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LHRH THERAPY IN TEN MALE AND TEN FEMALE PATIENTS

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ABSTRACT

We treated ten men and ten women suffering from hypogonadotropic hypogonadism with LHRH. Our method of treatment differed from others in that a minipump was not available at the onset of the study. Nine women were given injections via a heparinized indwelling catheter every 120 minutes for 14 days, i.e. the proliferative phase. After ovulation, 3000 IU human chorionic gonadotropin (HCG) was administered every two days. A minipump was used for only one patient. From among these nine female patients, three pregnancies occurred. In male subjects, 50-100 micrograms LHRH was subcutaneously self-administered twice daily, and 5000 IU HCG was given intramuscularly twice weekly. With this treatment, secondary sexual characteristics appeared after a few months, including nocturnal ejaculation, growth of testes, and elevation of serum testosterone levels.

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INTRODUCTION

LHRH therapy is widely used in endocrinology.[10-13] Many patients who had remained childless have been treated successfully and the treatment is safe for both male and female patients. In this report, the patients had been previously treated for many years with high doses of human chorionic gonadotropins without results, and were subsequently referred to our clinic, where they were successfully treated with LHRH.

MATERIALS AND METHODS

From early 1984 to mid-1987, ten male and ten female patients with hypogonadotropic hypogonadism

Table 1. Clinical characteristics of ten women with hypogonadotropic hypogonadism.

PATIENT	AGE	COMPLAINT	SECOND. SEX CHARAC.	GRADE OF HYPOTHAL. INSUFF.	HYPOSMIA	CHROMOSOMAL PATTERN
1	37	PA, INF	+ (EH)	III	–	XX
2	25	PA, INF	+ (EH)	III	–	XX
3	26	PA, INF	+ (EH)	III	–	XX
4	25	PA, INF	+ (EH)	II	–	XX
5	27	PA, INF	+ (EH)	III	*	XX
6	24	PA, INF	+ (EH)	II	–	XX
7	30	PA, INF	+ (EH)	III	–	XX
8	23	INF	PCO	–	–	XX
9	24	PA, INF	+ (EH)	III	–	XX
10	37	PA, INF	+ (EH)	III	–	XX

PA = Primary amenorrhea
INF = infertility
EH = exogenous hormone
* = positive in patient's sister

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Table II. Clinical characteristics of ten hypogonadotropic males.

PATIENT	AGE	HEIGHT	SIZE OF TESTIS	SEXUAL CHARAC.	COMPLAINT	HYPOSMIA	CHROMOSMAL PATTERN	SELLA TURCICA
1	24	tall	rudimen	–	IMP + INF	–	XY	N
2	32	tall	rudimen	–	IMP + INF	–	XY	N
3	27	tall	rudimen	–	IMP + INF	+	XY	N
4	27	tall	rudimen	–	IMP + INF	–	XY	N
5	37	short	rudimen	–	IMP + INF	–	XY	Sm
6	30	med	2 cm	+	IMP + INF	–	XY	N
7	29	med	rudimen	–	IMP + INF	+	XY	N
8	34	med	rudimen	–	IMP + INF	–	XY	N
9	16	tall	rudimen	–	IMP + INF	–	XY	N
10	27	tall	rudimen	+	IMP + INF	*	XY	N

rudimen = rudimentary
IMP = impotency
INF = infertility
* = positive in patient's mother

Table III. Hormonal status in ten female patients.

PATIENT	FSH ImU/ml	LH ImU/ml	ESTRADIOL pg/ml	PROGESTERONE ng/ml	PROLACTIN ng/ml	TESTOSTERONE ng/ml
1	3.8	5.0	–	0.4	30	–
2	0.6	1.4	20	–	280	6
3	1.0	0.9	20	–	198	–
4	1.8	0.9	–	–	8.9	–
5	4.8	1.6	10	–	8.9	–
6	0.5	0.5	–	–	37	30
7	2.2	1.1	20	–	150	–
8	8.0	20.0	–	–	–	–
9	2.1	3.0	–	1	11	0.2
10	1.8	2.0	20	3	10	–

Normal prolactin: 100-750 microunits/ml, up to 23 ng/ml

Table IV. Hormonal status in ten male patients.

PATIENT	FSH	LH	TESTOSTERONE	PROLACTIN
1	0.8	3.2	0.3	85
2	2.7	1.8	0.3	350
3	2.1	3.0	0.4	100
4	2.3	3.0	400 mi	–
5	9.6	2.0	0.3	125
6	1.2	1.2	0.2	–
7	3.0	3.9	0.3	–
8	3.0	2.4	0.4	–
9	5.0	4.7	0.6	–
10	UD	UD	0.4	–

UD = undetectable
Normal testosterone: 300 – 1000 ng/ml
Normal prolactin: 70 – 300 microunits/ml

were chosen from infertile patients who had been referred for infertility to the Rahnamun Hospital, and for the first time in Iran, were treated with LHRH. Most of the male patients were referred by endocrinologists, and the females by gynecologists. The patients received complete clinical and paraclinical workups (Tables I and II). Male patients ranged in age from 16 to 44 years, and female patients from 20 to 37 years. All patients had rudimentary testes and had been injected with 100 mg testosterone bi-weekly or monthly for maintenance of potency. Because of this affliction two of the patients had separated from their spouses. A spectrum of adolescent characteristics was seen due to previously incomplete treatment (Fig. 1). In women hypothalamic insufficiency (Table I) varied from grade II to grade III with the majority falling in grade II.[6] All female patients were of normal height, but body height was tall in all but one male. In three males, there was hyposmia and this defect was also present in the mother

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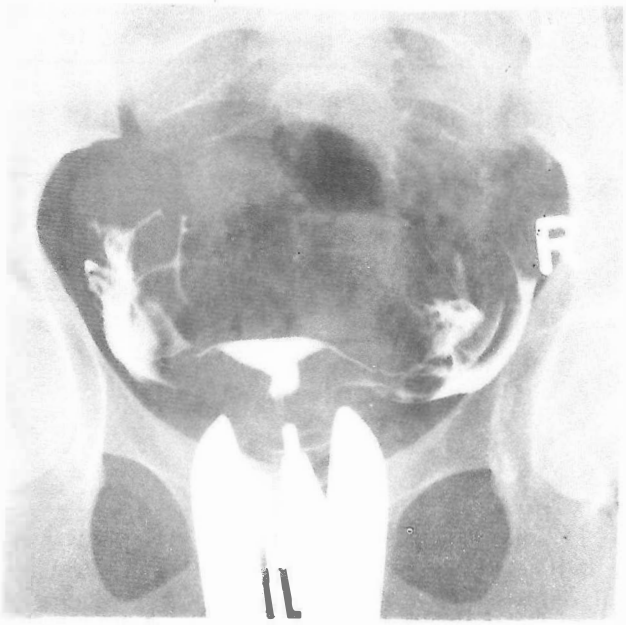

Fig 1: Hysterosalpingogram of an infertile woman, demonstrating infantile type uterus with patent ducts.

of a male patient and the sister of a female patient, without reproductive disturbance. Paraclinical investigations were performed in this order: hormonal assays including FSH, LH, proiactin, estradiol, progesterone, testosterone, and in some patients, LHRH (Tables III and IV), sella turcica radiography, karyotyping, etc. FSH, LH, estradiol (women) and testosterone (men) assays were all below normal and even near zero except in one male patient with small body features whose levels were relatively normal (Table IV).

All patients had low-normal prolactin levels. None of the female patients displayed hyperandrogenemia. All sella turcicas were normal radiographically, except in one patient, in whom it was slightly smaller than normal. The chromosomal pattern was normal in all patients (Tables I and II). Hysterosalpingogram demonstrated the shape of the uterus to be infantile with patent ducts (Fig. 1).

After all other possibilities were ruled out, hypogonadotropic hypogonadism was diagnosed and the following treatment initiated (Tables V and VI).

Firstly it was necessary to modify the standard method of treatment because of the difficult economic situation induced by the imposed war and the unavailability of a minipump. The modified method of treatment was as follows.

Female patients were hospitalized and 20 micrograms LHRH was injected via an indwelling catheter by nurses for 14 days. From the 10th day of treatment patients were examined clinically and sonographically for cervical score and follicle diameter (Table V). When cervical score was greater than eight and two follicles with diameters greater than 20 mm were observed (Figs. 2 and 3), the LHRH injections were discontinued and 3000 to 5000 IU hCG was administered every two days.[1] If pregnancy occurred, treatment was continued until the fourth month, otherwise the treatment was discontinued and another cycle started. This time after setting up a heparinized catheter, the patients were sent home and the drug was self-injected in the above manner. From the tenth day, patients returned to the clinic for cervical score determination and sonography. There was no change in the remainder of treatment. In some patients estradiol was measured from the 10th day.

In male patients, firstly testosterone injections were discontinued and 50-100 micrograms LHRH was self-administered twice daily subcutaneously, and because of complaints of relative impotence, 5000 IU hCG was added to the treatment. This new regimen was continued for a minimum of one year, after which a minipump was used (Table VI).

Table V. Management and results of LHRH therapy in 10 females with hypogonadotropic hypogonadism after six months.

PATIENT	DOSE (mcg)	LHRH FREQ	ROUTE	NO. OF FOLLICLES	LARGEST FOLLICLE (mm)	LUTEAL SUBSTITUTE	NO. OF CYCLES TREATED	OVULATION	PREGNANCY	RESULT
1	20	120	IV	3	17-19	HCG	1	+	TWIN	PREMATURE LABOR
2	20	120	IV	3	17-20	HCG	2	+	+	NORMAL DELIVERY
3	20	120	IV	3	15-17	HCG	5	+	−	−
4	20	120	IV	3	17-25	HCG	1	+	+	NORMAL DELIVERY
5	20	120	IV	2	15-20	HCG	4	+	−	−
6	20	120	IV	3	19-20	HCG	5	+	−	−
7	20	120	IV	3	20-24	HCG	1	+	−	−
8	minipump			2	21-24	HCG+LHRH	3	+	−	
9	20	120	IV	3	19-23	HCG	3	+	−	−
10	minipump			3	17-26	HCG	2	+	+	NORMAL DELIVERY

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Table VI. Management and results of LHRH therapy in 10 males with hypogonadotropic hypogonadism after six months.

PATIENT	ROUTE	LHRH DOSE (mcg)	HCG DOSE (IV)	APPEARANCE OF SEXUAL CHARACTERISTICS	LARGEST DIAM. OF TESTIS (cm)	TESTOSTERONE (ng/ml)	NOCTURNAL EJACULATION	SPERM
1	SC	50 bid	5000 tw	+	3.0	2.0	+	–
2	SC	100 bid	5000 tw	+	3.5	3.0	+	–
3	SC	50 bid	5000 tw	+	3.2	3.0	+	–
4	SC	50 bid	5000 tw	+	3.5	–	+	–
5	–	–	5000 tw	+	2.0	–	+	–
6	–	–	75 HMG daily	+	3.0	3.5	+	*
7	–	50 bid	5000 tw	+	3.0	2.2	+	–
8	–	50 bid	5000 tw	+	–	–	–	
9	–	minipump						
10	–	50 bid	5000 tw	+	3.8	3.1	+	

* 2 million/cc. 55% motile
tw= twice weekly

RESULTS

In three of the female patients, pregnancy occurred. The oldest female patient (37 yrs) became pregnant during the second cycle of treatment, with a twin pregnancy terminating in premature labor at 28 weeks of gestation.

The second patient became pregnant in the third cycle with a normal labor and delivery of a healthy baby girl.

The third patient conceived during the first cycle with the normal delivery of a healthy baby girl.

In male patients, after beginning treatment, the need for testosterone ceased. After a few months, secondary sexual characteristics appeared, as did nocturnal ejaculation. The largest testicular diameter increased from a rudimentary state to 3 cm, and serum testosterone levels reached 3-4 ng/ml.

In one patient, the sperm count was 20 million/cc with 50% motility without conception.* Because of failure of appearance of sperm in most patients, it was necessary to change the treatment to a minipump.

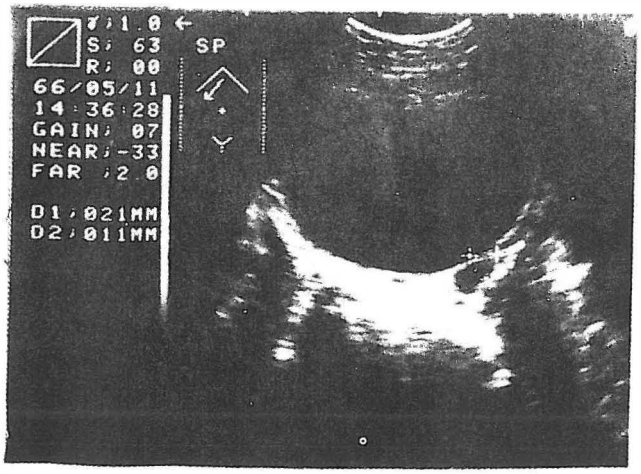
DISCUSSION

Female patients with hypogonadotropic hypogonadism, especially those with severe hypothalamic insufficiency, can be treated with intravenous self-administered LHRH. However, because of longevity and relative ineffectiveness of treatment in male patients, it must be completed by use of a minipump.

In all previously reported studies,[1-6] 5-20 micrograms LHRH has been used every 90 to 120 minutes subcutaneously or intravenously with a minipump.

In two reports,[9,10] high doses of LHRH (500-1000 micrograms) was used in ovulation and pregnancy, but this high dose produced unsatisfactory results.

* The patient's wife was four months pregnant at date of publication of this report.



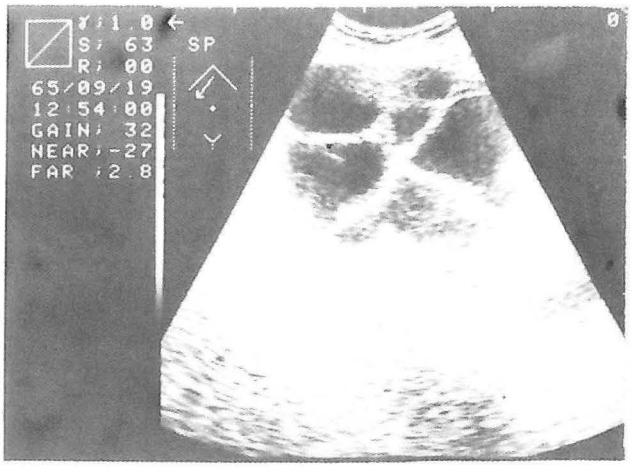


Fig 2, 3: Sonography of the ovaries for evaluation of the diameter of the follicles.

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Our results, using 20 micrograms LHRH every 2 hours, demonstrate that without the use of a mini-pump, female patients can be treated adequately. However, treatment of male patients proved to be satisfactory but incomplete.

We believe that the dosage of LHRH was insufficient in the male patients and perhaps if a higher dose or more frequent doses (three times a day) are used in future studies, the results could be improved.

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