

**Gonadotropin-Releasing Hormone agonist as a single luteal support –
What is its mechanism of action?**

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Background

Hormonal support during the luteal phase in in-vitro-fertilization (IVF) patients is intended to overcome the phenomenon of luteal phase deficiency [1], with the purpose to increase pregnancy rates. Different protocols for luteal support use progesterone, estrogen, human chorionic gonadotropin (hCG), or their combination. The field of IVF is rapidly developing with cumulating data regarding treatment efficiency and with more possibilities for treatment applications. There is still no consensus in the medical literature regarding the preferred treatment protocol for luteal support.

In recent years, Gonadotropin Releasing Hormone (GnRH) agonists have been used innovatively as an adjunct to progesterone or as a sole treatment for luteal support [1]. Different protocols for the administration of GnRH agonists were suggested, using single or repetitive doses. Drugs can be administered by subcutaneous (SC) injections like Triptorelin (Decapeptyl) and Leuprolide or intranasal like Nafarelin (Synarel). Intranasal administration using a nasal spray is considered a non-invasive route for drug delivery and can increase patient convenience, comfort, and compliance compared to injections or vaginal administration of other luteal support treatments.

In previous studies, a single dose of SC injection was given six days after ovum pick-up (OPU) [2-4]. Repetitive doses were administered either by injections or intranasal administration. SC injections were given in several studies at different points of time along the luteal phase; at six, seven, and eight days after OPU [5], three and six days after ET [6], and on the day of OPU, the day of ET, and three days afterward [7]. Alternatively, an intranasal GnRH agonist was daily administered for two weeks [8].

The supplementation of GnRH agonist at the luteal phase was found associated with increased pregnancies and live birth rates [1, 9-10].

A recent prospective randomized study conducted by our group found higher positive β hCG rates when luteal support with GnRH agonists was compared to standard progesterone support (45% vs. 23.3%, $p=0.034$) [11]. Previous studies suggested that the use of GnRH agonists improves fecundity, supports placental implantation [12-14], and may save corpus luteum (CL) from luteolysis [8].

As of today, the exact mechanism of action through which GnRH agonist improves pregnancy outcomes remains unexplained.

Several hypotheses have been proposed, including stimulation of LH secretion from the pituitary gland, a direct effect on the endometrium and the fetus through GnRH agonist receptors, and control of the production and secretion of β hCG by the placenta and the fetus in the pre-implantation phase [15-17].

Biologically, continuous administration of GnRH agonists is expected to suppress gonadotropin secretion from the pituitary gland through a desensitization mechanism, resulting in luteal phase deficiency [18].

However, GnRH agonists given at the luteal phase are thought to restore LH levels when administrated at an adequate dose and frequency [1].

One study explored serum LH levels during the luteal phase among patients who underwent mild ovarian stimulation and intrauterine insemination [17]. They compared different doses and duration (up to 14 days) of intranasal GnRH agonists with hCG for luteal support. The authors found that high levels of LH after ovulation induction declined during the luteal phase, but remained detectable and relatively high throughout the luteal phase in all patients given luteal support, without a significant difference between groups.

To the best of our knowledge, no study examined LH levels after treatment with GnRH agonists in IVF treatments, where pituitary suppression during the follicular phase was given.

If the administration of GnRH agonists results in increased LH levels, it could potentially enhance steroid production from the CL. Indeed, higher progesterone levels at the β hCG measurement day following GnRH agonist treatments suggest its luteotrophic effect [10,15].

As opposed to progesterone support that may be continued until luteo-placental shift (approximately 9 weeks of pregnancy), GnRH treatment is discontinued on the day of positive β hCG results (end of luteal phase support). The fact that pregnancies continue to develop after the termination of treatment strengthens the assumption that CL is rescued by GnRH treatment and keeps functioning independently.

Despite the efficacy of GnRH agonists as a treatment regimen used in IVF protocols, it is important to stress its limitations. First, previous studies discussed the possibility of suboptimal response to general treatment with GnRH agonists. This could be defined by relatively low LH levels in the morning after GnRH agonist administration when used for triggering [19] or low progesterone levels when used for luteal support [8]. It was speculated that such situations occur due to hypothalamic dysfunction, receptor mutations, or LH β -subunit polymorphisms resulting in decreased biological activity of LH [19].

An additional limitation is a possible association described in the medical literature between GnRH agonists given at the luteal phase and ovarian hyperstimulation syndrome (OHSS) [20]. Although GnRH agonists are considered relatively safe, especially among high responders [8], it is possible that some women are more prone to higher expression of OHSS mediators such as vasoactive substances when given the treatment.

Aim

We aim to investigate the mechanism of action of GnRH agonist as a sole treatment for luteal support, and to find predictors for treatment success or failure.

We would also stress the safety of treatment by investigating inflammatory cytokines and angiogenic factors associated with ovarian hyperstimulation syndrome (OHSS).

Primary outcome

1. Positive pregnancy rate after Synarel treatment for luteal support - defined as serum β hCG \geq 25 IU/L, measured 14 days after ET.

Secondary outcomes

1. Level of blood markers along the luteal phase under Synarel treatment – including LH, FSH (secreted from pituitary gland), steroid hormones, cytokines, and other proteins secreted from CL (Estradiol, Progesterone, Relaxin, Interleukin 6 (IL-6). Interleukin 8 (IL-8), Vascular endothelial growth factor (VEGF) and Pigment epithelium-derived factor (PEDF)).
2. Finding a threshold for sufficient levels of hormones indicating that supportive treatment can be stopped earlier.
3. Rate of under-response to treatment (women presenting with vaginal bleeding during treatment).
4. Levels of OHSS mediators (IL-6, IL-8, VEGF, PEDF) in the follicular fluid and blood tests of women who experienced OHSS and those who did not.
5. Clinical pregnancy (sonographic appearance of gestational sac)
6. Biochemical pregnancy (positive β hCG measurement and absence of clinical pregnancy)
7. Miscarriage (loss of pregnancy up to 21+6 days)
8. Live birth (delivery of a living offspring from 22+0 weeks of pregnancy)
9. Finding predictors in follicular fluid of M2 oocytes and fertilization rate.

Research Plan

The study is a prospective observational study, which will be conducted among women undergoing IVF treatments based on GnRH antagonist protocol with a single fresh embryo transfer (ET) at the IVF unit in Shaare Zedek medical center.

About 800 egg retrieval procedures take place at our unit every year, not including pre-implantation genetic testing (PGT) and oocyte cryopreservation cycles. Approximately 80% of the cycles use the

antagonist protocol. It is estimated that in 400 of them, patients are administrated with GnRH agonist for luteal support.

Women included in the study will be 18-41 years old, undergoing IVF treatments due to ovulation disorder, mechanical factor, primary ovarian insufficiency, or male infertility. All women will be at their first to the third cycle of treatment and will undergo a single 3-day ET.

Exclusion criteria will include repeated implantation failure (more than 3 cycles of good quality ET without implantation), moderate-severe endometriosis, hydrosalpinx, fibroid uterus, BMI more than 35 or less than 19, women with hypogonadotropic hypogonadism, PGT of embryos, use of surgical techniques for sperm retrieval, preference of the long GnRH-agonist protocol and women with rhinitis or nasal congestion.

Patients will be recruited for the study in accordance with the approval of the Institutional Helsinki Committee.

During the visit to the clinic, the women's demographic and clinical data will be collected.

All patients will undergo ovarian stimulation based on GnRH antagonist protocol: Ovarian stimulation with gonadotropins (150-225IU of recombinant FSH and/or hMG depending on patients' age, BMI, and basal serum FSH levels) will begin within the first 2-3 days of the menstrual period. When the leading follicle reaches a diameter of 13mm, treatment with daily injections of GnRH antagonist (0.25 mg Orgalutran or 0.25 mg Cetrotide) will be added and continued until the day of ovulation induction.

Once sonography will demonstrate three or more follicles at size ≥ 17 mm, ovulation triggering will be administrated. The stimulation for egg maturation will be performed by either recombinant hCG (250 mcg Ovitrelle), GnRH agonist (0.2 mg Decapeptyl), or a combination of the two -dual triggering (250 mcg Oviterelle plus 0.2 mg Decapeptyl). The stimulation type will be chosen according to the decision of the attending physician, usually based on the estimated risk of OHSS (based on laboratory and sonographic markers).

The eggs will be retrieved 36 hours after the ovulation triggering and fertilized by IVF or by intracytoplasmic sperm injection (ICSI). Fertilized embryos will be incubated until the day of ET. During incubation time and before ET, the quality of embryos will be evaluated and graded according to the accepted criteria in the laboratory. All patients will undergo a single ET to the uterine cavity.

Following egg retrieval, patients will receive luteal phase support with intranasal GnRH agonist - spray of 200 mcg Nafarelin (Synarel) twice a day or vaginal progesterone. Treatment will begin on the evening of the OPU day and continue for 14 days – until β hCG examination day.

Blood samples will be collected for each patient at the six following stages:

1. Ovum pick-up day
2. Day of ET
3. 7 days after ovum pick-up (mid-luteal phase)
4. 12 days after ET
5. 14 days after ET

In addition, follicular fluid from the OPU of each woman will be centrifuged and tested as well.

Laboratory markers will include LH, FSH, β hCG, Estradiol, and Progesterone. IL-6, Relaxin, IL-8, VEGF and PEDF will be analyzed by enzyme-linked immunosorbent assay (ELISA) using commercial kits. All samples will undergo appropriate freezing for future testing.

The Variables of the study include:

- Demographic characteristics – age, BMI, obstetric history (gravida, partum, spontaneous abortions, termination of pregnancy, ectopic pregnancy, cesarean section), infertile diagnosis, infertile classification (primary\secondary infertility), length of infertility.
- IVF cycle characteristics – gonadotropins stimulation (FSH or FSH+LH), total FSH units, stimulation duration, peak E2, maximum endometrial thickness, number of follicles >14mm, type of ovulation triggering (Ovitrelle, Decapeptyl or dual triggering), number of oocytes retrieved, number of mature oocytes, number of 2PN, fertilization rate, fertilization method (IVF/ICSI), embryo grade.
- Blood and follicular fluid markers - LH, FSH, β hCG, Estradiol, Progesterone, 17-Hydroxyprogesterone, Relaxin, IL-6, IL-8, VEGF and PEDF.
- Pregnancy outcomes - positive pregnancy (serum β hCG \geq 25 IU/L, measured 14 days after ET), clinical pregnancy rate, biochemical pregnancy rate, miscarriage rate, live birth rate, OHSS (based on clinical criteria including physical examination, laboratory results and US scan [21]), vaginal bleeding.

Statistical Analysis

Sample size – there are about 400 women every year who undergo IVF cycles with antagonist protocol followed by luteal support with Synarel. We expect to recruit for the research 150 patients within two years. Based on the previous study of our group [11], we predict that 45% of patients treated with Synarel will have a positive β hCG 14 days after ET.

Statistical Package for the Social Sciences (SPSS Inc. V27.0) will be used for all statistical analyses. Categorical variables will be compared using Pearson Chi-Square test, Fisher's exact test where

appropriate. Continuous variables will be compared using student t-test for normally distributed data and the non-parametric Mann-Whitney Test for non-normal distributed data. Logistic regression multivariable model will be used to adjust outcome measures, i.e. positive β hCG, of the study for confounding variables.

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