MSD

Symposium Abstracts

(13)

Towards a Center Of Excellence

2010

Indian Fertility Experts Meet

Creating a Patient-Oriented Best-in-Class *In Vitro* Fertilization Laboratory

Dr. Peter Sjöblom, UK

Integrating a Patient-Centered Approach in *In Vitro* Fertilization Practice

Prof. Jan I. Olofsson, Singapore

Gonadotropin-Releasing Hormone Antagonist in Controlled Ovarian Stimulation: Indian Perspective

Dr. Manish Banker, India

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Overview

The Indian Society for Assisted Reproduction (ISAR) is dedicated in providing information and updates in the field of reproductive medicine and assisted reproductive technology (ART). Recently, the society has put forward efforts to publishing the national ART registry of India from the year 2000.

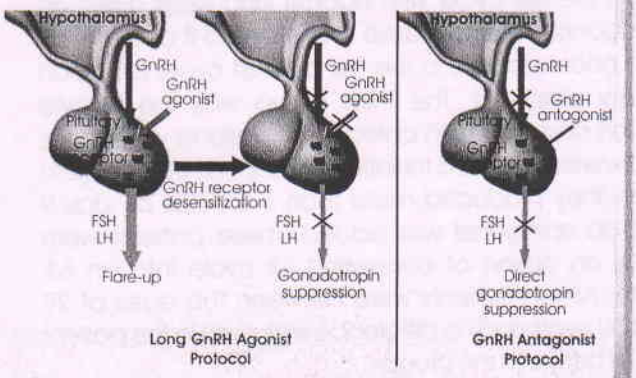
The society is now a part of the International Federation of Fertility Societies and all doctors practicing ART can volunteer to participate in the Indian National Registry for ART. The ISAR site contains all information related to ART right from the beginning of the cycle till the birth of a child, different types of *in vitro* fertilization (IVF) protocols, methods involving frozen transfer surrogacy, egg donation and embryo donation.[1]

Gonadotropin-Releasing Hormone Agonists, Antagonists and Assisted Conception

Gonadotropin-releasing hormone (GnRH) agonists and antagonists act differently. Agonists initially stimulate the release of gonadotropins from the pituitary (flare-up) for a short period of time, resulting in complete suppression of pituitary luteinizing hormone secretion after 2–3 weeks of pretreatment (see Slide 1).[2]

As opposed to the GnRH agonists, GnRH antagonists directly and rapidly suppress the gonadotropin release by blocking the pituitary GnRH receptor. Therefore, treatment with GnRH antagonists does not result in desensitization of the pituitary, allowing treatment to be restricted to the follicular phase.[2]

Slide 1: GnRH Agonist vs GnRH antagonist: Mechanism of action



GnRH=Gonadotropin-releasing hormone, FSH=follicle-stimulating hormone, LH=luteinizing hormone

Are Antagonists Patient-Centered?

Patient-centered IVF is important and the issues that are patient-centered involves safety, efficacy, efficiency, to ensure equity of access and timeliness of the procedure.[3] Antagonists are considered superior to agonists with respect to patient-centeredness because in many surveys, patients have been shown to prefer them and because of fewer incidences of ovarian hyperstimulation syndrome (OHSS), stress and return for another cycle more readily, less gonadotropin usage and afforadable treatment. More options for soft (or mild) ovarian stimulation are available, like clomiphene or letrozole. A recent study has shown that there is a trend towards higher pregnancy rates with agonists but not significantly different from antagonists both in terms of ongoing pregnancy and live birth rates.[4]

Experience with GnRH Antagonists

A retrospective study was conducted in Pulse Women's Hospital from the period of January to September 2009. Analysis was done in all cycles carried out in a 9-month period with the control group patients undergoing the first cycle using GnRH agonist protocol and compared with all the other patients on IVF on antagonist protocol. The antagonist protocol fell into four different patient categories. The first were those who were undergoing the first cycle on the antagonists either due to the patient's choice or due to suspected poor response on the basis of low anterior follicle count or high FSH.

The second group of patients were those who had failed the first cycle with agonist and were given an antagonist either because they wanted it or because of a poor response in the first agonist cycle (≤3 good quality embryos). The third group was the oocyte donors and the fourth category of patients were those who were stimulated for intrauterine inseminations (IUIs) when they produced more than 5 follicles on day 9 and an antagonist was added. These patients were given an option of converting IUI cycle into an IVF cycle. All the patients were between the ages of 29 and 30 years and no difference was seen in the patient profile between the groups.

Pregnancy outcome was different between the groups. A significantly higher pregnancy rate was seen in patients who had their first cycles on the antagonist compared to those who were on the agonist (see Table 1). Patients who had converted from IUI into IVF cycle had the best pregnancy rates as they were the most fertile among the entire group.

Table 1: Pregnancy outcome

	Pregnancies	Pregnancy rate
Group 1-Patients who are on first cycle on the antagonists	56/158	35.40%
Group 2-Patients who had failed the first cycle with agonist and were given an antagonist	15/51	29.40%
Group 3-Oocyte donors (Antagonist cycle)	48/140	34.30%
Group 4-Patients stimulated for intrauterine inseminations (IUIs) (>5 follicles on day 9) and received antagonist	11/14	78.60%
Control-agonist cycle	76/253	30.30%

The incidence of OHSS among the patients who had their first cycle on an agonist and an antagonist were practically the same but none of the other groups had any incidence of OHSS.

Exclusive Use of Antagonists in all ART Cycles

A change was made in the IVF protocol to use GnRH antagonist in all cycles, as of 1 January 2010. A study was done to assess the safety and efficacy of the antagonist protocol at Dr. Banker's pulse center. The protocol involves performing scan on day 2 of the cycle and a hormonal profile if required following which gonadotropin stimulation is started (see Slide 2).[5]

The patient is assessed after 5 or 6 days of stimulation after which antagonist is started with human chorionic gonadotropin (hcG) trigger. The protocol followed by Banker *et al*. involved a baseline scan on day 2 and the dose of stimulation decided for a particular patient and after 5 days of stimulation a second scan performed for the patient. The dose was modified if needed and the antagonist was started. The third scan was done on day 10 during which time the day and timing of hcG administration was decided.

A total of 283 patients were included in the 6-month period. This study finding showed that the treatment was effective with a pregnancy rate of 41%, 11.3% abortion rate and 5% ectopic pregnancy rates. Furthermore, average days of stimulation needed were found to be 10 and the average dose of the antagonist was four.

Total gonadotropins requirement for women aged less than 30 years was 2,312 International Units (IU); aged between 30 and 35 years was 2,718 IU; and for those aged >35 years was 3,193 IU. Average eggs were 9.29, mature eggs were 83%, average embryos transferred were 2.78, the average usable embryos were 5.6 and the implantation rate was 19.7%.

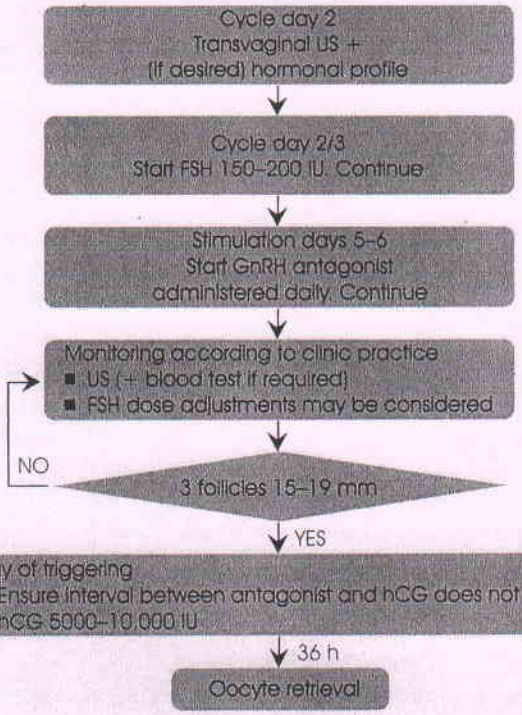
Safety of the Antagonist Protocol

There were nine cases of severe OHSS, twin pregnancy rate of 26% and triplet rate of 4.53%.

Slide 2: Suggested GnRH antagonist protocol

This suggested protocol represents a "best estimate" given the current data and clinical experience. Further data are required before more concrete recommendations can be made.

For regular IVF patients:
- 5–9 antral follicles per ovary
- Age <35 years
- No PCOS
- No history of poor responses
- No endometriosis



- ✓ No OCP pretreatment
- ✓ Check patient cycle day 2
- ✓ FSH 100–225 IU
- ✓ Antagonist earlier than later
- ✓ LH not necessary

Duration of treatment based on clinical judgment in consultation with patient (usually 2 USs)

US=ultrasonogram; OCP=oral contraceptive pill.

Devroey *et al. Hum Reprod.* 2009;24:764.

Summary

- Antagonists are simple to administer, efficacious and safe.
- No significant difference in pregnancy rates and other efficacy parameters was observed between the antagonist and the agonist.
- Use of antagonists can be considered as highly patient friendly.
- The future promises routine use of the antagonist especially in patients who prefer elective double embryo transfer.

References

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