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Ovulation induction with pulsatile gonadotropin-releasing hormone: a study of the subcutaneous route of administration*

Michael R. Soules, M.D.†‡
Molly B. Southworth, M.D.§
Mary E. Norton, M.D.†
William J. Bremner, M.D., Ph.D.§

University of Washington School of Medicine and Veterans Administration Medical Center, Seattle, Washington

The efficacy of ovulation induction with the use of intermittent gonadotropin-releasing hormone (GnRH) therapy was examined in seven infertile women with hypothalamic amenorrhea. GnRH was administered every 90 minutes via the subcutaneous route in doses ranging from 50 to 300 ng/kg. Analysis of the induced gonadotropin pulse pattern revealed normal to modestly increased luteinizing hormone secretory parameters (e.g., pulse amplitude) in six of the seven patients. Six of seven women and 15 of 16 treatment cycles (94%) were ovulatory. The conception rate was 43% per woman and 19% per cycle. However, detailed hormonal analysis of 13 treatment cycles revealed that only 1 cycle was entirely normal in terms of duration and/or steroid secretion. Fertil Steril 46:578, 1986

Women with infertility and clomiphene citrate (CC)-resistant chronic anovulation have long presented a clinical challenge. For several decades, exogenous gonadotropin therapy has been available and reasonably efficacious in treating these women.[1, 2] However, exogenous gonadotropin therapy is relatively expensive and its use carries a potential risk for serious adverse effects (e.g., ovarian hyperstimulation and multiple pregnancy).[3, 4] The clinical availability of gonadotropin-releasing hormone (GnRH), coupled with the realization that GnRH is secreted in an intermittent (pulsatile) pattern in ovulatory women,[5] set the stage for the use of GnRH as an alternative medication to exogenous gonadotropin therapy. It was reasoned that GnRH therapy may be safer than gonadotropin therapy, because it incorporates the body's normal endocrine feedback mechanisms. Successful ovulation induction and pregnancy with pulsatile GnRH therapy was first reported in 1980.[6, 7] Following these initial feasibility studies, more clinical reports have followed, describing the ovulation and pregnancy rates achieved with intermittent GnRH therapy.[8–17] From these clinical reports controversy regarding the optimal route of administration (intravenous or subcutaneous) for GnRH has evolved. The intravenous route of GnRH administration has been shown to be efficacious in terms of ovulation and pregnancy rates.[9, 12, 14, 17] However, the intravenous route carries the potential for serious complications, such as septicemia and phlebitis.[16, 17] The subcutaneous route generally is con-

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†Department of Obstetrics and Gynecology, University of Washington.

‡Reprint requests: Michael R. Soules, M.D., Department of Obstetrics and Gynecology, RH-20, University of Washington, Seattle, Washington 98195.

§Department of Medicine, Veterans Administration Medical Center and University of Washington.

Table 1. *GnRH Treatment: Patients*

Patient	Age	Parity	%IBW	Diagnosis	Duration	Other infertility factors	Pretreatment hormone levels		
							LH	FSH	E_2
	yrs				*yrs*		*ng/ml*	*ng/ml*	*pg/ml*
A	27	G0P0	103	Hypothalamic amenorrhea	2	Male factor	< 6	69.3	< 12
B	33	G0P0	91	Hypothalamic amenorrhea	8	Tubal factor	14.3	104.0	< 12
C	26	G0P0	94	Hypothalamic amenorrhea	4	None	9.1	120.8	20.8
D	32	G1P1 (hMG Rx[a])	87	Hypothalamic oligomenorrhea	2	None	8.4	109.3	< 12
E	28	G0P0	100	Hypothalamic amenorrhea (postpill)	3	None	6.3	35.0	< 12
F	26	G0P0	84	Hypothalamic amenorrhea (postpill)	10	None	7.7	72.3	< 12
G	27	G1P1 (spontaneous)	94	Hypothalamic amenorrhea (postpill)	1	None	17.9	102.1	32.4
							32.8[b]	159.8[b]	57.5[b]

[a]hMG, human menopausal gonadotropin treatment.
[b]Normal values (n = 5), mean levels, early follicular phase.[5]

sidered to be safer in terms of potential complications and to have a better level of patient acceptance, because a small subcutaneous needle is less invasive than an intravenous catheter and can be inserted by the patient at home. The controversy that has developed is in regard to the efficacy of subcutaneous GnRH therapy. Reports[8, 10-16] regarding the outcome of subcutaneous GnRH therapy, with similar methodologies, have varied from poor to excellent.

This study was undertaken to look into the discrepancy regarding the subcutaneous route of administration of GnRH for ovulation induction. We examined not only the ovulation and pregnancy rates with the use of subcutaneous GnRH, but the induced gonadotropin pulse patterns and subsequent ovarian responses. Other pertinent areas examined were dose-response relationships, the stimulation interval before ovulation, the quality of ovulation, adverse effects, and patient acceptance.

MATERIALS AND METHODS

The subjects were seven women (aged 26 to 33 years) with secondary amenorrhea and infertility. These women were diagnosed as having hypothalamic amenorrhea or oligomenorrhea after thorough endocrine testing. They all had low serum levels of estradiol (E_2) and gonadotropins (Table 1). A complete infertility evaluation was normal except for the ovulation problem in five of the women; two had mild additional infertility factors (Table 1). All had failed to have withdrawal bleeding to a progesterone (P) challenge and to ovulate on adequate doses of CC (100 to 250 mg/day).

Luteinizing hormone (LH), follicle-stimulating hormone (FSH), E_2, and P levels were tested daily during one or two treatment cycles per patient. Basal body temperature (BBT) charts were kept. Pelvic sonography was performed in the periovulatory period. Regular pelvic examinations were performed to monitor for hyperstimulation syndrome. The occurrence of ovulation was established with the use of pelvic sonography (e.g., decreased follicular size) and BBT charts and later verified when LH (surge) and P concentrations were determined.

Baseline and stimulated secretion patterns of LH and FSH were studied during a 12-hour admission to the Clinical Research Center (University of Washington) on day 1 of each patient's first treatment cycle. During this and subsequent admissions, blood samples were obtained every 20 minutes through an indwelling intravenous line. GnRH administration with an intermittent infusion pump was begun 6 hours into this admission. Also, patients were admitted and blood samples obtained for 6 hours after 1 week of treatment on each successive dose regimen. A pelvic ultrasound was performed with a sector scanner during every admission to assess ovarian follicular size.

GnRH (Factrel, Ayerst Laboratories, New York, NY) was administered with an intermittent infusion pump (Autosyringe Model A6H, Autosyringe Division of Travenol Laboratories, Hookset, NH). The GnRH was administered subcutaneously every 90 minutes with an infusion

Table 2. *Normal Control Values (n = 15)*

	Mean ± SD	95% confidence interval
Follicular phase		
Length (days)	16 ± 3	10–22
Days until E_2 > 100 pg/ml	9.8 ± 1.4	7.3–12.9
Preovulatory follicle diameter (mm) (LH surge day − 1)	20.1 ± 2.9	14.9–26.6
Peak E_2 (pg/ml)	299.7 ± 71.5	179.7–474.5
LH surge (ng/ml)	361.5 ± 121.9	181.1–653.7
Luteal phase		
Length (days)	13 ± 1	11–16
P peak (ng/ml)	20.2 ± 5.5	10.8–34.9
P area [(ng/ml)day]	138.3 ± 43.8	70.3–248.3
Total cycle length (days)	29 ± 3	23–36

interval of 2 to 6 seconds. Twenty-six-gauge right-angle needles were placed subcutaneously in the upper abdominal wall or high on the buttocks. Syringes and needles were changed every 2 to 7 days. An initial dose of 50 ng/kg of GnRH (2 to 4 μg/dose) was used for two patients and of 100 ng/kg for the remainder. (The higher initial GnRH dose was selected after the study began in an attempt to circumvent the problem with prolonged follicular phases.) If E_2 levels failed to rise after 1 week, the dose was doubled, to a maximum dose of 400 ng/kg (about 20 μg/dose). If ovulation occurred, support was provided for the corpus luteum in all patients. In the first two patients use of the pump was discontinued after ovulation and the women were given 3000 U of human chorionic gonadotropin (hCG) intramuscularly every four days. On all subsequent cycles the intermittent GnRH therapy was merely continued at the preovulatory dose and rate throughout the luteal phase. (Luteal support with intermittent GnRH therapy was used in most of the subjects because of patient preference over hCG injections.)

The control patients used for comparing daily serum hormone levels were 15 women of reproductive age (23 to 35 years). These women conformed to ± 10% ideal body weight (IBW) (Metropolitan Life Table, 1980) and were in good health and on no medications. They were determined to be normal by BBT charts, daily serum levels of LH, FSH, E_2, and P, and preovulatory ovarian ultrasound examinations performed daily until ovulation was confirmed (Table 2). The geometric means and 95% confidence intervals (± 2 standard deviations [SDs]) were determined after log transformation of their hormone data. A study patient's value was considered to be abnormal if it fell outside the confidence interval for the normal women. Luteal and follicular phase lengths (in days) were determined in relation to the LH surge. The pretreatment LH pulse parameters in the study patients were compared with early follicular (EF) levels in five of the control women.[5] While the study patients were receiving GnRH therapy, normal baseline and pulse values from the late follicular (LF, n = 5) phase were used for comparative purposes.[5]

The venous blood samples were analyzed for LH and FSH with the use of double-antibody radioimmunoassays (RIAs), according to a previously reported methodology.[18] Standard National Institutes of Health (NIH) reagents were used, with results expressed as ng/ml of the LER-907 reference preparation. The respective sensitivities of the LH and FSH assays were 6 ng/ml and 25 ng/ml; for the LH assay intraassay and interassay coefficients of variation were 5.5% and 8.4%, respectively; for the FSH assay intraassay and interassay coefficients of variation were 7.3% and 9.7%, respectively. Serum samples for plasma E_2 and P determinations were assayed in duplicate by RIA according to a previously reported methodology.[18] The sensitivity of the E_2 assay was 12 pg/ml; intraassay and interassay coefficients of variation were 6% and 7.8%, respectively. The sensitivity of the P assay was 140 pg/ml; intraassay and interassay coefficients of variation were 6% and 8%, respectively.

LH secretion patterns were analyzed using a modification of the Santen and Bardin method.[19] For each sample set, measurement error was assessed based on the assay replicate SD. A pulse was defined as an increase from nadir to peak that was greater than 2 SDs. Based on computer simulations, it was found that this procedure worked well when there were at least ten simulated pulses (in data sets consisting of 73 samples). When less than ten simulated pulses were present, false positives were a problem. Therefore, when the initial analysis indicated less than ten pulses; a more stringent criterion was set, requiring an increase of > 5 SDs.[20]

RESULTS

Before treatment was begun most of the LH secretion parameters (frequency, amplitude, and mean level) were found to be markedly sup-

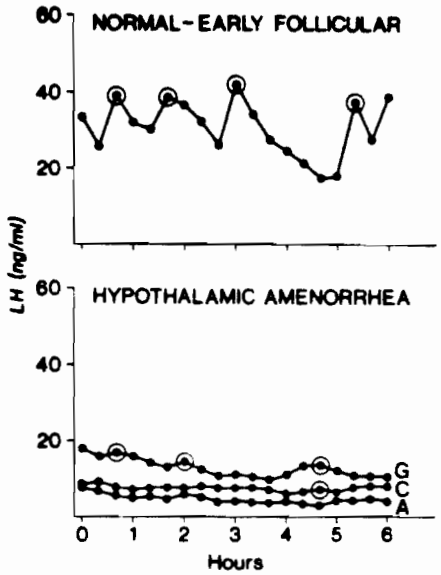

Figure 1
The LH secretory pattern over six hours is illustrated for a normal woman in the EF cycle phase (**top**) and for three different women with hypothalamic amenorrhea (**bottom**). Circled LH values indicate that a pulse was detected.

pressed in the study patients (Fig. 1; Table 3). Four of the women had normal LH pulse frequency as determined by our criteria, but all subjects had normal LH amplitude and mean levels. Three of the subjects had no LH secretory activity as detected by pulse analysis techniques. GnRH therapy induced a clear LH pulse pattern in six of the seven women treated (Fig. 2).

A total of 16 cycles were studied, 13 with daily serum hormone levels and 3 with levels determined two to three times per week. Ovulation was observed in 15 of the 16 treatment cycles (94%). Three of the seven patients conceived (43%), all during their third or fourth treatment cycle. One patient had a spontaneous abortion at 14 weeks; two have delivered at term. The pregnancy rate per cycle was 19%. These results are summarized in Table 4. Ovulatory cycles resulted with GnRH doses of 50 ng/kg, 100 ng/kg, and 200 ng/kg. Ovulation generally was achieved at a GnRH dose of 100 to 200 ng/kg. The one patient who failed to ovulate was treated in consecutive cycles with 100, 200, and 300 ng/kg of GnRH.

There were sufficient endocrine data to analyze in detail 13 of the treatment cycles (Table 5). The follicular phase was significantly prolonged in 9 of the 13 cycles. The follicular E_2 rise demonstrated several patterns. One E_2 pattern consisted of an acute increase > 100 pg/ml within 1 to 2 days of initiating treatment, which would then either proceed to ovulation or decline for several weeks before rising again, if it rose again at all. The second E_2 pattern was to remain relatively low for a period exceeding 2 weeks and then rise in a sustained manner until ovulation occurred. Two of the eight cycles that demonstrated this delayed pattern had significantly low peak E_2 levels just before ovulation. Only one of the 13 cycles demonstrated a normal E_2 response in terms of time and magnitude (Table 5). The data obtained from ovarian sonograms were sporadic and insufficient, considering the variability in

Table 3. *Pretreatment LH Secretory Parameters*

Patient	LH pulse frequency	Mean LH amplitude	Mean LH level
	no./24 hr	*ng/ml*	*ng/ml*
A	12	1.1	4.7
B	12	3.8	14.3
C	0	—	7.7
D	0	—	8.4
E	16	1.3	6.3
F	16	2.7	9.1
G	0	—	17.9
Mean ± SEM	8.0 ± 2.9	2.2 ± 0.6	9.8 ± 1.8
Normals[a]	14.4 ± 1.0	15.0 ± 2.4	32.8 ± 8.2

[a]Normal values (n = 5), mean levels ± standard error of the mean, early follicular phase.[5]

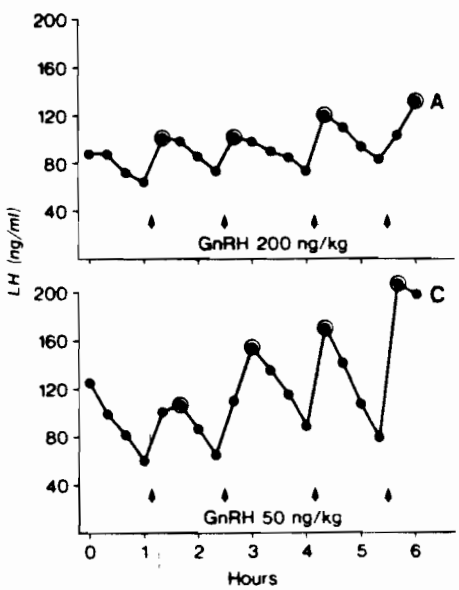

Figure 2
An LH "pulse" pattern has been induced with exogenous GnRH administered subcutaneously every 90 minutes (*arrows*) at a dose of 200 ng/kg (**top**) and 50 ng/kg (**bottom**). Circled LH values indicate that a pulse was detected.

Table 4. *GnRH Treatment: Cycle Outcome*

Patient	No. of cycles	Final GnRH Dose[a]	Ovulation	Pregnancy
		ng/kg		
A	3	200	+	−
		200	+	−
		200	+	+
B	2	100	+	−
		100	+	−
C	1	50	+	−
D	2	200	+	−
		200	+	−
E	4	100	+	−
		100	+	−
		100	+	−
		100	+	+
F	1	300	−	−
G	3	200	+	−
		200	+	−
		200	+	+
Total	16		15	3

[a]In a given cycle a patient may have been treated with increasing doses of GnRH. The dose indicated is the last dose administered.

follicular phase activity. However, it is noteworthy that four of the eight cycles that received scans close to ovulation had smaller-than-normal follicles in relation to the day of the LH surge. This trend toward a decreased follicular size is consistent with a similar trend toward a low or decreased preovulatory peak serum concentration of E_2 (Table 5).

A normal LH surge in terms of magnitude of rise occurred spontaneously in 12 of 13 cycles (Table 5). Three of ten cycles had short luteal phases, two with corresponding significant decreases in P secretion. There was an additional cycle that demonstrated a decreased P peak value, for a total of 40% of cycles with luteal phase deficiency (significant decreases in luteal length, P peak and/or area under P secretion curve) (Table 5). Eight of 14 cycles were of an abnormal total length (prolonged) secondary to increases in follicular phase length. Altogether, only one cycle (cycle 8) was found to have no significant deviations from normal during both cycle phases. The cycle (cycle 10) in which ovulation did not occur despite 60 days of treatment had four acute changes in LH serum concentration (each lasting several days) of sufficient magnitude to be LH surges. However, there was no rise in serum P following these increases in LH. Each of these LH surges occurred simultaneously with brief (3- to 5-day) increases in serum E_2 (range, 160 to 300 pg/ml).

The induced LH secretory (pulse) pattern was analyzed over a 6-hour sampling interval for GnRH doses ranging from 50 to 300 ng/kg (Table 6). Five of the women were studied at two different doses. In all but patient F, who failed to ovulate, a clear LH pulse was detected each time a dose was given. In the six ovulatory women, four pulses were not detected in each sampling interval, because sampling did not necessarily commence with a dose. Five ovulatory subjects were

Table 5. *GnRH Treatment: Cycle Summaries*

Patient	Cycles	Final GnRH Dose[a]	Follicular phase				LH surge	Luteal phase			Total cycle length	Comments
			Length	Days until E_2 > 100 pg/ml	Preovulatory follicular diameter	Peak E_2		Length	P peak	P area		
		ng/kg	*days*			*pg/ml*	*ng/ml*	*days*	*ng/ml*	*(ng/ml)·days*	*days*	
			16 ± 3[b]	9.8 ± 1.4[b]	20.1 ± 2.9[b]	299.7 ± 71.5[b]	361.5 ± 121.9[b]	13 ± 1[b]	20.2 ± 5.5[b]	138.3 ± 43.8[b]	29 ± 3[b]	
A	1	200	53[c]	48[c]	—	164[c]	272.4	15	10.6[c]	91.2	68[c]	Luteal phase deficiency
B	2	100	11	1[c]	Decreased[c]	263	272.6	15	14.6	120.2	26	Corpus luteum cyst
	3	100	30[c]	22[c]	Normal	325	165.1[c]	8[c]	7.6[c]	43.8[c]	38[c]	Luteal phase deficiency
C	4	50	13	5[c]	Decreased[c]	209	462.1	20[c]	29.0	318.7[c]	33	Luteal hCG treatment
D	5	200	46[c]	1[c]	Normal	143[c]	336.3	—	—	—	46+[c]	Probable ovulation
	6	200	47[c]	39[c]	Normal	417	200.0	16	12.3	—	63[c]	Luteal data inadequate
E	7	100	32[c]	16[c]	Decreased[c]	240	399.0	15	17.0	125.6	47[c]	Luteal hCG treatment
	8	100	10	7	Normal	350	300.6	13	24.6	164.4	23	
	9	100	16	16[c]	Decreased[c]	200	300.0	11[c]	9.5[c]	41.8[c]	27	Luteal phase deficiency
F	10	300	60[c]	2[c]	—	300	238.0	—	—	—	60[c]	Abnormal LH-follicular synchrony
G	11	200	68[c]	65[c]	—	514	371.4	18[c]	19.0	172.0	86[c]	No apparent reason for prolonged luteal phase
	12	200	55[c]	49[c]	—	155[c]	211.8	8[c]	11.7	91.2	63[c]	Luteal phase deficiency
	13	200	30[c]	20[c]	—	346	300.0	—	29.0	—	—	Pregnancy

[a]In a given cycle a patient may have been treated with increasing doses of GnRH. The dose indicated is the last dose administered.
[b]Normal values (n = 15), mean ± standard deviation (see Table 2).
[c]Connotes a significant difference from normal.

Table 6. *LH Secretory Pattern with Exogenous GnRH*

Patient	Cycle	Dose	LH Pulse frequency	Mean LH amplitude	Mean LH level	Ovulation	Pregnancy
			number/6 hr	*ng/ml*	*ng/ml*		
A	1	100	3	29.9	54.5		
		200	3	39.0	92.6	+	−
B	2	100	3	17.2	49.0	+	−
C	4	50	4	87.6	117.6	+	−
D	5	100	3	40.0	58.0		
		200	3	53.9	185.4	+	−
E	7	50	3	19.7	43.9		
		100	3	31.8	77.1	+	−
F	10	100	1	13.5	9.3		
		300	2	13.6	17.0	−	−
G	11	100	4	25.0	71.0		
		200	3	26.5	76.9	+	−
			2.8–6.8[a]	5.7–14.2[a]	16.2–63.2[a]		

[a]Normal values (n = 5), 95% confidence interval, late follicular phase.[5]

studied at the 100 ng/kg dose, which resulted in a mean LH pulse amplitude of 28.8 ng/ml (range, 17.2 to 40.0 ng/ml); this amplitude was significantly elevated in all five women. Three subjects were studied at the 200 ng/kg dose, which resulted in a mean LH pulse amplitude of 39.8 ng/ml (range, 26.5 to 53.9 ng/ml); all three women had significantly elevated amplitude levels. The mean LH level was in the normal range in four of the ten ovulatory studies. For the 100 ng/kg dose, the mean LH level was 61.9 ng/ml; for the 200 ng/kg dose, it was 118.3 ng/ml. The LH pulse parameters in the woman who failed to ovulate demonstrated an inadequate response to GnRH; not all doses resulted in detectable pulses, and her pulse amplitudes and mean LH levels were lower than corresponding levels found in GnRH-induced ovulatory cycles.

There were no adverse effects with the subcutaneous GnRH therapy during this study. In general, patient acceptance of the treatment was good, except for impatience with the frequently prolonged follicular phases.

DISCUSSION

Since GnRH was identified and synthesized in 1972, it has been administered to women by intramuscular, nasal, subcutaneous and intravenous routes in attempts to induce ovulation. In initial attempts at ovulatory induction with GnRH, the medication was administered in milligram quantities in a continuous fashion, with limited success.[21] The realization that GnRH needed to be administered in an intermittent manner led to its successful use for ovulation induction.[6, 7] Intermittent infusion pumps are now available and have been successfully used to induce ovulation with GnRH using both the subcutaneous and intravenous routes. The most appropriate patients for this therapy have been identified as infertile women with hypothalamic amenorrhea who failed to ovulate on relatively high doses of CC.

The method for the intravenous route of GnRH administration has been sufficiently defined as to lead to a predictable and acceptable rate of ovulation and pregnancy. The GnRH dose for the intravenous route is 2.5 to 5.0 μg/pulse administered every 90 to 120 minutes. Ovulation rates per cycle from 85% to 100% have been reported with intravenous GnRH therapy.[9, 12, 14, 17] The pregnancy rates per patient have varied from 33% to 80% with intravenous GnRH therapy administered over one to four cycles.[9, 12, 14, 17] Inadequacy of the luteal phase despite support has been reported to occur in 0% to 33% of luteal phases in intravenous GnRH-induced ovulatory cycles.[9, 11, 12] Therefore, intravenous pulsatile GnRH therapy appears to be a reasonable alternative to exogenous gonadotropins for ovulation induction. The incidence of reported adverse effects with intravenous therapy has been acceptable, consisting primarily of an occasional superficial phlebitis.[16, 17]

However, there is considerable disagreement and controversy regarding the intermittent administration of GnRH via the subcutaneous route. In 1981, Reid and colleagues[8] reported an attenuated LH pulse pattern in two patients associated with a poor ovarian response with 5 μg of GnRH administered subcutaneously. Likewise,

Leyendecker and Wildt,[14] in 1983, noted an ovulatory rate of 52% in 21 cycles treated with subcutaneous GnRH (dose, 5 to 20 μg/pulse). In a latter report, (1984) Reid and Sauerbrei[12] found a 20% ovulation rate and no pregnancies in six women treated with 5 μg GnRH subcutaneously. Similar findings (0% ovulation rate) were reported by Loucopoulos et al.[11] in 12 women treated with subcutaneous GnRH (5 to 20 μg). Molloy et al.[16] noted only a 33% ovulation rate per patient with subcutaneous GnRH (dose, 3 to 20 μg). In three of these five studies, the investigators achieved a 100% ovulatory rate and pregnancy rates from 33% to 100% when the same subjects were treated subsequently with intravenous GnRH at the same or lower dose.[8, 12, 14] There is a physiologic explanation for the apparent decreased efficacy of the subcutaneous route: the pharmacokinetics of intravenous therapy has been demonstrated to lead to sharper and more discrete LH pulses.[22]

However, authors of other studies[10, 13, 15] on subcutaneous GnRH therapy report success comparable to that for the intravenous route. Skarin et al.[10] reported an 85% ovulation rate per patient and a 57% conception rate per patient (n = 14) with subcutaneous GnRH (dose, 5 to 20 μg). Hurley and colleagues[13] likewise reported a 100% and 78% ovulation and pregnancy rate per patient respectively (n = 14) with subcutaneous therapy (dose, 5 to 15 μg). Seibel et al.[15] achieved ovulation in all four patients treated with subcutaneous GnRH (dose, 20 μg). Insufficiency of the luteal phase, as determined by varying criteria, has been reported to range from 20% to 50% per cycle with subcutaneous therapy, despite routine support of the corpus luteum with either the pump or hCG.[10, 12, 13]

This study was done to examine the apparent discrepancy in results with subcutaneous GnRH treatment. As evidenced by the baseline gonadotropins and LH secretory profile (Tables 1 and 3), the seven patients in this study had hypothalamic amenorrhea and therefore were appropriate subjects for comparing the results of their GnRH treatment with previous experience. The ovulation rate per treatment cycle (94%) and the conception rates (43% of patients; 19% of cycles) achieved compare favorably with the more successful and optimistic reports on subcutaneous GnRH therapy.[10, 13, 15] However, on closer inspection, beyond the ovulation and pregnancy rates, our subcutaneous GnRH-induced cycles were not often normal. The follicular phase was commonly prolonged, often to as many as 40 to 50 days, and often associated with a borderline or low peak E_2 level. Only one of 13 cycles had a normal follicular phase. Nevertheless, 12 of these cycles proceeded to ovulation. Luteal phase deficiency was present in 40% of the luteal phases studied. Altogether, only 1 of 13 subcutaneous GnRH-induced cycles was entirely normal in length and hormone parameters. A reasonable LH pulse pattern in terms of induced discrete pulses was present in six of the seven women so studied. The more effective GnRH doses for inducing ovulation (100 and 200 ng/kg) generally resulted in an increased LH pulse amplitude over normal late follicular levels. The induced mean LH levels were generally normal for the 100 ng/kg dose and modestly elevated for the 200 ng/kg dose. There was a moderate amount of variability in induced LH secretory parameters between individuals at a given dose. In summary, it seems that the ovary responds with a delayed and/or weak hormone response to what appears to be an adequate to increased gonadotropin pulse pattern induced with the subcutaneous administration of GnRH. It is inferred that the less discrete gonadotropin pulses induced with subcutaneous GnRH therapy, which less closely approximate endogenous gonadotropin pulses than intravenous-induced pulses, are the cause of this variable ovarian response.[22]

The reports[8-17] on intravenous and subcutaneous GnRH therapy are not all presented in sufficient detail to compare adequately the efficiency of induced ovulation by each route of administration. From our data and the overall high degree of success achieved with intravenous GnRH therapy, it appears that the subcutaneous route of GnRH administration is less predictable and efficient than the intravenous route. The subcutaneous route is efficacious for many women, but the duration of therapy is generally more prolonged and requires higher GnRH doses, which entails more expense. While the reported adverse effects with intravenous therapy are low, this route does carry more potential risk. The greater inconvenience with the intravenous route tends to be offset by the longer cycle duration with the subcutaneous route. Dependent upon patient and physician preference, it would be reasonable to initiate ovulation induction with GnRH by either the intravenous or subcutaneous route. If the subcutaneous route is selected and fails, then it

would be prudent to switch to intravenous GnRH therapy.

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