Original Articles

Effect of antagonists vs agonists on in vitro fertilization outcome

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Summary

Purpose: To compare outcome following in vitro fertilization-embryo transfer (IVF-ET) using controlled ovarian hyperstimulation (COH) regimens using either the gonadotropin-releasing hormone (GnRH) agonist leuprolide acetate vs the GnRH antagonist ganirelix.

Methods: Women needing IVF for conception were randomly assigned to 300 IU of gonadotropins with ganirelix used in the follicular phase when a follicle with a 14 mm average diameter was attained vs a regimen using leuprolide acetate from the mid-luteal phase of the previous cycle.

Results: There were no differences found in clinical, ongoing, delivered pregnancy rates or implantation rates between groups.

Conclusions: The use of GnRH antagonists do not seem to reduce IVF outcome compared to using GnRH agonists in COH regimens.

Key words: Agonists; Antagonists; GnRH; Implantation.

Introduction

Gonadotropin releasing hormone (GnRH) analogues, both agonists and antagonists, were designed to control the synthesis and release of follicle stimulating hormone (FSH) and luteinizing hormone (LH) by pituitary gonadotropins [1, 2]. Because of the histamine-releasing side-effects for antagonists [3], the agonists were the first to come on the market. The first GnRH agonist to be used to prevent premature LH surges during controlled ovarian hyperstimulation (COH) was leuprolide acetate [4].

Gonadotropin-releasing hormone antagonists were introduced to the market later after finally two antagonists were developed without histamine-releasing side-effects - Cetrorelix® (ASTA Medica AG; Frankfurt, Germany) and Ganirelix® (Organon, Oss, The Netherlands) [5-7].

There have been several studies demonstrating that these two antagonists are effective in preventing premature LH surge following COH protocols for purposes of in vitro fertilization (IVF) [8-14].

A multi-cooperative study found that GnRH antagonists used for COH for IVF-embryo transfer (ET) had equal efficacy to agonists in preventing the LH surge, in stimulation of retrieved oocytes in fertilization rates, and in embryo quality [15]. The same study found that ganirelix was superior to agonists in requiring a smaller dose of FSH needed for stimulation and 50% less frequency of ovarian hyperstimulation syndrome [15].

However the same study found that the GnRH antagonist was inferior to the agonist in producing lower serum estradiol (E2) levels at the time of follicular maturation, lower clinical and ongoing pregnancy rates, and lower implantation rates [15]. A prospective randomized phase III study by Albano *et al.* also concluded that there was a non-significant trend for lower pregnancy rates with ganirelix than buserelin [16].

There are published data suggesting that the adverse effect of the GnRH antagonist is more likely on the endometrium rather than the embryo itself based on finding very acceptable pregnancy rates following transfer of spare frozen-thawed embryos formed with larger dosages of ganirelix (> 0.5 mg/day) which results in lower implantation rates following fresh ET [17].

Another study suggested that the adverse effect on the endometrial environment may be associated with the demonstration of a higher incidence of the serum E2 level plateauing or even decreasing in the late follicular phase prior to the human chorionic gonadotropin (hCG) injection [18]. The lower serum E2 level may be associated with using higher dosages of the GnRH antagonist or possibly by decreasing the dosage of the gonadotropins.

The prospective study presented here compared IVF outcome following the use of leuprolide acetate beginning in the mid-luteal phase and continuing until the hCG injection versus a moderate dosage of ganirelix started later in the follicular phase on IVF outcome.

Materials and Methods

A randomized prospective study was conducted. Sixty couples requiring IVF or intracytoplasmic sperm injection (ICSI) were randomly assigned to one of two ovarian stimulation treatment groups.

The luteal phase leuprolide regimen required the subcutaneous administration of 0.5 mg qd of leuprolide acetate

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(Lupron, TAP) for ten days from the mid-luteal phase, then .25 mg once gonadotropins were started. Gonadotropins (300 IU in two divided doses) were administered intramuscularly (IM) or subcutaneously (s.c.) after suppression was observed.

The ganirelix (Antagon, Organon) regimen required the administration of 250 mcg of ganirelix beginning with the observation of at least one dominant follicle with a diameter ≥ 14 mm in conjunction with a serum estradiol (E2) level ≥ 1000 pg/ml. Gonadotropins (300 IU in divided doses) were administered beginning on day 3 of the cycle.

In both groups the gonadotropins included 300 IU of follitropin beta (Follistim, Organon) or 150 follitropin beta and 150 IU human menopausal gonadotropin (hMG). The decision to use hMG or not was usually based on financial considerations so that all follitropin beta was used with prescription plans and hMG was added to cut costs for those paying out of pocket. There was no step-down in gonadotropin dosage unless the patient exhibited potential ovarian hyperstimulation syndrome.

Human chorionic gonadotropins (10,000 IU) were administered 35-37 hours prior to oocyte retrieval. Embryo transfer (ET) was deferred if the patient was at risk for ovarian hyperstimulation syndrome or a poor uterine environment was detected during ultrasonographic monitoring (endometrial thickness < 8 mm or a homogeneous hyperechogenic echo pattern was present at peak serum E2).

The outcome measures were clinical pregnancy rates (PRs), viable PRs, and implantation rates. If ET was deferred, the outcome of the first frozen ET was analyzed.

The rates were compared by treatment group using chi-square analysis. A .05 level of significance was used.

Results

There were 24 retrieval cycles with ganirelix (protocol 1) and 30 with luteal phase leuprolide acetate (protocol 2). Three women assigned to protocol 1 became pregnant before the study started and three decided not to proceed with IVF at least at our IVF center.

In protocol 1, 17 were given follitropin beta only and seven had follitropin beta and hMG. In group 2, seven had follitropin beta only and 23 had follitropin beta and hMG.

No cycles were cancelled for premature luteinization. A comparison of the stimulation characteristics is given in Table 1. A summary of the outcomes is presented in Table 2.

Table 1. — *Comparison of stimulation characteristics.*

	Protocol 1 (Ganirelix)	Protocol 2 (Leuprolide acetate)
Age of patients	38.0 ± 5.0 (38.3)	32.7 ± 3.8 (32.9)
No. of stimulation cycles	24	30
No. of retrieval cycles	24	30
Gonadotropins		
Follitropin beta only	17 (70.8%)	7 (23.3%)
Follitropin beta +hMG	7 (29.2%)	23 (76.7%)
Avg. no. of oocytes harvested	9.6 ± 7.7 (7)	17.6 ± 10.1 (16.5)
Avg. fertilization rates (%)	67.0 ± 30.7 (75.9)	66.5 ± 23.2 (70.1)
No. of deferred transfers	10 (41.7%)	12 (40.0%)
Reasons for deferred cycles		
OHSS risk	1	6
Lining inadequate	2	0
Failed fertilization	2	0
Multi-factors	5	6

Ovarian hyperstimulation syndrome = OHSS

Table 2. — *Comparison of outcome by stimulation protocol.*

	Protocol 1 (Ganirelix)	Protocol 2 (Leuprolide acetate)
Fresh transfer		
No. of cycles	14	18
Avg. no. of embryos transferred	3.1 ± 1.7 (3)	2.9 ± 54 (2.5)
Clinical PR	35.7% (5/14)	33.3% (6/18)
Viable PR	35.7% (5/14)	27.8% (5/18)
Implantation rate	20.9% (9/43)	13.2% (7/53)
Frozen ET (deferred transfers only)		
No. of cycles	5	10
Avg. no. of embryos transferred	3.0 ± 71 (3)	2.4 ± 70 (2.5)
Clinical PR	20.0% (1/5)	60.0% (6/10)
Viable PR	20.0% (1/5)	40.0% (4/10)
Implantation rate	20.0% (1/5)	54.2% (13/24)
Results of first transfers for all patients (fresh & frozen)		
No. of cycles	19	28
Avg. no. of embryos transferred	3.1 ± 1.5 (3)	2.7 ± 64 (3)
Clinical PR	31.6% (6/19)	42.8% (12/28)
Viable PR	31.6% (6/19)	32.1% (9/28)
Implantation rate	20.7% (12/58)	26.0% (20/77)

There were 14 fresh transfers in group 1 and 18 in group 2. The clinical PRs per ET were 35.7% for protocol 1 and 33.3% for protocol 2 (p = NS). The viable PRs were 35.7% and 33.3%, respectively (p = NS). The implantation rates were 20.9% and 13.2%, respectively (p = NS).

When the outcomes of the first frozen ET for those patients who deferred transfer were included, the viable PR and implantation rates were 31.6% and 20.7% for protocol 1 and 32.15% and 26.0%, respectively, for protocol 2.

Discussion

In the IVF cycles using a non step-down gonadotropin regimen, where either the GnRH antagonist or agonist was used, the PRs and implantation rates following transfer of fresh embryos showed no significant difference.

If one even looks for a trend, based on the limited power of the study, one could argue that the implantation rate of 20.9% in the ganirelix group vs 13.2% in the leuprolide acetate group could be interpreted as demonstrating a trend suggesting that if anything the prolonged use of GnRH agonists may adversely affect the uterine environment. This is even more plausible based on the fact that the trend for higher implantation rates was achieved despite the fortuitous selection, despite randomization, of a much older group taking ganirelix (age 38 vs 32.7).

The suggestion that the agonist and not the antagonist may create a less favorable endometrium was further supported by finding a much higher implantation rate (54.2%) following frozen ET in those younger women taking the luteal phase leuprolide acetate who deferred fresh ET for various reasons (implantation rate only 13.2% in the fresh transfer cycles). The slightly higher implantation rate of 26.0% for the younger group taking agonists vs 20.7% for the older group taking antagonists when evaluating all first transfers (fresh and frozen) is what one might expect to see based on the fortuitous differences in age.

If larger studies confirm the trends shown in this study where implantation rates following fresh ET in IVF cycles

using a luteal phase agonist protocol were lower than when frozen ET with non-deselected embryos was performed, the conclusion could be made that GnRH agonists may inhibit implantation by adversely affecting the uterine environment rather than the embryo itself. The use of ganirelix showed almost identical implantation rates with fresh or frozen transfer. The trend for higher pregnancy and implantation rates with frozen transfer in the leuprolide vs ganirelix group is expected based on the age differential.

Thus these data suggest that a COH regimen using ganirelix at a dosage of 0.25 mg daily s.c. does not reduce implantation potential compared to the use of leuprolide acetate started in the luteal phase even when the dosage of leuprolide is reduced from that originally described by Meldrum [19]. This would apply to protocols not using a step-down of gonadotropins.

Possibly a better financial status and better insurance in older patients may have influenced the higher percentage use of exclusive follitropin beta in the ganirelix group. However, it is not likely that the use of a higher percentage of follitropin beta provided an advantage to the group using ganirelix since at least at the Cooper Center for IVF, higher pregnancy rates have been recorded for patients taking a mixture of recombinant FSH and hMG vs recombinant FSH alone [20].

More extensive studies, possibly with a larger cooperative study, are need to explore the possibility that this dosage of ganirelix has a less adverse effect on the uterine environment than the standard dosage leuprolide acetate. Possibly even this dosage of ganirelix could reduce the implantation potential relative to using no agonists or antagonists at all, but probably at the sacrifice of more cancellations related to premature luteinization. There were none in this study with either protocol.

More studies are needed on even smaller dosages of ganirelix above 0.125 mg but less then 0.25 mg to see if an even more ideal dosage can be found that effectively inhibits premature luteinization but allows an even higher implantation rate. Another option would be to start the ganirelix a little later possibly not until the follicle attains a 16 mm diameter.

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