A comparison of pregnancy rates following fresh and frozen embryo transfer according to the use of leuprolide acetate vs ganirelix vs cetrorelix

J.H. Check, C. Wilson, J.K. Choe, J. Amui, B. Katsoff

The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology & Infertility, Camden, NJ (USA)

Summary

Purpose: To determine if controlled ovarian hyperstimulation (COH) regimens using the gonadotropin releasing hormone (GnRH) agonist leuprolide acetate result in higher pregnancy and implantation rates than COH regimens using the GnRH antagonists cetrorelix or ganirelix following fresh and frozen embryo transfer. *Methods*: Retrospective analysis was performed evaluating the pregnancy rates with the first fresh and first frozen embryo transfer cycles according to which protocol was used. A haphazard decision was made on which protocol to use. Women were required to be < 40 years of age and have had ≥ 5 eggs retrieved. *Results:* Significantly lower implantation rates were seen with ganirelix compared to leuprolide acetate or cetrorelix. *Conclusions:* These data should hopefully encourage interest in a prospective study to determine if conclusions about the inferiority of ganirelix are not merely fortuitous.

Key words: Gonadotropin releasing hormone; Agonist, antagonist; Fresh and frozen embryo transfer.

Introduction

The use of gonadotropin releasing hormone (GnRH) agonists to be combined with gonadotropin stimulation for purposes of in vitro fertilization-embryo transfer (IVF-ET) was first described in 1988 [1]. This technique started the GnRH agonist in the mid luteal phase and become known as the "long protocol" [2]. One of the purposes of adding GnRH agonists was to prevent premature luteinizing hormone (LH) surge [3]. Prior to the use of GnRH agonists approximately 20% of controlled ovarian hyperstimulation cycles for IVF-ET had to be cancelled because of premature luteinization [4, 5].

The long acting GnRH agonists initially stimulate gonadotropins and then by ablating the pulsatility of FSH and LH secretion eventually suppress endogenous gonadotropins. Thus they have to be taken for a long length of time. The duration can be shorter than the three weeks used in the long protocol, but starting in mid-luteal phase when FSH and LH are maximally suppressed, provides the best chance for prevention of premature luteinization.

Development of GnRH antagonists where there is a substitution of two different amino acids in the decapeptide GnRH than the ones substituted for GnRH agonists occurred but they were too toxic to initially be introduced when GnRH agonists were introduced on the market. Eventually toxicity was reduced and these products were able to accomplish almost immediate gonadotropin suppression by blocking the GnRH receptor in a close dependent competitive fashion [6]. The main advantage of the GnRH antagonist over the agonist is the simplicity of the protocol. By starting it in the late follicular phase two cycles are not needed to achieve one controlled ovarian hyperstimulation. Also, elimination of the initial gonadotropin stimulation effects of GnRH agonists would help prevent follicular cysts.

However, one major disadvantage was that there were reports that the use of GnRH antagonist may lower the subsequent pregnancy rates when compared to GnRH agonists [7, 8].

The reason for the 5% difference in pregnancy rates in GnRH agonist vs antagonist protocols is not clear [7]. Various hypotheses for adverse effects of GnRH antagonists on oocytes, embryos, or endometrium have been proposed [8,9]. However some clinical trials found similar pregnancy rates between agonist and antagonist protocols [10-12].

The present study retrospectively evaluated pregnancy and implantation rates in similar types of patients according to whether they used GnRH agonists or antagonists. The GnRH antagonists used were either cetrorelix or ganirelix which are considered equally effective. Nevertheless, the possibility exists that there may be a difference between them as far as subsequent pregnancy or implantation rates. This study, therefore, was somewhat unique in that the pregnancy and implantation rates would be analyzed according to which antagonist was used. Finally the pregnancy and implantation rates would be analyzed following frozen embryo transfer according to the embryo having been formed by either agonist or antagonist and which antagonist was used. If, in fact, higher pregnancy or implantation rates were found with the GnRH agonist (as concluded by the aforementioned meta analysis) and if higher pregnancy rates with frozen

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embryo transfer in the agonist group were also found it would favor the adverse effect of an antagonist being on the oocyte or embryo. In contrast, if the fresh embryo but not frozen embryo pregnancy rates were lower with GnRH antagonists this would support that the adverse effect of GnRH antagonists was on the endometrium.

Materials and Methods

A retrospective cohort analysis of women having their first IVF cycles in our IVF center over a 3-year period was performed. Inclusion criteria were age ≤ 39.9 years and IVF cycles with ≥ 5 eggs retrieved.

The patients were first separated into antagonist and agonist (leuprolide acetate) groups. The antagonist group was further categorized by antagonist identity (ganirelix vs cetrorelix). The antagonists were administered with a 14 mm follicle at a dosage of 250 mcg daily. Leuprolide acetate began mid-luteal phase (10 IU) for ten days, then 5 IU through the follicular phase. Various brands of gonadotropins were utilized.

The decision on which COH regimen to use, i.e., agonist vs antagonist and which antagonist was not pre-determined but up to the choice of the physician. Frequently, the GnRH antagonists were used for timing convenience, i.e., the woman was already past mid-luteal and a whole month would be wasted if trying for an agonist protocol.

Results

Comparison of pregnancy rates following transfer of fresh embryos according to use of ganirelix vs cetrorelix or leuprolide acetate is shown in Table 1. The clinical pregnancy rates were significantly lower ($p < 0.05$) in ganirelix cycles as compared to the cetrorelix and leuprolide acetate cycles combined. There was a trend for lower pregnancy rates ($p = .080$) comparing ganirelix to cetrorelix alone. Implantation rates were significantly lower for ganirelix (21.7%, 95/437) versus cetrorelix (26.8%, 131/489) or leuprolide acetate (28.4%, 188/662) ($p < 0.01$).

Table 1. — *Live delivered pregnancy and implantation rates according to use of GnRH agonist or antagonist, and which one.*

	Ganirelix	Cetrorelix	Leuprolide acetate	*p* value
Fresh				
Clinical pregnancy rate	37.7% (55/146)	48.8% (84/146)	48.1% (117/243)	.080
Live delivered pregnancy rate	35.6% (52/146)	41.9% (72/146)	42.8% (104/243)	.349
Frozen				
Clinical pregnancy rate	30.8% (40/130)	47.2% (51/108)	42.0% (95/226)	.025
Live delivered pregnancy rate	28.5% (37/130)	36.1% (39/108)	35.4% (80/226)	.338

The table also shows pregnancy rates according to antagonist (and type) and agonist following frozen embryo transfer. A significantly lower clinical pregnancy rate per transfer was seen with ganirelix following frozen ET ($p = .025$).

No significant difference was found when comparing ongoing delivered pregnancy rates in either fresh or frozen ET cycles but the live/delivered pregnancy rates were still 20% lower with ganirelix.

Implantation rates were significantly lower with ganirelix (14.1%, 53/377) versus cetrorelix (24.7%, 73/295) versus leuprolide acetate (20.2%, 24/133) following frozen ET ($p < 0.01$, $p < 0.01$).

Discussion

For reasons still as yet undetermined, the use of the antagonist ganirelix during COH procedures yields both lower clinical pregnancy and implantation rates as compared to the antagonist cetrorelix and agonist leuprolide acetate. These data suggest that the lower rates may be attributable to adverse effects on the embryo rather than endometrium since the adverse effect was even more evident in frozen ET cycles.

Possibly one of the reasons for conflicting data as to whether antagonists adversely affect the chance of an embryo to implant may be related to which antagonist was studied. One should always be cautious about the conclusion made from a retrospective study, but the data suggests the need for a proper prospective study to better determine if ganirelix does, in fact, adversely effect embryo implantation.

A prospective study was proposed to the Ethics Committee for the Cooper Institute for Reproductive and Hormonal Disorders before requesting permission from the institutional review board of Cooper Hospital University Medical Center. The ethics committee concluded that in view of the data found in the respective study there would be no reason to subject a group of women placing their trust in physicians to provide the best medicine to treat them with a potentially inferior COH protocol that could lead to a lower pregnancy rate. Thus our IVF center will not be conducting the suggested prospective study to make sure that our findings that ganirelix rather than cetrorelix led to inferior pregnancy rates was not merely fortuitous. It is not clear why there should be a difference between the affect of these two antagonists. Possibly these data will encourage another reproductive center to perform this prospective study.

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Address reprint requests to:
J.H. CHECK, M.D., Ph.D.
7447 Old York Road
Melrose Park, PA 19027 (USA)
e-mail: laurie@ccivf.com