Single GnRH agonist administration as luteal phase support in insemination cycles: a randomized controlled trial

Abstract

Objective: To find out whether a single-administered GnRH agonist improves the live birth rate in real-life patients undergoing intrauterine insemination (IUI) cycles.

Study Design: A prospective, randomized controlled trial in a public single tertiary center in Tampere University Hospital, Finland. Altogether 251 IUI cycles in 163 patients were randomized to triptorelin and a control group between January 2017 and April 2019. In the triptorelin group, the participants had a single administration of a subcutaneous GnRH agonist triptorelin 0.1mg at the time of implantation. In the control group, there was no luteal phase support. The primary outcome measure was the live birth rate (LBR). The secondary outcome measures were clinical pregnancy rate (CPR) and miscarriage rate.

Results: Overall, the live birth rate was lower in the triptorelin group compared to the control group (7.9% vs. 12.1%; p=0.297). The clinical pregnancy rates were 12.6% and 13.7%, respectively. There were 2.4% miscarriages in the triptorelin group and no miscarriages in the control group. Ovarian stimulation with letrozole was associated with lower LBR among the triptorelin group, in comparison to the control group (0% vs. 14.7%, p=0.020). In contrast, when gonadotrophin was added to the letrozole, LBR was almost doubled compared to the control group (15.9% vs. 8.3%, p=0.341).

Conclusion: A single administration of GnRH agonist in the luteal phase does not improve LBR in IUI cycles.

Keywords: Triptorelin, Luteal support, Intrauterine insemination

Introduction

Triptorelin is a GnRH-agonist used as a luteal phase support mostly in IVF cycles, in which the advantage of its administration at the time of implantation has been proven [1]. The failure to induce early abortion with huge doses of a GnRH agonist led to several studies showing the favorable impact of a GnRH agonist on the implantation of the embryo in IVF and intracytoplasmic sperm injection (ICSI) cycles [2-5]. There are some prospective studies advocating the use of a GnRH agonist as a luteal phase supporter in frozen-thawed cycles, but there is a lack of firm evidence, and the quality of evidence and the safety issues regarding the clinical use of a luteal phase GnRH agonist are still questionable [6-10].

The role of the administration of a GnRH agonist at the time of implantation in the luteal phase is unclear in IUI cycles. In their randomized controlled trial in a small series comprising 23 patients, Pirard et al. found that the administration of a GnRH agonist (buserelin) worked alone without progesterone in the luteal phase of the IVF cycle. This observation suggested that the GnRH agonist could be administered without any other luteal support [11]. In contrast, the same authors published a small randomized trial with 24 patients showing no significant differences in the pregnancy rates [12]. To our knowledge, there is only one randomized controlled trial regarding the GnRH agonist triptorelin in the luteal phase, in IUI-treated patients [13]. In this study, all the patients were stimulated with gonadotrophins, and both triptorelin and vaginal progesterone were administered in the luteal phase, compared to the progesterone only group. There were no significant differences in the ongoing pregnancy rates.

The previous studies encouraged us to study connection between the pregnancy results and the single-administered triptorelin in the luteal phase. Usually in daily practice we have not used luteal phase support in the insemination cycles because of mild stimulation response. The hypothesis of our study is that in a stimulated insemination cycle, the pregnancy rates are higher in the group

treated with a single dose of triptorelin near the implantation window as luteal support, in comparison to the control group which received no luteal support.

Materials and methods

This study is a prospective randomized single-center trial. The patient recruitment and treatment were performed in Tampere University Hospital, Tampere, Finland, a tertiary center referral hospital. Participants signed a written, informed consent between January 2017 and April 2019. The study protocol was approved by the Research Ethics Committee of the Pirkanmaa Hospital District (ETL R16171M, EudraCT 2016-002321-11, ClinicalTrials.gov NCT03115307).

Study population

Altogether 167 patients with 255 IUI cycles were recruited. All the patients were treated because of their primary or secondary infertility problem lasting for at least one year. IUI was carried out on patients who were thought to benefit from the intrauterine insemination. Included were patients with ovulation problems, mild endometriosis, unexplained infertility, mild male infertility or combinations of those. The patients participating in the study represent real life (pragmatic) data from our clinic, and all the patients, planning to have IUI below the age of 42, had the opportunity to participate in the study. We used three kinds of ovarian stimulation protocols: aromatase inhibitors, gonadotrophins, and a combination of the two. We had no clomiphene cycles in our study, because clomiphene citrate was not available in Finland without a special permission.

The exclusion criteria included a failure in the ovarian stimulation cycle, failures in the execution of the insemination (problems passing the cervix), giving the sperm sample and no sperm after the preparation. There were no donor IUI cycles in our study. Patients with primarily planned

progesterone luteal support were also excluded. Patients with an allergy to gonadotrophins, triptorelin or some ingredients in the medicine were not allowed to participate in the study.

Study design

A flowchart of the study is presented in Figure 1. The patients were randomized to either the intervention group or the control group during their IUI cycle. The randomization was performed by the doctor responsible for the treatment with sealed opaque envelopes. The ratio for the intervention and control group was 1:1.

Ovarian stimulation was individually executed with the aromatase inhibitor letrozole, gonadotrophins, or a combination of letrozole and gonadotrophins in both groups. We used letrozole 2.5-5mg on cycle days 3-7 to obtain one or two mature follicles. We used letrozole for women who seemed to be in risk for responding with the growth of multiple follicles. In case of a thin endometrium or inadequate follicular growth with letrozole, we combined gonadotrophins in continuum with letrozole. Gonadotrophins were started on cycle day 5 with individually planned doses to patients without risk to high response.

The ultrasound was performed to estimate follicle maturation and measure the thickness of the endometrium. Follicle maturation was monitored by transvaginal ultrasound on cycle days 9-11, and the monitoring was repeated if needed by transvaginal ultrasound. One or two leading follicles were accepted, and when the leading follicle was over 18mm, hCG 5000 IU (human chorionic gonadotrophin Pregnyl®, MSD) was administered. Insemination was performed 38 hours after the hCG injection. Due to weekends, the time period between the insemination and the hCG injection in some cases was shorter than 38 hours. In the intervention group, triptorelin (Gonapeptyl® 0.1mg/ml, Ferring) was administered on the eighth day after the injection of hCG, near the implantation time. In the control group, the participants did not use any luteal phase support at all.

In both groups, the hCG level was measured from a home urine test two weeks after the insemination and the following pregnancy was evaluated by the ultrasound in the first trimester.

If the patients were first randomized into the intervention group and the pregnancy test was negative in the first cycle, the following IUI cycle was executed in the control group and vice versa. After a live birth it was not possible to participate in the study again.

Outcome measures

The primary aim of this study was to clarify the role of the gonadotrophin agonist as a luteal phase support. The primary endpoint was the live birth rate (LBR). The benefit of the treatment was secondarily measured by the clinical pregnancy (CPR) and miscarriage rates. We also compared the impact of various induction methods on the pregnancy rates in both the intervention and the control group.

Statistical analyses

All analyses were performed using version SPSS 25.0. Numeric data were showed with median, minimum and maximum values, and categorical data with the number and percentage. All analyses were performed according to the intention-to-treat principle. The differences in the pregnancy rates were compared using Fisher's exact test. A P-value <0.05 was considered significant.

The sample size calculation was based on the hypothesis that the live birth rates would have a group difference of 15%. With the alpha risk $p=0.05$ and power 0.80, a total of 242 intrauterine insemination cycles (121 cycles per group) were needed for the study to observe statistical differences in the live birth rates.

Results

Of the total 255 cycles randomized into the triptorelin or the control groups, 4 cycles (1.6%) in four patients were ruled out because they did not meet the inclusion criteria. Two of the patients had used intravaginal progesterone as a luteal phase support, one had used clomiphene citrate, and one had too many leading follicles in her cycle leading up to the IVF treatment. There were no serious adverse effects related to triptorelin.

The characteristics of the participants in the study groups are presented in Table 1. There were no significant differences in any of characteristics studied. No etiologies regarding the infertility were excluded. Some of the patients had more than one etiology for infertility, for example anovulatory and male infertility. Other reasons included tubal etiology (only one patent fallopian tube), a uterine anomaly and diminished ovarian capacity.

The primary endpoint was the live birth rate, which was 4.2% lower in the triptorelin group than in the control group (7.9% vs. 12.1%; p=0.297), although the difference was not statistically significant. Participants had similar positive pregnancy test results 12.6% and 13.7% (p=0.853) in the triptorelin and control groups, respectively. The clinical pregnancy rate was 2.7% lower in the triptorelin group than in the control group (10.2% and 12.9%; p=0.557), respectively. There were no miscarriages in the control group and only 2.4% in the triptorelin group (p=0.247). There were no extrauterine pregnancies in either group. In the triptorelin group, one of the patients with a live birth had vaginal progesterone in her cycle despite of the study protocol.

The participants in the triptorelin group and the control group had various ovarian stimulation protocols. The live birth rate and clinical pregnancy rate in the subgroups are shown in Table 2. In the subgroups, there were no statistical differences in the characteristics of the participants between the triptorelin and the control group. To our knowledge, this is the first study to present the results of using letrozole and triptorelin in the same IUI cycle.

Discussion

In the current study, we examined the pregnancy results with a single administration of the GnRH agonist triptorelin among the IUI patients representing a real-life series of patients planning to have the treatment. We found that there was no statistical difference in the live birth rate between the intervention group and the control group. However, in the subgroups formed from the basis of the ovarian stimulation protocol, the effect of triptorelin was dependent on the stimulation method used. A stimulation protocol by letrozole only was associated with no live births at all, whereas letrozole combined with gonadotrophin doubled the LBR compared to the control group.

Aromatase inhibitor in the early phase of the menstrual cycle increases the gonadotropin synthesis by decreasing estrogen levels. In most cases, only one leading follicle grows. The effect of the aromatase inhibitor on the ovarian androgen synthesis is another mechanism for ovarian stimulation [23]. Ovarian stimulation with the aromatase inhibitor letrozole has been shown to enhance endometrial receptivity in comparison to a natural cycle [24,25]. Gonadotropin injections stimulate the follicle growth directly and may cause a strong ovarian response with high estrogen production. All three stimulation protocols that we used could cause distinct type of physiological response. This increases heterogeneity in our study population.

A GnRH agonist shares close structural similarities with the original GnRH and it has a great affinity to the GnRH receptor [15]. Triptorelin acetate (Gonapeptyl®) has a short terminal half-life - in healthy persons approximately from three to five hours and a total clearance within 24 hours. Binding GnRH agonists to the GnRH receptors has a stimulatory effect on the pituitary gonadotrophins leading to increasing levels of gonadotrophins (a “flare-up effect”). Later, if the binding of the GnRH agonists to the GnRH receptors continues, the result is a fall of the gonadotrophin levels [16].

There can be several mechanisms behind the effect of a GnRH agonist during the luteal phase. A GnRH agonist as a luteal support can stimulate LH-secretion and increase the secretion of E2 and progesterone via corpus luteum [1]. There are various other proposals as to the influence of the GnRH agonist but the exact mechanism is not clear. It has been postulated that the GnRH agonist could have a direct beneficial effect on the blastocyst embryo due its antiapoptotic effect, or it may have also a stimulatory effect on the endometrium by affecting the motility of decidualized stromal cells at the time of implantation [2,11,18].

On the other hand, there are also doubts as to the controversial effects of the GnRH agonist on the hormonal environment during the luteal phase [19-22]. The mechanisms behind these phenomena include the downregulation of the corpus luteum and the disturbance of the endometrium. The effect of a single dose of a short-term GnRH agonist on the corpus luteum and endometrium near the implantation window is different from the effect of its continuous administration. In a retrospective analysis with 214 patients with fresh embryo transfer, the administration of a GnRH agonist as luteal support was emphasized to be safe and effective [17]. There is still a need for complementary data regarding the safety of the administration of a GnRH agonist during the luteal phase [6,17].

Previous reports have shown the benefit of a single administration of GnRH agonist in IVF cycles. A systematic review and meta-analysis of the six randomized, controlled trials verified the role of GnRH agonist administration during the luteal phase [1]. The live birth rate was significantly higher among patients who received a GnRH agonist as a luteal support in addition to progesterone, in comparison to the patients without a GnRH agonist as a luteal support in IVF cycles. The beneficial effect on the pregnancy rates is likewise shown in the oocyte-donation program [2]. However, there are also controversial outcomes showing no beneficial effect on the pregnancy rates with a single GnRH agonist administration [14]. There is no strong evidence to recommend to the use of a GnRH agonist as a luteal support in frozen embryo transfer cycles [7,8].

In our study, we had only a few multiple pregnancies due to the mild ovarian stimulation and allowing usually only one or two leading follicles to grow. In a randomized controlled study with 344 patients, multiple pregnancy rates were high after insemination and more common in the placebo group than in the triptorelin group (36.8% vs. 10.3%, p=0.006) [13]. The stimulation was different compared to our study, using only gonadotropins, and the luteal phase support was also different, containing both vaginal progesterone and triptorelin. The live birth rates were not measured.

Our study population represents real-life IUI patients in the fertility clinic. Because of the various ovarian stimulations and etiologies of infertility, our study population is heterogeneous, which may bear an influence on the results. The subgroups with different ovarian stimulation protocols were quite small but there was a significant difference between the live birth rates in the triptorelin and the control group among the patients using letrozole (0 vs 14.7%, p=0.020). It may be possible that somehow during the same cycle, the letrozole in the early follicle phase and the triptorelin in the luteal phase have a harmful impact on the embryo-endometrium interaction, the embryo or the corpus luteum. The result could also be coincidence because of the quite small subgroups using letrozole (n=38 vs n=34). Conversely, the administration of the GnRH agonist buserelin in the luteal phase during the aromatase inhibitor stimulated cycle resulted in promising pregnancy rates in the study with 24 patients [12]. It is possible that the GnRH agonist at the time of implantation may require progesterone luteal support to maintain the corpus luteum function in IUI cycles.

Conclusions

As a conclusion, the single-administered GnRH agonist near the implantation window seems not to improve pregnancy results in IUI cycles. The mechanisms of GnRH agonists as a luteal support are

still under investigation and more research is needed to find the best stimulation protocols and luteal supports to be used in IUI cycles.

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