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Failure to preserve fertility in patients with Hodgkin's disease

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Summary. The hypothesis that the "down-regulated" gonad is less vulnerable to the effects of cytotoxic chemotherapy for advanced Hodgkin's disease has been investigated. Thirty men and eighteen women were randomly allocated to receive an agonist analogue of gonadotrophin-releasing hormone prior to, and for the duration of, cytotoxic chemotherapy. Buserelin (*d*-Ser-[TBU]^6 LHRH ethylamide) was prescribed in two different dosage schedules to twenty men, and in a single dosage schedule to eight women. A standard gonadotrophin-releasing hormone test (GnRH 100 μg) was performed 1 week prior to and on day 1 of each cycle of chemotherapy. In all patients peak luteinizing hormone responses to GnRH were suppressed throughout treatment. The higher of the two dosage schedules used in the men caused more effective suppression of luteinizing hormone, and both regimens led to an initial suppression of peak follicle-stimulating hormone responses to GnRH, which was not maintained. At follow-up assessment up to 3 years from the completion of treatment, all men treated with buserelin were profoundly oligospermic and four of the eight women were amenorrhoeic. All ten male controls were profoundly oligospermic, and six of nine female controls were amenorrhoeic. In the dosages and schedules investigated, buserlin was ineffective in conserving fertility.

Introduction

Prolonged survival is now expected for a high proportion of young people treated with cytotoxic chemotherapy for advanced Hodgkin's disease. This is due to the introduction of MOPP (mustine, vincristine, prednisolone and procarbazine) chemotherapy and its variants [10]. Amongst the long-term complications of treatment is gonadal damage. This results in infertility with nonetheless normal potency in men and an early menopause, dyspareunia, reduced libido and premature osteoporosis in women. As many as 80% of patients become sterile as a result of this treatment, whose gonadal toxicity correlates with age and sex [5, 6, 21]. The possibility of administering an adjuvant treatment that might limit the gonadal damage caused by an otherwise successful treatment programme is attractive.

The agonist analogues of gonadotrophin-releasing hormone were initially introduced as stimulatory [7]. However, repeated administration results in decreased secretion of the pituitary gonadotrophins [1, 2]. This effect has been used to advantage in precocious puberty [8], endometriosis [17], contraception [2, 16], uterine leiomyomata [14], menorrhagia [19], prostatic cancer [4, 20, 22] and carcinoma of the breast [15]. It may be that decreased secretion of the pituitary gonadotrophins, by decreasing ovarian and testicular function, could protect against the sterilizing effects of treatment. The evidence that reduced secretion of the gonadotrophins decreases germ cell activity comes from the finding of arrested spermatogenesis in patients proceeding to orchiectomy after treatment with buserelin [23] and the observation that both men and women with Kallmann's syndrome have hypogonadism. Although the findings are controversial, as children treated for malignancy are less vulnerable than adults to the sterilizing effects of chemotherapy [3, 24] and prepubertal rats are less liable to radiation-induced testicular damage than adult rats [9], it may be that the repeated administration of an agonist analogue of gonadotrophin-releasing hormone could protect against infertility. This hypothesis has been investigated.

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Patients and methods

Details of the patients are provided in Table 1. The following hormonal assessment was performed in all patients: basal blood samples were taken at 9 am for measurement of prolactin (mean of 3 levels sampled at 10-min intervals), sex hormone-binding globulin, testosterone, 17 B oestradiol, and progesterone; and a standard GnRH test was performed. Concentrations of luteinizing hormone, follicle-stimulating hormone and prolactin were measured by specific double-antibody radio-immunoassay, using Medical Research Council standards 68/40, 78/549 and 75/504, respectively. Concentrations of 17 B oestradiol, progesterone and testosterone were measured by standard radio-immunoassay, and sex hormone-binding globulin by saturation radio-immunoassay [11]. After 2 days' abstinence from intercourse seminal analysis was performed. This was repeated on at least two occasions to confirm oligospermia, and thrice if the analysis was normal, to allow for cryoperservation of semen. In both sexes, if randomisation was to "gonadal protection" treatment was started with buserelin at 200 μg thrice daily intranasally. Eleven men and eight women were randomized to receive and ten men and ten women not to receive buserelin. In men, 6-weekly depot testosterone supplements (Sustanon 250 1 ml i. m.) were given to potentiate the effect of the agonist analogue and to prevent loss of libido. After 1 week, the hormonal

Table 1. Details of the patients

	Number of patients	Age (years)		Follow-up (years)	
		Mean	Range	Mean	Range
Men					
Buserelin-treated	20	27.1	18–44	2.3	1 –3
Controls	10	27.1	18–43	1.9	1 –2.5
Women					
Buserelin-treated	8	28.5	17–34	2.3	1.8–2.5
Controls	10	25.9	17–46	2.0	1 –2.5

profile was repeated and cytotoxic chemotherapy given. Adjuvant treatment continued with buserelin for the duration of chemotherapy and for a further 3 days after its completion. Each patient was treated with up to six cycles of standard MVPP (mustine 6 mg/m^2 i. v. on days 1 and 8, vinblastine 6 mg/m^2 i. v. on days 1 and 8, procarbazine 100 mg/m^2 p. o. on days 1–14 and prednisone 40 mg on days 1–14) chemotherapy. Subsequent to the early results of this study, the dosage regimen of buserelin was altered. An additional nine men received 1 mg buserelin daily s. c. for 1 week prior to chemotherapy, and then 200 µg thrice daily intranasally during treatment, which was increased to 200 µg five times daily for 3 days before day 1 of each treatment cycle. Five men in this group were treated with ChlVPP (chlorambucil 6 mg/m^2 p. o. on days 1–14, vinblastine 6 mg/m^2 i. v. on days 1 and 8, procarbazine 100 mg/m^2 p. o. on days 1–14, prednisone 40 mg p. o. on days 1–14) and four with MVPP. Patients were followed for up to 3 years after completing treatment. In men seminal analysis was repeated, and in women menstruation was assessed together with measurement of day-20 to day-22 progesterone.

Results

Details of the results of serum gonadotrophin assays are provided in Fig. 1 a–e. The results for two men who were non-compliant, another who developed treatment-related hypersensitivity, two men who relapsed, and one woman who died during treatment are included up to the point where chemotherapy was altered or non-compliance demonstrated.

A. Women

Menstruation. All women receiving buserelin, and three of ten who did not, developed amenorrhoea during treatment. Four of eight women treated with buserelin, and six of nine controls, menstruated after treatment.

Serum hormone concentrations. In comparison with pretreatment levels there was persistent significant suppression of concentrations of luteinizing hormone ($P < 0.05$: Student's *t*-test) but not follicle-stimulating hormone measured at 20 and 60 min after injection of 100 µg LHRH. The results of sequential GnRH tests have been plotted in Fig. 1 a and b. Two patients who had received buserelin were shown to have ovulated during the period of follow-up, as was one control patient (progesterone on day 20–22 of menstrual cycle >30 nmol/l). An additional patient in the control group has become pregnant. In patients who were treated with buserelin low 17 B oestradiol levels persisted throughout therapy and were consistently in the postmenopausal range in two of eight women. Serum testosterone, sex hormone-binding globulin and prolactin levels did not significantly change with buserelin treatment.

B. Men

Seminal analysis. Thirteen of thirty men had abnormal seminal analysis at presentation (total sperm counts less than 20×10^6 or less than 50% sperm motile). All men were profoundly oligospermic, with total counts less than 0.6×10^6, at follow-up examinations up to 3 years later.

Serum hormone concentrations. Basal follicle-stimulating hormone concentrations and levels of both gonadotrophins at 20 and 60 min after 100 µg GnRH were significantly suppressed ($P < 0.05$; Student's *t*-test) by buserelin after 1 week's treatment with both dosage regimens. After the institution of treatment luteinizing hormone, but not follicle-stimulating hormone, responses to GnRH were suppressed throughout treatment. The results of sequential GnRH tests have been plotted in Fig. 1 c, d an e. An overall Chi-square test compared their differences. Luteinizing hormone alone was more significantly suppressed ($P < 0.002$) by the higher dosage regimen. No significant change in the serum concentrations of testosterone, progesterone, prolactin, sex hormone-binding globulin or 17 B oestradiol occurred comparing patients treated with buserelin and controls.

Discussion

This study investigated whether suppression of the pituitary gonadotrophins in patients receiving sterilizing chemotherapy resulted in the preservation of fertility. It has been demonstrated that with the dosages and schedules investigated, buserelin resulted in the suppression of peak responses of luteinizing hormone to GnRH in both men and women throughout the cytotoxic chemotherapy. In men both high and low dosage buserelin regimens led to an initial suppression of follicle-stimulating hormone, which ceased after one course of cytotoxic chemotherapy. At follow-up, all men were profoundly oligospermic, whilst four of eight women who received buserelin and six of nine controls continued to menstruate. Menstruation was found to be ovulatory in two treated women and two controls.

Two similar experiments have been reported in animal

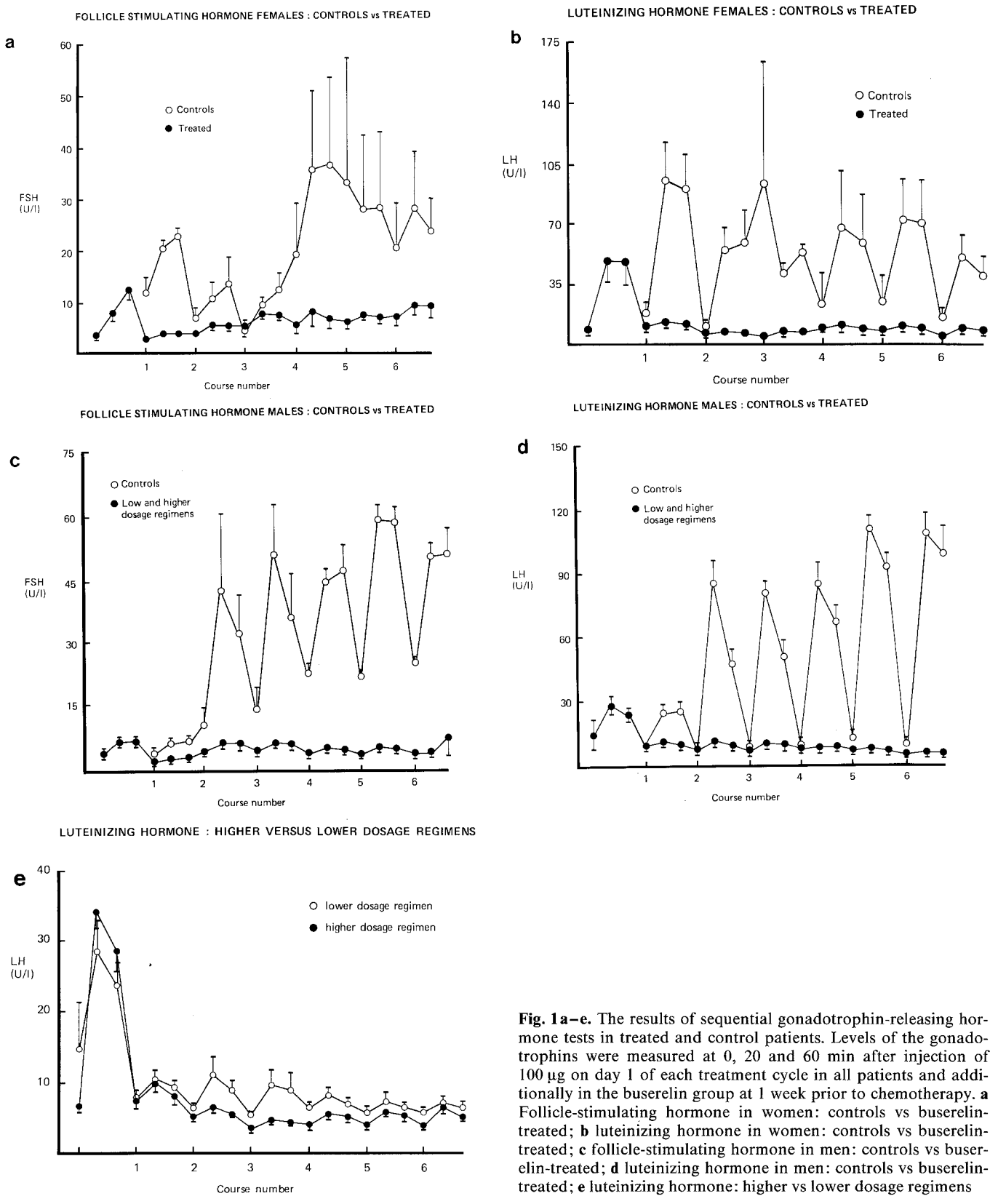

Fig. 1a–e. The results of sequential gonadotrophin-releasing hormone tests in treated and control patients. Levels of the gonadotrophins were measured at 0, 20 and 60 min after injection of 100 µg on day 1 of each treatment cycle in all patients and additionally in the buserelin group at 1 week prior to chemotherapy. **a** Follicle-stimulating hormone in women: controls vs buserelin-treated; **b** luteinizing hormone in women: controls vs buserelin-treated; **c** follicle-stimulating hormone in men: controls vs buserelin-treated; **d** luteinizing hormone in men: controls vs buserelin-treated; **e** luteinizing hormone: higher vs lower dosage regimens

models. The first described the effects of a single dosage of cyclophosphamide in mice pretreated with *d*-Leu^6 pro^9 LHRH ethylamide. The authors demonstrated a protective effect of this agonist upon spermatogenesis [12]. This study was criticized because GnRH analogues do not decrease gonadotrophin levels in mice and neither do they return them to the prepubertal state. In addition, a single dose, as opposed to repeated administration, of alkylating agents does not generally cause infertility.

In the second experiment, dogs were treated with D-

Nal(2)[6] LHRH for between 48 and 51 weeks at 2 μg/kg/day s.c. At 7 weeks after the initiation of treatment, the animals received cyclophosphamide either 3.5 or 6 mg/kg p.o. thrice weekly, concomitantly with the agonist. The dogs were castrated 6–9 weeks after the completion of treatment. Controls treated with cyclophosphamide alone had atrophic seminiferous tubules. Those dogs treated with agonist and alkylating agent had active spermatogenesis that was decreased compared with that in dogs treated with agonist alone [13].

From the evidence of these two animal models, it may well be that the hypothesis investigated is correct, but the decreased secretion of gonadotrophins achieved was inadequate. This may be because the pretreatment interval was too short or because the dosage of buserelin given was insufficient. There is little opportunity in the management of Hodgkin's disease to delay chemotherapy whilst adequate gonadal down-regulation is achieved. However, it is possible that GnRH antagonists may suppress gonadotrophin levels more quickly than agonist analogues. Alternatively, treatment might be altered to less frequently used regimens that are said not to be sterilizing [18].

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Addendum. Further details of the hormonal results will be supplied on request.

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