Comparison of GnRH antagonist cycles with and without oral contraceptive pretreatment in potential poor prognosis patients

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Summary

Purpose: To evaluate the effect of oral contraceptive pill (OCP) pretreatment in patients undergoing IVF cycles with an antagonist.

Methods: In this retrospective study, 194 cycles of women with diminished ovarian reserve undergoing IVF with a protocol using GnRH antagonists were evaluated. Oral contraceptive pretreatment was used in 146 cycles.

Results: Pregnancy rates were the same in both groups. Patients using OCPs required more gonadotropins (5,890 IU) compared to patients not undergoing OCP pretreatment (4,410 IU),

Conclusions: Pregnancy outcomes were the same whether or not OCP pretreatment was implemented in poor responders using an antagonist protocol. While OCP pretreatment may help with scheduling flexibility, the higher dose of gonadotropins needed for ovarian stimulation should be considered.

Key words: IVF; Antagonist; Poor responders; Oral contraceptive pills.

Introduction

One of the most difficult challenges in in vitro fertilization (IVF) practice today is the management of patients with diminished ovarian reserve. Women in their waning reproductive years constitute a large proportion of the IVF population, as many women are tending to delay childbirth. Often, these women have a suboptimal response to standard stimulation protocols.

Multiple attempts have been made to formulate an ideal stimulation protocol for these difficult patients [1]. Various researchers have advocated alternative stimulations using microdose GnRH agonist flare or GnRH antagonist regimens [2, 3]. Direct comparison of these two approaches has shown them to be comparable [4].

GnRH antagonist treatment offers several advantages over traditional GnRH agonists. The immediate suppression of gonadotropin secretion allows for its use in the late follicular phase preventing premature luteinizing hormone (LH) surges while at the same time avoiding the excessive suppression that can occur with the traditional long protocols [5, 6].

The use of oral contraceptive pills (OCPs) has been employed as a pretreatment before controlled ovarian hyperstimulation in order to abolish persistent corpus luteum function [1]. They also work to achieve suppression of the pituitary ovarian axis [7, 8]. OCPs can be employed to assist in the coordination and efficient timing of the IVF cycles. However, patients are often eager to start immediately after a failed cycle and the need for OCPs may delay their continued treatment.

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In previous studies, the use of OCPs has been shown to decrease the time needed for suppression, improve ovarian stimulation, decrease the amount of gonadotropins, and eliminate premature LH surges, and in some studies improve pregnancy rates [8-12]. However, these studies examining the effects of OCPs have not been in conjunction with an antagonist protocol. A recent report commented on seeing no difference in pregnancy rates with OCP pretreatment and antagonist use [13] but did not compare other cycle parameters. The aim of this study was to evaluate the impact of oral contraceptive pills on pregnancy outcome and on the amount of gonadotropins used to achieve adequate follicular maturation in cycles using a GnRH antagonist.

Materials and Methods

We reviewed all IVF cycles using a GnRH antagonist protocol at Stanford University Medical Center between the months of August 2001 and August 2002. A total of 194 cycles in 138 patients were included in this retrospective study. The use of OCPs was determined primarily by scheduling availability. Patients were included if they had had a previous poor response (fewer than 4 oocytes retrieved), elevated FSH (> 10 IU/l), or were over 40 years old. Patients were excluded if they were over 44 or had an FSH > 15IU/l.

Information on patient characteristics was gathered from medical records including age, number of previous failed IVF cycles, and day 3 FSH. Data collected on the IVF cycle included the protocol type, number of cancellations, amount of gonadotropins used, number of follicles, number of oocytes retrieved, and normal fertilization rate. Pregnancy outcome data were collected, including number of serum positive pregnancies, and number of viable pregnancies documented by cardiac activity on ultrasound examination at eight weeks' gestation.

Oral contraceptive pills (Desogen, Organon, Inc., West Orange, NJ or Ortho Novum 1/35, Ortho-McNeil Pharmaceuticals, Inc. Raritan, NJ) were used in 146 cycles (Group 1). Pretreatment with OCPs was started on cycle day 2-4 and used for 15-30 days before stimulation. Forty-eight cycles did not include pretreatment with oral contraceptive pills (Group 2). Stimulation consisted of a mixed protocol of recombinant FSH (Gonal-F, Serono Laboratories, Randolph, MA or Follistim, Organon) and HMG (Pergonal, Serono or Repronex, Ferring Pharmaceuticals, Inc. Tarrytown, NY). Antagonist (Antagon 250 mcg, Organon, or Cetrotide, 250 mcg, Serono) was started when the lead follicle reached 14 mm.

All patients received monitoring throughout the cycle by transvaginal ultrasounds. Patients were given hCG (Profasi 10,000 IU, Serono or Ovidrel 250 mcg, Serono) when the lead follicle was approximately 18 mm. Oocytes were retrieved transvaginally 35 hours later. Embryo transfer was performed three to five days later.

Chi square and the Student's t-test were used for statistical analysis. Significance was set at $p < 0.05$. Institutional Review Board approval was obtained for retrospective chart review for this study.

Results

Oral contraceptive pills were used as pretreatment in 146 cycles and 48 cycles were not pretreated with OCPs. Table 1 summarizes the characteristics and outcomes of the study patients as the mean with standard deviation. There were no significant differences in patient characteristics between the two groups. Most patients had day 3 embryo transfers, and there was no statistical difference in the number of blastocyst transfers, number of cryopreserved embryos, or the use of intra cytoplasmic sperm injection (ICSI) in the two groups. The average number of embryos transferred per retrieval was 2.79 in the group using OCPs and 2.23 in the group that did not use OCPs, which was not statistically significant. Patients pretreated with OCPs required a higher amount of gonadotropins.

Table 1. — *Outcomes of cycles with and without OCP pretreatment.*

Parameter	OCP (n = 146)	No OCP (n = 48)	p value
Age (mean)	38.4 ± 3.4	37.7 ± 4.2	NS
Day 3 FSH	7.6 ± 3.3	8.5 ± 3.0	NS
IVF cycle #	2.4 ± 1.7	2.5 ± 2.3	NS
Total dose FSH (IU)	5,890 ± 5,442	4,410 ± 1,890	0.009
Oocytes retrieved	7.2 ± 5.5	7.3 ± 5.0	NS
Fertilization rate	51.4%	49.5%	NS
+ Serum HCG/cycle (> 10 IU)	17.8% (26/146)	22.9% (11/48)	NS
Viable pregnancy/cycle	10.6% (15/146)	14.6% (7/48)	NS
Implantation rate	6.3% (24/379)	11.1% (10/90)	NS
Term delivery/Cycle	9.6% (14/146)	14.6% (7/48)	NS

Discussion

A GnRH antagonist offers an alternative approach to the use of a GnRH agonist in the management of IVF patients with diminished ovarian reserve. These protocols have been shown to have equivalent efficacy to the microdose agonist flare protocol for poor responders in a previous small study [4]. The advantage of the antagonist protocol, however, is that it requires a smaller number of injections for fewer days. In addition, it offers the option of not using OCP pretreatment, unlike the microdose agonist flare protocol which typically uses OCP suppression

IVF programs have used OCPs to assist in scheduling and planning cycles. By manipulating cycle starts with OCPs, personnel can be coordinated and increased efficiency and flexibility can be achieved. Oral contraceptive pills have been shown in some studies to improve ovarian stimulation, decrease the dose of gonadotropins needed and reduce premature LH surges [9, 10]. In contrast, Lindheim *et al.* did not show any difference in gonadotropin use between cycles with or without OCPs [11]. However, studies have shown increased pregnancy rates when OCPs were used with either gonadotropins alone or with GnRH agonists [10, 11]. No studies have been reported examining the use of OCPs with antagonist cycles and impact on gonadotropin use.

The present study found that pretreatment with oral contraceptives did not have any positive or negative effects on the number of oocytes, fertilization rate, or viable pregnancy rate. However, a significant negative effect on the dosage of gonadotropins required was found with OCP use.

Our study was limited by the fact that it was a retrospective review, but the use of OCPs was determined primarily by scheduling constraints. Because of this, more patients ended up in the OCP group, but there was no difference in patient characteristics of age and day 3 serum FSH between the two groups. Although there is the potential for selection bias, patients were started randomly on OCPs, depending on whether space was available at the time of their menses.

Previous studies performed with GnRH agonists have not shown an increased need for gonadotropins with OCP use [10]. It is likely that the suppression brought about with GnRH agonist down-regulation is significant enough that the additional effect of OCPs is minimized. In antagonist cycles, the OCP effect is the only presuppression the patient is exposed to at the time of gonadotropin start and thus may become a significant variable in influencing the requirement for gonadotropins. Correlated with this, a small study examining OCP pretreatment showed profound pituitary suppression in a subset of women, who then had a poor response to gonadotropin use alone [14].

Conclusion

In this population of potential poor prognosis patients using a GnRH antagonist protocol, the use of OCPs did not improve viable pregnancy rates in contrast to some previous studies of GnRH agonist protocols [10, 11]. Furthermore, our study found that OCP pretreatment had a negative effect in that more gonadotropins were needed to achieve adequate follicular maturation.

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