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Effect of taking a one time injection of one mg leuprolide acetate three days after embryo transfer on pregnancy outcome and level of first beta human chorionic gonadotropin (beta-hCG) level

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Summary

Purpose: To determine if the injection of a gonadotropin releasing hormone agonist (GnRHa) three days after embryo transfer will improve pregnancy and implantation rates. *Materials and Methods:* One mg s.c. of leuprolide acetate was randomly given based on patient decision three days after embryo transfer to some patients undergoing in vitro fertilization-embryo transfer (IVF-ET). *Results:* For women aged ≤ 43 the clinical pregnancy rate for those not taking the GnRHa was 39.5% (68/122) *vs.* 54.5% (42/77) for those taking leuprolide acetate (Chi-square, $p = 0.0275$). The respective implantation rates were 22.6% *vs.* 30.2% ($p = 0.0495$). There was no difference in first serum beta human chorionic gonadotropin (beta-hCG) levels according to whether leuprolide was used or not. *Conclusions:* Leuprolide acetate similar to other GnRH agonists can improve implantation rates following IVF-ET when injected once in mid-luteal phase. The beneficial effect may be on GnRH receptors in the endometrium rather than the embryo (which had been hypothesized to direct increased placental production of hCG).

Key words: Leuprolide acetate; Mid-luteal phase; Endometrial GnRH receptor; Improved implantation.

Introduction

In 2004 in an oocyte donation model, Tesarik *et al.* found an enhancement of embryo development potential by a single administration of a gonadotropin releasing hormone agonist (GnRHa) at the time of embryo implantation [1]. The benefit of luteal phase GnRHa in mid-luteal phase was confirmed by Pirard *et al.* [2]. Iwashita *et al.* found that GnRHa increased human chorionic gonadotropin (hCG) levels suggesting that this results from its action on placental GnRH receptors [3]. The higher levels of hCG suggested to Tesarik *et al.* that the GnRHa may have a direct beneficial effect on the embryo itself causing it to secrete more hCG which favors successful implantation [4]. The study by Lin *et al.* provided support for this theory by demonstrating expression of the human GnRH receptor gene in the placenta and found a functional relationship to hCG secretion [5].

The objective of this study was to determine if the GnRHa leuprolide acetate at a one-mg dosage could improve implantation and live pregnancy rates after in vitro fertilization-embryo transfer (IVF-ET) similar to the other GnRHa, e.g., buserelin by Pirard et al and triptorelin by Tesarik *et al.* [2, 4]. Furthermore the study would determine if the use of a GnRH agonist in mid-luteal phase is more or less beneficial according to female age. Finally, the study would corroborate or refute the suggestion that the use of GnRHa in mid-luteal phase is associated with a higher first serum beta-hCG levels.

Materials and Methods

During a four month time period, all patients were given the opportunity of taking one mg leuprolide acetate in mid-luteal phase. They were advised of previous studies suggesting increased pregnancy rates [1-5]. However, they were explained that the present authors have no personal experience with this treatment.

To ensure they received the medication, one requirement was that they would have to receive the injection at the present institution at the same time as their evaluation by pelvic sonography to determine if they reached a homogeneous hyperechogenic endometrial echo pattern [6].

Only cycles using controlled ovarian hyperstimulation with a gonadotropin releasing hormone antagonist (cetrorelix or ganirelix) were included followed by IVF-ET. There were no exclusions for previous failed IVF cycles or degree of ovarian reserve as evidenced by normal or increased day 3 serum FSH.

The women were stratified into age groups of ≤ 35, 36-39, 40-42, and ≥ 43. Clinical (ultrasound evidence of pregnancy at

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Table 1. — *Pregnancy and implantation rates and first serum beta-hCG level according to age and use or non-use of a single one-mg injection of leuprolide acetate in mid-luteal phase.*

	Without LA in the luteal phase			With leuprolide		
Age	≤35	36-39	40-42	≤35	36-39	40-42
# transfers	72	36	41	38	20	11
# clinical pregnancy	32	17	14	24	11	5
% clinical/transfer	44.4	47.2	34.1	63.2	55.0	45.5
% delivered/ongoing	37.5	41.7	22.0	57.9	45.0	27.3
Avg. # embryos transfer	2.2	2.5	2.8	2.0	2.4	3.0
Implantation rate (%)	30.6	29.7	15.9	42.9	29.2	18.2
Avg. level 1st beta-hCG (mIU/ml)	280.8	336.4	192.5	290.5	221.9	186.8

eight weeks) and % delivered/ongoing (viable fetus past 12 weeks) and implantation rates were compared according to whether the s.c injection of one mg leuprolide acetate three days after a day 3 embryo transfer was given or not. The average first serum beta-hCG level in those who were pregnant was also compared according to whether leuprolide acetate was given or not. The first serum beta-hCG was taken 14 days after oocyte retrieval.

Results

There were 172 women who did not take the leuprolide acetate *vs.* 77 who did take it. The most common reason for not taking the leuprolide injection was the requirement to actually return to the present IVF center for the administration since a significant percentage of the present practice is not local. The requirement for the administration in this facility was not made as much to ensure delivery of the medication but was created to allow an unbiased control group without randomization since the latter would require a more extensive IRB approval which would not have been time sensitive.

The pregnancy outcome according to three age groups (35-42) in women not taking *vs.* taking the one mg leuprolide acetate injection three days after embryo transfer is seen in Table 1. For each age group there was a higher clinical and live delivered ongoing pregnancy rate in those taking the GnRHa *vs.* those who did not. The implantation rates were higher for those taking *vs.* not taking leuprolide acetate with the exception of the age group 36-39 where they were the same. The greatest difference was seen in women aged ≤ 35.

There were 23 women aged ≥ 43 who did not take the GnRHa *vs.* eight who did. The clinical and live delivered pregnancy rates were 8.7% and 4.3% *vs.* 25% and 12.5%, respectively.

Combining all cases the clinical pregnancy rate without leuprolide acetate was 39.5% (68/172) *vs.* 54.5% (42/77) with the GnRHa ($p = 0.0275$, chi-square analysis). The implantation rate for all women combined was 22.6% for those not taking the leuprolide *vs.* 30.2% in those taking the drug ($p = 0.0495$, chi-square analysis).

Table 1 also shows the average first serum beta-hCG for those conceiving without and with leuprolide acetate supplementation. No increased level or trend was found for higher serum beta-hCG levels in those conceiving with *vs.* without leuprolide supplementation.

Conclusions

This study confirms the previous studies by Tesarik *et al.* and Pirard *et al.* that a single use of a GnRHa in mid-luteal phase can increase pregnancy rates following embryo transfer [1, 2, 4]. This is the first study showing that the GnRHa leuprolide acetate can improve implantation rates similar to buserelin and triptorelin.

These data do not corroborate previous data suggesting that the mechanism for improved successful implantation following mid-luteal GnRHa may be by enabling the embryo to make more hCG. These data more suggest a possible direct effect of the GnRHa on the endometrium. GnRH receptors have been found in murine endometria [7]. The human uterus also has LH receptors [8]. Thus the GnRHa could stimulate an increased amount of endometrial LH to explain the beneficial effect of these agents on improving pregnancy rates.

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