Evidence that the main adverse effect of ganirelix on pregnancy and implantation rates is on the embryo rather than the endometrium

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Summary

Purpose: To compare pregnancy rates following the transfer of thawed frozen embryos according to the type of GnRH antagonist or agonist used during controlled ovarian hyperstimulation (COH). *Methods:* Retrospective review of frozen embryo transfers according to whether a GnRH agonist or antagonist was used. Furthermore to determine if a specific antagonist/agonist resulted in higher pregnancy rates than the other. *Results:* The pregnancy rates in two different age categories were similar whether the COH regimen used the GnRH agonist leuprolide acetate or the GnRH antagonist cetrorelix. However, lower pregnancy rates were found with the GnRH antagonist ganirelix. *Conclusions:* These data reached similar conclusions as was found comparing these three agents in fresh embryo transfer.

Key words: GnRH agonist; GnRH antagonist; Frozen embryo transfer.

Introduction

Some studies have suggested that the use of gonadotropin releasing hormone (GnRH) antagonists, e.g., ganirelix or cetrorelix, are associated with lower pregnancy rates when used for controlled ovarian hyperstimulation (COH) compared to COH protocols using leuprolide acetate [1, 2].

At the 2008 Pacific Coast Reproductive Society we compared clinical and live delivered pregnancy rates according to whether ganirelix or cetrorelix was used as the GnRH antagonist for IVF-ET and found a significantly lower clinical and live delivered pregnancy rate with ganirelix [3]. If this is an adverse effect of ganirelix inhibiting embryo implantation theoretically it could either be involving the endometrium or the embryo directly.

The present study compared clinical and live delivered pregnancy rates and implantation rates following frozen embryo transfer. The hypothesis was that if the pregnancy and implantation rates were also lower with ganirelix compared to the other agents the evidence would favor the adverse effect of ganirelix to be on the embryo rather than the endometrium.

Materials and Methods

All frozen embryo transfer cycles over a 5-year period where at least two embryos were transferred were retrospectively compared. Clinical (viable pregnancy at 8 weeks), viable (viable pregnancy at 12 weeks) and live delivered pregnancy rates and implantation rates were determined according to whether the COH regimen used the GnRH agonist leuprolide acetate or the GnRH antagonist ganirelix or the GnRH antagonist cetrorelix prior to oocyte retrieval.

The average number of blastomeres per embryo transfer according to these three groups was also determined. The data was also stratified according to two age groups: ≤ 35 and age 36-39 counting the age of when the female partners had the oocyte retrieval.

Embryos were frozen using a simplified protocol using a one-step removal of the cryoprotecant 1,2 propanediol [4]. Assisted embryo hatching was performed prior to the transfer of these day 3 embryos [5]. No cycles were included if leuprolide was used to prepare for the graduated estradiol/progesterone protocol used to develop the endometrium for the frozen ET.

Results

A summary of the outcome following frozen embryo transfer according to whether a GnRH agonist or GnRH antagonist was used and according to which GnRH antagonist was used during the oocyte retrieval cycle divided into two age groups is seen in Table 1. In both age groups the women who had taken cetrorelix or leuprolide acetate for their COH protocol had similar pregnancy and implantation rates but the pregnancy and implantation rates were lower in those whose COH protocol used ganirelix (Table 1).

Comparing women aged ≤ 39, the clinical pregnancy rate per frozen ET was 30.0% (52/173) for those whose COH protocol used ganirelix vs 42.5% (289/680) for those taking either cetrorelix or leuprolide acetate (p = 0.0038, chi-square). The live delivered pregnancy rates were also lower with ganirelix – 24.8% (43/173) vs 34.5% (235/680) (p = 0.019). The implantation rates were also significantly lower with ganirelix: 13.1% (69/525) vs 20.9% (506/1937) ($p < 0.001$).

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Table 1. — *Frozen embryo transfer pregnancy rates according to use of ganirelix, cetrorelix or leuprolide acetate during the oocyte retrieval cycle.*

	Ganirelix			Cetrorelix			Leuprolide acetate		
Age at retrievals	Totals	≤ 35	36-39	Totals	≤ 35	36-39	Totals	≤ 35	36-39
# Transfers	173	116	57	244	179	65	436	369	67
Avg. # blastomeres	6.5	6.6	6.5	6.3	6.5	6.2	6.4	6.4	6.3
# pregnancies (beta-hCG >200 mIU/ml)	62	40	22	116	86	30	220	191	29
% pregnant/transfers	35.8	34.5	38.6	47.5	48.0	46.2	50.5	51.8	43.3
# clinical pregnancies	52	33	19	103	76	27	186	161	25
% clinical/transfers	30.1	28.4	33.3	42.2	42.5	41.5	42.7	43.6	37.3
# viable	45	28	17	87	62	25	163	140	23
% viable/transfers	26.0	24.1	29.8	35.7	34.6	38.5	37.4	37.9	34.3
# miscarriages	9	6	3	24	21	3	30	25	5
% miscarriage/preg.	17.3	18.2	15.8	23.3	27.6	11.1	16.1	15.5	20.0
# deliveries/ongoing	43	27	16	79	55	24	156	136	20
% delivered/ongoing	24.9	23.3	28.1	32.4	30.7	36.9	35.8	36.9	29.9
# total embryos transferred	525	329	196	677	474	203	1254	1038	216
Avg. # embryos transferred	3.0	2.8	3.4	2.8	2.6	3.1	2.9	2.8	3.2
# sacs implanted	69	44	25	136	102	34	270	232	38
Implantation rate (%)	13.1	13.4	12.8	20.1	21.5	16.7	21.5	22.4	17.6

The difference in pregnancy rates could not be accounted for by embryos having fewer blastomeres. Fragmentation indices were not evaluated but recent data suggest that the number of blastomeres of day 3 embryos is a better indicator of pregnancy outcome [6].

Discussion

Not all IVF centers share our observation that the use of ganirelix leads to lower pregnancy rates following fresh embryo transfer compared not only to the use of a GnRH agonist but also the other GnRH antagonist cetrorelix.

Whatever the reasons as to why our methodology leads to lower pregnancy rates with ganirelix, the present study aimed to determine if that adverse effect was on the endometrium or the embryo.

The demonstration that lower pregnancy and implantation rates result from frozen ET when no antagonists or agonists are used in the COH protocol strongly suggests that for those centers whose methodology leads to similar findings as to our IVF center (i.e., that ganirelix lowers pregnancy rates) the adverse mechanism seems to have some direct effect on the embryo rather than the endometrium.

This study by showing lower pregnancy rates even with frozen ET where embryos were developed using ganirelix corroborated our previous conclusions that for some reason, in some IVF centers, ganirelix leads to lower pregnancy rates compared to the other GnRH antagonist cetrorelix.

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