

Controlled Ovarian Hyperstimulation through Gonadotrophin releasing Hormone Agonist for Patients at Risk of Hyperstimulation Syndrome

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Abstract

Background: Patients at high risk of OHSS can experience difficulty in completing an IVF cycle with the administration of gonadotrophins. Here, we test a unique low-dose GnRH agonist protocol.

Methods: 0.1mg triptorlin acetate (decapeptyl) was administered to 18 patients at high risk of OHSS from day 5 of the menstrual cycle. Oocyte retrieval was performed 36 hours after the administration of 10000 IU human chorionic gonadotrophin, when follicles of 18-20mm were observed. Oocytes were fertilised in vitro and embryos transferred on day 3.

Results: Patients produced a mean of 4.1 ± 0.96 oocytes. After ICSI, a mean of 3.0 ± 0.84 embryos were transferred to the uterus. A total of 5 pregnancies were obtained from the 18 cycles. No patients were affected by OHSS.

Conclusions: Low-dose injections of GnRH analogues can cause multiple follicular development, mature oocytes and pregnancies in patients at risk of OHSS. This novel COH protocol appears safe and applicable as a valuable alternative to the natural cycle.

Keywords: GnRH agonist; Controlled ovarian hyperstimulation; Ovarian hyperstimulation syndrome; Assisted reproduction technology

Introduction

During controlled ovarian hyperstimulation protocols (COH) for assisted reproduction, the occurrence of severe ovarian hyperstimulation syndrome (OHSS) is a risk factor in which the excessive response of the ovaries to exogenous follicle stimulating hormone (FSH) leads to a pathology which can be life threatening [1-4]. The risk of occurrence of OHSS is poorly predicted in the female population, although some factors such as polycystic ovary syndrome (PCOS) are known to be high risk factors [1,2,5,6]. Since the best cure for OHSS is the removal of exogenous FSH i.e. 'coasting' [7] or cancellation of the COH cycle [1-3], patients noted to be highly sensitive to exogenous FSH can experience difficulties in proceeding with IVF due to the impossibility of completing the stimulation regime.

Advances in treatment protocols and pharmaceuticals available for COH have reduced the incidence of OHSS. Classical IVF protocols combined the use of large doses of GnRH agonists (3.75mg, 8-10) to enable the suppression of endogenous gonadotrophin production, followed by the administration of exogenous gonadotrophins to enable multiple follicle development. Initially, gonadotrophins purified from urinary sources were the only products available. It was suggested that the flare of FSH and luteinizing hormone (LH) produced by the GnRH agonists, or contaminants in the purified preparations, were associated with the onset of OHSS [8]. However, neither commencing the GnRH agonist on the 21st day of the preceding cycle, nor the introduction of recombinant gonadotrophins, has completely eliminated the risk of OHSS [9,10]. GnRH antagonists, that block the production of endogenous gonadotrophins without causing a gonadotrophin flare, have also assisted in the control of the risk of OHSS [10]. Another development, the daily application of low doses of GnRH agonists (0.1mg), has enabled a fine level of control of endogenous GnRH suppression with minimal flare [9-11]. However, since the sensitivity of the ovaries to COH is patient-dependent, OHSS is an ever present risk because some ovaries will always respond excessively to the introduction of exogenous gonadotrophins.

Several protocols exist for patients at high risk of OHSS. Low

doses of gonadotrophins together with agonists or antagonists have been used, however these can result in a poor response of follicular development, and do not eliminate the risk of OHSS. As an alternative, normal stimulation regimes can be applied followed by coasting to lower oestradiol levels [6-7]. Coasting has been successfully used for IVE, but neither eliminates the ongoing risk of OHSS, nor is effectively applied to ART since oocyte quality is often negatively affected by coasting [12]. The natural cycle can be followed together with the administration of antagonists to enable the control of ovulation. Although this protocol gives reasonable results, a single follicle is produced and therefore the patient encounters the possibility that no oocytes are retrieved, that the oocyte obtained is immature, or that no fertilisation occurs, leading to a high rate of cycle cancellation. The pregnancy rate after a single embryo transfer further remains low, reducing patient acceptance of the protocol.

In this case series, we describe the use of low-dose agonist as the unique source of gonadotrophins for patients at high risk of OHSS. The protocol enables both the production of a small amount of endogenous gonadotrophins and the control of ovulation. Pregnancies were obtained without clinical complications to the patients, suggesting that the protocol is applicable to assisted reproduction.

Materials and Methods

Patients

Couples attending the 'Centro Fecondazione Assistita', Naples, Italy

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in which the female partner was known to be at high risk of OHSS due to more than 1 previous cycles cancelled for excessive follicular development, agreed to test the new stimulation regime in a cycle of assisted reproduction. All couples signed an informed consent form. Couples were included in the trial in cases in which 3 previous cycles of COH were due to the onset of severe OHSS. Patients were characterised by a basal FSH of 4-8 IU/l, body mass index (BMI=weight (kg)/height (m)²) <29 and menstrual cycle with range 25 ± 4 days. Both partners had a normal karyotype. The male partner was normospermic. The mean maternal age was 34.8 ± 3.9 years at the initiation of the cycle (mean ± sd, n=18).

Stimulation protocols

A single member of the medical staff co-ordinated all stimulation protocols, ensuring standardisation. 0.1mg triptorlin acetate (decapeptyl, Ipsen) was administered from day 1,3,5 or 7 of the menstrual cycle (where day 1 was defined as the first day of menstrual bleeding). Development of follicles was followed by ultrasound measurement of follicular growth on days 7 and every successive 2 days until administration of human chorionic gonadotrophin (hCG), or cycle cancellation. Follicular development was also analysed through blood serum measurement of 17 β-oestradiol levels.

Oocyte retrieval was performed 36 hours after the administration of 10,000 IU hCG when 2-3 follicles of 18-20 mm diameter were observed by ultrasound examination, and blood 17 β-oestradiol levels reached 150-200 pg/ml/follicle over 18mm. Luteal phase supplementation was achieved with intramuscular injections of Progesterone (Prontogest, IBSA), 50mg/day. All oocytes in the present project were treated with ICSI 3 hours after oocyte retrieval (60 minutes after removal of the cumulus complex). A single team of biologists co-ordinated all biological work, ensuring that both culture protocols and embryo assessment were standardised. Oocytes were processed for ICSI using commercial IVF medium (COOK, Limerick, Ireland), pre-equilibrated to 37°C and 6% CO₂. Sperm samples were collected by masturbation and examined after liquefaction. All samples were washed using a silicon-based gradient of 40% overlaid over an 80% silicon solution (COOK Sperm Gradient, Ireland). The sample was centrifuged for 20 minutes at 1000 G, followed by a wash in Hams F-10. The final precipitate was re-suspended to a final concentration of 1x10⁶ sperm/ml and conserved in an atmosphere of 37°C and 6% CO₂ until required. Sperm samples were placed in a drop of PVP in a Falcon 1006 ICSI dish (Beckton Dickinson, New Jersey, USA), selected with a 40x objective equipped with Nomarski optics and injected into oocytes using Narishige micromanipulators and COOK microtools (ICSI and holding pipette, COOK, Ireland). Zygote quality was scored 16-17 hours after ICSI. Embryo quality on day 3 was assessed 64-65 hours after insemination. Zygote and embryo evaluation was performed

	Day 1	Day 3	Day 5	Day 7
Patients	11	5	18	6
Mean age (years)	33.2 +/- 3.7	32.2 +/- 2.9	34.8 +/- 3.9	33.0 +/- 2.9
Follicles produced mean +/- sd (range)	0.2 +/- 0.4 (0-1)	0.4 +/- 0.5 (0-1)	4.9 +/- 0.9 (4-7)	1.4 +/- 0.5 (1-2)
Peak oestradiol (pg/ml)	33.9 +/- 34.5	43.0 +/- 28.9	750.3 +/- 110.8	152.6 +/- 59.6
Cycles to pick-up	0	0	18	0
Number oocytes retrieved mean +/- sd (range)	0	0	4.1 ± 0.9 (3-6)	0

Notes: All data is presented as mean +/- sd with range in parentheses. Day refers to the first day of initiation of GnRHa

Table 1: Development of stimulation protocol.

Patients	18
Number of follicles produced (mean +/- sd/patient)	88 (4.9 +/- 0.9)
Number of mature oocytes retrieved (mean ± sd)	74 (4.1 ± 0.9)
Number of oocytes fertilised (mean ± sd/patient %)	54 (3.0 ± 0.8%)
Number of grade A embryos (% of total)	44 (81.5%)
Number of transfers	18
Number of embryos transferred (mean ± sd/transfer)	54 (3.0 ± 0.8)
Number of grade I embryos transferred	44
Number of clinical pregnancies (% pregnancies/transfer)	5 (27.7%)
Number of fhb's^b (Implantation rate %)	7 (15.9%)
Pregnancies to term (% clinical pregnancies)	5 (100%)
Live births (% fhb's detected)	7 (100%)

Table 2: Biological data for GnRHa – only trial.

according to previous data [13]. Two or three embryos were transferred in all cases on the third day after oocyte retrieval. The establishment of a pregnancy was considered as a positive β-hCG test of over 60 IU/l 14 days after embryo transfer. The implantation rate was calculated by the observation of foetal heart beats after ultrasound analysis, 8 weeks after the establishment of pregnancy. A clinical pregnancy is defined as a pregnancy to term. Live birth rate is defined as the number of babies born per gestational sacs observed.

Results

Establishment of GnRHa protocols

GnRH agonist administration was initiated on days 1, 3, 5 or 7 of the menstrual cycle. Day 1 and 3 initiation of administration resulted in no follicular development (Table 1). This is presumably due to the suppression of endogenous FSH levels prior to the production of receptors and the sensitisation of the lead follicle to FSH. The initiation of the stimulation regime on day 7 of the menstrual cycle led to the production of a single follicle and therefore no advantage over the patients' natural cycle (Table 1). We assume that this is because the lead follicle has already developed and others repressed. The initiation of GnRHa administration on day 5 however led to the production of 4-5 follicles. We therefore followed this protocol for all stimulation regimes with GnRH agonists. A total of 18 patients were treated with this protocol.

Of the 18 patients in which the GnRH agonist protocol was applied, no patients were cancelled due to a poor response. Patients produced an average of 4.9 ± 0.9 follicles (mean ± sd, n=18, Table 2) and a total of 4.1 ± 0.9 (mean ± sd, n=18) metaphase II oocytes were retrieved. After ICSI, 3.0 ± 0.8 (mean ± sd, n=18) oocytes were observed to have fertilised, and all embryos formed were transferred into the uterus. A total of 5 pregnancies were observed, of which 7 healthy babies have been born. No patient had any signs of OHSS at any point in the treatment cycle.

Discussion

Ovarian hyperstimulation syndrome remains a life threatening risk factor in IVF cycles because of the excessive response of the ovaries to exogenous gonadotrophins. Often, the response of patients to exogenous FSH cannot be predicted in anticipation of the COH regime, indicating that the risk of OHSS in patients attending for assisted

reproduction will be difficult to eliminate. Furthermore, some patients are characterised by a persistent, highly sensitive response to exogenous FSH despite changes in the stimulation protocol, causing difficulties in the completion of an IVF cycle without the onset of OHSS.

GnRH analogues are characterised by the suppression of endogenous gonadotrophins through the persistent occupation of GnRH receptors. The agonistic nature of these pharmaceuticals however causes the release of endogenous gonadotrophins as a 'flare'. The introduction of low-dose suppression with daily injections of 0.1mg agonist has reduced the clinical relevance of the 'flare', enabling fine control of COH regimes.

Patients in whom the sensitivity of the ovaries causes an excessive response to exogenous gonadotrophins can often not be treated with classical COH protocols because an increased risk of OHSS is present. Often, the unique solution for these patients is a natural cycle, with a single oocyte produced per IVF cycle. In the present report, we have tested a simple low-dose agonist as a COH protocol in patients in which the high sensitivity to exogenous gonadotrophins precluded all other protocols. The daily low-dose analogue regime, when initiated on day 5 of the menstrual cycle, caused multi-follicular development. Patients produced a mean of 4.9 ± 0.9 (mean \pm sd, n=18) follicles, from which 4.1 ± 0.9 oocytes were retrieved. Five pregnancies resulted from the treatment group (27.8% pregnancy rate). Seven gestational sacs were observed and all 7 arrived to term.

These data suggest that daily low-dose administration of GnRH analogues in patients at high risk of OHSS can be successfully applied in cycles of assisted reproduction. The protocol appears to cause minimal risk of OHSS, is fully applicable to COH, produces a suitable number of oocytes for the completion of the cycle and patients can successfully achieve pregnancy with this protocol.

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