Journal of Fertilization : In Vitro, IVF-Worldwide, Reproductive Medicine, Genitics & Stem Cell Biology

Horowitz et al., J IVF Reprod Med Genet 2013, 1:2
DOI: 10.4172/2375-4508.1000107

Case Report

More Indications for the Use of GnRH Antagonists

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Abstract

Purpose: Due to their ability to effectively suppress the LH surge, the primary use of GnRH antagonists is to prevent premature luteinization and ovulation during ovarian stimulation. We describe two cases which represent new indications for the use of GnRH antagonist that may prevent distressing complications associated with infertility therapy.

Methods: A 25-year-old anovulatory woman with PCOS who was treated with clomiphene citrate exhibited an excessive response. The second case involved a 45-year-old egg recipient who underwent hormonal preparation with estradiol valerate. At an early stage of treatment a dominant follicle developed that could result in undesired premature ovulation and cycle cancellation. A GnRH antagonist was administered in both cases.

Results: In the first case OHSS was prevented, and a singleton pregnancy was achieved. In the second case, spontaneous ovulation was avoided and a singleton pregnancy was accomplished as well.

Conclusions: GnRH antagonists can be used for the prevention of distressing complications of clomiphene citrate treatment and for the prevention of unwanted spontaneous ovulation during hormonal preparation in oocyte recipients.

Keywords: GnRH antagonists; Clomiphene citrate; Multiple pregnancies; OHSS; Oocyte donation

Introduction

The introduction of Gonadotrophin-Releasing Hormone (GnRH) agonists has greatly improved the results of IVF by decreasing the cancellation rate through prevention of premature LH surge and luteinization. Recently, the GnRH antagonists have been introduced into Assisted Reproductive Technology (ART) treatment cycles to prevent premature LH surges while reducing the length of the treatment and the gonadotropins requirements compared to the long agonist protocol [1,2]. Currently, the major indication for using GnRH antagonists in ART is prevention of premature ovulation in IVF.

Additionally, in conditions other than Controlled Ovarian Stimulation (COS) prior to ART, constant treatment with GnRH antagonists can inhibit and withdraw gonadotropin stimulation from growing follicles. Without gonadotropin induction for developing follicles, their growth and development can be arrested and may lead to their atresia and disappearance.

In the present report, we describe two cases in which we have effectively used a GnRH antagonist to prevent unwanted complications associated with infertility therapy. In the first case, the possible complications of intensified response to clomiphene citrate, namely Ovarian Hyperstimulation Syndrome (OHSS) and multiple pregnancy were prevented. In the second case, spontaneous ovulation during hormonal preparation in an oocyte recipient was prevented. Spontaneous ovulation at an early stage of treatment in this case, would have definitely caused cycle cancellation. To the best of our knowledge, these forms of use of GnRH antagonists have not been previously described.

Case 1

The first case involved a 25-year-old female and a 26-year-old male who presented with 1 year of primary infertility due to chronic anovulation. The female partner was healthy, except for hypercholesterolemia that was treated medically in the past. Treatment was withdrawn once the patient considered pregnancy. She was diagnosed with Polycystic Ovarian Syndrome (PCOS), as evidenced by oligomenorrhea, chronic anovulation and the typical appearance of polycystic ovaries by Transvaginal Ultrasound (TVS). The patient's infertility work-up revealed normal day 3 FSH (5.1 IU/L), LH (6.7 IU/L) with no clinical or biochemical signs of hyperandrogenism. Her Body Mass Index (BMI) was 21. The husband's past medical history was non remarkable. He denied the consumption of prescribed medications and smoked 10 cigarettes a day. His semen analysis was normal.

The female was prescribed clomiphene citrate (Ikaclomin, Teva Pharmaceuticals, Petah-Tikva, Israel) 50 mg/day, to be taken on cycle days 5-9. On her first monitoring visit, at cycle day 11, TVS revealed multiple follicles (>10) ranging 11-13 mm in diameter, serum estradiol (E2) was 2754 pmol/L and serum progesterone (P) was 3 nmol/L. The couple was counseled regarding the potential risks of multiple pregnancy and OHSS. They were advised to abort the current cycle by avoiding unprotected sexual intercourse and to prevent further follicular development by introduction of GnRH antagonist therapy. On that day, daily SC cetrorelix treatment (Cetrotide, Merck-Serono, Geneva, Switzerland) 0.25 mg was begun. Two days later, multiple follicles ranging 13-17 mm in diameter were seen by TVS, serum E2 was 2725 pmol/L and serum P was 3.7 nmol/L. Three days later (cycle day 16), serum E2 level dropped to < 200 pmol/L, serum P was 1.6 nmol/L, and follicles of similar size and number were seen on TVS. Cetrorelix treatment was halted on that day. The last monitoring session took place on cycle day 20. Serum E2 level was 325 pmol/L, serum P was 2.5 nmol/L, and TVS revealed five follicles ranging 13-17 mm in diameter. The couple was again counseled that the high risk for complications was now effectively reduced, and that no further monitoring was necessary. On cycle day 46, after reporting a missing period, nausea and fatigue, a pregnancy test was done, and serum hCG level was 210 IU/L. Three weeks later, TVS revealed an intrauterine gestational sac, containing a viable singleton pregnancy compatible with gestational 7.3 weeks. By retrospective analysis, the presumed time of ovulation was around cycle

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Received June 27, 2013; **Accepted** July 27, 2013; **Published** July 29, 2013

Citation: Horowitz E, Ravhon A, Nahum H, Golan A, Levran D, et al. (2013) More Indications for the Use of GnRH Antagonists. J IVF Reprod Med Genet 1: 107. doi:10.4172/2375-4508.1000107

day 31. The pregnancy was uneventful and resulted in the birth of a healthy baby.

Case 2

This case involved a 45 year old female and a 36 year old male who presented at our clinic with 5 years of secondary infertility of unexplained origin. The female partner was in good health, with a non remarkable medical history, a non-smoker, and had a BMI of 19. In her twenties she had two uneventful induced abortions, and at the age of 39 years she conceived spontaneously without difficulties and had an uneventful pregnancy and a term cesarean delivery of a healthy baby girl. At the age of 45 years, the patient had regular cycles of 26 days duration, elevated basal FSH levels (day 3 FSH 14.2 IU/L), a normal pelvic ultrasound and a normal uterine cavity as evidenced by both hysterosalpingography (HSG) and hysteroscopy. The male partner was healthy, a non-smoker and denied use of chronic medication. His semen analysis was normal. During the last 3 years, the couple had undergone 8 unsuccessful IVF-ET cycles. The couple was counseled regarding their extremely poor prognosis for further IVF treatment using autologous eggs and was offered the option of oocyte donation, which they accepted.

Because of her relatively short and ovulatory cycles, in order to achieve optimal synchronization with the donor, the patient first received a depot preparation of the GnRH agonist triptorelin (Decapeptyl 3.75 mg, Ferring, Kiel, Germany). After pituitary down-regulation was achieved, the patient received estradiol valerate 2 mg t.i.d. (Progynova, Schering AG, Berlin, Germany). On the day that donor eggs were received, the endometrial thickness was 12 mm, and the patient commenced progesterone therapy, consisting of vaginal tablets (Endometrin, Ferring, 100 mg b.i.d.), and I.M progesterone in oil (Gestone, Ferring) 50 mg every other day. Two embryos were transferred, but pregnancy was not achieved.

A second egg donation cycle was carried out several months later. This time, however, there was no time to achieve pituitary suppression, and the patient had therefore started estradiol valerate therapy (Progynova 2 mg t.i.d.) on day 2 of a spontaneous menstrual cycle. After one week of estradiol therapy, TVS revealed a 15 mm follicle on the left ovary, and endometrial thickness of 9.8 mm. Serum E2 level was 198 pmol/L and serum P was 2.2 nmol/L. The patient was informed that spontaneous ovulation at this point would lead to cycle cancellation and was advised to add daily SC injections of cetrorelix acetate (Cetrotide 0.25 mg) to the treatment regimen. Two days later, the follicle size was reduced to 12 mm, endometrial thickness was 6.2 mm, serum E2 235 pmol/L and P was 1.3 nmol/L. The patient continued estradiol valerate and cetrorelix for another five days, after which she returned for monitoring. On TVS no follicular activity could be demonstrated, the endometrial thickness was 8.5 mm, serum E2 was 987 pmol/L and P 1.9 nmol/L assuming that the development of a dominant follicle was abolished and the risk of spontaneous ovulation was removed, the use of cetrorelix was discontinued, and further therapy consisted of estradiol valerate alone. On cycle day 24, when donor eggs were received, the endometrial thickness was 10.5 mm, no follicular activity was evident by TVS, serum E2 was 668 pmol/L and P was 2.2 nmol/L. The patient commenced P therapy as described above and three days later three embryos were transferred into the uterine cavity. A singleton pregnancy was achieved that resulted in the birth of a healthy baby.

Discussion

GnRH antagonists block pituitary GnRH receptors by competitive binding, resulting in immediate gonadotropin suppression. Because of their ability to effectively suppress the LH surge, they have been widely introduced into clinical practice for prevention of premature luteinization and ovulation during ART treatment cycles [1,2].

In addition, continuous administration of GnRH antagonists can withdraw gonadotropin support from growing follicles, in situations other than COS prior to ART. Withdrawal of gonadotropin support from developing follicles can abolish their further growth and development, and can subsequently lead to their atresia and disappearance.

In the two cases described above, we have successfully used GnRH antagonist treatment to prevent two complications associated with infertility therapy. In the first case, the potential complications of exaggerated response to clomiphene citrate, namely OHSS and multiple pregnancies were prevented. In the second case, spontaneous ovulation during hormonal preparation in an oocyte recipient was prevented. Spontaneous ovulation at an early stage of treatment in this case, would have undoubtedly caused cycle cancellation.

In anovulatory patients with PCOS, clomiphene citrate is often the first line of treatment. It is not unusual for young and lean PCOS patients to respond to a low daily starting dose of 50 mg in an "explosive" manner. Ovarian enlargement and multifollicular development can be seen during monitoring, accompanied by highly elevated serum E2 concentrations. The risk for high order multiple pregnancies is extremely high in this situation, but can be effectively prevented by refraining from unprotected sexual intercourse. Unlike in gonadotropin therapy, where ovulation and luteinization will not take place without exogenous hCG triggering, in clomiphene citrate cycles, a spontaneous LH surge will most likely occur, leading to massive luteinization. Therefore, such patients are at high risk for developing either OHSS or the complications of massive ovarian enlargement such as abdominal pain, cyst formation and ovarian torsion.

To the best of our understanding, the only effective way to prevent further ovarian enlargement and ovulation under such circumstances is by blocking the clomiphene-induced gonadotropin stimulation by GnRH antagonist administration. As far as we know, this treatment approach has not been described before. Our case revealed that after several days of GnRH antagonist treatment, serum E2 levels first plateaued, and then dropped to <200 pmol/L, representing most likely follicle atresia due to gonadotropin deprivation. This was accompanied by a gradual reduction in the size and number of follicles seen on TVS. To our surprise, the patient later conceived during the same cycle. Fortunately, it was a singleton pregnancy and the patient reported no further complications.

By retrospective analysis of gestational age according to the fetal size on ultrasound, ovulation took place at around cycle day 31, more than 2 weeks after the cessation of GnRH antagonist therapy. The resumption of follicle development and finally ovulation can be attributed to the long half-life of clomiphene citrate. Clomiphene citrate is cleared through the liver and excreted in stool. Five days after oral administration of clomiphene, 51% has been excreted; however, some clomiphene continues to be excreted for at least 6 weeks [3] and levels of the less active isomer zu-clomiphene remain detectible in the circulation for more than a month after treatment. Thus, the late action of clomiphene in our case was much milder, probably due to relatively lower serum concentrations at this stage.

In a natural cycle of normal ovulatory women, GnRH antagonist administration acutely inhibits the LH surge and ovulation, even when administered as late as the onset of the LH surge [1]. Discontinuation of GnRH antagonist treatment results in rapid, predictable recovery of the pituitary-gonadal axis, as the pituitary receptor system remains intact. Ditkoff et al. [4] provided evidence that spontaneous follicular

rescue recurred in eight of 10 cycles after 3 to 4 days of administration of the GnRH antagonist Nal-Glu. The subsequent luteal phase also was normal. Since our patient was anovulatory, as mentioned above, continuous exposure to clomiphene citrate was most likely the cause for ovulation and conception.

In women with functioning ovaries undergoing egg donation, safe and efficient synchronization between endometrial and embryo development is often achieved by using pituitary down-regulation with a GnRH agonist to avoid spontaneous ovulation before sequential administration of estradiol and progesterone. Without pituitary suppression, ovulation can occur during hormonal supplementation, leading to embryo/endometrial asynchrony and decreased pregnancy rates after embryo replacement.

Remohi et al. [5] used increasing doses of oral estradiol valerate from as early as day 3 of menstruation in women with functioning ovaries receiving donated oocytes and demonstrated histological evidence of ovulation in almost 40% of those studied, proving that ovarian function continued despite steroid treatment. When the pituitary is not suppressed by using a GnRH agonist, it is very important to start estradiol treatment in the early follicular phase (on cycle day 1 or 2). With this approach, although initial follicular activity is sometimes present, spontaneous ovulation seems to be inhibited [6]. Starting estradiol treatment after day 3 of the cycle might lead to an increased incidence of LH surge and luteinization of the endometrium. Even when estrogen supplementation is started on day 1 of menstruation, premature luteinization and/or ovulation cannot be completely prevented [7,8]. Using such a regimen prior to frozen embryo transfer, the rate of premature luteinization was reported to be as high as 3.2% [6].

Although pituitary suppression by a GnRH agonist allows the establishment of well-controlled and uniform conditions for exogenous steroids to work unopposed, this treatment regimen is lengthy, and therefore requires ample time for patient preparation. First, waiting for the proper timing for GnRH agonist administration (early follicular or mid-luteal phase), and secondly, the achievement of pituitary suppression usually takes approximately 12-14 days, but may be further complicated and prolonged because of ovarian cyst formation.

In the second case we described, the first oocyte donation cycle was conducted under GnRH agonist pituitary suppression, and was successful in terms of synchronization between the donor and the recipient. Pregnancy, however, was not achieved. In the second cycle, because of the short notice given regarding the availability of donor eggs, it was not possible to achieve pituitary down regulation prior to estradiol treatment. Despite the fact that estradiol treatment was introduced on cycle day 2, a dominant follicle had developed and the risk for premature ovulation and cycle cancellation became clearly high. The introduction of cetrorelix therapy effectively withdrew gonadotropin support from the growing follicle, leading to its complete disappearance within several days of therapy. Once the follicle had disappeared, cetrorelix therapy was discontinued, and serum progesterone levels remained un-elevated during the last week of estradiol treatment, until donor eggs were received and exogenous progesterone was added to the treatment regimen. The establishment of an ongoing pregnancy was the definite proof of a well-prepared and synchronized endometrium.

In summary, in the two cases we hereby describe, we present two new indications for the use of GnRH antagonists in daily clinical practice. Common to both indications is the induction of gonadotropin deprivation from growing follicles. An exaggerated response to clomiphene citrate may put at risk patients to develop OHSS and/or high-order multiple pregnancies. In case of hormonal preparation of egg recipients, untimely ovulation may lead to cycle cancellation. The administration of a GnRH antagonist under such circumstances can effectively prevent these distressing complications.

Capsule

Endogenous gonadotropin suppression by GnRH antagonists can be used to prevent untimely ovulation during donor eggs recipient preparation or ameliorate ovarian response to clomiphene citrate stimulation.

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