-antagonist protocol enables cycle scheduling without compromising cycle outcome and patient's age is not a limitation in decision making for the use of this approach.

H. Pinkas · O. Sapir · O. M. Avrech · A. Ben-Haroush · J. Ashkenzi · B. Fisch · J. Farhi
Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

H. Pinkas (✉) · O. Sapir · O. M. Avrech · A. Ben-Haroush · J. Ashkenzi · B. Fisch · J. Farhi
Infertility and IVF Unit, Helen Schneider Hospital for Women, Rabin Medical Center, Petach Tikva 49100, Israel
e-mail: haimpin@clalit.org.il

Introduction

Gonadotropin-releasing hormone (GnRH) antagonist protocols are characterized by shorter stimulation period and use of lower quantities of gonadotropins as compared with the long GnRH-agonist protocol [1–3]. However, in a long GnRH-agonist protocol there is flexibility in the starting day of gonadotropin stimulation, which is lacking in the GnRH-antagonist protocol. This flexibility is beneficial for both the patients' convenience in controlling their time of stimulation and for the IVF units for controlling their workload. To overcome this limitation in the GnRH antagonist protocol, patients can be offered the use of pretreatment with oral contraceptive pills (OCP) [4–7]. Moreover, a previous study has shown that OCP pretreatment before GnRH antagonist led to higher numbers of oocytes retrieved compared to the standard GnRH antagonist protocol [8]. On the other hand, longer stimulation

periods and increased consumption of recombinant FSH (rFSH) were needed for stimulation [8–10].

The available data on OCP pretreatment before GnRH antagonist protocol is scant, and mainly based on rather small study groups of relatively young patients. There is also the question of the effect of the OCP on pregnancy outcome as in one study OCP pretreatment was associated with significantly higher early pregnancy loss [10].

In our IVF unit, pretreatment with OCP prior to GnRH antagonist protocol is routinely used for cycle scheduling either for the patients' convenience or IVF unit workload control. The aim of this study was to summarize our data and assess the impact of OCP pretreatment prior to GnRH-antagonist protocol in a large patient population.

Materials and methods

Patients

Between June 2003 and June 2006, a GnRH-antagonist protocol was used in 1,236 patients treated in 1,799 cycles. In 604 of these cycles, OCP pretreatment was administered for cycle scheduling. The use of pretreatment with OCP was for cycle scheduling either for the patients' convenience or for IVF unit workload control.

To investigate the effect of OCP pretreatment by age, patients were divided into those ≤35 years old ("young group") and those ≥36 ("older group"). In the young group (691 patients, 927 cycles) there were 224 patients treated in 281 cycles of OCP pretreatment GnRH antagonist protocol and 467 patients treated with 646 cycles without OCP. In the older group (545 patients, 872 cycles) there were 222 patients treated with 323 cycles of OCP pretreatment GnRH antagonist protocol and 323 patients treated in 549 cycles without. Institutional Review Board approval was obtained for retrospective analysis of IVF data.

Ovarian stimulation protocols

OCP pretreatment was administered for 12–17 days, starting on cycle days 2–3. At the end of the OCP period prior to gonadotropin stimulation, vaginal ultrasound was performed to establish ovarian and uterine quiescence. Five days after OCP discontinuation, ovarian stimulation was commenced using either rFSH (Gonal F®, Serono, Switzerland) alone or in combination with human menopausal gonadotropin (hMG) (Menogon®, Ferring GmbH, Germany) at a starting dose of 150 to 300 IU/day depending on the patient previous ovarian response to stimulation. The dose was adjusted after 5 to 6 days according to the patient's individual E2 response and follicular development.

In the non-OCP protocol, gonadotropin stimulation was started on day 3 or 4 of the menstrual cycle, with a similar policy for the starting dose as in the OCP protocol.

In both protocols, GnRH-antagonist (Cetrotide® 0.25 mg, Serono, Switzerland) was started when the leading follicle reached ≥14 mm in diameter, and was continued until the day of human chorionic gonadotropin (hCG) administration. Ovulation was triggered with 250 mcg of choriogonadotropin alfa (Ovitrelle®, Serono, Switzerland) when at least three follicles measuring 17 mm were detected by ultrasound scan. Oocyte collection, fertilization, in vitro incubation, and luteal phase support were performed in the same manner in both protocols, in accordance with our clinical and laboratory standard of care and practice. Adhering to the Israel Ministry of Health recommendations, we routinely replaced two embryos, with a gradual increase in number in patients with repeated failed IVF-ET cycles. No more than four embryos were replaced per cycle.

Pregnancy was diagnosed based on two consecutive positive β-hCG tests performed 2–3 days apart with at least doubling of the serum level. Clinical pregnancy rate was defined as the presence of an intrauterine gestational sac by ultrasound scan 4 weeks after oocyte retrieval.

Statistical analysis

The variables of interest in this study were analyzed using General Linear Modelling (GLM) methods [11]. For continuous random variables, a traditional analysis of variance technique was performed using a 2 × 2 factorial structure, the factors being Age (Young/Old) and Treatment (OCP/Non-OCP). The GLM [11] procedure for proportions (Implantation Rate etc) involved a transformation onto the logistic scale, after which Maximum Likelihood was used to carry out the analysis. For ease of interpretation however, the results from those analyses are presented on the original scale of proportions.

Since this is a retrospective study and furthermore since the patients had exercised their preference with regard to the treatment employed, it was necessary to make some assumptions in order to validate the findings. The main assumption of course is that the patients' preferences to use OCP for cycle scheduling did not influence the physiological responses in any way. As with most retrospective studies one must also assume that no variable, both recorded or not recorded, exercised a systematic effect on the treatments of interest in the study. In effect this is equivalent to assuming that the treatments could be regarded as being randomly allocated to the patients, which should apply in a prospective study.

A variable number of cycles were recorded for the patients, and the analyses were carried out (a) on all recorded cycles, and (b) on the first treatment cycle per

Table 1 Comparison of background characteristics of patients undergoing GnRH-antagonist stimulation with or without OCP pretreatment, by age group

	Young (≤35 years)			Older (≥36 years)		
	OCP	Non-OCP	*P*	OCP	Non-OCP	*P*
Number of patients	224	467		222	323	
Age (year)	29.8±3.5	29.8±3.6	0.99	40.8±2.6	40.6±2.5	0.27
Previous IVF attempts	3.0±2.1	2.9±2.5	0.79	4.0±3.0	3.7±3.2	0.18
1^0 infertility, %	58.4	55.0	0.34	44.2	38.2	0.08
Infertility type, %	–	–	0.42	–	–	0.08
Male	51.9	52.9		26.1	35.1	
Unexplained	24.3	25.7		55.7	45.4	
Tubal	12.3	10.5		12.0	14.1	
Anovulation	7.0	7.9		2.4	2.6	
Endometriosis	2.1	2.5		1.7	0.8	
Other	2.4	0.5		2.1	2.0	

Results are presented as mean ± SD
OCP = oral contraceptive pill

patient. The main findings were very similar however and the results presented below were derived from the analyses using all cycles.

Results

There were no differences within each age group between the pretreated OCP and non-OCP treated patients in demographic and baseline clinical parameters (Table 1). The IVF cycle characteristics and laboratory data are presented in Table 2. In addition to the customary, and expected, differences between the younger and the older patients on several variables, there was evidence of an 'Oral Contraceptive' effect for the variables 'Length of Stimulation' & 'Endometrium thickness.' The stimulation for the patients taking the oral contraceptive was on average of longer duration than for the Non-OCP group. Also the endometrial thickness was on average lower for the contraceptive group.

Table 2 IVF cycle characteristics in OCP and non-OCP cycles according to age groups

	Young (≤35 years)			Older (≥36 years)		
	OCP (281 cycles)	Non-OCP (646 cycles)	*P*	OCP (323 cycles)	Non-OCP (549 cycles)	*P*
COH						
Stimulation length (days)	11.30±0.15	9.08±0.10	<0.0001	11.37±0.14	8.74±0.11	<0.0001
Total dose of FSH (IU)	3210± 1898	2565±1500	<0.0001	4973±2010	3983±1815	<0.0001
hCG day						
Endometrium (mm)	9.26±0.14	9.78±0.09	0.087	8.64±0.13	9.27±0.10	<0.0001
E_2 (pmol/l)	4828±181	5116±121	<0.01	4519±169	3990±131	<0.01
Follicles (=14 mm)	8.81±0.22	8.38±0.15	0.59	5.70±0.21	5.49±0.16	0.29
IVF laboratory data						
Oocytes retrieved	10.41±0.35	10.16±0.23	0.91	6.66±0.32	6.19±0.25	0.49
Fertilization rate (%)						
Insemination	57.6	62.0	0.87	60.3	59.0	0.69
ICSI	59.5	59.9	0.70	54.2	58.0	0.20
Embryos transferred	2.1±1.0	2.06±0.94	0.42	2.1±1.4	2.1±1.4	0.98
Embryos frozen	1.5±2.6	1.6±2.9	0.70	0.5±1.5	0.4±1.7	0.85

Stim. Length (Days) All OCP (11.34±−0.10) > all Non-OCP (8.92±−0.07) (*P*<0.001)
Endom. (mm) All OCP (8.96±−0.09) < All Non-OCP (9.53±0.07) (*P*<0.001)
All Young (9.60±−0.08) > All Old (9.05±−0.08) (P<0.01)
Follicles (>14 mm) All Young (8.53±−0.13) > All Old (5.56±0.13 (*P*<0.001)
Ooctyes Retrieved All Young (10.25±−0.19) > All Old (6.34±−0.20) (*P*<0.001)
For each of the nominated variables, the estimated mean values and standard errors are presented for each of the four sub-classes.

Table 3 Implantation and pregnancy outcome with and without OCP pretreatment by age group

	Young (<35 years)			Older (=36 years)		
	OCP (281 cycles)	Non-OCP (646 cycles)	*P*	OCP (323 cycles)	Non-OCP (549 cycles)	*P*
Implantation rate, %	12.0±14	11.4±9	0.49*(0.19)	5.7±9	4.9±6	0.40*(0.82)
Positive β-hCG, % (*n*)	23.0 (64)	19.9 (129)	0.29*(0.24)	11.1 (36)	9.9 (54)	0.56*(0.69)
Clinical pregnancy rate, %	20.3	18.6	0.62*(0.26)	9.0	8.6	0.68*(0.61)
Pregnancy outcome, %						
Biochemical pregnancy %	12.9	6.5	0.19	17.1	15.7	0.51
Clinical abortions %	21.8	16.4	0.36*(0.72)	32.1	44.2	0.27*(0.04)
Extra-uterine pregnancy %	0	3.4	–	0	0	–
Deliveries %	65.3	73.7	0.47	50.1	39.1	0.61

Results are presented as mean ± SD
OCP = oral contraceptive pill
*(*P* value) = for comparison of the first antagonist cycle per patient

For the variable E_2 there was statistical evidence of an interaction between the age effect and the OCP effect. From Table 2 we note that the sense of the interaction was that; whereas in the younger group of patients the OCP subgroup had the lower E_2 values, this was reversed in the older group of patients. There was no evidence of an 'OCP effect' on the number of oocytes retrieved, nor on the Fertilization, Implantation, Pregnancy or Abortion rates. Comparison of all data using only the first antagonist cycle per patient, either with or without OCP, did not change statistical significance (Tables 2 and 3).

Discussion

In this study we evaluated the effect of OCP pretreatment prior to GnRH-antagonist protocol for cycle scheduling in IVF treatment. This study presents the largest series to date on this treatment modification with a specific emphasis on the impact of patient's age on the ovarian response, cycle characteristics and outcome. We found that OCP pretreatment in both age groups, younger and older then 35 years, was associated with a longer length of stimulation and an increase in the total dose of gonadotropins needed for stimulation. The OCP pretreatment did not affect the magnitude of the ovarian response in both age groups in terms of the number of oocytes retrieved. The implantation and pregnancy rates were not affected by OCP pretreatment in both age groups. Endometrial thickness was not affected by OCP use in the young group but in the older population there was a statistically significant thinner endometrium following OCP. Although statistically valid, this difference in endometrial thickness does not seem to have a clinical significance as implantation, pregnancy and abortion rates were similar.

There is limited body of data in the literature on the use OCP pretreatment prior to GnRH antagonist protocol including three prospective randomized studies [8–10]. However, these studies focus only on the young IVF population and include relatively small numbers of patients and cycles. Overall, our findings on the effect of OCP pretreatment prior to GnRH antagonist protocol on cycle characteristics, magnitude of ovarian response and pregnancy outcome are in accordance with these studies [8–10]. In all studies including this study, longer stimulation period and higher total dose of gonadotropins were needed in the OCP pretreatment cycles [8–10]. Similar to our results, in two studies [9, 10], OCP pretreatment had no effect on the final number of mature follicles whereas in one study [8] the OCP pretreatment resulted in an increase in the number of mature follicles and in the number of oocytes retrieved. Finally, in our study as in previous studies, the implantation and pregnancy rates were not affected by the use of OCP pretreatment [9, 10].

There is no previous data in the literature on the effect of OCP pretreatment in different age groups. As all previous data is related to relatively young IVF patients, we looked into the effect of cycle scheduling with OCP in the older IVF population over 35 years of age. Within these patients there were no differences caused by the use of OCP in the number of oocytes, or fertilization, implantation, pregnancy and abortion rates. We did find a thinner endometrium following OCP on hCG day in the older patients. A thinner endometrium was also noted in an earlier study [10] on day 6 of stimulation but disappeared by the time of hCG administration. Taken together, this may indicate a slower endometrial recovery rate in older patients owing to the OCP suppression of the uterine hormonal milieu. Nevertheless, there was no effect on the implantation and pregnancy rate in the OCP pretreatment cycles.

In summary, OCP pretreatment for cycle scheduling in GnRH-antagonist protocol is a valid modality with comparable IVF outcome to the non-OCP protocol. The longer stimulation and higher total dose of FSH are the only drawbacks that we found in this modification. The weight of these drawbacks has to be measured against the gain in enabling cycle scheduling. The age of the patients is not a limitation in decision making for the use of this treatment approach.

References

1. Albano C, Felberbaum RE, Smitz J, Riethuller-Winzen H, Engel J, Diedrich K, et al. Ovarian stimulation with HMG: results of a prospective randomized phase III European study comparing the luteinizing hormone-releasing hormone (LHRH)-antagonist cetrorelix and the LHRH-agonist buserelin. European Cetrorelix Study Group. Hum Reprod 2000;15:526–31.
2. Hohmann FP, Macklon NS, Fauser BC. A randomized comparison of two ovarian stimulation protocols with gonadotropin-releasing hormone (GnRH) antagonist cotreatment for in vitro fertilization commencing recombinant follicle-stimulating hormone on cycle day 2 or 5 with the standard long GnRH agonist protocol. J Clin Endocinol Metab 2003;88:166–73.
3. Al-Inany H, Aboulghar M. GnRH antagonist in assisted reproduction: a Cochrane review. Hum Reprod 2002;17:874–85.
4. Obruca A, Fischl F, Huber JC. Scheduling OPU in GnRH antagonist cycles. J Reprod Fertil 2000;4:37.
5. Cedrin-Durnerin I, Grange-Dujardin D, Laffy A, Parneix I, Massin N, Galey J, et al. Recombinant human LH supplementation during GnRH antagonist administration in IVF/ICSI cycles: a prospective randomized study. Hum Reprod 2004;19:1979–84.
6. Barmat LI, Chantilis SJ, Hurst BS, Dickey RP. A randomized prospective trial comparing gonadotropin-releasing hormone (GnRH) antagonist/recombinant follicle-stimulating hormone (rFSH) versus GnRH-agonist/rFSH in women pretreated with oral contraceptives before in vitro fertilization. Fertil Steril 2005;83:321–30.
7. Meldrum D, Scott R, Levy MJ, Alper M, Noyes N. A pilot study to assess oral contraceptive (OC) pretreatment in women undergoing controlled ovarian hyperstimulation (COH) in ganirelix acetate cycles. Fertil Steril 2002;78(3 Suppl 1):S176 Abstract P-182.
8. Huirne JA, Van Loenen ACD, Donnez J, Pirard C, Homburg R, Schats R, et al. Effect of an oral contraceptive pill on follicular development in IVF/ICSI patients receiving a GnRH antagonist: a randomized study. Reprod Biomed Online 2006b;13(2):235–45.
9. Rombauts L, Healy D, Norman RJ, on the behalf of the Orgalutran Scheduling Study Group. A comparative randomized trial to assess the impact of oral contraceptive pretreatment on follicular growth and hormone profiles in GnRH antagonist-treated patients. Hum Reprod 2006;21:95–103.
10. Kolibianakis EM, Papanikolaou EG, Camus M, Tournaye H, Van Steirteghem AC, Devroey P. Effect of oral contraceptive pill pretreatment on ongoing pregnancy rates in patients stimulated with GnRH antagonists and recombinant FSH for IVF. A randomized controlled trial. Hum Reprod 2006;21:352–7.
11. McCullagh P, Nelder JA. Generalised linear models. London: Chapman and Hall; 1989.