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ORIGINAL ARTICLE

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Significant reduction of the incidence of ovarian hyperstimulation syndrome (OHSS) by using the LHRH antagonist Cetrorelix (Cetrotide®) in controlled ovarian stimulation for assisted reproduction

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Abstract A prospective, randomized study was performed to compare the efficiency of hormonal stimulation for IVF (in vitro fertilization) in either the long luteal protocol, using the LHRH agonist Buserelin, or the multiple dose LHRH antagonist protocol, using the LHRH antagonist Cetrorelix. Here we present the data on the incidence of ovarian hyperstimulation syndromes (OHSS). 85 and 188 patients were recruited for the stimulation in the LHRH agonist and in the LHRH antagonist protocol, respectively. The groups were comparable regarding anamnestic data. The incidence of WHO °II and °III OHSS was significantly lower in the Cetrorelix than in the Buserelin group (1.1% vs. 6.5%, p=0.03). Additionally 3 patients in the Cetrorelix group (1.6%) and 5 patients in the Buserelin group (5.9%) did not receive hCG because of a threatening OHSS. The follicle maturation was more homogeneous in the Cetrorelix protocol, with less small follicles on the day of hCG administration but a similar number of oocyte cumulus complexes retrieved. The pregnancy rates per cycle were not significantly different in the Cetrorelix and Buserelin protocol (22% vs. 26%). The Cetrorelix multiple dose protocol is advantageous compared to the long protocol regarding the incidence of OHSS, a potentially life threatening complication of controlled ovarian stimulation.

Keywords LHRH antagonist · Cetrorelix · Ovarian hyperstimulation syndrome

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Introduction

Ovarian hyperstimulation syndrome (OHSS) is one of the most severe complications arising from ovarian stimulation for assisted reproductive technologies (ART), e.g. in vitro fertilization and embryo transfer (IVF-ET). By a still unknown pathophysiology a fluid transition from the intravasal compartment to the third space, i.e. intraabdominal and pleural cavity, takes place, leading to ascites, pleural effusions and a rise in hematocrit [5, 7]. This can lead to hemoconcentration, and finally to renal failure and/or thrombo-embolic events and – possibly – death [14], especially in cases when additional risk factors like e.g. an activated protein C (APC) resistancy is present [9].

It is well known, that certain factors increase the risk of OHSS during ovarian stimulation. These factors are some endocrinological disorders, a high estradiol value on the day of hCG administration, a high number of oocytes retrieved, and different ovarian stimulation protocol used [7]. Especially the introduction of the long protocol with LHRH agonists and gonadotrophins has resulted in an increase in the incidence of OHSS [11, 15].

Herewith we present data on the occurrence of OHSS from a prospective, randomized, controlled phase III trial, comparing the stimulation using a conventional long luteal protocol with a LHRH-agonist preparation (Buserelin) and an antagonist multiple dose protocol with the LHRH antagonist Cetrorelix.

Materials and methods

Patients

The study was done in a multicenter approach. Study design, inclusion and exclusion criteria were previously described (Albano et al. 2000).

Ovarian stimulation

The LHRH-agonist group started on cycle day 18 to 22 with 0.6 mg/d of a nasal spray of buserlin (Suprefact®, Hoechst Marion

Roussel, Bad Soden, Germany) (intention to treat population ITT=85). HMG (human menopausal gonadotrophin; Menogon®, Ferring Arzneimittel GmbH, Kiel, Germany) was initiated 14–21 d after the start with the LHRH agonist, aiming at complete desensitization of the pituitary, confirmed by hormonal analysis. In the antagonist protocol stimulation with HMG started on day 2 or 3 of a spontaneous menstrual cycle, the LHRH antagonist Cetrorelix (Cetrotide®, ASTA Medica AG, Frankfurt, Germany and Serono GmbH, Unterschleissheim, Germany) (ITT=188) was given starting on stimulation day 5 or 6 in the minimal effective dose of 0.25 mg per day s.c. in a multiple dose protocol as previously described [2, 6]. Both LHRH analogues were given up to and including the day of hCG. HMG starting dose was 2 ampoules per day (150 IU) for 5 days. Thereafter, the dose was individualized according to the ovarian response. Patients suffering from polycystic ovarian syndrome were excluded from the study.

Final oocyte maturation was achieved by 10000 IU hCG (human chorionic gonadotrophin) when at least one follicle was ≥20 mm or an estradiol value of 1200 pg/mL were present, oocyte pick up was done in a routine fashion. A maximum of three embryos were transferred into the uterine cavity two days after oocyte pick up. HCG injection was withheld when too many follicles were present (>12 follicles with a diameter ≥15 mm) or estradiol ≥4000 pg/mL. Luteal phase support was performed according to centers rule. However, if estradiol levels were >2000 pg/ml, no hCG was allowed to be given.

If present, OHSS was defined and recorded at each visit according to the WHO criteria as mild (°I), moderate (°II) or severe (°III) (WHO 1973). Patients were seen routinely for blood sampling on 6–8 days after embryo transfer. A final visit was scheduled for 21 to 25 days after embryo transfer.

A clinical pregnancy was recorded during a further follow up, in case that embryonic heart beats were present.

Statistical analysis

Statistical analysis was done using Fisher's exact test (2-sided) or analysis of variances (ANOVA) adjusted for center.

Results

The numbers of retrieved cumulus oocyte complexes and clinical pregnancies were comparable for the two treatment group (Table 1). Other parameters, as e.g., patients age, duration of infertility, number of previous IVF or ICSI trials and parity were also comparable. 181 patients in the Cetrorelix group (96.3%, 181/185) and 77 in the Buserelin group (90.6%, 77/85) received an hCG injection. The WHO °II and °III OHSS cases were significantly more frequent in the Buserelin group (6.5%, 5/77) than in the Cetrorelix group (1.1%, 2/181) (p=0.03, Fisher's exact test; odds ratio: 6.2, 95% confidence interval: 1.4–27.1). Additionally 3 patients in the Cetrorelix group (1.6%) and five patients in the Buserelin group (5.9%) did not receive hCG because of a threatening OHSS. Here the protocol criteria defined in the study protocol were fulfilled, and hCG was withheld because of the presence of too many follicles (≥12 follicles with a diameter ≥15 mm) and/or of too high estradiol levels (≥4000 pg/mL). All cases of OHSS could be controlled by the investigators and in no case any sequelae were reported. In two of the OHSS cases and in one additional patient at risk for an OHSS, all from the Buserelin group, no embryo transfer was performed for safety reasons and all embryos were cryopreserved.

All patients in the Buserelin and Cetrorelix group, who had an embryo transfer and developed OHSS, received several hCG injections for luteal phase support. Three of these five patients got pregnant. The two patients from the Buserelin group, who did not have an embryo transfer because of a threatening OHSS did not receive any luteal phase support.

Overall, 19.4% (13/67) in the Buserelin group and 16.6% (26/157) in the Cetrorelix group got only hCG for luteal phase support. The remaining patients received progesterone for luteal phase support. No patient was supplemented with a combination of both medications. The estradiol values during ovarian stimulation and the luteal phase in the Cetrorelix and Buserelin group are shown in Fig. 1. There was a statistically significant difference in the values on the day of ovulation induction (p<0.001), due to a more rapid increase of estradiol serum concentrations in the Buserererelin group at the end of ovarian stimulation.

Ovarian stimulation required a mean of 1 day more in the Buserelin group than in the Cetrorelix group until the criteria for hCG injection were obtained.

The distribution of small, intermediate and large follicles as measured during transvaginal sonographic folliculometry are shown in Fig. 2 for the days hMG6 up to the day of hcG. The growth dynamics of small, intermediate and large follicles in the two groups show, that in the Buserelin group, despite there were less small follicles at the beginning, these patients ended up with more small

Table 1 Results of the two different stimulation procedures

	Cetrorelix		Buserelin	
	IVF	ICSI	IVF	ICSI
Patients recruited (*n*)	188		85	
Patients with hCG injection (*N*)	181		77	
Patients with oocyte pick up (*n*)	178		77	
Patients with oocytes obtained (*n*)	175		77	
Patients with embryo transfer (*n*)	157		67	
Mean number of cumulus-oocyte-complexes	7.1±4.2	10.1±5.6	9.4±5.5	11.7±7.5
Mean estradiol levels on day of hCG[a]	1659±919 pg/mL		2313±1155 pg/mL	
Mean number of embryos transferred	2.1±0.6	2.3±0.7	2.1±0.7	2.2±0.9
Incidence of OHSS °II or °III (%)	1.1%[b] (*n*=2)		6.5%[b] (*n*=5)	
– OHSS II (*n*)	2		4	
– OHSS III (*n*)	–		1	
Clinical pregnancies (%) (per attempt)[c]	22% (42)		26% (22)	

[a] Evening values, statistically significant different using ANOVA (p<0.0001)
[b] Statistically significant different using Fisher's exact two-sided test (p=0.03)
[c] Clinical pregnancy is defined as positive embryonic heart activity by ultrasound, including clinical abortions and ectopic pregnancies

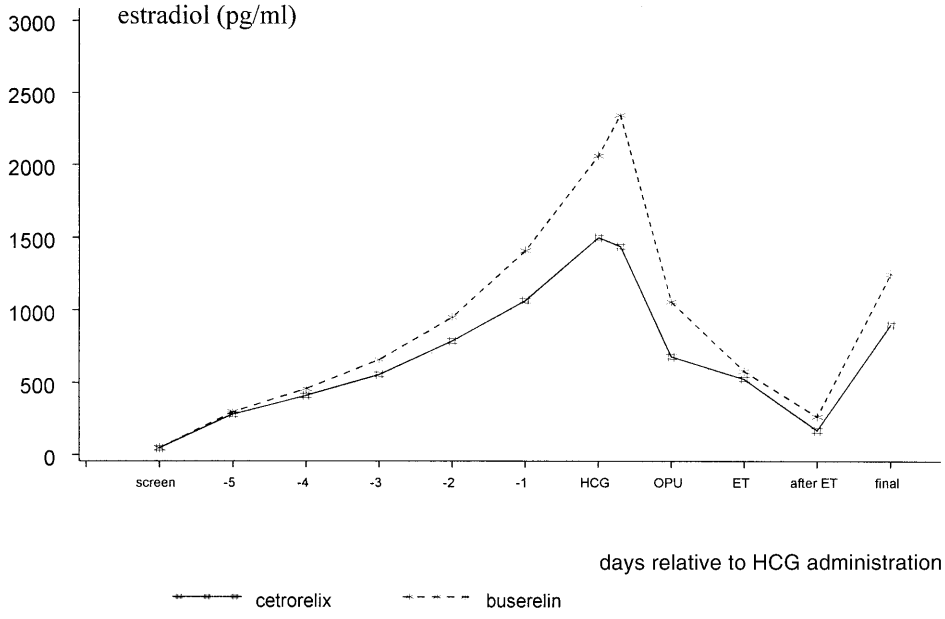

Fig. 1 The time course of median estradiol serum levels during the stimulation procedure. Levels on day of hCG are significantly higher in the Buserelin compared to the Cetrorelix group. Screen: levels on the day of screening; HCG: day of hCG; OPU: day of oocyte pick up; ET: day of embryo transfer; after ET: day 6–8 after embryo transfer; final: 21–25 days after day of embryo transfer

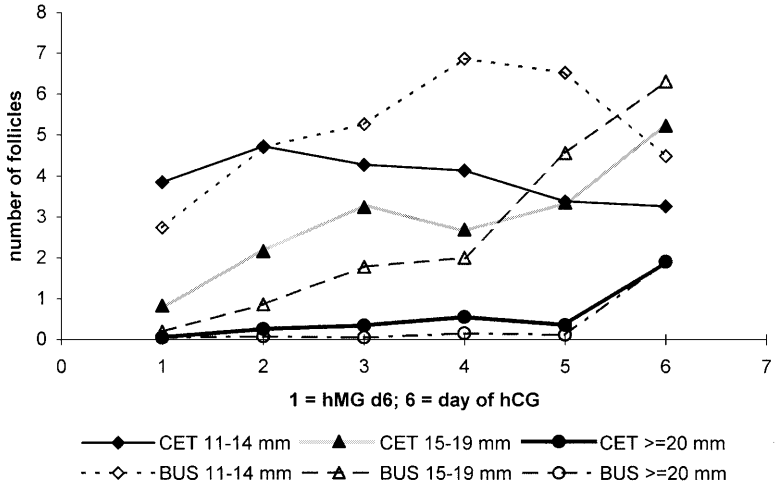

Fig. 2 The presence of follicles of different sizes at different time points during the ovarian stimulation procedure in the Cetrorelix and Buserelin group. Shown are the dynamics of mean number of follicles during certain times points of ovarian stimulation

follicles on the day of hCG. This maybe due to an unproportionate rise in the recruitment of more small follicles in the Buserelin group, instead of a more homogeneous number of recruited follicles in the Cetrorelix group throughout the stimulation cycle.

Discussion

In the presented prospective, randomized study the incidence of WHO °II and °III OHSS cases was significantly lower in the Cetrorelix multiple dose compared to the long luteal protocol (1.1% vs. 6.5%, p=0.03). Furthermore, three patients in the Cetrorelix group (1.6%), and five patients in the Buserelin group (5.9%) did not receive hCG because of a threatening OHSS. Additionally, estradiol levels were significantly higher on the day of hCG in the Buserelin group and there were more small follicles (1–14 mm) recruited during the stimulation procedure in the Buserelin compared to the Cetrorelix group. Despite this advantage of the Cetrorelix protocol, there were no differences in the clinical pregnancy rates.

From the data shown, it seems that ovarian stimulation in the Cetrorelix protocol leads to a more physiological way of follicular recruitment than does ovarian stimulation in a long luteal protocol. The more homogeneous way of follicular recruitment throughout the cycle (Fig. 2) explains the lower estradiol values on the day of hCG administration, since the small follicles contribute to the final estradiol concentration to an important degree and are – to some extend – responsible for the incidence of OHSS [4, 12]. This may be explained by the production of several vasoactive factors by these immature small follicles. If one considers, that OHSS is an iatrogenic condition, which can lead to severe complications like thromboembolism [7] or even myocardial infarction [10], and is potentially life

threatening, these findings are of utmost clinical importance. Although strict safety criteria regarding cancellation of cycles and luteal phase support to be applied had been used, and although there was no difference in the percentage of cycles, which were supplemented with either hCG or progesterone between the two groups, the differences in incidence of OHSS became significant. It is extremely important to realize, that all patients, who experienced a WHO °II or °III OHSS, were from the group of patients, who received hCG for luteal phase support – well known risk factor for the development of OHSS [7].

One can conclude from the presented data that the use of Cetrorelix in controlled ovarian stimulation protocols can significantly reduce the rate of WHO °II and °III OHSS. Less small and intermediate follicles mean a lower amount of granulosa cells, a source of e.g. VEGF (vascular endothelial growth factor), which has been shown to be a pathogenetic factor in OHSS in vitro as well as in vivo [1, 8, 13]. Ovarian stimulation can be performed more safely and convenient for the patients using Cetrorelix. It seems, that during pituitary suppression using the LHRH antagonist Cetrorelix the follicles grow more homogeneously and too high and rapidly rising estradiol levels are avoided.

Reverences

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