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*Assisted Reproduction*

# Modified Natural Cycle Using GnRH Antagonist Can Be an Optional Treatment in Poor Responders Undergoing IVF

**Shai E. Elizur,[1,2,3] Dilek Aslan,[1,2] Adrian Shulman,[1,2] Boaz Weisz,[1,2] David Bider,[1,2] and Jehoshua Dor[1,2]**

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***Purpose*:** To investigate the efficacy of gonadotrophin-releasing hormone (GnRH) antagonist supplementation during natural cycles in poor responders undergoing IVF-ET treatment.
***Methods*:** We retrospectively evaluated 540 cycles of 433 suitable patients who were divided by treatment protocol into modified natural, antagonist, and long agonist groups. There were 52 modified natural cycles with GnRH antagonist supplementation, 200 stimulated cycles with GnRH antagonist, and 288 long GnRH agonist cycles. Cycle characteristics and treatment outcomes were compared between the groups.
***Results*:** The mean number of oocytes retrieved in the modified natural group was significantly lower than in the stimulated antagonist and long agonist groups ($1.4 \pm 0.5$ vs. $2.3 \pm 1.1$ and $2.5 \pm 1.1$, respectively, $p < 0.05$). The respective implantation and pregnancy rates were 10% and 14.3%, 6.75% and 10.2%, and 7.4% and 10.6%. Cycle outcome and cycle properties were similar.
***Conclusions*:** Modified natural IVF cycle with GnRH antagonist supplementation is a feasible alternative to ovarian stimulation protocols in poor responders.

**KEY WORDS:** GnRH antagonists; IVF; natural cycle; ovulation induction; poor ovarian response.

## INTRODUCTION

Poor response to ovulation induction despite various therapeutic strategies is very common in IVF cycles (1). Patients diagnosed as having a poor response often require greater doses of gonadotrophins but ultimately have fewer oocytes and with poor quality (2). Various ovulation induction regimens have been used to improve the success rate in those particularly difficult cases (3–7). Among these protocols, ovarian stimulation combined with gonadotrophin releasing hormone (GnRH) agonist is associated with increased doses of gonadotrophin (4,5). Recent studies pointed out the efficacy of GnRH antagonists in poor responders (8–10). These hormones are added to the stimulation protocol in the follicular phase and are short-acting. Thus, prior desensitization for a long duration is not necessary to prevent premature luteinization, which is the main cause for cycle cancellation in these patients.

IVF following natural cycles was reported to be as valuable as stimulated cycles in poor responders. The main concern about natural IVF cycles is the disadvantage of a high cancellation rate because of premature luteinizing hormone (LH) surges (11). There are limited data on the use of GnRH antagonists for preventing premature luteinization in natural cycles of poor responders.

We investigated the efficacy of GnRH antagonists in natural IVF cycles of poor responders compared

[1] IVF Unit – Department of Obstetrics and Gynecology, Chaim Sheba Medical Center, Tel-Hashomer, Israel.
[2] Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel.
[3] To whom correspondence should be addressed; e-mail: shaieliz@netvision.net.il.

to poor responders undergoing stimulated IVF cycles receiving GnRH antagonist or a long protocol GnRH agonist.

## MATERIALS AND METHODS

### Patients

The study population consisted of 433 poor responders who had undergone 540 IVF cycles between January 2001 and October 2002 at the IVF Department of Chaim Sheba Medical Center, Israel. All the women signed an informed consent to participate. Poor response was defined as ≤4 oocytes obtained at ovum pick-up (OPU) or an E2 level <1000 pg/mL on the day of human chorionic gonadotrophin (hCG) administration (11). Treatment protocols were chosen according to periods. In the first period we used the long agonist protocol and in the second the antagonist protocol. The women that were included in the modified natural group were failures of a previous treatment with one of the other protocols. Patients were divided into long agonist, antagonist, and modified natural groups according to treatment protocol. Cycle characteristics and treatment outcomes were compared between the groups.

### Ovarian Stimulation Protocols

The "modified natural" protocol group consisted of 43 women who underwent 52 natural cycles with GnRH antagonist supplementation. GnRH antagonist treatment (0.25 mg/day, Cetrorelix, Cetrotide, Serono International SR, Geneva, Switzerland) was started when a follicle of 13 mm was present. Two to three ampoules of hMG (Menogon, Ferring) were added daily during the antagonist treatment (12).

The antagonist group consisted of 179 patients who underwent 200 cycles. Ovulation induction was started on day 2 of the cycle with hMG (Menogon, Ferring) or recombinant FSH (follitropin alfa, Gonal-F, Serono, Aubonne, Switzerland) at a minimum dose of 225 IU/day. GnRH antagonist treatment (0.25 mg/day, Cetrorelix, Cetrotide, Serono International SR, Geneva, Switzerland) was started when a follicle of 13 mm was present.

The long agonist group consisted of 211 women who underwent 288 cycles. Ovarian suppression was achieved with either single dose of GnRH analog (GnRHa) (D-Trip-6-LHRH microcapsules: Decapeptyl Depot 3.75 mg microcapsules: Ferring Ltd, Mlemo, Sweden) or a multiple dose of daily Decapeptyl 0.1 mg given on day 21 of the previous cycle; ovarian stimulation was carried out with hMG or recombinant FSH (follitropin alfa, Gonal-F, Serono, Aubonne, Switzerland) with a minimum dose of 225 IU/day 15 days after verification of complete ovarian suppression.

All subjects underwent basal hormone evaluation and transvaginal ultrasound examination. Follow up of estradiol, progesterone, and LH levels were carried out up to a follicle size of 18 mm. Transvaginal ultrasound-guided oocyte retrieval was performed 32–36 h after hCG administration.

### Main Outcome Measures

The following measures were analyzed: cancellation rates, number of gonadotrophin ampules required to achieve ovarian stimulation, estradiol level on the day of hCG administration, number of retrieved oocytes, fertilization rate, embryo quality, and implantation and pregnancy rates.

### Statistics

Unpaired Student's $t$-test, $\chi^2$ test, and Fisher's exact test were used for the comparison of groups, as appropriate. $p < 0.05$ was considered as statistically significant.

## RESULTS

The study participants' demographic features and cycle characteristics are shown in Table I. The women were well-matched for age. Basal FSH levels were significantly higher in the modified natural group compared to the antagonist and long agonist groups. The estradiol level on the day of hCG administration and the mean number of retrieved oocytes were significantly lower in the modified natural group compared to the other two groups (Table I). Fertilization rate were similar for the three groups. The mean number of transferred embryos was significantly lower in the modified natural group compared to the antagonist and long agonist groups.

The implantation and pregnancy rates of modified natural, antagonist, and long agonist treatment groups were 10% and 14.3%, 6.75% and 10.2%, 7.4% and 10.6%, respectively. The number of cancelled cycles was significantly ($p < 0.05$) higher in the modified natural group compared to the antagonist and long agonist groups. In order to clarify these

**Table I.** Women's and Cycle Characteristics

| | Modified natural (mean ± SD) | Antagonist (mean ± SD) | Long agonist (mean ± SD) | *P* value |
|---|---|---|---|---|
| No. of cycles | 52 | 200 | 288 | |
| Women's age (years) | 39 ± 5.8 | 38.4 ± 4.7 | 38.1 ± 6 | NS |
| FSH (day 3) (IU/L) | 10.5 ± 5.8* | 8.7 ± 4.3 | 7.8 ± 3.0 | |
| $E_2$ (on HCG day) (pg/mL) | 349.3 ± 223.4* | 599.5 ± 345.5 | 770 ± 478.3 | |
| No. of oocytes retrieved | 1.4 ± 0.5* | 2.3 ± 1.1 | 2.5 ± 1.1 | |
| No. of canceled cycles (%) | 17/52 (32.6)* | 34/200 (17) | 53/288 (18.4) | |
| Fertilization rate (%) | 80 | 70.8 | 75.3 | NS |
| No. of embryos transferred | 1.1 ± 0.3* | 1.8 ± 0.9 | 1.9 ± 0.9 | |
| Implantation rate (%) | 10 | 6.75 | 7.4 | NS |
| Clinical pregnancy/cycle (%) | 9.6 | 8.5 | 8.6 | NS |
| Clinical pregnancy/transfer (%) | 14.3 | 10.2 | 10.6 | NS |

*Note*. FSH – follicle-stimulating hormone; HCG – human chorionic gonadotrophin.
*$p < 0.05$ (modified natural vs. antagonist and long agonist protocol).

findings we further analyzed the cancelled cycles with regard to the women's age (above and below 40 years old) and the cancellation etiology (early luteinization or ovarian failure to response) (Table II). The percentage of canceled cycles in patients in the modified natural group who were older than 40 years of age was higher compared to the antagonist and long agonist groups (21.4%, 10.1%, and 4.8%, respectively; $p < 0.05$).

## DISCUSSION

The ideal approach has yet to be defined for patients who had previously shown poor response to IVF-ET treatment. Various studies have attempted to determine the most efficient protocol for patients with poor ovarian response, such as increasing the dose of gonadotrophins (13,14), the use of recombinant FSH (15), supplementation of growth hormone (16), and altered time and dose of administration of GnRH agonists (7,17). No convincing advantage for one protocol over another has been established to date (18). We have recently described our results using natural cycles in poor responder patients, and showed a success rate of 20% (11). The discovery of GnRH receptors in the ovary led to the assumption by some investigators that GnRH agonists may have a direct and unfavorable effect on the ovary, a factor that could be particularly critical for poor responders to IVF-ET treatment (8). Administration of GnRH antagonists in poor ovarian response has been examined in a number of studies (8–10), and GnRH antagonist treatment protocols were shown to have the advantage of not involving early folliculogenesis.

Although the first successful IVF treatment was performed in a natural cycle (19), this practice was abandoned due to premature LH surges and subsequent high cancellation rates. In a review by Pelinck *et al*., the cancellation rate in natural cycles was reported to range from 14.3 to 62.5% with 16.6% of canceled cycles being due to premature LH surge (20). In our study, cancellation rates were considerably higher in the modified natural group compared to the antagonist and long agonist groups (32.6%, 17%, and 18.4%, respectively, $p < 0.05$). The vast majority of cancellations (13.5%), however, was seen in patients older than 40 years of age and was due to failure of ovarian response and not to early luteinization.

Our current study revealed that the use of GnRH antagonists during natural IVF cycles can be an optional treatment in poor responders. Moreover, the basal FSH levels that were found to be higher in patients undergoing a modified natural cycle and their

**Table II.** Cancelled Cycles According to Women's Age and Etiology*

| | Modified natural $n = 52$ | | Antagonist $n = 200$ | | Long agonist $n = 288$ | |
|---|---|---|---|---|---|---|
| Age (years) | <40 | ≥40 | <40 | ≥40 | <40 | ≥40 |
| Early luteinization (%) | 3 (5.7) | 4 (7.7) | 6 (3.0) | 10 (5.0) | 8 (2.7) | 5 (1.7) |
| Ovarian failure (%) | 2 (3.8) | 7 (13.5)* | 6 (3.0) | 6 (3.0) | 9 (3.1) | 4 (1.3) |

*Note*. Canceled cycles due to other reasons are not included.
*$p < 0.05$.

failure in previous IVF treatments also suggest that the modified natural group had a less favorable prognosis compared to the other two groups. Pregnancy rates per cycle, however, were similar for all three protocols.

Since the cancellation rate was higher in the modified natural group, we further analyzed pregnancy rates per total number of cycles, including cancelled ones and found that the pregnancy rates were still not significantly different between the three groups (Table I).

Lindheim *et al*. reported lower fertilization and implantation rates in stimulated cycles of poor responders compared to natural cycles due to lower oocytes and embryo quality (21). In our study, the fertilization rates were similar for the three protocols.

Although natural cycle IVF has several advantages, including low patient burden and low cost, it was claimed that they have the disadvantage of a high cancellation rate due to premature LH surge (20). In our "modified natural" protocol, the supplementation of GnRH antagonists into natural cycles seems to diminish this adverse effect thus conserving the advantage of the recruitment of more natural follicles in the follicular phase prior to ovarian suppression. In light of the fact that the addition of GnRH antagonist into the natural cycle may decrease the secretion of FSH leading to follicular atresia (12), we added HMG into the treatment protocol starting from the day of antagonist administration.

## CONCLUSIONS

We are encouraged by the results of the use of GnRH antagonists during natural IVF cycles in poor responders. Our experience suggests that this patient-friendly protocol can be of value for patients with poor ovarian response leading to similar results in the modified natural protocol together with reducing the doses of gonadotrophins used and cost. Further studies preferably randomized prospective studies are needed to confirm our observations.

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