

Case Report: Opposite Responses to the Addition of Leuprolide Acetate to Human Menopausal Gonadotropin Therapy in Two Perimenopausal Women

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ABSTRACT: Leuprolide acetate was used to suppress the endogenous gonadotropins in order to prevent premature luteinization in two women under ovulation induction therapy. One patient had previously developed premature luteinization with clomiphene citrate, but consistently produced only one mature follicle with hMG therapy. However, when leuprolide acetate was started prior to hMG during an attempt for in vitro fertilization, it failed to stimulate even a mild rise in her serum estradiol. The other patient, who was not able to make a mature follicle with hMG alone because of premature luteinization, was enabled to make mature follicles with leuprolide therapy alone (without hMG). The exact mechanism for these totally different responses to leuprolide acetate in two perimenopausal women is not known.

INTRODUCTION

PREMATURE LUTEINIZATION, DEFINED as a rise of serum progesterone above 2 ng/mL prior to full follicular maturation (i.e., estradiol >200 pg/mL and follicular diameter >18 mm) in the follicular phase is not an uncommon phenomenon during ovulation induction. One possible method of eliminating it is by the suppression of endogenous gonadotropins, using a gonadotropin-releasing-hormone agonist such as leuprolide acetate (LPL), followed by ovulation induction using human menopausal gonadotropin (hMG). This approach is

similar to its use in the treatment of polycystic ovarian syndrome.¹ Two cases are presented wherein this approach was adopted to overcome premature luteinization yet, surprisingly, with quite opposite outcomes.

CASE REPORTS

Case 1

The patient is a 44-year-old woman with 10 years of primary infertility because of anovulation, pelvic adhesions, endometriosis, and oligospermia in the

husband. Following surgery to improve her pelvic pathology and clomiphene treatment for her husband's oligospermia, she was treated with clomiphene citrate for four cycles to induce ovulation. In each of the four clomiphene cycles, she developed premature luteinization; hMG therapy was then initiated, with the goal of maturing the follicle earlier in the cycle. This technique successfully induced a single ovulation (never multiple ovulation) in each of seven cycles, but she failed to conceive. Subsequently she decided to enter the in vitro fertilization program. Because of her history of premature luteinization, she was placed on LPL (1 mg subcutaneously daily), followed in each cycle by hMG ovulation induction. The hope was that with LPL, and with premature luteinization less likely, there would be a better chance of inducing multiple follicles with higher dosages of hMG; hMG was started after 2 weeks of LPL. Despite a high dose of hMG (started with 4 ampules/day, 75 IU each), with the ovarian response monitored using sonograms and serum estradiol (E) and progesterone (P) levels to adjust subsequent dosages, she failed to develop even a single maturing follicle, as evidenced by her E level failing to rise above 20 pg/mL. She was given 66 ampules over 14 days of therapy. The next cycle she resumed hMG without LPL and reached a 250 pg/mL E level with just 13 ampules of hMG. A sum-

mary of the steroid and gonadotropin levels in some typical cycles is shown in Table I.

Case 2

The patient is a 41-year-old woman with a 5-year history of secondary infertility. Previously she had normal childbirths at age 26 and 36. Because of her recent anovulatory status, she was placed on clomiphene therapy for six cycles without any success. During the subsequent hMG therapies (10 to 30 ampules of 75 IU hMG per cycle during 10 to 15 days of treatment), she frequently developed premature luteinization around day 9 of therapy, with the E level never rising above 200 pg/mL despite multiple folliculogenesis. In order to overcome this problem, she was placed on daily LPL medication; hMG was planned to be added after 14 days of LPL. Surprisingly, she developed three mature follicles, with E level of 641 pg/mL, at the ninth day of LPL treatment alone and had a normal ovulation. In the subsequent two cycles of solely LPL treatment, she produced one mature follicle in each cycle, with E levels of 315 and 377 pg/mL and without premature luteinization. She conceived in the last cycle of LPL treatment, and had a live birth. A summary of the steroid and gonadotropin levels in some typical cycles is seen in Table II.

TABLE I
Hormone profile of patient no. 1.

	Day of Cycle						
	7	9	11	16	19	23	25
hMG therapy only							
E ₂ (pg/mL)	122	464					
P (ng/mL)	0.4	1.7					
LH (mIU/mL)	23	50					
FSH (mIU/mL)	28	—					
Follicles (diam. in mm)	rt. 14.2 lt. 10.0	rt. 21.6 lt. 13.6	rt. ↓ 12.3 lt. 14.3				
Total hMG units employed	1,650	10 ³ IU hCG 2,250					
Combined leuprolide acetate-hMG therapy							
E ₂ (pg/mL)			<20	<20	<20	<20	<20
P (ng/mL)			0.2	0.3	0.3	0.4	<0.1
LH (mIU/mL)			22	22	21	24	20
FSH (mIU/mL)			28	46	44	49	55
Follicles (diam. in mm)			none	none	none	none	none
Total hMG units employed			525	1,650	2,550	4,050	4,950

TABLE II
Hormone profile of patient no. 2.

	Day of Cycle					
	8	9	10	11	12	13
Clomiphene citrate therapy (50 mg days 3-7)						
E ₂ (pg/mL)		65	92		94	61
P (ng/mL)		0.9	1.4		2.8	5.1
LH (mIU/mL)		23	31		28	14
FSH (mIU/mL)		19	22		20	18
Follicles (diam. in mm)		rt. 12.6	rt. 14.5		rt. 17	
hMG therapy only						
E ₂ (pg/mL)	72	99	110	82		
P (ng/mL)	0.9	1.7	3.5	6.5		
LH (mIU/mL)	10	18	27	15		
FSH (mIU/mL)	15	28	22	26		
Follicles (diam. in mm)	none	none	14.5	14		
Total hMG units employed		600	750	900		
First cycle of leuprolide acetate therapy						
E ₂ (pg/mL)			641		135	
P (ng/mL)			0.5		3.2	
LH (mIU/mL)			14		8	
FSH (mIU/mL)			10		6	
Follicles (diam. in mm)			rt. 21.3		21.3 ↑ 25	
			11.7		11.7 ↑ 13.7	
			lt. 17.7		17.7 ↓ <10	
			15.7		15.7 ↑ 17.3	
Units hCG employed			10,000		5,000	
Leuprolide acetate therapy—cycle of conception						
E ₂ (pg/mL)	188	276	377			
P (ng/mL)	0.3	0.2/0.3	0.4			
LH (mIU/mL)	27	23	19			
FSH (mIU/mL)	16	13	10			
Follicles (avg. diam.)	11.6	15.3	20.7			released
Units hCG employed				10,000		

DISCUSSION

Two perimenopausal patients with a similar problem of premature luteinization during ovulation induction therapy responded quite differently to leuprolide acetate treatment. The ovaries of the first patient were unresponsive to a high dose of hMG when she was under LPL medication, despite her previous favorable response to a lower dose of hMG when LPL was not added. In contrast, the second patient ovulated with just LPL medication, without additional hMG treatment.

Both patients, despite being in their early 40s,

were still in their premenopausal period, with normal serum gonadotropin levels. It is unclear how LPL induced such a different response. The possibility exists that LPL can exert a negative effect on ovarian responsiveness to gonadotropins. However, it is possible that fortuitously there were no follicles in a state responsive to gonadotropins in that one cycle when leuprolide was given, so that, perhaps, hMG alone would not have been successful during that cycle in inducing a mature follicle either. Previously, we have reported that LPL was capable of inducing proper follicular maturation and subsequent ovulation in a woman with ovarian

failure.² Case 2 demonstrates that in a woman with premature luteinization, LPL alone may be more effective in some cases than hMG alone. The treating physician should, therefore, not automatically use LPL for 2 weeks and then add hMG, but should evaluate the patient during therapy with LPL alone, looking for possible follicular maturation before the hMG is started. Perhaps, when more cases are treated with LPL, some common factor may be identified to predict in which patients LPL will act as an agonist, and in which cases it may not only act to suppress endogenous gonadotropins but also inhibit ovarian sensitivity to exogenous gonadotropins.

REFERENCES

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