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Shrinkage of uterine fibroids by preoperative LHRH analogue injection

H R McClelland, A J Quinn

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SUMMARY

Six patients with large uterine fibroids were given a single subcutaneous implant of an LHRH analogue (goserelin 3·5 mg) prior to elective hysterectomy. Overall fibroid volume decreased by 30 – 47% within six weeks of implantation. All patients reported improvement in their symptoms of pressure and pain, and were rendered amenorrhoeic prior to surgery.

INTRODUCTION

Goserelin, a high potency luteinizing hormone-releasing hormone (LHRH) analogue is available as a slow release subcutaneous implant (Zoladex ICI), which has been shown to produce consistent, reversible suppression of the pituitary-ovarian axis.[1] The release of follicle stimulating hormone and luteinizing hormone from the pituitary gland is under the control of pulsatile release of LHRH from the hypothalmus. Continuous administration of LHRH analogues causes pituitary gonadotrophes to become desensitised, which induces a state of hypogonadotrophic hypogonadism, a process known as pituitary down-regulation. As a result of this oestrogen output from the ovary decreases and serum oestrogen levels fall to values in the postmenopausal range.

LHRH analogues are increasingly advocated in the management of common oestrogen-dependent gynaecological conditions, notably uterine fibroids,[2,3] endometriosis[4,5] and menorrhagia,[6] and may also be effective in the management of metastatic breast cancer.[7] Recent work[2,3] has shown the effectiveness of both buserelin and goserelin in shrinking uterine fibroids to about 50% of their original size (assessed by ultrasonic measurement), but both these studies showed regrowth of the fibroids to their former size within months of stopping therapy. This work prompted Shaw to suggest that LHRH analogues should be used as an adjunct to the surgical management of fibroids.[2]

The aim of the present study was to measure the effect of a single implant of goserelin on large fibroid masses prior to elective surgery, to determine its effect on the patients' symptoms and to record side effects.

Gynaecological Unit, The Ulster Hospital, Dundonald, Belfast.

H R McClelland, MB, BCh, MRCOG, Senior Registrar.

A J Quinn, MB, BCh, Senior House Officer.

Correspondence to Dr H R McClelland, Gynaecological Unit, Belfast City Hospital, Lisburn Road, Belfast BT9 7AB.

PATIENTS AND METHODS

Six patients, aged 42 – 50 years, parity 0 – 2, were recruited to the study from the gynaecological clinic of the Ulster Hospital. All had menorrhagia, dysmenorrhoea and generalised lower abdominal pain and pressure.

On clinical examination each patient had a firm abdominal mass equivalent in size to a 16 – 20 week pregnancy. Clinically these were fibroid masses and ultrasound examination supported this diagnosis. The patients were offered abdominal total hysterectomy and bilateral salpingo-oophorectomy with postoperative hormone replacement therapy as the treatment of choice. Each was given an admission date within 4 – 8 weeks.

After informed consent for the present study was obtained, each patient received a 3·5 mg goserelin implant into the anterior abdominal wall after local infiltration with 1% lignocaine. They were then reviewed weekly for ultrasonic assessment of the maximum length (a), depth (b) and width (c) of the tumour. Measurements (a) and (b) were taken in the longitudinal plane and (c) in the transverse plane. Ultrasound scanning was performed on an Ultramark 4 machine by one observer. After obtaining a picture of what was regarded as the maximum size of the mass, the ultrasonographer freeze-framed the picture and turned the screen away. The second observer performed the measurements and obtained hardprint copies of these. Fibroid volume was determined by the formula of an ellipsoid according to Shawker's method.[8] Weekly measurements of serum FSH, LH and 17β-oestradiol values were obtained, symptoms were reviewed and any side effects noted. Following operation the fibroid volume was measured immediately by fluid displacement in a measuring jug.

RESULTS

Overall fibroid volume estimated by ultrasound showed a 30 – 46% reduction in the study period (Table I), the shrinkage being obvious within two weeks in all cases and maximum by four weeks (Fig 1). This reduction was evident on palpation. The shrinkage coincided with the postmenopausal levels of oestradiol (< 50 pmol/l) achieved with the treatment. These levels were reached in all cases by four weeks from implantation (Fig 2). These coincided with hypogonadotrophic levels of FSH and LH (< 2 IU/l).

TABLE I

Ultrasonic estimates of original and immediate preoperative fibroid volume and percentage reduction in size

Patient	*Original fibroid volume (ml)*	*Preoperative fibroid volume (ml)*	*Shrinkage*
OA	1033	557	46%
JC	951	581	39%
ED	815	453	44%
MM	660	353	46%
FS	600	420	30%
JH	542	350	33%

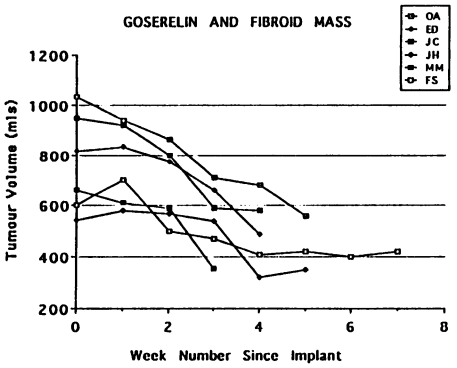

Fig 1. Ultrasonic estimate of fibroid volume in the weeks following goserelin implant up to the day before surgery.

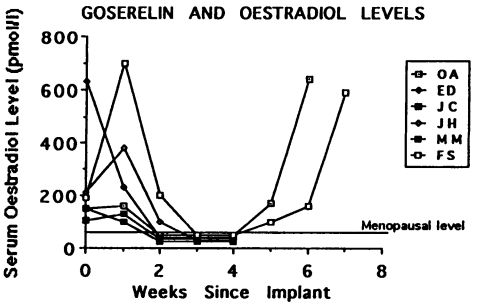

Fig 2. Serum oestrogen levels after goserelin implantation.

The estimated volume by scan prior to surgery corresponded to within 5 – 14% of the actual volume of the surgical specimen (minus ovaries and tubes) as determined by fluid displacement (Table II). The ultrasound volumes were all under-estimated.

TABLE II

Comparison of ultrasonic estimation of immediate preoperative fibroid volume and actual volume of surgical specimen measured by fluid displacement

Patient	*Preoperative estimated fibroid volume (ml)*	*Actual fibroid volume (ml)*	*Discrepancy*
OA	558	636	– 14%
JC	581	648	– 11%
ED	453	475	– 5%
MM	353	385	– 9%
FS	420	441	– 5%
JH	350	388	– 10%

All patients reported improvement in their symptoms of pain and pressure, evident between the second and third week of treatment. One patients had slight vaginal staining during the treatment, but menstruation was delayed in all patients prior to hysterectomy. One patient was just commencing menstruation at the time of hysterectomy, 61 days after her implant. The only side effects noted were hot flushes (four patients) which coincided with the low oestradiol levels.

Despite shrinkage of the fibroid mass in all patients, a debulking procedure (myomectomy) was required in two patients in order to gain access to the uterine pedicles. Postoperatively the only complication was one self-limiting episode of paralytic ileus. Histopathology confirmed the diagnosis in all cases: in two endometriosis was found in the ovaries.

DISCUSSION

We report major shrinkage of large uterine fibroids following a single subcutaneous implant of goserelin. Some studies have suggested that medical management of fibroids with a LHRH analogue is an alternative to surgery[9,10] but others[2,3] have shown complete regrowth of fibroids within months of cessation of this therapy. The long-term use of LHRH analogue with subsequent hypooestrogenism has not been studied but this therapy does induce a premature menopause with the associated problems of climacteric symptoms and, in the long-term, potential atherosclerotic and osteoporotic changes. We would agree with Shaw[2] who suggested that the LHRH analogue should be used as an adjunct to surgical management. The implant could be repeated at four-weekly intervals if surgery was delayed. Surgery also allows full histological assessment with a firm diagnosis and rules out malignancy.

Important aspects of this combined chemosurgical approach include full patient compliance and acceptability, improvement in symptoms and absence of serious side effects. Goserelin is expensive (£114 per implant) but this must be weighed against other positive factors and potential savings. The cessation of menses over the treatment period should allow anaemia to be corrected by simple haematinics and might save the need for blood transfusion in some patients with severe menorrhagia.[6] Surgery could also be made easier in several ways. Matta *et al* have shown by Doppler blood flow studies that the blood supply to fibroids and the uterus is decreased after a LHRH analogue.[11] In our series, a debulking procedure (myomectomy) still had to be performed in two cases but blood loss was not a problem. Access to the uterine pedicles should be easier when fibroids are smaller and the surgical incision might be modified from a longitudinal midline incision to a transverse lower abdominal incision.

One important factor in the selection of patients is to exclude the possibility of an ovarian tumour. Fibroids have a characteristic ultrasonic appearance and shrinkage is obvious both clinically and ultrasonically within three weeks. It is unlikely, therefore, that a misdiagnosis would be made, but with this chemosurgical approach, surgery would be performed within a few months and the time factor involved would make little difference in prognosis.

The fibroids appeared to demarcate prior to shrinkage and one huge mass appeared to separate into the various fibroids making up the mass. It has been shown that fibroids have increased cytoplasmic oestrogen receptors compared to adjacent myometrium[12] but our impression on serial scanning was that the myometrium shrank around the fibroid first, which allowed the fibroids to demarcate.

Concern has been expresed regarding the potential side effects of the LHRH agonists. The only side effects recorded by our patients were tolerable hot flushes and these were offset by relief of pain and pressure. In theory, long-term usage of a LHRH analogue could be associated with bone loss or coronary artery disease. Our patients did not show any change in serum calcium or alkaline phosphatase during the short period of this study. Van Leusden and Dogterom did not find any bone loss following six months of continuous treatment with a LHRH analogue.[13] We contend that this chemosurgical approach to large fibroids is safe, effective and beneficial to the patient. One implant produces significant benefits and this

schedule could be incorporated into standard clinical practice. Close follow-up of patients preoperatively seems unnecessary as there are few side effects.

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