Cetrotide confirmatory trial of cetrorelix/0.25 mg in 26 women undergoing ovarian stimulation with recombinant follicle stimulating hormones for IVF, ICSI and embryo transfer (ET)

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Summary

Background: There have been numerous double-blind, randomised, dose-finding studies of the gonadotrophin-releasing hormone (Gn-RH) antagonist Ganirelix (Org 37462) [2] and the Gn-RH antagonist Cetrorelix [4].

Methods: We performed a clinical trial with 26 patients undergoing ovarian stimulation with the recombinant human follicle stimulating hormone (FSH) by applying rec. FSH in a flexible daily dose, depending on the estradiol levels of the patient, from day 3 of the cycle onwards in a controlled ovarian hyperstimulation (COH) protocol. A single dose of 0.25 mg was injected daily subcutaneously from day 7 of the cycle onwards until the day of HCG application. The recombinant FSH dose was adjusted according to ovarian response. Fifteen patients were treated for IVF and nine for ICSI. In two patients egg retrieval was not performed. Estradiol and LH levels were measured on the day of HCG application.

Results: The mean number of recovered oocytes in the 24 patients was 5.5. A fertilisation rate of 64% was achieved in the IVF group and 69% in the ICSI group. In Germany a maximum of three embryos per patient is permitted to be transferred. Pregnancy occurred in ten patients: 5 IVF patients and 5 ICSI patients. In this small group of IVF patients a 33% pregnancy rate per follicular puncture and a 50% pregnancy rate per embryo transfer resulted. The ICSI group showed a 55% pregnancy rate per follicular puncture and a 62% pregnancy rate per embryo transfer.

Conclusion: Within an IVF/ET, ICSI programme the Gn-RH-antagonist *Cetrorelix* in combination with rec. FSH gave optimal pregnancy results.

Key words: Gn-RH antagonists; ICSI/IVF; Ovarian stimulation; Recombinant FSH; LH surge prevention.

Introduction

An increasing number of gonadotrophin releasing hormones, analogues, Gn-RH agonists and antagonists are used for a variety of reproductive disorders in which reversible suppression of the pituitary-gonadal axis is desired [1]. This has been achieved mainly by the application of Gn-RH agonists. Only recently have antagonists also been administered within ovarian stimulation protocols for the immediate suppression of pituitary gonadotrophin receptors [13, 14]. Discontinuation of Gn-RH antagonist treatment leads to a rapid and predictable recovery of the pituitary-gonadal axis [5, 7]. Gn-RH antagonist treatment is administered only for a few days to women undergoing ovarian stimulation. It was the aim of this paper to test the application of the Gn-RH antagonist. Cetrorelix in a dose of 0.25 mg to prevent the occurrence of LH surge during ovarian stimulation of patients enrolled in our IVF, ICSI and ET programme.

Material and Methods

Patients

A total of 26 patients with indications for ovarian stimulation were screened and treated in our in vitro fertilisation (IVF) and intracytoplasmatic sperm injection (ICSI) programme. The ovarian stimulation was selectively carried out with rFSH.

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Study Design

This study, performed in 1999, is a Phase III clinical trial study of the Gn-RH antagonist Cetrorelix with ovarian stimulation from day 3 of the menstrual cycle onwards. The patients received daily dosages of recombinant FSH (at varying levels depending on the individual estradiol response) in a controlled ovarian hyperstimulation (COH) programme. From day 7 of the cycle (day 5 of stimulation) until the day of HCG application 0.25 mg Cetrorelix was administered daily subcutaneously. Once the three leading follicles had reached a diameter of 18-20 mm, as measured by transvaginal ultrasound, and estradiol levels indicated satisfactory follicular response, ovulation was induced with 10,000 IU HCG. Cetrorelix was provided by courtesy of the Asta Medica Company, Frankfurt, Germany. All follicles were punctured according to clinical practice (ultrasound guided follicular puncture under slight analgesia using an automatic puncture device) [12]. A maximum of three embryos were transferred; in patients under the age of 35 years only two. The corpus luteum phase was supported by daily administration of a vaginal gel with 90 mg progesterone (Crinone®).

Results

All patients tolerated the stimulation with Cetrorelix and recombinant FSH well without displaying any side-effects. Table 1 shows the results of 26 cycles. All follicles were aspirated. Two patients were not punctured (no follicles >15 mm). In two patients no cleavage and in four patients no fertilisation occurred. The number of transferred embryos varied between 1 and 3. Pregnancy

Table 1. — *Pregnancy outcome in 26 IVF-ICSI/ET patients regulated with the Gn-RH antagonist: Cetrorelix (0.25 mg per day) and rec. FSH/HCG stimulation (▽ = per patient cycle, □ = per patient transfer).*

Patients (n)			E2 pg/ml at HCG			LH mU/l at HCG			Oocytes n		Fertilised Oocytes				Transferred Embryos		Pregnancies n			
IVF	No puncture	ICSI	IVF	No puncture	ICSI	IVF	No puncture	ICSI	IVF	ICSI	IVF n	IVF %	ICSI n	ICSI %	IVF n	ICSI n	IVF n	IVF %	ICSI n	ICSI %
1			1182			2.1			10		7	70			3		1			
		2			738			1.6		5			3	60		3			1	
3			197			1.3			1		1	100			1		0			
		4			1312			2.0		9			4	44		3			0	
5			600			1.9			4		0	0			0		0			
		6			779			0.7		5			4	80		3			0	
		7			845			1.4		4			3	75		3			0	
8			2015			1.9			11		10	91			3		1			
		9			1680			2.3		8			5	62		2			1	
10			2200			1.6			11		10	91			2		0			
		11			625			0.9		3			3	100		2			1	
		12			1485			1.8		6			6	100		3			1	
13			784			2.1			2		2	100			1		0			
		14			120			14.2		1			1	100		0			0	
15			1204			1.2			8		6	75			3		1			
	16			448			3.9													
17			510			0.5			9		8	89			3		1			
		18			342			1.1		4			2	50		2			1	
19			306			0.8			6		3	50			2		0			
20			180			1.3			3		0				0		0			
21			405			2.0			1		0				0		0			
	22			131			4.1													
23			549			1.5			5		2	40			0		0			
24			1844			0.7			4		0				0		0			
25			1357			>0.5			10		6	60			3		1			
26			129			2.9			2		1	50			1		0			
Σ ▽15	2	▽9							87	45	56	64	31	69	22 in □10 pts	21 in □8	5 ▽33		5 ▽55	
																	□50		□62	

rates assessed per patient (per stimulated cycle) and per transfer resulted in ten pregnancies. The five resulting pregnancies in the IVF group represent a 38% pregnancy rate per stimulated cycle and a 50% pregnancy rate per embryo transfer; the five pregnancies in the ICSI group a 55% pregnancy rate per stimulated cycle and a 62% pregnancy rate per embryo transfer. The average dose of recombinant FSH (100 IU per ampoule) administered per patient varied between 22 and 28 ampoules.

Discussion

This was our first study to prove the effectiveness of the Gn-RH antagonist Cetrorelix in preventing premature LH surge [13, 14] using a controlled ovarian hyperstimulation protocol. In view of the satisfactory pregnancy rate with a daily dose of 0.25 mg Cetrorelix from day 7 of the stimulated menstrual cycle onwards, we are now treating our first patients with 3 mg Cetrorelix (Cetrotide®). In spite of the eight dropouts in this small evaluation (no egg retrieval [2], no fertilisation [4] and no cleavage [2]) high pregnancy rates have been achieved among the first 26 patients treated with Cetrorelix. The pregnancy rate appears higher than that achieved over the last ten years during the administration of GN-RH agonists in our IVF/ICSI programme. However, no conclusion can be drawn in comparison to Gn-RH agonists/FSH protocols as the patient number is very small.

The use of Gn-RH agonists for the purpose of ovarian homogenous stimulation is one of the important endocrine achievements following the early synthesis of Gn-RH analogs [8-11] which helped solve many of the difficulties and drawbacks in in vitro fertilisation and embryo transfer. In our department the rate of 16% of cycles which had to be terminated due to LH surges was reduced to about 2%. Endogenous hormone production by Gn-RH analogs followed by HMG stimulation has developed from a second line to a first line therapy. Parallel to the development of Gn-RH agonists, other anaologs have been synthesised which also bind to the pituitary Gn-RH receptors. These compounds are more complex than the Gn-RH agonists with modifications in molecular structure not only at positions 6 and 10 but also at positions 1, 2, 3 and 8. In comparison to the Gn-RH agonists, the pharmacological mechanisms by which Gn-RH antagonists suppress the liberation of gonadotrophins are different. Whereas the agonists act on chronic administration through the down regulation of receptors, the antagonists bind competitively to the receptors and therefore prevent endogenous Gn-RH from exerting its stimulatory effect

on the pituitary cells. A "flare-up" is avoided. The allergic side-effects due to induced histaminic release impeded the clean development of these compounds. The modern Gn-RH antagonists such as Ganirelix (Organon, Oss, The Netherlands) and Cetrorelix (Asta Medica, Frankfurt, Germany) have solved these problems. After many tedious dose-finding studies [3-6, 15, 16] Ganirelix and Cetrorelix have been approved by many National Health organisations and become medically available. Gn-RH antagonists significantly reduce the length of the stimulation cycles as no more "flare-ups" occur. In our study no premature LH surge occurred. Cetrorelix, administered in a single daily dose of 0.25 mg, allows sufficient LH to be secreted from the pituitary gland for normal estradiol secretion under stimulation with preparations of recombinant FSH without inducing any LH activity itself. The pituitary response is maintained and it is possible to induce ovulation by Gn-RH or Gn-RH agonists.

In this study we applied HCG to trigger ovulation and experienced no ovarian hyperstimulation syndrome; however, we are investigating results without HCG application. Nowadays, both Ganirelix and Cetrorelix are successfully applied in dosages of 0.25 mg per day or one single dosage of 3 mg during the cycle. Other studies [6] show similar high pregnancy rates to those described in this paper.

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