THERAPEUTIC VALUE OF A SINGLE DOSE OF SYNTHETIC LH-RH IN ANOVULATORY INFERTILITY

by

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Introduction

It is now well established that synthetic Luteinising Hormone-Releasing Hormone (LH-RH) not only increase the output of Follicle Stimulating Hormone (FSH) and Luteinising Hormone (LH) but it also induces ovulation. It has been used as a therapeutic agent for the induction of ovulation. The plasma oestradiol and pregnandiol are also increased by the release of endogenous gonadotrophins in response to LH-RH.

The aim of the present study was to induce ovulation with a single intravenous 100 μg dose of LH-RH in the middle of the menstrual cycle.

Material and Methods

Each ampoule contained 100 μg LH-RH in 1 ml. water. A policy was adopted to administer 100 μg LH-RH intravenously around the middle (day 12-14) of the menstrual cycle. 10 mls of blood was drawn before and 20 minutes after the injection of the drug for estimation of serum FSH and LH. A twenty-four hour sample of urine was collected 48 hours later for estimation of total oestrogens and pregnandiol. Presumptive ovulation was assumed by the rise of basal body temperature and urinary pregnandiol level at or above 2.5 mg in twenty-four hours.

Ten patients of different ages (27-42 years) with varying duration of infertility (6-20 years) were chosen. The tubal patency was confirmed both by insufflation test and hysterosalpingogram. The husband's sperm counts were analysed and postcoital tests were performed before embarking on treatment. The endocrine status of the patients were assessed by the following parameters: serum gonadotrophins (FSH and LH), total urinary oestrogens and pregnandiol, thyroid function and adrenocortical function test. Thyroid function tests (T3, T4 and free thyroxin index) and adrenocortical functions (17-oxo and oxogenic steroid) were normal in all cases.

The policy of the Unit was to commence treatment with Clomiphene, 50 mg daily for 5 days, and gradually increasing the daily dose upto 200 mg with a blank month in between the increasing doses. If Clomiphene failed to induce ovulation and conception Clomiphene and Pregnyl were tried. Pergonal and Pregyl were used as a final mode of treatment.

All but 1 case of the present series, were of primary infertility. In 10 cases, ovulation followed by conception occurred with Clomiphene and Pregnyl on two occasions but the patient aborted at 8 weeks gestation. This patient did not ovulate with Clomiphene only. The case is included in this study to determine the therapeutic value of LH-RH instead of using combined treatment of Clomiphene and Pregnyl.

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Accepted for publication on 17-7-81.

Results

Patients age, duration and degree of infertility attendance at the infertility clinic, endometrial biopsy and 24 hours urinary oestrogens and pregnendiol readings are summarised in Table I.

All patients had anovulatory cycles as evidenced by endometrial biopsy and 24 hour total urinary oestrogens and pregnandiol (and basal boy temperature charts). The serum FSH and LH level and their response to LH-RH are summarised in Table II.

Serum FSH was less than normal in 2 cases but reached a normal range in 1 (Case 3) in response to LH-RH whereas in the other (Case 8) it remained unchanged. The LH level was also less than normal in Case 8 but attained a normal range following the injection of the drug.

A high urinary oestrogen (263 μg) in 1 (Case 1) and a low oestrogen reading was observed in 2 patients (Cases 7 and 8) in response to LH-RH. Despite a high urinary oestrogen, the pregnandiol reading was 1.4 mg%/24 hours in Case 1. Urinary pregnandiol was not detected in Cases 7 and 8 respectively. Six patients ovulated and 2 of them conceived (Case 9 and Case 10) in the same cycle.

Discussion

Reviewing the literature and from the present study, it is now obvious that the Synthetic LH-RH is a potential therapeutic agent for the induction of ovulation. Serum FSH and LH were increased in all the cases except in 1 (Case 8) where serum FSH level remained less than 1 unit 1. Yen *et al* (1972) promulgated that despite a satisfactory rise in serum LH level the FSH response was comparatively less marked following the administration of LH-RH.

Of the 6 ovulated, 2 conceived in the same treatment cycle following a single intravenous 100 μg dose of LH-RH in the middle of the menstrual cycle. This indicates that the synthetic LH-RS has a definite role in the treatment of anovulatory infertility and we believe that LH-RH is worth trying, particularly to those patients where other conventional treatment failed to achieve conception. One of our illustrated patients (Case 9), the duration of infertility was 20 years and was attending the Clinic for 10 years. Clomiphene, Pregnyl and Pergonal were tried and although ovulation was induced on few occasions but required larger doses of Pergonal and Pregnyl. There is always a risk of multiple pregnancy due to hyperstimulation of the overy. Amniocentesis was carried out in this patient at 14 weeks gestation in order to exclude Down's Syndrome. The report of the amniocentesis was of a normal foetus. Alphafeto protein level was also normal. Elective caesarean section was performed on this patient at 38 weeks gestation and a healthy normal female baby was delivered. The other patient also delivered a normal baby at term.

Zarate *et al* (1972) reported 2 pregnancies out of 10 by daily intramuscular injections of 50 μg LH-RH for 10 days, whereas Kastin *et al* (1971) were able to induce one patient by injecting 600 μg of Porcine LH-RH by intravenous infusion for 24 hours supplemented with two rapid intravenous injections of 300 μg LH-RH at 8 hours and 24 hours respectively. Keller (1972) reported 2 pregnancies out of 12 with combined treatment of Clomiphene and LH-RH.

From the foregoing discussion it appears that our result is better in comparison to the others so far as the incidence of pregnancy is concerned with a single dose of LH-RH and no untoward effect

was observed in any patient in the present series. It remains to be seen whether larger doses or multiple smaller injections of LH-RH over a long period will correct serum FSH and LH in Case 8.

Summary and Conclusion

The discovery of Synthetic LH-RH brings a new era in the field of infertility treatment. Not only does it provide a valuable test for pituitary function in the study of diseases of pituitary-gonadal axis but it also helps to induce ovulation. The availability of the drug should also provide a potential therapeutic agent for the treatment of anovulatory infertility. A total of ten patients were studied. All but one were of primary infertility and all had anovulatory cycle. Six patients ovulated following a single intravenous injection of 100 μg LH-RH around the middle of the menstrual cycle and two patients conceived in the same cycle.

The level of serum FSH and LH were increased in all cases in response to LH-RH injection except one where there was no alteration of serum FSH level. A high urinary oestrogen (263 μg) in one patient and a low urinary oestrogen was noted in two patients following the intravenous injection of LH-RH.

TABLE I

Case	Regd. No.	Age	Duration on infertility in years	Degree	Attendance in clinic	Endometrium	Total 24 hours oestrogen in μg	Urine Pregnandiol in mg (24 Hrs.)
1. M.B.	U36373	33 years	10	Primary	1970	Proliferative	29	2.1
2. S.C.	U67567	33 ,,	9	,,	1972	,,	6	1.8
3. M.A.B.	U66851	30 ,,	8	,,	1972	,,	2	2.1
4. G.S.	U23073	27 ,,	18	,,	1969	,,	8	0.23
5. J.D.	U510074	29 ,,	8	,,	1969	,,	29	2.4
6. J.P.	U68932	32 ,,	8	,,	1972	,,	10	1.6
7. C.R.	U36093	27 ,,	6	,,	1972	,,	10	0.5
8. B.T.	U70627	28 ,,	6	,,	1972	,,	10	0.4
9. J.E.F.	U510656	42 ,,	20	,,	1964	,,	21	1.4
10. S.C.	U33493	32 ,,	8	Secondary	1970	,,	51	1

Acknowledgement

The author thanks Mr. K. M. Mackenzie, F.R.C.S., F.R.C.O.G., Consultant Obstetrician and Gynaecologist, Essex County Hospital, Colchester, Essex, for his encouragement and help during this investigation and would also like to express his thanks to Mrs. Imray and the Department of Biochemistry and Pathology, Essex County Hospital, Colchester, Essex.

TABLE II

Response with LH-RH VJJ mg intravenously in the middle of menstrual cycle

Case	Serum FSH in unit/1 (normal unit/1)		Serum LH in unit/1 (Normal 10 units/1)		Urinary oestrogen in μg/24 hours	Urinary pregnandiol in mg/24 hours	Results
	Control	After LH-RH	Control	After LH-RH			
1.	6.7	9.3	38.5	140	263	1.4	—
2.	2.1	6.8	17.4	100	24	4.4	Ovulation
3.	1.7	3	26.8	100	37	1.3	—
4.	3.1	5.8	8.7	53.6	10	2.5	Ovulation
5.	3	7.6	16.8	75	19	2.7	Ovulation
6.	6.3	15	49.6	100	54	2.7	Ovulation
7.	7.6	16.7	45.6	67	4	Not detected	—
8.	1	1	4	10	9	,,	—
9.	2.3	2.5	13.9	90	24.4	4.4	Conceived with LH-RH in the same cycle. Amniocentesis carried out at 14/52. Normal female foetus 46XX without evidence of Down's Syndrome. Delivered a normal female by Caesarean Section.
10.	3.4	4.6	28.1	50.9	14	3	Conceived with LH-RH in the same cycle. Delivered a normal healthy baby.

References

1. Kastin, A. J., Schally, A. V., Gual, C., Midgley, A. R., Miller, M. C. and Cabeza, A.: J. Clin. Invest. **50**: 1551, 1971.
2. Keller, J. P.: Lancet. **I**: 570, 1972.
3. Yen, S. S. C., Rebar, R., Vendenberg, G., Naftolin, F., Ehara, Y. and Englon, S.: J. Clin. Endocrinol and Metab. **34**: 1108, 1972.
4. Zarate, A., Canales, E. S., Schally, A. V., Ayala-Valdes, and Kastin, A. J.: Fertil. Steril. **23**: 672, 1972.