Beneficial Effect of Luteal-phase Gonadotropin-releasing Hormone Agonist Administration on Implantation Rate After Intracytoplasmic Sperm Injection

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SUMMARY

Objective: To evaluate the effect of gonadotropin-releasing hormone (GnRH) agonist, administered in the luteal phase, on intracytoplasmic sperm injection (ICSI) outcome.

Materials and Methods: One hundred and eighty women undergoing ovarian stimulation for ICSI were enrolled in this study. Patients were randomly assigned to receive a single dose of GnRH agonist or placebo. Implantation rate and clinical pregnancy rate were the main outcomes.

Results: Administration of 0.1 mg of the GnRH agonist triptorelin on day 3 after embryo transfer led to a significant improvement in implantation rate (12.3% *vs.* 7.3%) and clinical pregnancy rate (25.5% *vs.* 10.0%) as compared with placebo.

Conclusion: Luteal phase GnRH agonist administration enhances ICSI clinical outcomes. [*Taiwan J Obstet Gynecol* 2009;48(3):245–248]

Key Words: embryo implantation, GnRH agonist, intracytoplasmic sperm injection, luteal phase support

Introduction

Luteal phase deficiency is a common feature of cycles resulting from stimulation of follicular development, in cycles downregulated with gonadotropin-releasing hormone (GnRH) agonist as well as those using a GnRH antagonist [1,2]. It is characterized by premature regression of the corpus luteum, leading to a shortened luteal phase of less than 10 days, low progesterone levels, and delayed secretory transformation of the endometrium [3]. The consequences of luteal phase deficiency are a reduced embryo implantation rate, a lower pregnancy rate, and an increased miscarriage rate when pregnancy is established; thus, luteal phase support is a common practice in assisted reproductive technology (ART) to significantly improve embryo implantation, clinical pregnancy rate, and delivery rate [2]. The therapeutic regimens routinely used for supporting the luteal phase are intramuscular human chorionic gonadotropin (hCG) or vaginal progesterone with or without estrogen. hCG administration is associated with increased risk of ovarian hyperstimulation syndrome (OHSS), and progesterone is the preferred choice [4]. Recently, the beneficial effect of GnRH agonist for luteal phase support has been suggested in some studies [5–7]. The mechanism of the presumed beneficial effect of luteal phase agonist administration is poorly defined. It was hypothesized that GnRH agonist may support the corpus luteum by stimulating the secretion of luteinizing hormone by pituitary gonadotroph cells, or by acting directly on the endometrium through the locally expressed receptors [8]. Tesarik et al reported a direct effect of GnRH agonist on the embryo in oocyte donors [5]. The aim of this study was to assess the effect of single dose GnRH

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agonist administration, as luteal phase support, on intracytoplasmic sperm injection (ICSI) outcome.

Materials and Methods

Patients

In order to study the effect of GnRH agonist administration on pregnancy outcome, a total of 180 women who were candidates for ICSI, and who were referred to the Research and Clinical Center for Infertility in Yazd, were screened. Patients older than 40 years old and poor responders in previous cycles (defined as day 3 follicle-stimulating hormone > 10 IU/mL or less than four follicles at the time of hCG injection in the previous cycle) were excluded from the study. The patients were randomly divided into two groups: an experimental group ($n = 90$) and a control group ($n = 90$). Random selection to either group was performed by drawing a piece of paper from a bag containing equal numbers of papers assigned to each group.

The baseline characteristics of the two groups, especially age, duration of infertility, duration and dosage of hormonal stimulation, number of retrieved oocytes and transferred embryos, were not statistically different (Table 1).

Written informed consent was given by the patients in the case group. This prospective study has been approved by the ethics committee of the Research and Clinical Center for Infertility, Yazd University of Medical Sciences.

Ovarian stimulation protocol

For pituitary downregulation and endogenous gonadotropin depletion, patients in both groups were treated by daily injection of subcutaneous buserelin 500 μg (Suprefact; Aventis, Frankfurt, Germany) from day 21 of the menstrual cycle, followed by 250 μg daily from the first day of vaginal bleeding. Follicular stimulation was initiated from day 2 of the menstrual cycle with daily use of recombinant follicle-stimulating hormone 150–225 IU (Gonal-F; Serono, Aubonne, Switzerland) and was continued until at least two follicles with diameter ≥ 18 mm were observed by vaginal ultrasonography. Oocyte maturation was induced by 10,000 IU of hCG intramuscularly (Pregnyl; Organon, Cambridge, UK).

Oocyte retrieval was performed 34–36 hours after hCG administration by a 17-gauge needle (Cook, Queensland, Australia) under vaginal ultrasound guidance. Two or three embryos were transferred within 48–72 hours by a Labotect catheter (Labotect GmbH, Gottingen, Germany). The luteal phase was supported by administration of progesterone 800 mg (Cyclogest; Alpharma, Barnstaple, UK) daily and was continued to week 11 of pregnancy. In the study group, women were given a single dose of triptorelin 0.1 mg (Decapeptyl; Ipsen Pharma, Barcelona, Spain) subcutaneously on day 3 after embryo transfer. The controls received placebo at the same time. Chemical pregnancy was determined by measuring serum β-hCG level 14 days after embryo transfer. Clinical pregnancy was defined as the presence of an intrauterine gestational sac with embryonic cardiac activity observed by vaginal ultrasound.

Statistical analysis

The SPSS 15.0 software (SPSS Inc., Chicago, IL, USA) was used to analyze data of all patients. The baseline characteristics of the two groups of patients were compared by the Mann-Whitney *U* test. Differences in the pregnancy outcome in the study and control group were analyzed using the χ^2 test. The implantation rate was calculated as the ratio of the number of embryonic sacs detected by sonography to the total number of embryos transferred. The rate of clinical pregnancy was expressed

Table 1. Basic demographic and ovarian stimulation cycle characteristics of the gonadotropin-releasing hormone (GnRH) agonist treatment group and placebo group*

Characteristics	Patient groups†	
	Luteal phase GnRH agonist ($n = 90$)	Placebo ($n = 90$)
Age (yr)	29.96 ± 3.93	29.73 ± 3.92
Serum estradiol on day 14 after ICSI (pg/mL)	58.12 ± 26.44	96.92 ± 32.8
Serum progesterone on day 14 after ICSI (ng/mL)	21.35 ± 7.18	25.16 ± 13.38
Duration of FSH therapy (d)	10.72 ± 1.90	10.11 ± 2.11
Total amount of FSH given (ampule)	22.9 ± 7.5	22.9 ± 7.7
Oocytes retrieved, *n*	5.42 ± 2.54	5.89 ± 2.81
Embryos transferred, *n*	2.25 ± 0.78	2.40 ± 0.79

**Values are mean ± standard deviation; †the differences between the two groups was not significant ($p > 0.05$). ICSI = intracytoplasmic sperm injection; FSH = follicle-stimulating hormone.*

as the ratio of the number of patients in whom clinical pregnancy was diagnosed to the total number of patients who underwent embryo transfer. A p value of ≤ 0.05 was considered statistically significant.

Results

Infertile couples continued to be assessed until 90 patients were assigned to each of the treatment and placebo groups.

Patient characteristics were similar between the treated group and controls. There were no differences in the concentration of estradiol, progesterone, duration and dose of hormonal stimulation, number of retrieved oocytes, and number of embryos transferred (Table 1). Moreover, no cases of OHSS were found in either the study or control groups.

An implantation rate of 12.3% was detected in the GnRH group compared with 7.3% in controls, and the increase was statistically significant ($p = 0.042$). The clinical pregnancy rate was significantly higher in women experiencing GnRH administration than in the placebo group (25.5% *vs.* 10.0%; $p = 0.015$; Table 2).

Discussion

The luteal phase is the result of intermittent stimulation of the corpus luteum by pituitary luteinizing hormone, and it is different in ART cycles compared with natural cycles. Luteal phase deficiency is a common feature of cycles resulting from stimulation of follicular development [9] and leads to a decreased embryo implantation rate, a lower pregnancy rate and an increased miscarriage rate when pregnancy is established [2]. The reasons for luteal deficiency are not yet fully understood.

Table 2. Implantation rate and clinical pregnancy rate in gonadotropin-releasing hormone (GnRH) agonist and placebo groups

Variables	Patient group		p
	Luteal phase GnRH agonist ($n = 90$)	Placebo ($n = 90$)	
Implantation rate, %	12.3	7.3	0.042
Clinical pregnancy rate, n (%)	23 (25.5)	9 (10.0)	0.015

To cope with this problem, luteal phase support can be provided by hCG or progesterone. According to some studies, GnRH agonist administration can support the luteal phase [5–8].

Based on the above observation, we investigated the effect of GnRH agonist administration in this prospective randomized study, in a single dose 3 days after embryo transfer, on luteal phase characteristics and clinical outcome. Significant differences in implantation and clinical pregnancy rate were found among women with GnRH administration compared with the control group. It is in line with the study of Tesarik et al [5] which showed that mid-luteal GnRH agonist administration in oocyte donors increased the implantation rate. A similar study reported that administration of 0.1 mg of the GnRH agonist triptorelin on day 6 after ICSI led to a significant improvement in implantation and live birth rates as compared with placebo [8]. In addition, Pirard et al [6] administered intranasal buserelin for luteal phase support and showed that it was associated with a good pregnancy rate.

Theoretically possible effects of GnRH agonist are improvements in the function of the endometrium and corpus luteum and a direct effect on the embryo, or some combination of these possibilities. In this study, an improvement in the implantation rate and clinical pregnancy rate in the GnRH agonist-treated group appeared not to result from the effect of GnRH agonist on the corpus luteum, because we did not observe any difference in the serum levels of estradiol and progesterone between the two groups. We also carried out endometrial support by administering vaginal progesterone after embryo transfer which may show a possible effect of GnRH agonist on the embryo. A direct effect of the agonist on the endometrium mediated through locally present GnRH agonist can certainly not be ruled out. The hypothesis of a direct effect of a GnRH agonist on the embryo by Tesarik et al [8] has been suggested by the observation of higher levels of serum β-hCG in patients who achieved a single pregnancy after administration of GnRH agonist compared with controls. Previous research has shown that GnRH increased serum hCG in pregnant women [10] by acting on a placental GnRH receptor [11]. However, we did not observe in our study any differences in serum β-hCG level among pregnant women in the study group and controls. The present data showed a positive effect on pregnancy outcome of single-dose GnRH agonist administration as luteal phase support. More information is needed about the possible mechanism of action of a single dose of agonist as luteal phase support, and also detailed knowledge has to be gained with regard to optimal treatment (minimally effective dose

and timing). Early studies suggested that the GnRH agonist has a dose-dependent effect on the corpus luteum. Administration of the GnRH agonist buserelin at a dose of 500 μg (as used for downregulation in ART cycles) may act as a luteolytic agent; but in one study, it was shown that buserelin at lower doses (100 μg) had a stimulatory effect on the corpus luteum [6].

In the present study, in accordance with the study of Tesarik et al [8], we did not observe any increase in the development of OHSS in GnRH agonist-treated patients. A question may arise about a possible increase in the incidence of OHSS because of a higher level of hCG by administering luteal phase GnRH agonist, and it may question the safety of GnRH agonist in high-risk patients. In some animal studies, it has been shown that administration of GnRH agonist during the luteal phase not only decreased the expression of vascular endothelial growth factor receptors, but also might prevent OHSS [12]. Therefore, it seems that luteal phase support by GnRH agonist does not have any adverse effect, but caution is recommended until more details on the effect of luteal phase GnRH agonist administration are available.

The results of this study showed a beneficial effect of GnRH agonist administration as luteal phase support on pregnancy outcomes in ART as in previous studies, but more studies investigating the optimal dose and exact mechanism of the beneficial effect of a GnRH agonist are needed.

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