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Effective Management of Single Dominant Follicle with Continuous Administration of Gonadotropin-Releasing Hormone Agonist

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=Abstract=**With the widespread use of gonadotropin-releasing hormone agonist (GnRH-a) for in vitro fertilization(IVF) program, the cancellation rate during controlled ovarian hyperstimulation(COH) is much lowered. However, poor responders with poor estradiol(E2) rise or single dominant follicle still persist in GnRH-a combined COH, and the decision to cancel the cycle and the counselling of further cycles remain very perplexing. Three poor responders with single dominant follicle during GnRH-a combined COH for IVF were, rather than being cancelled, managed by continuous administration of GnRH-a and restimulation with initial low dosage and subsequent high dosage of follicle-stimulating hormone until an appropriate number of follicles was obtained. While no pregnant case treated in this way, the management resulted in a higher E2 level, and more oocytes and embryos. We suggest that this approach could serve as an alternative to cancellation in GnRH-a combined COH.**

Key Words: *IVF, COH, GnRH-a, Poor responders, Single dominant follicle*

INTRODUCTION

Recently the use of gonadotropin-releasing hormone agonist(GnRH-a) has been frequently indicated in controlled ovarian hyperstimulation(COH) for in vitro fertilization (IVF) program and satisfactory results have been obtained in terms of the cancellation and pregnancy rates (Katavama *et al.* 1988; Serafini *et al.* 1988; Droesch *et al.* 1990).

Poor responders, especially with poor estradiol(E2) rise or single dominant follicle, are a particularly challenging group of patients encountered in COH. At present, except for an oocytes donation program, COH with GnRH-a is the last resort for poor responders. Even though the cancellation rate is low, cancelled cases persist in the GnRH-a combined COH and the main reason for cancellation is the growth of fewer follicles(Porter *et al.* 1984; Meldrum *et al.* 1989). When using the GnRH-a combined COH, the decision to cancel the cycle is difficult and counselling of further cycles in these patients is even more difficult. As we have experienced rather successful management of single dominant follicle during the GnRH-a combined COH with the continuous administration of GnRH-a followed by high

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dosage of exogenous gonadotropins, we here describe three cases.

MATERIALS AND METHODS

Case 1

A 35-year old woman with gravida 4, para 2, abortion 2, and 2 living babies who had previously undergone tubal ligation was enlisted on the IVF register for desiring further pregnancy. During COH, 1 mg of leuprolide acetate (Lupron; TAP Pharmaceuticals, Chicago, IL) was first given on day 21 of the menstrual cycle(MCD #21) for pituitary down-regulation, and after identification of ovarian suppression which was evaluated on day 3 of the next menstrual cycle with ultrasound (no follicle 〉 10mm in diameter) and by measurement of serum E2 (≤30pg/ml), the stimulation was begun with a combination of human menopausal gonadotropin(hMG, Pergonal; Serono, Switzerland) and follicle-stimulating hormone(FSH, Metrodin; Serono, Switzerland)(Chang *et al.* 1990). Due to a high basal FSH, a high dosage of gonadotropins was administered : 3 ampules (225IU) of FSH on the first and second day of stimulation (S 1 and S 2) and 3 ampules(225IU) of hMG from S 1. As a single dominant follicle was seen on S 10, we switched to a continuous administration of Lupron only. After 18 days of suppression with Lupron only, ovarian suppression was confirmed and stimulation was restarted with 4 amplules of FSH at 6 PM on S 1 and S 2, and 4 ampules at 10 AM from S 3. In addition, 4 ampules of hMG were administered at 6 PM on S 3 and S 4. After S 5, dosage adjustment of FSH and hMG administered was made according to serum E2 and ultrasonographic findings up to one day before 10,000 IU of human chorionic gonadotropin(hCG, Profasi; Serono, Switzerland) injection(Day -1). Serum E2, LH, FSH and β-hCG were determined using radioimmunoassay techniques.

Case 2

A 30-year old woman, nulligravida, underwent her first attempt at IVF due to irreparable tubal damage. One hundred μg of D-Trp6-luteinizing hormone-releasing hormone analogue(Decapeptyl; Ferring, Sweden) was started on MCD #21. After ovarian suppression, the stimulation was made with a pure FSH regimen : 2 ampules of FSH were administered at 10 AM on S 1 and S 2, and 2 ampules of FSH at 6 PM from S 1. On S 9, a single dominant follicle was seen. Once again, we switched to a continuous administration of Decapeptyl only. After identification of ovarian suppression 28 days later, we began restimulation with 3 amplules of FSH at 6 PM from S 1 and with 3 ampules of FSH at 10 AM on S 3 and S 4. After S 5, dosage adjustment of FSH administered was made.

Case 3

A 41-year old woman, nulligravida, had previously undergone tubal ligation. She was enlisted on our IVF register due to her advanced age. Short protocol of GnRH-a was adopted for COH. Decapeptyl was administered from MCD #2 for flare-up effect. Due to her age and a high basal FSH, a high dosage of FSH was administered : 4 ampules of FSH at 10 AM on MCD #4 & #5 and 4 ampules of FSH at 6 PM from MCD #4. On MCD #10,a single dominant follicle was seen. we again switched to a continuous administration of Decapeptyl only, and began to restimulate 26 days later after ovarian suppression with 4 amplules of FSH at 6 PM from S 1 and with 4 ampules of FSH at 10 AM on S 3 and S 4. After S 5, dosage adjustment was also made.

RESULTS

A summary of the comparison of the outcome of COH in the three patients is presented in Table 1. In Case 1, after the continuous administration of GnRH-a and restimulation with hMG and FSH, peak serum E2 level was 1,249 pg/ml and the number of follicles observed on the day of hCG injection(Day 0) was 4. On transvaginal aspiration, 2 mature oocytes were retrieved. After in vitro fertilization and culture, 2 embryos were transferred. In

Case 2, after further suppression with GnRH-a for 28 days and restimulation with FSH for 11 days, 13 follicles were observed and 11 oocytes were retrieved. Four embryos were transferred, and another 4 embryos were cryopreserved. In Case 3, after further suppression with GnRH-a for 26 days and restimulation with FSH for 14 days, 7 follicles were observed and 3 oocytes were retrieved. But no embryo was obtained. Unfortunately, no pregnancy occurred in all three patients.

Table 1. Comparison of outcome of controlled ovarian hyperstimulation in three patients

	Case 1		Case 2		Case 3	
	initial	later	initial	later	initial	later
Age(yr)	35		30		41	
Basal FSH (mIU/ml)	20.1		9.8		33.0	
Basal LH (mIU/ml)	9.6		12.3		14.7	
Dosage(ampules)						
FSH	6	24	4	49	36	95
hMG	27	32	-	-	-	-
Duration(days)						
Suppression	17	18	18	28	-[a]	26
Stimulation	9	10	10	11	7	14
E2 peak(pg/ml)	472	1,249	290	2,045	650	1,821
Follicles						
10 - 15 mm	1	1		7	1	3
15 - 20 mm	1	2	1	6	1	4
〉 20 mm		1				
Total	2	4	1	13	2	7
Oocytes	-	2	-	11	-	3
Embryos		2		8		0
≥ 4-cell		2		4		
Pregnancy		No		No		No

a : Short protocol of GnRH-a was used.

DISCUSSION

The use of GnRH-a in COH has resulted in improved oocyte retrieval rates by more recruitment of follicles and prevention of endogenous LH surge(Katavama *et al.* 1988; Serafani *et al.* 1988; Droesch *et al.* 1990; Porter *et al.* 1984; Meldrum *et al.* 1989). It was assumed that COH after pituitary desensitization with GnRH-a might result in the growth of a more synchronous cohort of follicles later(Gougeon 1986; DeZiegler *et al.* 1987). In poor responders, the pituitary desensitization with GnRH-a has allowed better responses during COH(Serafini *et al.* 1988; Droesch *et al.* 1990; Porter *et al.* 1984; DeZiegler *et al.* 1987).

Whereas this GnRH-a combined COH reduces the cancellation rate, certain patients still show a poor response. Especially, poor responders with a high basal FSH level and the growth of few follicles, usually less than 2, are a challenging group. Such COH cycles might be cancelled and restarted a few months later with no further hope.

To reduce the cost and achieve a flare-up effect, recently the short protocol has been widely used. But conflicting findings have been reported. Some reports have shown that short protocol improves the number of preovulatory oocytes and embryo quality(Katavama *et al.* 1988; Droesch *et al.* 1990). In contrast, short protocol had no improved outcome and resulted in fewer oocytes with more atretic oocytes(Serafini *et al.* 1988; Bryzski *et al.* 1988; Garcia *et al.* 1990). This finding has been presumed to result from the initial rise of LH (Bryzski *et al.* 1988; Loumaye *et al.* 1989) since a high basal LH is shown to be detrimental to normal oocyte development and fertilization (Stanger and Yovich 1985). But some authors have reported that an initial high LH is not detrimental to oocyte development and quality (Garcia 1990). Furthermore, others have shown that initial high LH is beneficial to COH and results in many more oocytes and a better IVF outcome(Pallida *et al.* 1990). They have suggested that an initial high LH results in the elevation of E2, which might in turn increase the number of FSH receptors to allow more recruitment of follicles and oocytes of good quality.

It has been postulated that after about 85 days of growth, small antral follicles attain

preovulatory size(Gougeon 1986). Folliculogenesis by increasing FSH, due to a decline in progesterone level, is started in an antecedent luteal phase, and such recruited follicles reach class V of Gougeon's growth stage(Gougeon 1986) at the beginning of the ongoing menstrual cycle(Baird 1987). In the natural cycle, low FSH is presumed to prevent luteal phase folliculogenesis(McNatty *et al.* 1975). Some authors have reported that exogenous gonadotropins administered in the luteal phase can override this process and resume folliculogenesis in experimental animals (Zeleznik and Resko 1980) and humans (Sharma *et al.* 1989). On the other hand, Sharma *et al.* (1989) reported that FSH administered in midluteal phase is not beneficial, despite the observed recruitment and growth of follicles.

Recently, Gougeon *et al.* (1990) reported that the mitotic activity of granulosa cells was subject to the menstrual cycle day and this difference is presumed to result in the absent midfollicular response of follicles to gonadotropins. This suggests that there might be an inhibitory activity, possibly ovarian, designed to suppress the selection and maturation of the less developed antral follicles from the midfollicular phase of the spontaneous menstrual cycle. In the same manner, long protocol of GnRH-a started in midluteal phase results in the pituitary desensitization and the subsequent increment of the gonadotropin level has little effect on the follicles, resulting in prevention of recruitment. After ovarian suppression, exogenous gonadotropins might simultaneously stimulate the cohort of follicles and allow synchronous multiple follicular growth. As Brown(1978) suggested, a threshold level of FSH might be present to promote the growth of follicles beyond the small antral stage.

It has been shown that, on suspicion of ovarian hyperstimulation syndrome, withholding hCG injection and continued GnRH-a administration with later stimulation after ovarian suppression did not incur any detrimental effect on IVF outcome(Forman *et al.* 1990). When a poor response was encountered during short protocol of GnRH-a, the switch to long protocol was beneficial(Germond *et al.* 1990). Studies in primates have shown that the prevention of a decline in FSH below a critical level during the cycle can promote the growth of follicles otherwise destined for atresia(Zeleznik and Kubik 1986). In addition, Brown(1978) postulated that the growth of small antral follicles(< 4mm) requires a low level of FSH.

In summary, we managed three poor responders with single dominant follicle during GnRH-a combined COH by continuing the administration of GnRH-a and, after confirmation of ovarian suppression, by beginning stimulation with an initial low dosage and subsequent high dosage of FSH until an appropriate number of follicles (>12mm) was obtained. Though there were no pregnant cases, we suggest this approach as an alternative to cancellation.

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