We should like to thank Miss P. Townshend, the sisters and nursing staff of the S.C.B.U. at the John Radcliffe Hospital, and the many excellent registrars and residents on the unit without whose scrupulous care these results would not have been possible. The infants in this study were under the care of J.P.M.T. and Drs. H. L. Ellis, B. D. Bower, and D. Pickering.

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An Abnormality of Oestrogen Feedback in Amenorrhoea-Galactorrhoea

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British Medical Journal, 1975, 3, 274-275

Summary

Fourteen patients with amenorrhoea and hyperprolactinaemia but no evidence of pituitary tumours were each given an intramuscular injection of 1 mg oestradiol benzoate. Thirteen patients failed to release luteinizing hormone in response to the oestrogen. This hypothalamic abnormality may help to explain the menstrual disturbances in subjects with hyperprolactinaemia.

Introduction

The many physiological and pathological conditions in which serum prolactin levels are consistently raised are usually associated in women with amenorrhoea. Prolactin is increased when hypothalamic control of the pituitary is lost, presumably because of a lowered secretion of prolactin-inhibiting factor.¹ Recently it has been shown in vitro that raised prolactin levels may inhibit ovarian steroid biosynthesis.² It has therefore been suggested that in-vivo steroid feedback to the hypothalamic-pituitary unit is reduced, with subsequent amenorrhoea.³ Prolactin could also conceivably inhibit directly pituitary release of gonadotrophins, though there is no evidence to substantiate this.

Much evidence indicates that exogenously administered oestrogens can produce both negative and positive feedback effects on gonadotrophin release in regularly menstruating women.⁴⁻⁷ If reduced steroid feedback is the correct explanation for the anovulation in hyperprolactinaemia the administration of exogenous oestrogens should produce a normal release of gonadotrophins. We tested this by giving oestradiol benzoate to women with amenorrhoea and galactorrhoea associated with hyperprolactinaemia and measuring the changes produced in serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Methods

Patients.—Fourteen patients with consistently raised serum prolactin levels and amenorrhoea of more than 12 months' duration were investigated. Five presented with accompanying galactorrhoea, galactorrhoea was first noted on examination of the breasts in eight, and in the remaining patient only clear serous fluid could be expressed from the breasts. Patients with radiologically apparent pituitary tumours were excluded from this study.

Test Procedure.—Oestradiol benzoate B.P. 1 mg was given intramuscularly and venous blood samples taken at 0 hours and after 24, 48, 56, 72, and 96 hours. Serum oestradiol and progesterone were estimated at 0 hours to exclude recent ovulation and LH and FSH were measured in all samples. A positive response was defined as an increase in LH of 8 U/l and in FSH of 3 U/l above mean baseline values within 96 hours.⁸ The gonadotrophin release in response to LH-RH was assessed in all patients after injection of 100 µg LH-RH (Hoechst Pharmaceuticals) as previously described.⁹

Hormone Measurements.—Serum LH, FSH, oestradiol, and progesterone were estimated using specific radioimmunoassays (R.I.A.).⁹ Serum prolactin was measured by a double antibody R.I.A. using a modification of Sinha *et al.*'s method.¹⁰ The prolactin preparation HPr V-L-S No. 1, supplied by the National Institute of Arthritis and Metabolic Diseases, U.S.A., was used as standard and label. Iodination was by the method of Redshaw and Lynch¹¹ using sodium hypochlorite 1 mmol/l as an oxidant. The product was passed through Sephadex (Pharmacia Fine Chemicals, Sweden) G25 and G100 columns before use to remove free iodide and polymerized material. Prolactin antibody was supplied by Dr. A. S. McNeilly.^{12, 13} Donkey anti-rabbit serum (Burroughs Wellcome) was used for final separation. The normal values of 30 regularly menstruating women ranged from 6-32 µg/l (Mean ± S.D., = 12.6 ± 6.0 µg/l) and were similar to those reported by McNeilly.¹²

Results

Basal serum prolactin, oestradiol, and gonadotrophin estimations and LH-RH responses of the patients are summarized in the table. Prolactin was clearly raised above the upper limit of normal in all patients. Basal oestradiol and gonadotrophins were within the normal range (mean ± 2 S.D.) for the early follicular phase.⁹ LH and FSH release after LH-RH were either normal or exaggerated when compared with the responses of normal women in the early follicular phase.⁹

After administration of the oestradiol benzoate circulating levels of FSH, and LH in most cases, were initially suppressed in all patients. Only one patient (case 14) responded normally as defined by an increase in LH 72 hours after the oestradiol benzoate (see fig.). The remaining 13 failed to release gonadotrophin (see fig., case 11).

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Basal Serum Prolactin, Oestradiol-17 β , and LH and FSH Levels and LH-RH Test and Oestrogen Provocation Test Responses in Patients with Amenorrhoea and Hyperprolactinaemia

Case No.	Diagnosis	Basal Levels				Responses to LH-RH		Positive Feedback Response to Oestradiol
		Prolactin (μ g/l)	Oestradiol (pmol/l)	LH (U/l)	FSH (U/l)	LH	FSH	
1	Post partum	47	64	1	1	Normal	Exaggerated	Absent
2	"	73	141	3	1	Normal	Normal	Absent
3	"	81	164	4	4	Normal	Normal	Absent
4	"	185	66	<1	4	Exaggerated	Exaggerated	Absent
5	Post pill	83	224	5	1	Normal	Normal	Absent
6	"	112	155	1	2	Normal	Normal	Absent
7	"	186	222	1	8	Exaggerated	Exaggerated	Absent
8	No apparent cause	71	131	8	3	Exaggerated	Exaggerated	Absent
9	"	110	<40	2	2	Exaggerated	Normal	Absent
10	"	120	367	2	4	Normal	Normal	Absent
11	"	184	130	3	7	Exaggerated	Normal	Absent
12	"	199	481	1	4	Normal	Normal	Absent
13	"	290	141	3	1	Normal	Normal	Absent
14	"	207	161	3	5	Exaggerated	Exaggerated	Present

Conversion: SI to Traditional Units—Oestradiol: 1 pmol/l $\approx$ 0.27 pg/ml.

Serum LH and FSH changes in case 14 and case 11 after 1 mg oestradiol benzoate at 0 hours. Response in case 14 was normal, with release of LH and FSH at 72 hours. Response in case 11 was abnormal, with no release of LH and FSH; levels of LH from 24 to 72 hours were undetectable (< 1 U/l).

Discussion

The negative and positive influences of oestrogen on the release of gonadotrophins in normal women⁴⁻⁶ have also been recognized in some women with amenorrhoea,¹⁴⁻¹⁵ though in other women with amenorrhoea and normal serum prolactin levels these mechanisms are abnormal.⁸ We have shown a similar abnormality in oestrogen feedback mechanisms in all but one of 14 women with hyperprolactinaemia. This abnormality might explain the anovulation of our patients since positive feedback is necessary to cause the ovulatory surge of gonadotrophins.⁵

Our findings do not negate observations of an apparent anti-gonadotrophic action of raised prolactin values at a gonadal level,^{2-3,17} but the failure of positive feedback in most patients accounts for the variable response to clomiphene alone and the need to give human chorionic gonadotrophin in addition to achieve apparent ovulation.¹⁶ Our results have also confirmed earlier findings of normal basal gonadotrophin and oestradiol levels and normal or exaggerated release of FSH and LH after

LH-RH administration in patients with hyperprolactinaemia and amenorrhoea.¹⁸⁻¹⁹

In conclusion, our results suggest that there is a hypothalamic abnormality of oestrogen feedback mechanisms as well as the possible hypothalamic defect causing hyperprolactinaemia. Suppression of raised serum prolactin levels is associated with a return of normal hypothalamic-pituitary and ovarian function,²⁰⁻²³ but the precise mechanism is unknown. Our data suggest that the return of normal function could be due partly to a restoration of normal oestrogen feedback.

This work was supported by grants from the United Birmingham Hospitals Endowment Fund and the Medical Research Council. We thank the National Institute of Arthritis, Metabolism and Digestive Diseases for supplying the prolactin standard, Dr. A. S. McNeilly for the prolactin antiserum, and Hoechst Pharmaceuticals for the synthetic LH-RH.

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