Upsala J Med Sci 89: 99–106, 1984

Peptide Contraception in Women

Inhibition of ovulation by chronic intranasal LRH agonist therapy

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ABSTRACT

Seventy-one healthy female volunteers used the LRH superagonist D-Ser(TBU)^{6}-EA^{10}-LRH (buserelin) for contraception during 3-26 months. One daily dose of 200-600 μg was administered by the nasal route. No pregnancy occurred during the 628 treatment months. The bleeding pattern varied from fairly regular menstrual bleedings (n=26) to oligomenorrhoea (n=27) and amenorrhoea (n=18). No severe or dysfunctional bleeding disturbances were observed. No signs of hyperplastic changes of the endometrium were found in 57 endometrial biopsies. After cessation of the long-term treatment normal ovulation and menstruation returned after 41.3 days, on average. Thus, intranasal administration of an LRH agonist for inhibition of ovulation is a promising new contraceptive method for women.

INTRODUCTION

Peptide contraception is based on analogues of the hypothalamic gonadotrophin-releasing hormone LRH (8, 11-13, 17). Inhibition of ovulation can paradoxically be obtained by daily administration of a stimulatory analogue to LRH a new lead contraception (10). The first reports of this peptide method of fertility control have been very encouraging (1-7, 14, 15). No pregnancies and no serious side effects have occurred. Here we summarize our experience with a superagonist of LRH, buserelin, as a contraceptive agent in 71 women.

SUBJECTS AND METHODS

Seventy-one healthy women, aged 18-41 years (mean 29) volunteered for the study. All the women had normal ovulatory pretreatment menstrual cycles, as judged by basal body temperature (BBT) curves and progesterone determinations in serum.

Treatment

The superactive LRH agonist D-Ser(TBU)^{6}-EA^{10}-LRH (buserelin, Hoechst AG, Frankfurt/Main, FRG) was administered once daily by a nasal spray. The spray applicator delivered 100 µl solution containing 100 µg of the LRH agonist at each application. Fifty-one volunteers were treated with 400 µg (n=27) and 600 µg (n=24) daily. Twenty women were treated with an improved spray applicator, which delivered smaller droplets. The dose could then be reduced to 2-400 µg daily. Ten of these women received 200 µg and the remaining 10 women 400 µg daily. The therapy was instituted within the first three days of the menstrual bleeding and continued for 3-26 months. The treatment was monitored by regular clinical examinations, BBT recordings, bleeding schedules and frequent venous blood samples for determination of oestradiol and progesterone. Repeated endometrial biopsies were obtained during the prolonged study periods.

Hormone assay methods

Immunoreactive oestradiol in serum was measured by a radioimmunological technique, using an antiserum to an oestradiol-6-oxime-BSA conjugate. With this antiserum the oestradiol levels during the early follicular phase of the menstrual cycle varied between 60 and 200 pmol/l and the pre-ovulatory oestradiol range was 500-1 300 pmol/l. Progesterone was determined by a similar radioimmunological technique. The normal mid-luteal phase progesterone levels for our laboratory are more than 30 nmol/l.

RESULTS

A total of 628 treatment months were completed by the 71 women (Table 1). Twenty-two of the women used the nasal spray as their only contraceptive for 12 months and nine of them for two years. Only three presumptively ovulatory cycles were recorded. They occurred during the first treatment month and were probably caused by initial technical problems with the spray applicator. No pregnancies have occurred.

Table 1. Summary of results

Intranasal dose (μg)	Subjects (n)	Treatment months (n)	Ovulatory treatment months (n)
200	10	174	0
400	37	329	2
600	24	125	1
Total (n)	71	628	3

A summary of the bleeding pattern during treatment is shown in Table 2. Twenty-six women (37%) had fairly regular uterine bleedings, 27 (38%) had oligomenorrhoea and 18 (25%) amenorrhoea. There was a tendency towards a prolongation of menstrual bleeding intervals during the course of the long-term treatment. The first menstrual bleeding during treatment was somewhat heavier than a normal menstrual bleeding in about 15 per cent of the women. No dysfunctional bleedings occurred. Five women experienced spottings of short duration.

The only untoward side effects reported by some women were slight nasal irritation and headache at initiation of treatment. The acceptability of this contraceptive method was very high. Five women discontinued therapy after 3-8 months because of desire of pregnancy (n=3), lack of spray (n=1) and mild psychosomatic symptoms unrelated to the treatment (n=1).

Table 2. Bleeding patterns during treatment

	Subjects	LRH agonist dose (μg)		
		200	400	600
	(n)	(n)	(n)	(n)
Regular uterine bleedings	26	4	14	8
Oligomenorrhoea	27	3	11	13
Amenorrhoea	18	3	12	3
Total (n)	71	10	37	24

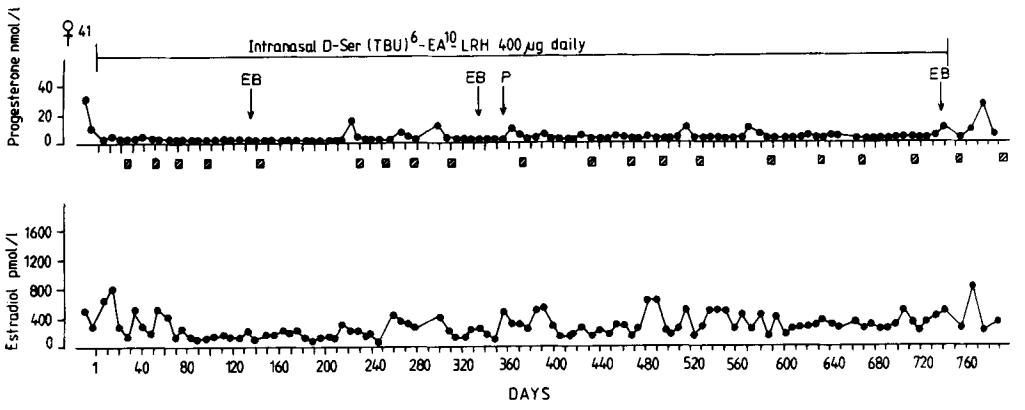

Fig. 1 Serum progesterone and oestradiol levels during 2 years of buserelin treatment of a healthy female volunteer. □ Uterine bleedings. EB = Endometrial biopsies. P = Progesterone challenge test (50 mg intramuscularly).

Hormone and bleeding patterns from a healthy woman during two years of intranasal LRH agonist therapy are shown in Fig. 1. The menstrual bleedings were fairly regular during the prolonged treatment. Repeated endometrial biopsies showed weak proliferative changes of the epithelium. A progesterone challenge test was positive. Slightly raised progesterone levels in serum were recorded on some occasions during treatment. Oestradiol and progesterone levels in a healthy woman with amenorrhoea throughout a 761-day treatment course with the LRH agonist are shown in Fig. 2. No signs of follicular maturation were noticed. After cessation of treatment, normal ovulatory menstrual cycles rapidly returned.

The serum oestradiol levels decreased during the course of the treatment, being highest during the first month. The mean oestradiol level during buserelin therapy was in the range of the early to mid-follicular phase of the normal menstrual cycle. The progesterone levels were slightly raised (range 5.0-20 nmol/l; mean 8.6 nmol/l) during 53 treatment months, indicating luteinization of follicles or a defect luteal function.

A total of 57 endometrial biopsies were taken during the long-term treatments. The predominant histological picture of the endometrium was inactive or weak proliferative gland with slightly atrophic stroma (n=46). No signs of hyperplastic changes were found.

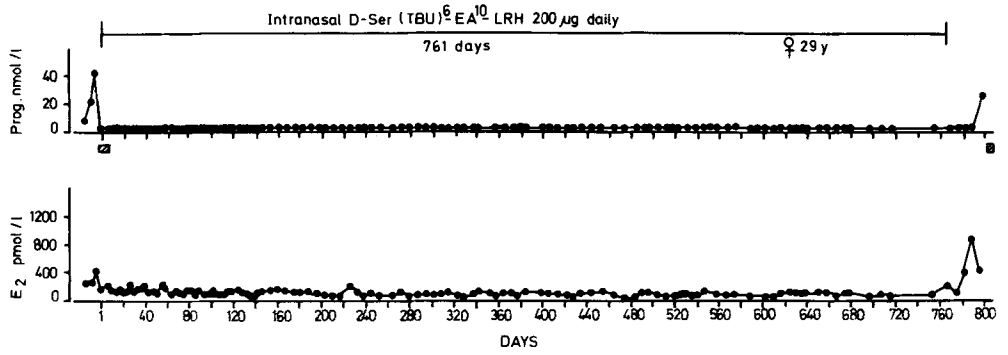

Fig. 2 Serum progesterone and oestradiol levels during more than 2 years of buserelin treatment of a healthy female volunteer. □ Menstrual bleedings.

After discontinuation of treatment, all the 71 women regained normal ovulatory cycles. The first menstrual bleeding occurred after 41.3 days, on average. The 18 women with amenorrhoea during treatment experienced their first menstrual bleeding somewhat later than the 26 women with regulary menstrual bleedings (55.7 and 36.9 days, on average, $p < 0.01$).

DISCUSSION

This contraceptive study with buserelin, a potent LRH agonist, confirms that inhibition of ovulation by continous intranasal superagonist treatment is an effective and most interesting new approach to fertility control in women. No pregnancy occurred during the 628 treatment months. After discontinuation of prolonged treatment, even for 1-2 years, ovulation and fertility promptly returned.

A major advantage of using prolonged LRH agonist therapy instead of steroid treatment for inhibition of ovulation is the fact that the LRH analogues have specific actions on the hypothalamic-pituitary-gonadal system and lack systemic effects. They are therefore less likely to cause metabolic derangements and other generalized side effects.

No adverse effects except bleeding disturbances caused by the induced anovulation were observed. None of the women discontinued the therapy because of bleeding problems. Dysfunctional bleeding did not occur and no hyperplastic changes were found in endometrial biopsies.

Chronic LRH agonist therapy leads to desensitization of the pituitary processes responsible for gonadotrophin release. It has therefore been suggested that they may be useful for induction of inadequate luteal function, luteolysis and early abortion in women. However, the contraceptive effectiveness of such approaches remains to be demonstrated. The luteolytic effects of present superagonists of LRH are prevented by exogenous and endogenous human chorionic gonadotrophin. Human ovulation can, however, be effectively and reversibly inhibited for prolonged periods of time by chronic intranasal LRH agonist therapy. This new method of birth control has been shown to provide acceptable, effective and safe contraception in women.

ACKNOWLEDGEMENTS

We thank Farbwerke Hoechst, Frankfurt (Main), FRG for supply of buserelin, Ass. Professor Anders Lindgren at the Department of Pathology for professional evaluation of the endometrial biopsies, and Mrs Birgitta Bohman and Karin Mattsson for expert secretarial assistance.

The studies were supported by the International Committee for Conraception Research of the Population Council and the Swedish Medical Research Council. The financial support provided to the Population Council by the International Development Research Centre of Canada, The Ford Foundation, The Rockefeller Foundation and the Geo. J. Hecht Fund is gratefully acknowledged.

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