Drugs 1996 Feb; 51 (2): 319-346
0012-6667/96/0002-0319/$28.00/0

Goserelin

A Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Use in Benign Gynaecological Disorders

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Summary

Synopsis

Goserelin is a gonadotrophin-releasing hormone (GnRH) analogue which, during continuous administration, down-regulates the pituitary-ovarian gonadal axis and reduces levels of the gonadotrophins, luteinising hormone and follicle-stimulating hormone. In women, this results in suppression of ovarian steroidogenesis and a decline in estrogen to levels similar to those observed after menopause or following surgical oophorectomy. Thus, goserelin has a useful role in the management of some benign estrogen-dependent gynaecological disorders. Goserelin is available as a biodegradable sustained release depot 3.6mg injection which is administered every 28 days.

In women with endometriosis, monthly injections of depot goserelin were effective in achieving resolution of endometriotic implants and in improving pelvic symptoms, including pain and dyspareunia. Randomised clinical comparisons of depot goserelin with danazol indicate that goserelin is at least as effective as danazol and is better tolerated in the treatment of endometriosis.

In the management of uterine leiomyomata (fibroids), goserelin depot injections reduce uterine size and the size of uterine leiomyomata, with maximum clinical benefit achieved approximately 3 to 4 months after initiation of treatment. When used as an adjunctive pretreatment for women undergoing surgical removal of uterine leiomyomata, goserelin was associated with technically easier surgical procedures, reduced intraoperative blood loss and reduced transfusion requirements around the time of surgery. As an alternative to surgery, therapeutic use of goserelin is limited by the rapid regrowth of leiomyomata following cessation of treatment. However, goserelin may be a useful treatment for women approaching menopause, in whom uterine leiomyomata shrink naturally as endogenous estrogen levels decline.

In women with dysfunctional uterine bleeding, treatment with depot goserelin before surgery facilitates resection and ablative procedures by suppressing endometrial growth and thinning the endometrial mucosa. Goserelin is also an effective alternative to surgery in this patient group.

As adjuvant therapy for women undergoing assisted reproduction procedures, goserelin is associated with reduced cycle cancellation rates and with an increase in the rate of oocyte retrieval.

The tolerability profile of goserelin is characterised by adverse effects typical of hypoestrogenism, including hot flushes, loss of libido and loss of bone mineral density. However, concomitant 'add-back' hormone replacement therapy appears to effectively reduce these hypoestrogenic symptoms.

In summary, the availability of depot goserelin has broadened the spectrum of effective treatments for benign estrogen-dependent gynaecological disorders. As goserelin is effective as a sustained release depot formulation suitable for administration on a monthly basis, it is also a convenient and practical treatment choice.

Pharmacodynamic Properties

Goserelin is a gonadotrophin-releasing hormone (GnRH) analogue which is approximately 100 times more potent than endogenous GnRH. In women with benign gynaecological disorders, goserelin initially induces a transient increase in luteinising hormone (LH) and follicle-stimulating hormone (FSH) levels. Continuous administration of goserelin results in down-regulation of the anterior pituitary gland and a subsequent decline in LH and FSH levels. Within 14 days of administration of a depot injection of goserelin 3.6mg, LH and FSH levels

decline to levels below baseline and remain suppressed for up to 5 weeks. Since LH and FSH control ovarian steroidogenesis, suppressing the release of these gonadotrophins results in reduced levels of estrogen. In healthy women and those with benign gynaecological disorders, estradiol is reduced to levels similar to those occurring after menopause or after surgical oophorectomy.

Limited data are available on the relative hypoestrogenic effects of goserelin and other long- and short-acting GnRH analogues. In a small comparative study, depot goserelin was less effective than depot leuprorelin or depot triptorelin in reducing FSH levels. By the third month of treatment there was evidence of incomplete ovarian suppression, which was more marked with depot goserelin than with depot leuprorelin, depot triptorelin or the short-acting formulation of buserelin.

In contrast to danazol, an established treatment of endometriosis, goserelin had no effect on serum insulin or plasma glucagon levels in women with endometriosis. In addition, goserelin had an overall beneficial effect on haemostatic risk factors which resulted in preservation of the fibrinolytic defence mechanism.

Pharmacokinetic Properties

As goserelin is inactivated by intestinal peptidases when given orally, it is administered by subcutaneous injection. Goserelin is formulated as a sustained release depot injection which contains 3.6mg of the drug dispersed in a biodegradable poly (*d,l*-lactide-co-glycolide) polymer rod. The drug is released continuously over a 28-day period, thus avoiding the need for daily injections.

The pharmacokinetic properties of goserelin have been determined in men with prostate cancer, healthy volunteers and in women with benign gynaecological disorders. In men with prostate cancer, an initial transient mean serum concentration peak (C_{max}) of 0.2 to almost 2.0 μg/L is reached at between 2 and 8 hours, which is followed by a second mean C_{max} of approximately 2 to 3 μg/L, 14 to 15 days after administration of a single 3.6mg depot injection. In women with benign gynaecological disorders a mean C_{max} value of 1.4 μg/L is reached 15 days after the first and second monthly doses of depot goserelin 3.6mg. There is no evidence of drug accumulation when 3.6mg depot goserelin injections are administered monthly over a period of 6 months.

Goserelin is excreted primarily in the urine and has a mean body clearance of 8 L/h. Mean body clearance is reduced and the terminal elimination half-life is prolonged in patients with severe renal impairment, but dosage adjustment is not required.

Therapeutic Efficacy

In women with endometriosis, goserelin (usually administered as a 3.6mg depot injection every 28 days for a maximum of 6 months) was effective in achieving resolution of endometriotic implants as demonstrated by improvements in laparoscopic measurements of mean (revised) American Fertility Society (RAFS) endometriosis classification scores. Goserelin also significantly improved pelvic symptoms, including pain and dyspareunia. Randomised clinical comparisons of depot goserelin with danazol have shown that goserelin is at least as effective as danazol in the treatment of endometriosis. In a comparative study, more marked reductions in mean total RAFS and mean RAFS implant scores were observed in goserelin recipients than in danazol recipients. The addition of concomitant 'add-back' estrogen/progesterone hormone replacement therapy (HRT) to goserelin for the treatment of endometriosis did not appear to reduce the therapeutic efficacy of goserelin. Moreover, this therapeutic strategy reduced the hypoestrogenic adverse effects of goserelin treatment.

Noncomparative and comparative studies of goserelin in women with uterine leiomyomata have shown the drug to be effective in reducing the size of leiomyomata, thus facilitating surgical removal of these benign neoplasms. Goserelin treatment before surgery was also associated with technically easier surgical procedures (compared with women who had not received goserelin), a reduction in intraoperative blood loss, an increase in haemoglobin levels and, therefore, a reduction in blood transfusion requirements.

As an alternative to surgical management of uterine leiomyomata, goserelin appears to be of limited clinical benefit. Although uterine volume is reduced during treatment with goserelin, most shrinkage in volume occurs during the first 4 months' treatment. Importantly, discontinuation of goserelin treatment is followed by the rapid regrowth of uterine leiomyomata. Thus, goserelin may be most useful as treatment for women approaching menopause in whom these neoplasms might be expected to degenerate naturally.

In women with dysfunctional uterine bleeding, surgical pretreatment with goserelin suppressed endometrial growth and reduced uterine size, endometrial thickness and fluid absorption associated with surgical ablation, thus facilitating surgical ablative or resection procedures. Goserelin was also an effective alternative to surgery in women with dysfunctional uterine bleeding, significantly improving evaluated haematological parameters of anaemia.

Goserelin was also effective as adjuvant therapy prior to ovarian stimulation in women undergoing assisted reproduction procedures (*in vitro* fertilisation and gamete intrafallopian transfer). In this clinical setting, goserelin adjuvant treatment was associated with reduced cycle cancellation rates and improved rates of oocyte retrieval. There was a higher pregnancy rate in women who received a single 3.6mg dose of depot goserelin than in recipients of oral clomifene (100 mg/day for 5 days) as adjunctive pretreatment prior to ovarian stimulation with human menopausal gonadotrophin.

Tolerability

The tolerability profile of goserelin in premenopausal women is characterised by adverse effects typical of a hypoestrogenic state, including hot flushes (reported in 89% of women who received the drug in several clinical studies), vaginal dryness, headaches and loss of libido. In addition, bone mineral density loss of about 4.6% occurs during 6-month courses of goserelin. However, several studies have shown that concomitant 'add-back' estrogen/progesterone HRT reduces the incidence of hypoestrogenic adverse effects and bone mineral density loss. Local reactions at the site of injection are observed in approximately 3% of women receiving goserelin.

Dosage and Administration

In the treatment of women with benign gynaecological disorders the recommended dosage of depot goserelin is 3.6mg, injected subcutaneously into the anterior abdominal wall every 28 days for a maximum of 6 months. Repeat courses of goserelin are not recommended at the present time because of concern regarding bone mineral density loss. Dosage modification of goserelin is not required in women with renal or hepatic impairment.

As goserelin is contraindicated in pregnancy, pretreatment examination of fertile women is necessary to exclude pregnancy. In addition, nonhormonal methods of contraception should be used during goserelin treatment.

Goserelin is a synthetic agonist analogue of gonadotrophin-releasing hormone (GnRH) [luteinising hormone-releasing hormone (LHRH), or gonadorelin] with similar pharmacodynamic properties to GnRH. GnRH, produced by the hypothalamus in pulses at approximately 90-minute intervals, stimulates the release of luteinising hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. In women, LH is responsible for ovarian androgen production, luteinisation of the ruptured Graafian follicle and the subsequent production of progesterone. FSH stimulates the production of estrogens from ovarian androgens in the follicular granulosa cells. Continuous, rather than pulsatile, administration of GnRH or a GnRH analogue, such as goserelin, renders the pituitary gland refractory to stimulation, as a result of receptor desensitisation and/or down-regulation of the hypothalamic-pituitary-ovarian axis.[1] The resultant effect in women is a transient increase followed by a decrease in circulating LH and FSH levels, suppression of ovarian steroidogenesis and reduction of estrogen to levels similar to those observed in women after menopause or following surgical oophorectomy.[2] Thus, goserelin is potentially useful in the treatment of benign estrogen-dependent gynaecological disorders including endometriosis, uterine leiomyomata and dysfunctional uterine bleeding.[3]

The pharmacology and clinical use of goserelin in sex hormone–related conditions has been previously reviewed in *Drugs*.[1] This review further evaluates the role of goserelin in the treatment of benign gynaecological disorders and includes more recent data, which are supplemented with key information from the earlier review.

Goserelin is prepared as a depot sustained release biodegradable lactide-glycolide co-polymer rod which is administered as a 3.6mg dose by subcutaneous injection every 28 days. The majority of studies discussed in this review utilised this treatment regimen. Goserelin is also formulated as a 10.8mg dose for 12-weekly administration.

1. Pharmacodynamic Properties

Goserelin is a structural modification of GnRH which is more hydrophobic, possesses a greater affinity for GnRH receptors, has increased stability in blood and a longer plasma elimination half-life than GnRH, and is approximately 100 times more potent than its endogenous counterpart.[4-6]

An overview of the pharmacodynamic properties of goserelin (administered subcutaneously as a 3.6mg depot injection in most studies) is presented in table I.

1.1 Effect on Gonadotrophins

Goserelin initially stimulates the anterior pituitary gland to secrete LH and FSH, resulting in a sharp increase in serum LH and FSH levels 2 to 3 days after administration of the depot formulation in women with benign gynaecological conditions.[1,7,8] With continued exposure to goserelin, desensitisation of the pituitary gland occurs and LH and FSH levels rapidly decline to below baseline levels and remain suppressed for the duration of treatment (table I).[7]

Although substantial data confirm the activity of depot goserelin in suppressing the pituitary-ovarian gonadal axis [table 1] (see previous reviews of goserelin in *Drugs*[1] and *Drugs & Aging*[20]), incomplete suppression of ovarian function by depot goserelin has been reported in 1 study.[21] In this comparative study, groups of 10 women with male-related infertility, endometriosis or uterine leiomyomata who had normal menstrual cycles received either depot subcutaneous goserelin 3.6 mg/month, depot intramuscular leuprorelin 3.75 mg/month, depot intramuscular triptorelin 3.75 mg/month, or the short-acting subcutaneous formulation of buserelin 300μg every 12 hours.[21] All 3 depot GnRH analogues produced a profound suppression of LH during the study, but by the third month of treatment FSH levels were significantly higher in recipients of depot goserelin or leuprorelin than in those receiving the comparators ($p < 0.05$). Interestingly, there was evidence of an incomplete block of ovarian func-

Table I. Overview of the pharmacodynamic properties of goserelin, administered as a subcutaneous 3.6mg depot injection, in healthy women and in women with benign gynaecological disorders

Effect	Comments
Effects on gonadotrophin levels	
•↑ LH, ↑ FSH initially	Initial surge of LH and FSH with maximum levels reached 24 to 72h after subcutaneous administration of 3.6mg depot goserelin.[1,7,8] Increases in FSH generally less marked than increases in LH levels[8]
•↓ LH, ↓ FSH after initial surge	Rapid decline in LH and FSH levels about 3 days after administration of goserelin to healthy women and women with benign gynaecological disorders. Levels of LH and FSH decline to below baseline within 4wk after administration of a 3.6mg depot injection,[1,7-9] and remain suppressed for 4-5wk after a single dose.[7,8] During continued monthly administration, LH and FSH levels sustained at between 25 and 50% below baseline.[1] LH and FSH levels return to pretreatment levels 9wk after administration of a third dose of goserelin in women with premature ovarian failure[9]
Effects on sex hormones	
•↑ Serum estradiol levels initially	Increase in serum estradiol during the first 3 days[7,8,10] to almost 800 pmol/L[10]
•↑ Serum progesterone levels initially	Initial peak in serum progesterone after 2 days[1] to 50 to 100 nmol/L[10]
•↓ Serum estradiol levels	Goserelin about 10-fold more effective than GnRH in inhibiting estradiol synthesis.[1] Following single and repeated doses of goserelin, serum estradiol levels decrease to levels within the menopausal range (<100 pmol/L).[2,7,8,11-14] Estradiol levels increase to the normal range 2mo after treatment discontinuation[14]
•↓ Serum testosterone levels	Mean serum testosterone levels decrease[13,14] by 21%* 4wk after goserelin administration[12]
•↓ Serum progesterone levels	Serum progesterone levels decrease to early follicular phase values.[14] Suppression of progesterone reported by day 7 to 14 of therapy[1,10,15] to levels <50 nmol/L[10]
•No significant effects on insulin and glucagon	In nonobese women with minimal endometriosis, no changes in serum insulin, plasma glucagon levels or responses to orally administered glucose during and after treatment with goserelin[16]
•↑ Estradiol receptors in uterine leiomyomata and myometrium	Significantly higher estradiol receptor populations in uterine leiomyomata and myometrium of women who received goserelin for 3mo* compared with untreated women[17]
•↓ Binding of EGF to myometrium and fibroids	Specific binding of radiolabelled [^{125}I] EGF to myometrial and fibroid homogenates significantly less after 11wk of treatment with goserelin than in untreated women***[18]
Effects on haemostatic risk factors	
•Overall beneficial effect on evaluated haemostatic variables	In women with endometriosis there was a significant increase in antithrombin III†, protein C**, plasminogen activator inhibitor and tissue plasminogen activator levels during and after goserelin (3.6 mg/mo for 6mo), compared with controls.[11] Overall beneficial effect on the balance of haemostatic variables and preservation of the fibrinolytic defence mechanism against thromboembolic disease
Effects on the plasma lipid profile	
•Favourable effect (↓) on the atherogenic index (cholesterol/HDL-C ratio); favourable effect (↑) on the ApoA-1/ApoB ratio	Beneficial effect on plasma lipid risk factors for coronary heart disease in women with endometriosis.[12,19] Significant increase in HDL-C (31.4%***), HDL_2-C (23.9%*) and HDL_3-C (45.7%***) after 6mo of treatment with goserelin. No significant changes in LDL-C or ApoA-1 and ApoB and a nonsignificant increase in the apolipoprotein ratio[12]

Abbreviations and symbols: ApoA-1 = apoprotein A-1; ApoB = apoprotein B; EGF = epidermal growth factor; FSH = follicle-stimulating hormone; GnRH = gonadotrophin-releasing hormone; HDL-C = high density lipoprotein-cholesterol; HDL_2-C = high density lipoprotein-cholesterol minor subfraction; HDL_3-C = high density lipoprotein-cholesterol minor subfraction; LDL-C = low density lipoprotein-cholesterol; LH = luteinising hormone; mo = months; wk = weeks; ↑ indicates increase; ↓ indicates decrease; *$p < 0.05$; **$p < 0.02$; ***$p < 0.01$; †$p < 0.005$ *vs* baseline.

tion during the third treatment cycle in the goserelin recipients which was more marked than in the other treatment groups.[21] Filicori and colleagues[4] suggested that this effect may have been the result of the rod-shaped depot formulation of goserelin having different diffusion dynamics to

the other depot GnRH analogues used in the study. However, it is important to note that the small numbers of patients included in each treatment group preclude firm conclusions being drawn from this study regarding the comparative effects of these agents. In another comparative study, women with normal menstrual cycles who were receiving treatment for either uterine leiomyomata or endometriosis experienced similar significant ($p < 0.05$) declines in serum LH and FSH levels while receiving either monthly subcutaneous injections of goserelin or intramuscular injections of triptorelin for 6 months.[13]

Although ovulation has been reported to occur after women with premature ovarian failure have received treatment with some GnRH analogues,[9] this was not observed in 12 women with premature ovarian failure who received depot goserelin 3.6mg monthly for 3 months.[9] After treatment discontinuation, no ovarian follicles (determined by regular ultrasonography) were observed in any of the study participants.[9] Whether this is a typical response to goserelin remains to be determined as this is the only published study that has investigated the effect of goserelin in this clinical setting. Importantly, at the present time there is no clear evidence that GnRH analogues can initiate ovulation following premature ovarian failure and it is noteworthy that occasional ovulation has been reported in women with premature ovarian failure with or without medication; also, some women may have premature ovarian failure that is spontaneously reversible.

1.2 Effects on Estrogen and Progesterone

In animal studies, goserelin was approximately 10-fold more potent than repetitive or continuous GnRH administration in inhibiting estradiol and progesterone synthesis in the presence of FSH and testosterone.[1]

Following administration of a single depot 3.6mg goserelin injection to healthy menstruating women and women with benign gynaecological disorders, mean serum estradiol levels initially increased, then decreased (table I).[1,7,8,10]

During repeated monthly administration of goserelin (during the follicular phase) to 7 premenopausal women with uterine leiomyomata or premenstrual syndrome, estradiol levels were reduced 3 days after the dose had been administered,[15] and in 20 women with endometriosis, mean estradiol levels declined from 282 to 23 pmol/L during 6 months' goserelin treatment.[2] As with serum estradiol, mean serum progesterone levels initially peaked, but progesterone was suppressed to below 50 nmol/L by day 7 to 14.[1,10] In 8 women with genital endometriosis, serum progesterone levels were reduced to early follicular levels and serum testosterone and prolactin levels also declined 1 month after depot goserelin was administered.[14]

In a comparison of the hypoestrogenic effects of depot goserelin 3.6mg with depot intramuscular triptorelin 3.75mg in 15 women with either endometriosis or uterine leiomyomata,[13] serum estradiol levels were reduced to levels within the hypogonadal range in both treatment groups during 6 months' treatment. Prolactin and sex hormone binding globulin levels decreased during triptorelin treatment but remained unaltered in the goserelin recipients,[13] whereas testosterone levels tended to decrease during goserelin treatment but were unaltered during triptorelin treatment.[13]

Shaw[10] reported that the extent of ovarian suppression (determined by reductions in estradiol levels) achieved by depot goserelin 3.6 mg/month in women with endometriosis was greater and more consistent than that achieved by the comparator analogues intranasal buserelin 300μg 3 times a day or intranasal nafarelin 200μg twice a day. 20 women with endometriosis were included in each treatment group. In addition, all 3 GnRH analogues suppressed estradiol levels to a greater extent than danazol [200mg 3 times a day ($n = 20$)].

Epidermal growth factor (EGF) is a peptide hormone with cell proliferative activity which has been shown to bind to specific high affinity binding sites on the myometrium and on uterine leiomyomata.[22] Specific binding of radiolabelled [^{125}I] EGF to myometrial and fibroid homogenates

was significantly less in 13 women who had received monthly depot injections of goserelin for approximately 11 weeks before surgery than in 14 untreated women ($p < 0.01$).[18] In another small study of 13 women with uterine leiomyomata, the concentration of estradiol receptors (measured in homogenates for myometrium and fibroids) was significantly higher in recipients of goserelin 3.6 mg/month than in untreated controls ($p < 0.05$), whereas concentrations of EGF and progesterone receptors were significantly lower than in untreated women ($p < 0.01$ and $p < 0.05$, respectively).[17] As lower concentrations of EGF receptors may be related to the hypoestrogenic state, this finding may partly explain why uterine leiomyomata regress during treatment with goserelin.[17,22] Additionally, goserelin-induced hypoestrogenism leads to uterine blood flow and a subsequent decrease in the size of uterine leiomyomata (see section 3.2.2).[23]

1.3 Other Effects

Depot goserelin has similar activity to danazol in the suppression of endometriosis (see section 3.1). However, hyperinsulinaemia and insulin resistance are well-documented adverse effects of danazol treatment which are not observed in recipients of goserelin (table I).[16] In a comparative study that included 12 nonobese women with minimal endometriosis, serum insulin and plasma glucagon levels and responses to orally administered glucose increased significantly after danazol treatment ($p < 0.05$). In contrast, there were no changes in these parameters during or after goserelin treatment.[16] In addition, the free testosterone index also increased significantly in the danazol treatment group ($p < 0.01$) while there was no significant change in the testosterone index during goserelin treatment.[16]

Postmenopausal women and women who have undergone surgical oophorectomy have an increased incidence of cardiovascular disease, since low estrogen levels increase the activity of haemostatic risk factors for thromboembolism, cardiovascular disease and stroke.[11] During and after treatment with depot goserelin for 6 months, plasma levels of plasminogen activator inhibitor (PAI-1) and plasminogen activator (t-PA) significantly increased. In addition, protein-C and antithrombin III activity increased, resulting in a balance of haemostatic variables and preservation of the fibrinolytic defence mechanism against thromboembolic disease.[11]

Declining levels of estrogens in menopausal women are associated with changes in cholesterol metabolism and with an increase in the risk of cardiovascular disease.[12] In 2 studies that compared the effects of goserelin with danazol on the plasma lipid profile,[12,19] goserelin had a beneficial effect on plasma lipid coronary risk markers. In contrast, the plasma lipid profile of danazol recipients indicated that there was an increased risk of coronary heart disease in this patient group.[12,19]

2. Pharmacokinetic Properties

The pharmacokinetic properties of goserelin have been determined from investigations in animals and in men with prostate cancer. The reader is referred to the previous reviews of goserelin in *Drugs*[1] and *Drugs & Aging*[20] which comprehensively cover these data. In addition, the pharmacokinetic properties of goserelin have recently been investigated in healthy women and in women with benign gynaecological disorders.[24] Key pharmacokinetic data derived from studies of goserelin in men with prostate cancer, healthy volunteers and women with benign gynaecological disorders are summarised in table II. In most studies, depot goserelin 3.6mg was administered subcutaneously into the abdominal wall.

Goserelin is prepared as a sustained release depot injection formulation, in which 3.6mg of the drug is dispersed in a biodegradable poly (*d,l*-lactide-co-glycolide) polymer rod that allows uninterrupted drug delivery over a period of 4 weeks.[1,4] More recently, using the same delivery system, an ultra long-acting formulation containing 10.8mg goserelin has been developed which is suitable for administration every 12 weeks.[20] However, as no clinical data are available regard-

Table II. Overview of the pharmacokinetic properties of goserelin in men with prostate cancer, healthy volunteers and women with benign gynaecological disorders after single dose subcutaneous administration unless otherwise stated

Patient population	Pharmacokinetic parameter (mean value)	Dose	Value	Comments	Reference
Absorption					
Healthy volunteers (sex not stated)	C_{max} (μg/L) [t_{max}]	3.6mg depot	1.1 [15]		24
Women with benign gynaecological disorders	C_{max} (μg/L) [t_{max}]	3.6mg depot[a]	1.4 [15][b], 1.9 [15][c]	No evidence of accumulation after the second or sixth monthly sequential depot injection	24
Men with prostate cancer	C_{max} (μg/L) [t_{max}]	3.6mg depot	0.2-2.0 (first C_{max}) [2-8h], 2-3 (second C_{max}) [14-15days]		25-28
	C_{ss} (μg/L) [time to C_{ss} (days)]	120 μg/day infusion[d]	0.9-2.75 [2-4]	C_{ss} reached more rapidly (within 2-4 days) during continuous SC infusion[26] than with once-daily SC injections	26
	Release rate (μg/day)	3.6mg depot 1.8mg depot 0.9mg depot	120 60 30	Similar dose-proportional serum concentration profiles after depot SC injections of 0.9, 1.8 and 3.6mg	25-28
Distribution and plasma protein binding					
Men with prostate cancer	Vd (L)	250μg	13.7	As this value is similar to the normal extracellular fluid volume (12L), this suggests drug distribution outside the circulation with minimal plasma protein blinding[1]	26
Elimination					
Men with prostate cancer	$t_{½β}$ (h)	250μg[e]	4-5	Goserelin is excreted principally in the urine[1]	29
		250μg[f]	12		29
	CL (L/h)	250μg[e]	8		29
		250μg[f]	1.9	Dosage adjustment does not appear to be necessary in patients with severe renal impairment since clearance is sufficient to prevent accumulation of the drug	29

a Patients received depot goserelin monthly for 6mo.

b C_{max} and t_{max} after first and second monthly dose of goserelin depot.

c C_{max} and t_{max} after sixth monthly dose of goserelin depot.

d Patients received multiple doses of goserelin.

e Patients with normal renal function.

f Patients with severe renal impairment (creatinine clearance 0.6-1.2 L/h).

Abbreviations and symbols: C_{max} = maximum serum concentration; C_{ss} = steady-state serum concentration; CL = total body clearance; SC = subcutaneous; t_{max} = time to reach C_{max}; $t_{½β}$ = terminal elimination half-life; Vd = volume of distribution.

ing use of the 10.8mg formulation of goserelin in the treatment of women with benign gynaecological disorders, the pharmacokinetics of this preparation are not discussed in this section. Goserelin is administered by subcutaneous injection, as it is inactivated by intestinal peptidases when given orally, and variable absorption has been reported after intranasal administration.[1]

After subcutaneous administration of a single depot injection of goserelin 3.6mg to men with prostate cancer, there were 2 mean serum concentration peaks (C_{max}). The initial transient C_{max} was

0.2 to almost 2.0 μg/L at between 2 and 8 hours after administration; subsequently, there was a second mean C_{max} of approximately 2 to 3 μg/L, 14 to 15 days after the drug had been administered.[25,26] In women with benign gynaecological disorders (n = 50), a mean C_{max} value of 1.4 μg/L was reported 15 days after administration of the first and second of 6 sequential monthly doses of depot goserelin 3.6mg (table II). There was no evidence of drug accumulation over the 6 month investigation period (table II).[24] Depot goserelin has a dose-proportional serum concentration profile,[25,27,28] as demonstrated in a comparison of the release rates of goserelin from 3.6, 1.8 and 0.9mg subcutaneous depot injections (table II). In a comparative study, goserelin was demonstrated to have a consistent and reproducible controlled release profile from the polymer rod formulation when administered to patients with prostate cancer, whereas there was an initial surge in the release of triptorelin or leuprorelin following the first dose of microcapsule formulations of these GnRH analogues.[30]

Goserelin is excreted primarily in the urine and has a mean body clearance value of 8 L/h. Although clearance of the drug is reduced (and the terminal elimination half-life prolonged) in patients with severe renal impairment, dosage adjustment is not required as the rate of clearance is adequate to avoid accumulation.[29]

Following administration of a research aqueous nondepot formulation of goserelin (dose not stated) to 6 healthy volunteers, clearance of the drug was rapid (approximately 24 hours) and occurred via a combination of metabolism and urinary excretion.[24] The plasma elimination half-life and clearance of a single dose of a research aqueous nondepot formulation of goserelin (dose not stated) was unaltered in men and women with varying degrees of hepatic impairment (number of study participants not stated) compared with the same parameters in individuals with normal hepatic function.[24]

3. Therapeutic Efficacy in Benign Gynaecological Disorders

As goserelin has a suppressive effect on the pituitary-ovarian gonadal axis that leads to down-regulation of pituitary gonadotrophin secretion and sustained hypoestrogenaemia (see section 1), it is effective in the treatment of estrogen-dependent benign gynaecological disorders. The therapeutic efficacy of goserelin has been documented in numerous clinical studies conducted since the late 1980s, which have included women with endometriosis, uterine leiomyomata or dysfunctional uterine bleeding. Generally, most comparative studies were randomised but were not blinded because of the inherent difficulties involved in performing double-blind comparisons with drugs administered in different dosages and by different routes of administration. Goserelin has also been shown to be an effective treatment for women with ovarian hyperandrogenism, the majority of whom presented with hirsutism caused by polycystic ovary syndrome.[31,32] Earlier studies of goserelin in polycystic ovary syndrome were discussed in the previous review of goserelin in *Drugs*.[1] In addition, goserelin is well established as an adjunctive pretreatment prior to ovarian stimulation in women undergoing assisted reproduction. In all of the clinical investigations discussed in the following sections, women received the biodegradable depot formulation of goserelin, which was administered by subcutaneous injection into the abdominal wall every 28 days.

3.1 Treatment of Endometriosis

Endometriosis is an estrogen-dependent gynaecological disorder characterised by the presence of functioning endometrial tissue in an area outside the uterus, reportedly affecting 1 in 15 premenopausal women.[3] Abnormal endometrial tissue may develop between the muscle fibres of the myometrium or in other areas of the pelvic cavity, including the ovaries. The most commonly observed symptom of endometriosis is dysmenorrhoea, which is reported to occur in approximately 70%

of women presenting with this condition;[33] dyspareunia, pelvic pain and tenderness are also frequently reported symptoms.[33] There is an association between severe endometriosis and infertility which has been well documented.[34,35] As the ectopic endometrium is responsive to cyclical secretion of estrogen and progesterone, the rationale behind the treatment of endometriosis with goserelin is suppression of estrogen synthesis and subsequent establishment of amenorrhoea.[1] Other treatment options include alternative GnRH analogues, danazol, oral contraceptives, progestogens or surgery.[33]

3.1.1 Noncomparative and Comparative Studies

The clinical efficacy of goserelin in the treatment of women with endometriosis [revised American Fertility Society (RAFS) stages I, II, III and IV; minimal, mild, moderate and severe disease] has been documented in numerous noncomparative[1,36-40] and randomised comparative studies,[34,41-45] which are summarised in table III. Objective endpoints used to determine treatment efficacy were based on laparoscopic findings and included RAFS implant (endometriosis) and adhesion scores, and the additive diameter of implant (ADI) scores. In most studies, women underwent staging classification by laparoscopy before treatment was initiated. In addition, self-rated subjective responses (including symptomatic relief of dysmenorrhoea, dyspareunia and/or pelvic pain) were assessed during and after completion of treatment. For most goserelin recipients, amenorrhoea was achieved 1 to 2 months after initiation of goserelin treatment, thus preventing further endometrial seeding of viable endometrial fragments and the development of symptomatic endometriosis.

In a small dose-ranging study (n = 17), a 3.6mg dose of depot goserelin was significantly more effective than either a 1.8mg or a 0.9mg dose of the drug in improving objective parameters of endometriosis,[36] and in another small study (n = 18) a similar level of clinical improvement was achieved whether goserelin was administered in the midluteal or in the early follicular phase.[46]

Since the previous review of goserelin in *Drugs*,[1] which reported preliminary findings indicating that goserelin and danazol were similarly effective in the treatment of endometriosis, 2 large nonblind comparative studies have been published (table III).[34,41] In both of these studies, women with RAFS grades I to IV endometriosis experienced objective and subjective improvements (notably in pelvic pain and dyspareunia) during and after 6 months' treatment with either goserelin or danazol (table III). Goserelin was effective in the resolution of endometriotic implants, with mean total RAFS scores decreasing by 53.0 and 59.1% after goserelin treatment and by 33.0 and 51.7% after danazol treatment (table III).[34,41] While there were no significant differences in mean total RAFS and implant scores between either treatment group, there was a more marked reduction in mean total RAFS and implant scores after treatment with goserelin than after danazol (fig. 1).[34]

When women with stage IV endometriosis were analysed separately, a significantly higher proportion ($p = 0.01$) of goserelin recipients than danazol

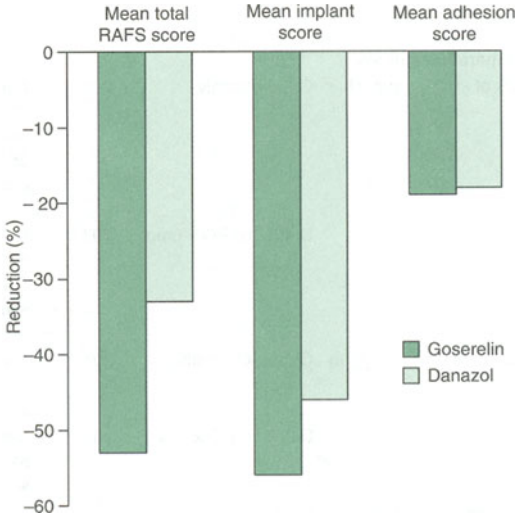

Fig. 1. Percentage reductions in mean revised American Fertility Society (RAFS) endometriosis scores. Study participants received either subcutaneous depot goserelin 3.6 mg/month (n = 208) or oral danazol 400mg twice daily (n = 107), for 6 months.[34]

Table III. Summary of noncomparative and comparative studies of depot goserelin (G) administered subcutaneously for 6 months in the treatment of women with endometriosis, RAFS stages I-IV

Reference	Study design	Dosage regimen (mg)	No. of patients enrolled	Objective response	Subjective response (mean symptom severity scores at baseline and after treatment using various scales)	Overall efficacy
Noncomparative and dose-ranging studies						
Magini et al.[46]	nb, r	G 3.6 monthly [administered during early follicular phase] (regimen A)	6	Mean total RAFS score ↓ for endometriotic lesions**	NR	A ≡ B ≡ C
		G 3.6 monthly [administered in luteal phase] (regimen B)	4	Mean total RAFS score ↓ for endometriotic lesions*	NR	
		G 3.6 twice monthly [day 3 and day 17 of the menstrual cycle] (regimen C)	8	Mean total RAFS score ↓ for endometriotic lesions**	NR	
Reichel et al.[37]	mc, nb	G 3.6 monthly	146	Mean implant score ↓ 71.9%, mean total implant and adhesion score ↓ 50%, mean total additive implant diameter ↓ 78%	Mean total subjective score ↓ 86%, mean total pelvis symptom score ↓ 93%	
Uemura et al.[36]	Dose-ranging, nb	G 0.9 monthly	5			G 3.6 > G 1.8 > G 0.9
		G 1.8 monthly	5			
		G 3.6 monthly	7			
Venturini et al.[38]	nb	G 3.6 monthly	32	Mean total RAFS score ↓ 47.3%	% of women with severe/very severe symptoms ↓ from 56.3 to 15.6%***, % of asymptomatic women/women with mild symptoms ↑ from 18.7 to 90.6%***	
Comparative studies						
Rock et al.[34]	mc, nb, r	G 3.6 monthly	208	Mean total RAFS score ↓ 53%; mean implant (endometriosis) score ↓ 56%; mean adhesion score ↓ 19%	Total subjective symptom scores ↓†; marked reduction in total pelvic symptom scores throughout treatment and during 72wk post-treatment phase	G ≡ D
		D 400 bid PO × 6mo	107	Mean total RAFS score ↓ 33%; mean implant score ↓ 46%; mean adhesion score ↓ 18%	Total subjective symptom scores ↓†; marked reduction in total pelvic symptom scores throughout treatment and during post-treatment phase	
Shaw et al.[41]	mc, r, nb	G 3.6 SC monthly	204	Mean total RAFS score ↓ 59.1%†; mean implant score ↓ 81.4%†	Mean total subjective scores ↓*	G ≡ D
		D 200 tid PO × 6mo	103	Mean total RAFS score ↓ 51.7%†; mean implant score ↓ 73.5%†	Mean total subjective scores ↓*	
Vercellini et al.[42]	r, nb	G 3.6 monthly	29	NR	Deep dyspareunia ↓, nonmenstrual pain ↓	G ≡ OC
		OC 1 t/d × 6mo	28	NR	Deep dyspareunia ↓, nonmenstrual pain ↓, dysmenorrhoea ↓	

Table III. Contd

Reference	Study design	Dosage regimen (mg)	No. of patients enrolled	Objective response	Subjective response (mean symptom severity scores at baseline and after treatment using various scales)	Overall efficacy
Comparative studies using 'add-back' therapy						
Howell et al.[43]	nb, r	G 3.6 monthly	25	Mean total RAFS score ↓ from 19.4 to 13.3 (↓ 31.4%)	Mean pain score ↓ from 7.5 to 1.4 (↓ 81.3%)	G ≡ G+ E + M
		G 3.6 monthly + E 25μg twice weekly TD + M 5/day PO	25	Mean total RAFS score ↓ from 17.7 to 10.4 (↓ 41.2%)	Mean pain score ↓ from 7.2 to 1.6 (↓ 77.8%)	
Kiilholma et al.[44]	db, pc, r	G 3.6 monthly + E 2/day + N 1/day	43	Mean total RAFS score ↓ from 22.3 to 10.7 (↓ 52%),† mean total additive implant diameter ↓ from 31.8 to 12.1 (↓ 62%)†		G ≡ G + E + N
		G 3.6 monthly + E placebo 1 tab/day + N placebo 1 tab/day	45	Mean total RAFS score ↓ from 19.9 to 9.2 (↓ 54%),† mean total additive implant diameter ↓ from 33.6 to 8 (↓ 76%)†		
Schlaff et al.[45] [abstract]	db, pc, r	G 3.6 monthly + CE placebo 1 tab/day + M placebo 1 tab/day (day 15 to week 22)	119		Rapid reduction in pelvic symptoms by wk 4. Pain relief maintained over 24wk treatment period	G ≡ G + CE + M
		G 3.6 monthly + CE 0.3/day + M 5/day (day 15 to week 22)	113		Rapid reduction in pelvic symptoms by wk 4. Pain relief maintained over 24wk treatment period	
		G 3.6 monthly + CE 0.625/day + M 5/day (day 15 to week 22)	113		Rapid reduction in pelvic symptoms by wk 4. Pain relief maintained over 24wk treatment period	

Abbreviations and symbols: bid = twice daily; CE = conjugated estrogens; D = danazol; d = day(s); E = 17β-estradiol; M = medroxyprogesterone; mc = multicentre; mo = months; N = norethisterone; nb = nonblind; NR = not reported; OC = oral contraceptive containing ethinyl estradiol 0.02mg and desogestrel 0.15mg per tablet; pc = placebo-controlled; PO = orally; r = randomised; RAFS = revised American Fertility Society; tab = tablet; T/D = transdermally; tid = 3 times daily; wk = week; ↓ = decreased; ↑ = increased; > indicates superior efficacy; ≡ indicates equivalent efficacy; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; †$p < 0.0001$ *vs* baseline.

recipients experienced a 50% or greater reduction in the RAFS score from the pretreatment value.[34]

As oral contraceptive therapy has been shown to be effective in alleviating pelvic pain in women with endometriosis,[42] the efficacy of goserelin in relieving symptoms of endometriosis was compared with that of low-dose oral contraceptive therapy (table III).[42] After 6 months' treatment, a significant reduction in deep dyspareunia and nonmenstrual pain was reported for women in both goserelin and oral contraceptive treatment groups. After discontinuation of treatment, symptoms recurred with similar severity in women in both groups.[42]

In a large noncomparative study (n = 146),[37] 31% (20 of 64) of previously infertile women conceived within 12 months of discontinuing a 6-month course of goserelin therapy.[37] In a comparative study[47] in which women with genital endometriosis received either depot goserelin 3.6 mg/month or intranasal buserelin 900 μg/day, 60% of previously infertile women in the whole study group became pregnant during the 6 months following discontinuation of drug treatment. How-

ever, as neither of these studies included a control group, it cannot be concluded that the restoration of fertility in these patients was the result of drug treatment.

Depot goserelin, given monthly for 3 months, was an effective treatment of women with ovarian cysts (prior to cyst drainage) [n = 40],[48] reducing cyst size and glandular mitotic activity. In contrast, a comparator group of women with similar clinical characteristics (n = 40) who underwent cyst drainage without goserelin pretreatment experienced a rapid recurrence of ovarian cysts.[48]

3.1.2 Studies Using 'Add-Back' Therapy

Although goserelin is an effective treatment for endometriosis, its use as a single agent is hampered by hypoestrogenic adverse effects such as hot flushes, sweating, vaginal dryness and loss of libido (see section 4).[49] In addition, long term goserelin therapy has been reported to have a negative effect on bone mineral density.[43,50] Concomitant 'add-back' estrogen/progesterone hormone replacement therapy (HRT) has been shown to reduce bone mineral density loss in women being treated with goserelin (see section 4) and this was confirmed in a randomised comparative study conducted to determine the clinical efficacy of 'add-back' HRT therapy in combination with goserelin in the treatment of endometriosis (table III).[43] No significant differences in clinical efficacy (determined by objective and subjective evaluation criteria) were observed between recipients of goserelin single-agent therapy and recipients of the combination regimen (table III). However, significantly fewer recipients of the combination regimen experienced hot flushes and loss of libido than recipients of goserelin single-agent therapy ($p < 0.01$) [see section 4].[43] Similarly, in a placebo-controlled study,[44] 'add-back' estrogen/progesterone therapy resulted in a diminishing of postmenopausal adverse effects associated with goserelin treatment while the therapeutic efficacy of goserelin was not reduced. In another recent multicentre study (published as an abstract),[45] estrogen/progesterone 'add-back' therapy maintained effective pelvic symptom relief for patients with endometriosis and reduced bone mineral density loss and other hypoestrogenic adverse effects related to goserelin treatment. Although there was evidence of some bone loss in all treatment groups, the rate of bone mineral density loss was significantly less in both groups of women who received goserelin with HRT ($p < 0.005$) than in patients who received goserelin with placebo HRT.[45]

3.2 Treatment of Uterine Leiomyomata

Uterine leiomyomata (fibroids) are benign, often asymptomatic,[3] estrogen-dependent tumours which are composed of smooth muscle and connective tissue.[51] These slow-growing tumours are estimated to occur in approximately 20% of women of reproductive age[3] with symptomatic individuals often presenting with an enlarged uterus and menorrhagia.[52] Traditionally, surgical intervention [hysterectomy or myomectomy (extirpation of myoma)] has represented the mainstay of uterine leiomyoma management. However, more recently goserelin has demonstrated efficacy as adjunctive pretreatment of women with uterine leiomyomata prior to surgery and has been used as an alternative to surgery in the management of uterine leiomyomata. Results of studies that have evaluated the efficacy of goserelin in the management of uterine leiomyomata are summarised in table IV. In most studies, the presence of fibroids and the uterine response to treatment were determined by ultrasound.

3.2.1 Prior to Surgery

As pretreatment of women requiring surgery, goserelin has been shown to reduce leiomyoma size, thus facilitating surgical removal of these tumours. In noncomparative and comparative studies,[53-59,63,64] goserelin treatment prior to surgery led to shrinkage of uterine leiomyomata and reduction in uterine volume. The extent of reduction in uterine volume reported by Lumsden and colleagues[56] after women with uterine leiomyomata (awaiting hysterectomy) received either goserelin or placebo for 3 months is shown in figure 2.

In addition, goserelin surgical pretreatment was associated with technically easier surgical proce-

Table IV. Summary of comparative studies of depot goserelin (G) administered subcutaneously at monthly intervals in the treatment of premenopausal women with uterine leiomyomata

Reference	Study design	Treatment regimen (mg) [duration]	No. of patients enrolled	Mean operative blood loss (ml)	No. of patients requiring blood transfusions (%)	Mean uterine volume (ml)		Mean leiomyoma volume (ml) post-treatment (% change)
						pre-treatment	post-treatment (% change)	
Goserelin adjunctive pretreatment for women requiring surgery for removal of uterine leiomyomata								
Audebert et al.[53]	nb, r	G 3.6 [6mo]	35	188	0	323.8	207.5 (40↓)	96.8 (↓42)
		Immediate surgery	36	289	7 (19)	495.1	419.5 (15↓)	252.2 (↑6)
Benagiano et al.[54]	mc, db, r, pc	G 3.6 [3mo] + PFe [3mo]	60	251	7 (12)	383	(37↓)*	(47↓)*
		G 3.6 [3mo] + Fe 600/day [3mo]	62	342	4 (6)	400	(40↓)*	(44↓)*
		PG [3mo] + Fe 600/d [3mo]	63	389	11 (17)	457	(7↓)	(7↓)
Gerris et al.[55]	mc, nb, r	G 3.6 [3mo]	123	NR[a]	9 (7)		295	93.2
		Immediate surgery	124	NR[a]	15 (12)		457	156.3
Lumsden et al.[56]	pc, db, r	G 3.6 [6mo]	35	187**	NR	295	224 (22.4↓)	
		P [6mo]	36	307	NR	444	458.6 (3.3↑)	
McClelland & Quinn[57]	nb	G 3.6 [1mo]	6					452 (↓39.6 [range 30-46])
Vercellini et al.[58]	nb, r	G 3.6 [6mo]	41	186[b], 132[c]	0	528	251 (52.5↓)	
		Immediate surgery	92	351[b], 264[c]	40[b] (43), 7[c] (8)	555		
Goserelin treatment for uterine leiomyomata (as an alternative to surgery)								
Costantini et al.[62]	nb, r	G 3.6 [6mo]	21				<30%↓ 3/21[f], 30-60%↓ 8/21[f], >60%↓ 10/21[f]	<30%↓ 3/21[f], 30-60%↓ 10/21[f], 60%↓ 8/21[f]
		B 500μg SC tid × 10 days then 200μg IN × 6mo	21				<30%↓ 4/21[f], 30-60%↓ 7/21[f], >60%↓ 10/21[f]	<30%↓ 5/21[f], 30-60%↓ 7/21[f], >60%↓ 9/21[f]
Cagnaccini et al.[59]	nb	G 3.6 [6mo]	22				(50↓)	(50↓)
		G 3.6 [12mo]	8				(50↓) [maximum shrinkage after 12mo treatment]	(50↓) [maximum shrinkage after 6mo treatment]
Maheux et al. [60]	nb[d]	G 3.6 [3mo], then G 3.6 + HRT PO [9mo]	10					(↓49.3 during first 3mo); no significant further changes
Maheux et al.[61]	nb, r	G 3.6 [6mo]	NR					(↓37.4)
		G 7.2 [6mo]	NR[e]					(↓46.4)***

a Data for operative blood loss was log transformed and presented as a ratio of mean operative blood loss for goserelin patients divided by the mean operative blood loss for patients in the surgery alone group. The estimated ratio was 0.77 (p = 0.01).
b Abdominal hysterectomy.
c Vaginal hysterectomy.
d Noncomparative study.
e 46 women in entire study group.
f Number of responding patients.

Abbreviations and symbols: B = buserelin; db = double-blind; Fe = iron; HRT = hormone replacement therapy (conjugated equine estrogens 0.3mg on days 2-5 of the cycle for 12mo plus medroxyprogesterone 5mg on days 16-25 of the cycle); IN = intranasally; mc = multicentre; mo = months; nb = nonblind; NR = not reported; pc = placebo-controlled; PFe = placebo iron; PG = placebo goserelin injection; PO = orally; r = randomised; SC = subcutaneously; tid = 3 times daily; ↑ indicates increased; ↓ indicates decreased; *p = 0.0001 *vs* iron-only treatment group; **p < 0.05 *vs* placebo; ***p ≤ 0.0001 *vs* 3.6mg.

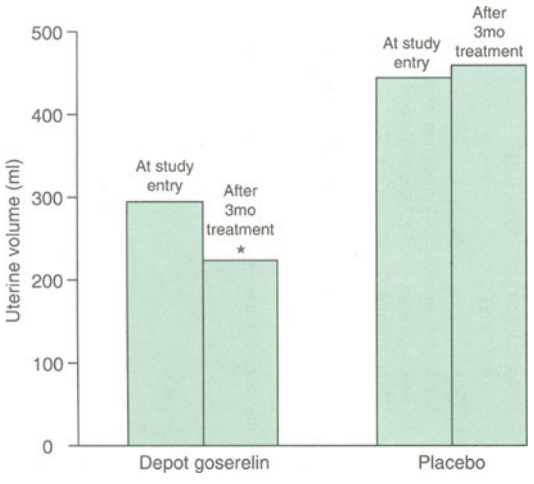

Fig. 2. Mean uterine volume (ml) of women with uterine leiomyomata before and after 3 months' treatment with either subcutaneous depot goserelin 3.6 mg/month (n = 35) or placebo (n = 36).[56] *p = 0.002 *vs* placebo.

dures[53,55,56] and with higher rates of vaginal, rather than abdominal, hysterectomy[58] compared with untreated women with similar clinical characteristics undergoing immediate surgery,[58] or compared with women who received placebo for 3 months prior to surgery.[56]

As a result of goserelin-induced leiomyoma shrinkage and reduced leiomyoma blood flow (measured by Doppler ultrasound[65]), bleeding decreased during and after hysterectomy and transfusion requirements were reduced.[1,64,65] In earlier studies reviewed by Chrisp and Goa,[1] 3 to 4 months' goserelin treatment prior to hysterectomy effectively reduced intraoperative blood loss and reduced blood transfusion requirements around the time of surgery. These findings were subsequently confirmed in several more recent studies,[53,55,58,64,65] including a placebo-controlled study which demonstrated that median operative blood loss during hysterectomy was significantly lower in 35 women pretreated with goserelin (blood loss = 187ml) than in 34 evaluable women who received placebo (blood loss = 307ml) [$p < 0.05$].[56] Similarly, mean operative blood loss was significantly less in women who had received goserelin for 6 months before surgery than in untreated controls [186 *vs* 351ml for abdominal hysterectomy ($p < 0.0001$); 132 *vs* 264ml for vaginal hysterectomy ($p < 0.01$)]. Whereas no goserelin recipients required blood transfusions (as a result of preoperative correction of severe iron deficiency anaemia) 51% of untreated control patients required transfusions before, during or after surgery.[58]

Goserelin adjunctive surgical pretreatment was shown to increase haemoglobin levels in women who had low haemoglobin levels (as a result of leiomyoma-associated menorrhagia) in several studies.[56,58,64,65] This was achieved through the establishment of amenorrhoea.[64] Increased haemoglobin levels prior to surgery represent another factor contributing to the reduced transfusion requirements of goserelin recipients before, during or after surgery compared with their untreated counterparts.[55,56,58,66] Depot goserelin, administered for 6 months to 41 women with myoma-associated menorrhagia, was associated with a 56% increase in mean haemoglobin levels before surgery.[58] Similarly, a comparison of haemoglobin levels after 3 months' goserelin treatment (prior to hysterectomy or myomectomy) with immediate surgery[53] reported a significantly higher mean haemoglobin level (12.63 g/dL) in goserelin recipients at the time of surgery than untreated patients (11.79 g/dL) [$p = 0.02$]. Postoperatively, there was a greater difference in these values [11.47 g/dL for the goserelin recipients and 10.20 g/dL for the untreated group (p value not reported)].

Recently, a combination of goserelin with orally administered iron was reported to be an effective adjunctive treatment of women with anaemia prior to surgery.[54] During the study, patients were only allowed iron supplements as indicated in the study protocol. Preoperative mean serum haemoglobin concentrations increased in all groups, but the increase in women who received goserelin plus iron was more marked than in the other treatment groups. Uterine and fibroid volumes decreased in women in all groups but the reduction was significantly greater in women who received goserelin than in women who received iron only (table IV).

Preoperative goserelin treatment (3.6 mg/month for 2 months) significantly reduced the size of large submucous fibroids and decreased fluid resorption in a study that included 60 women requiring myomectomy by hysteroscopy.[67] In addition, haemoglobin levels were restored to within the normal range.

3.2.2 As an Alternative to Surgery

In recent years the GnRH analogues have also become recognised as an effective (though temporary[59,68]) alternative to surgery in the management of uterine leiomyomata. As in surgical adjunctive pretreatment, therapeutic efficacy was achieved through induction of a hypogonadal state and subsequent shrinkage of leiomyomata and of uterine volume.[1,62,65,68-71] In women with uterine leiomyomata, goserelin induced a consistent reduction of ≤60% in uterine volume after 3 to 6 months' treatment (table IV).[1,52,71] Most shrinkage in uterine volume occurred during the first 4 months' treatment.

As the GnRH analogue buserelin has also demonstrated efficacy in the treatment of uterine leiomyomata, a randomised nonblind study was conducted to compare the therapeutic efficacy of buserelin with that of goserelin.[62] Both drugs produced similar reductions in mean uterine volume (table IV).[62] At present, there are no other published comparisons of goserelin with other GnRH analogues in the treatment of uterine leiomyomata, despite the proven efficacy of other GnRH analogues in this indication.

In a small study (n = 13) which compared goserelin with danazol in the treatment of menorrhagia in women with uterine leiomyomata, goserelin recipients experienced a significant increase in mean haemoglobin levels after 3 months' treatment ($p < 0.01$), while the increase in haemoglobin levels observed in danazol recipients after 3 months' treatment did not achieve statistical significance.[72]

The therapeutic efficacy of a combination goserelin/HRT regimen was demonstrated in a small nonblind noncomparative study.[60] Ten women with uterine leiomyomata received depot goserelin as a single agent for 3 months after which estrogen/progesterone HRT was added to the goserelin regimen on a cyclical basis for a further 9 months (table IV). After 3 months' goserelin treatment, leiomyoma size and symptomology were reduced. These improvements were sustained during the period of combination treatment. Additionally, during combination treatment bone mineral density was conserved and other goserelin-related adverse effects were reduced (see section 4).[60]

Although, as discussed, uterine leiomyomata may be effectively treated with goserelin, treatment with this agent has been limited by a lack of sustained benefit, with rapid regrowth of leiomyomata occurring 3 to 4 months after discontinuation of treatment.[60,71,73-75] However, as a nonsurgical treatment, goserelin may be useful for women approaching menopause in whom uterine leiomyomata are likely to degenerate naturally.[52,74]

3.3 Treatment of Dysfunctional Uterine Bleeding

Dysfunctional uterine bleeding is a gynaecological disorder associated with considerable morbidity,[76] which is reported to affect approximately 20% of premenopausal women.[77] Women with this disorder usually present with excessive blood loss; management often involves surgical intervention (hysterectomy, surgical ablation or surgical resection).[76,78] In women with dysfunctional uterine bleeding, monthly depot goserelin 3.6mg injections have proved to be an effective adjunctive surgical pretreatment, suppressing endometrial growth, reducing uterine size and depth of the endometrium, and, as a consequence, facilitating surgical ablation or resection.[79,80] In addition, fluid absorption, which may occur as a potentially serious complication of surgical ablation,[77] has been shown to be significantly reduced following goserelin treatment.[79,80] The therapeutic success of goserelin in this indication is, as in the treatment of endometriosis and uterine leiomyomata, achieved through the induction of sustained

hypogonadism and the establishment of amenorrhoea.

In 270 women with dysfunctional uterine bleeding, 2 months' preoperative treatment with goserelin (administered at the end of the luteal phase after weeks 4 and 8) facilitated endometrial ablation (using laser techniques) by suppressing endometrial growth and by reducing endometrial thickness and vascularity.[79] As the total intrauterine surface area was reduced, rapid endometrial ablation was achieved and hysterectomy avoided. Thus, the duration of hospital stay and the morbidity associated with this procedure were reduced.[79]

When administered 6 and 2 weeks prior to radiofrequency endometrial ablation, goserelin effectively produced an inactive endometrium and reduced uterine cavity size.[81] In another study (n = 60), goserelin administration 4 to 6 weeks prior to endometrial ablation facilitated surgery; a further dose of goserelin administered after surgery enhanced rates of amenorrhoea thus allowing scar formation by suppressing endometrial growth.[82]

As goserelin induces mucosal thinning, decreases bleeding and reduces mucous debris in women with dysfunctional uterine bleeding,[83] administration prior to surgical intervention may increase hysteroscopic visibility, facilitating hysteroscopic endometrial resection. In a recent randomised study,[83] women with menorrhagia either received goserelin for 2 months prior to surgery (n = 33) or underwent hysteroscopic endometrial resection only (n = 22) during the proliferative phase of the menstrual cycle.[83] Goserelin recipients experienced a 19% reduction in mean uterine volume ($p < 0.05$) and a 16% increase in haemoglobin levels ($p < 0.01$). Furthermore, hysteroscopic endometrial resection was performed significantly more quickly in the goserelin treatment group [$p = 0.002$] (22% reduction in mean operating time) than in the control group. Goserelin pretreatment was also associated with improved intrauterine operating conditions: these were reported to be 'good' or 'excellent' in 64% of goserelin recipients and 27% of the control patients.[83]

Goserelin has also been reported to be an effective nonsurgical management strategy for women with dysfunctional uterine bleeding and abnormal endometrial growth, thus offering a useful alternative to surgical ablation for women with severe symptoms.[76] Goserelin improved haematological parameters of anaemia in 23 women with chronic heavy anovulatory uterine bleeding (associated with endometrial hyperplasia) who had severe iron-deficiency anaemia.[84] After 6 months' goserelin treatment, the mean haemoglobin level increased from 7.9 to 13.8 g/dL, mean haematocrit from 26.3 to 41.6%, mean serum iron from 19.8 to 63.3 μg/dL (3.5 to 11.3 μmol/L) and mean serum ferritin from 6.2 to 35.3 μg/L. Mean percentage increases in these parameters are shown in figure 3. At follow-up biopsy endometrial regression was evident in all 11 patients who had endometrial hyperplasia before treatment.[84]

As danazol has also demonstrated efficacy in thinning the endometrium,[85] several recent large studies have compared the relative efficacies of danazol with goserelin in women with dysfunctional uterine bleeding.[85-87] In 2 studies,[85,87] which enrolled a total of 220 women with dysfunc-

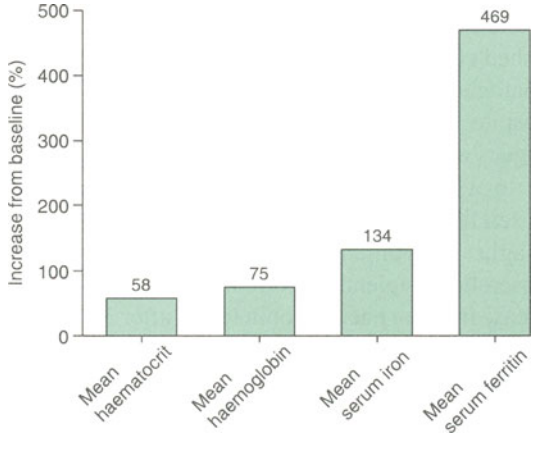

Fig. 3. Mean percentage increases from baseline in mean haematocrit, haemoglobin and mean serum iron and ferritin in women with chronic anovulatory uterine bleeding after treatment with subcutaneous depot goserelin 3.6 mg/month for 2 months.[84]

tional uterine bleeding, goserelin was at least as effective as danazol in thinning the endometrium. In another study (n = 120),[86] goserelin was significantly more effective than danazol in reducing endometrial thickness when assessed by vaginal ultrasound and histologically ($p < 0.03$).

Goserelin was administered in combination with cyclical 'add-back' HRT (estradiol 1 mg/day for 11 days + norgestrol 1 mg/day for the subsequent 11 days) to 20 women experiencing heavy menstrual loss, to counteract hypoestrogenic complications and bone demineralisation associated with goserelin single-agent treatment.[76] During 3 treatment cycles, patients experienced a significant reduction in blood loss ($p < 0.001$) and a significant decrease in the median length of menstruation ($p < 0.001$) compared with pretreatment. Combination treatment also resulted in a significant reduction in the number of women experiencing dysmenorrhoea, premenstrual symptoms, menstrual flooding, and passage of blood clots ($p < 0.005$).[76] Similarly, in another study that determined the efficacy of a combination regimen of goserelin and HRT therapy,[78] improvements in dysfunctional bleeding and reduced endometrial overstimulation were observed. As in studies of the drug in the treatment of uterine leiomyomata (see sections 3.2.1 and 3.2.2), haemoglobin levels increased significantly ($p < 0.001$) during treatment. Moreover, histological analysis revealed the restoration of adequate endometrial proliferation and differentiation.[78]

One small noncomparative study (n = 21) reported that a combination regimen of goserelin 3.6 mg/monthly and HRT (estradiol valerate 1 mg/day and medroxyprogesterone 5 mg/day started 3 weeks after the first dose of goserelin) was an effective treatment regimen for women with pelvic pain and venous congestion.[88] After 13 weeks' combination therapy, significant reductions in median uterine area (approximately 30%) and in median endometrial thickness ($p < 0.01$ *vs* baseline) were reported. In addition, the incidence of goserelin-related estrogen-deficiency adverse effects was reduced (see section 4).

3.4 Goserelin as Adjuvant Therapy in the Treatment of Fertility Disorders

Concomitant administration of GnRH analogues with drugs that induce ovulation is a widely accepted method of producing ovarian stimulation used in many assisted reproduction programmes worldwide.[4] In this clinical setting, GnRH analogues are used to down-regulate the pituitary gland, thus preventing a premature preovulatory LH surge, in order to synchronise follicular growth[6,89] before ovarian stimulation in *in vitro* fertilisation (IVF) or gamete intrafallopian transfer (GIFT).[1,33] This treatment strategy has been shown to improve ovulation induction rates and to increase the success rate of assisted reproduction procedures.[4]

In most clinical investigations of the efficacy of goserelin in this setting, depot goserelin 3.6mg effectively down-regulated the pituitary gland prior to controlled ovarian stimulation with menotropins [human menopausal gonadotrophins (LH and FSH)] for IVF or GIFT,[1,6,90-95] preventing a surge in LH levels and subsequent premature luteinisation. As a result, the inherent risk of cancelled cycles was reduced, leading to an increase in the numbers of oocytes recovered.[6,90] Goserelin was generally administered in the mid-luteal phase of the cycle, after which superovulation was induced with human menopausal gonadotrophin (HMG) administered about 2 weeks later, i.e. as a 'long' regimen.[93] After the leading 2 to 3 follicles reached a diameter of approximately 20mm, an ovulatory dose of human chorionic gonadotrophin was given and oocytes were recovered 24 to 36 hours later.

No data are currently available regarding the use of goserelin in 'flare-up' or 'short' protocols in which the GnRH analogue and exogenous gonadotrophins are administered concomitantly, with a resultant elevation of endogenous gonadotrophins.[4] However, long ovulation induction regimens (such as those described with depot goserelin) appear to be superior to short regimens and are used more widely in assisted reproduction centres.[4]

As both short- and long-acting GnRH analogues have been used in IVF programmes, a randomised study was conducted to compare the pituitary down-regulating efficacy of a single 3.6mg subcutaneous dose of goserelin administered between days 21 and 23 of the cycle (n = 49) with that of intranasal buserelin 200μg 5 times daily (n = 51) administered on days 21 to 23 of the menstrual cycle. Both treatments were equally effective in suppressing pituitary function on day 1 of HMG administration; however, goserelin recipients required significantly more ampoules of HMG to achieve follicular maturation than buserelin recipients ($p < 0.05$). The respective oocyte recovery rates for the goserelin and buserelin treatment groups were 6.7 and 6.3% and both groups reported similar pregnancy rates; 11 and 12 pregnancies, respectively. The tolerability and acceptability profile for goserelin was superior to that of buserelin, offering a 'less stressful' alternative for women requiring IVF.[6,90]

In general, GnRH analogue adjunctive pretreatment of women undergoing IVF of GIFT has been used in women for whom either HMG or clomifene have proved to be unsatisfactory in achieving follicular stimulation.[96] In a comparison of the efficacy of goserelin with clomifene as adjunctive pretreatment, women were randomised to receive either a single dose of depot goserelin 3.6mg administered 2 to 3 weeks before HMG stimulation (n = 152), or clomifene 100 mg/day administered for 5 days before ovarian stimulation with HMG (n = 151). Goserelin/HMG was the more effective stimulation protocol, as determined by the virtual absence of cancelled cycles and the increase in retrieved oocyte numbers in the goserelin treatment group. As a consequence, there was a significantly increased pregnancy rate in the patients treated with goserelin (36.8%) compared with that in the clomifene treatment group (24.5%; $p < 0.02$).[96] However, since significantly more HMG ampoules were required to produce follicular stimulation in goserelin recipients than in clomifene recipients (44.9 *vs* 9.9; $p < 0.0001$) the cost of one cycle's treatment with goserelin/HMG was 40% more than the clomifene regimen.[96]

A retrospective analysis of the fertilisation and aneuploidy rates achieved by either goserelin (n = 43) or clomifene (n = 233) [in combination with HMG] in infertile women undergoing IVF revealed significantly higher fertilisation rates in goserelin recipients than in clomifene recipients.[91] Although the incidence of aneuploid oocytes was significantly greater in goserelin recipients than in clomifene recipients ($p < 0.001$), when selection against chromosomally abnormal oocytes was performed, goserelin was found to have no intrinsic effect on the chromosomal complement of the oocyte.

One small study has also demonstrated the efficacy of goserelin (given in combination with HMG) in infertile women with ovarian polycystosis unresponsive to clomifene.[97]

4. Tolerability

As the GnRH analogues suppress gonadal steroidogenesis and decrease serum estradiol levels (see section 1), the tolerability profiles of these drugs are characterised by adverse effects associated with suppression of ovulation and induction of the hypoestrogenic state.[1,33,34,41] These adverse effects are similar to the symptoms that occur in postmenopausal women[98] and include hot flushes, vaginal dryness, headache and decreased libido.[34,41] Importantly, hot flushes have been reported to be a persistent adverse effect during treatment with various GnRH analogues and may be severe enough to compromise patient compliance.[99] In a review of several clinical studies in which women had received goserelin for various benign gynaecological disorders, hot flushes were reported as the most frequently observed adverse effect of goserelin therapy, occurring in 89% (763 of 862) of women.[100] The incidence of hot flushes and other hypoestrogenic adverse effects reported in this study is shown in figure 4.

In 2 large clinical studies that compared depot goserelin with oral danazol in women with endometriosis,[34,41] goserelin-related adverse effects

were, as expected, of a hypoestrogenic nature, while danazol recipients reported androgenic adverse effects,[34,41] including acne, oily skin, weight gain and hirsutism. In one study,[34] significantly more patients withdrew from danazol treatment (16.8%) than from goserelin treatment (7.2%), because of treatment-related adverse effects. Local reactions at the site of injection are observed in approximately 3% of women receiving goserelin.[34]

Loss of bone mineral density [particularly from the lumbar spine and proximal femur[99,101-104] (important sites for the development of osteoporosis[103])] is also a well-documented adverse effect of goserelin and other GnRH analogues.[105,106] In women with benign gynaecological disorders, bone mineral density losses have ranged from 4 to 12% (using quantitative computerised tomography scanning) after 6 months' treatment with GnRH analogues;[102] during goserelin treatment, bone mineral density losses from the lumbar spine have been reported to be approximately 4.6% (using dual x-ray absorbtiometry) although in some women no bone loss is observed.[75,102] However, it is important to note that different methods, with varying reliabilities and precision, have been used to determine bone mineral density losses during and after treatment with goserelin and other GnRH analogues.[105] In addition, as bone losses may be measured at various sites, it may be difficult to compare results from different studies. Importantly, the clinical relevance of bone mineral density loss varies from patient to patient and depends, at least in part, upon the bone mineral density of a patient before treatment with a GnRH analogue is initiated.

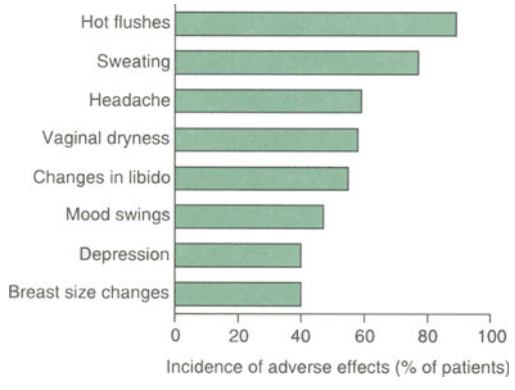

Fig. 4. Incidence of hypoestrogenic adverse events in women with benign gynaecological disorders treated with subcutaneous depot goserelin 3.6 mg/month. The data presented are pooled from several clinical studies (total n = 862).[100]

In one study,[103] premenopausal women who received goserelin for the treatment of endometriosis experienced a higher rate of bone loss than would be expected for postmenopausal women. This observation may be explained by the suppression of ovarian steroidogenesis occurring more rapidly during goserelin treatment than during menopausal transition.[103] Whether bone mineral density loss is a reversible complication of goserelin single-agent treatment is controversial.[75] Although there is evidence to suggest that losses are, at least, partially reversible after treatment discontinuation,[100,102] there have also been reports of bone mineral density losses being irreversible after cessation of goserelin treatment.[102,107,108] Importantly, longer periods of follow up than have been reported at present may be necessary to accurately determine the maximum extent of recovery of bone mineral density following discontinuation of goserelin treatment.

Dodin and colleagues compared bone mass in women with endometriosis after completion of a 6-month course of either depot goserelin 3.6 mg/month (n = 17) or oral danazol 400mg twice daily (n = 9).[103] Before initiation of study medication there were no significant differences in the trabecular bone content of the lumbar spine and femoral neck between women with endometriosis randomised to receive study medication and 26 age-matched healthy controls. Three and 6 months after initiation of treatment, the goserelin recipients experienced bone losses from the femoral neck and lumbar spine ($p < 0.05$ *vs* controls). In contrast, there were no significant changes in bone mineral content in the danazol treatment group or in the controls. Six months after discontinuation of study medication, bone loss was still evident in the

goserelin recipients but bone mineral content values did not differ significantly from those reported for the controls or the danazol recipients.[103]

As estrogen/progesterone HRT has been shown to prevent bone loss in postmenopausal women,[101] several studies have investigated the efficacy of this treatment approach in terms of conserving bone mineral density (and in reducing other hypoestrogenic adverse effects) in women with benign gynaecological conditions receiving depot injections of goserelin.[43-45,60,88,101,102,109] A double-blind, placebo-controlled study (n = 60)[101] (reviewed by Fogelman and colleagues)[102]) compared bone mineral density loss (measured using dual x-ray absorptiometry) in 60 women with premenstrual tension (aged 21 to 45 years) who received one of the following 3 regimens: depot goserelin + estradiol valerate 2 mg/day + norethisterone 5 mg/day on days 22 to 28 of the cycle (HRT) [n = 21]; placebo goserelin + placebo HRT (n = 20); or depot goserelin + placebo HRT (n = 19). Recipients of depot goserelin + placebo experienced a substantial loss in bone mineral density from both the lumbar spine (4.75%) and the proximal femur (3.2%) [compared with pretreatment levels] after 24 weeks' treatment (fig. 5). After a further 24-week follow-up period, bone mineral density losses (though reduced) were still substantial. In contrast, women who received 'add-back' HRT had a marked reduction in bone mineral density loss compared with recipients of goserelin single-agent therapy during and after discontinuation of goserelin treatment.

Other hypoestrogenic adverse effects of goserelin treatment have also been shown to be reduced by the addition of 'add-back' estrogen/progesterone HRT to the goserelin treatment regimen. In 1 study (n = 50),[43] significantly fewer recipients of goserelin + estrogen/progesterone HRT experienced hot flushes and loss of libido than recipients of goserelin single-agent therapy ($p < 0.01$) [see section 3]. Moreover, in women with dysfunctional uterine bleeding (n = 21), goserelin-related hypoestrogenic adverse effects (hot flushes, night

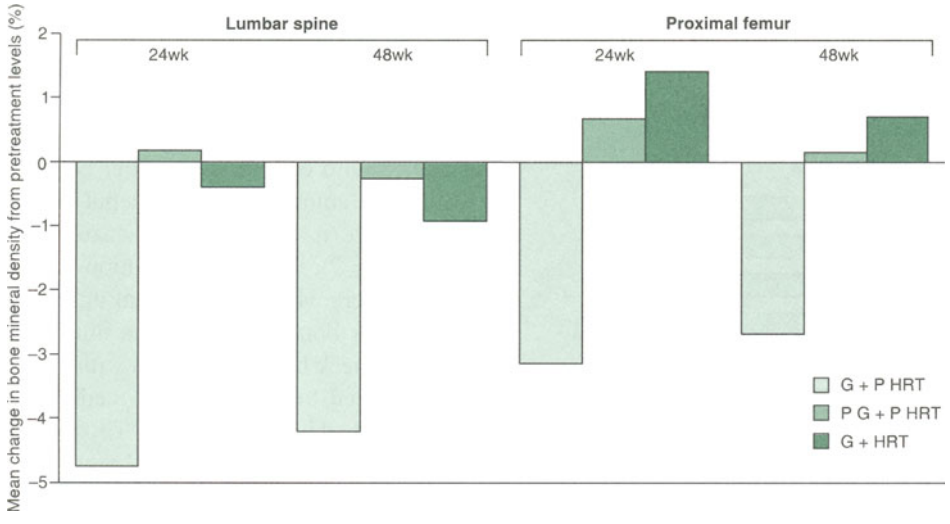

Fig. 5. Mean percentage changes in bone mineral density (measured using dual x-ray absorptiometry) reported in a placebo-controlled study conducted by Leather et al.[101] and reviewed by Fogelman et al.[102] Women with premenstrual syndrome received either 24 weeks' treatment with either goserelin 3.6mg + placebo hormone replacement therapy (G + P HRT) [n = 19], or placebo goserelin + placebo HRT (P G + P HRT) [n = 20], or goserelin 3.6mg + HRT (G + HRT) [n = 21]. HRT consisted of oral estradiol valerate 2 mg/day + oral norethisterone 5 mg/day administered on days 22 to 28 of the cycle. Goserelin was administered monthly. Results at 48 weeks were reported by Fogelman et al.[102]

sweats, vaginal dryness and mood changes) were reduced by the addition of estradiol valerate 1 mg/day and medroxyprogesterone 5mg/day started 3 weeks after the first dose of goserelin.[88]

Thus, the addition of 'add-back' HRT is a promising therapeutic strategy for reducing bone loss and for minimising the incidence of other adverse effects related to estrogen deficiency in women being treated with goserelin for benign gynaecological disorders,[88,102,109] possibly enabling women to receive further courses of goserelin.[102] However, more data are required before firm conclusions can be drawn regarding optimal therapeutic 'add-back' HRT regimens.

Veralipride, an antidopaminergic agent which has been shown in previous studies to reduce the incidence of vasomotor symptoms in postmenopausal women,[99]) has also been reported to be effective in alleviating hot flushes in women receiving goserelin.[99] In a nonblind observational study of premenopausal women (n = 25), veralipride 100 mg/day administered for 28 days (initiated during the third month of goserelin treatment) reduced the frequency and intensity of hot flushes in 92% of women. These beneficial effects were sustained for the remaining 2 months of goserelin treatment even though veralipride had been discontinued.[99] Adverse effects related to veralipride (breast tension, asthenia, drowsiness and galactorrhoea) all subsided after the drug was discontinued.[99]

Few data are available on the effect of goserelin on pregnancy. However, findings from an investigation in animals suggest that goserelin administration in very early pregnancy is associated with a poor pregnancy outcome,[110] possibly explained by the effect of the drug on the corpus luteum and on placental function during pregnancy.[110] Although no published studies have investigated the tolerability of goserelin in pregnant women being treated for benign gynaecological disorders, 1 case of multiple gestation (sextuplets) in a woman who had received goserelin for minimal endometriosis has been described.[111] The authors of the report postulated that the patient received goserelin during the mid-follicular phase of the cycle which resulted in a rapid rise in estrogen levels and a subsequent surge in LH levels before complete desensitisation of the pituitary gland.[111] Alternatively, if goserelin was administered in the early follicular phase of the cycle this may have produced supraphysiological levels of estrogen, hence overcoming the effect of pituitary desensitisation.[111] This case report highlights the importance of ascertaining the date of the last menstrual period before goserelin treatment is initiated, to avoid inadvertent treatment initiation during the follicular phase of the cycle.[111]

5. Dosage and Administration

In the treatment of women with benign gynaecological disorders the recommended dose of the biodegradable depot formulation of goserelin is 3.6mg injected subcutaneously into the anterior abdominal wall every 28 days.[112] As there are no long term clinical data regarding the use of goserelin in women with these disorders, the drug should be administered for a maximum of 6 months. At present, repeat courses of goserelin are not recommended because of concern regarding bone mineral density loss. Dosage modification for patients with renal or hepatic impairment is not required. As goserelin should not be administered to pregnant women, pretreatment examination of fertile women is necessary to exclude pregnancy. In addition, women being treated with goserelin should use nonhormonal methods of contraception during courses of treatment.[111,112]

Although the data available suggest that goserelin-induced bone mineral density loss is reduced by concomitant estrogen or estrogen/progestogen HRT, further studies are required to determine the optimal dose of HRT required to minimise bone losses.

6. Place of Goserelin in the Management of Benign Gynaecological Disorders

Since the late 1980s, numerous clinical studies have confirmed the therapeutic efficacy of depot goserelin, a long-acting GnRH analogue, in the

treatment of some benign estrogen-dependent gynaecological disorders.

In women, continuous release of goserelin from a depot biodegradable co-polymer matrix results in down-regulation of the pituitary-ovarian gonadal axis, suppression of gonadotrophins and a decrease in estrogen and progesterone levels. Importantly, prompt reversal of pituitary-ovarian suppression is achieved after discontinuation of goserelin treatment, a beneficial characteristic of the drug. Although endometriosis, uterine leiomyomata and dysfunctional uterine bleeding are distinctly different estrogen-dependent gynaecological disorders, the clinical efficacy of goserelin in the treatment of all of these disorders is achieved by the induction of a state of hypoestrogenism and subsequent establishment of amenorrhoea.

'Medical oophorectomy' achieved by treatment with goserelin and other GnRH analogues is a favourable alternative to radical surgery for women with endometriosis, particularly for women with severe disease who wish to retain their fertility. Danazol represented the mainstay of treatment for endometriosis during the 1970s and 1980s (before the introduction of the GnRH analogues into clinical practice), but its tolerability profile is characterised by significant physical, psychological and metabolic adverse events.[1,13] Moreover, as danazol requires twice daily oral administration, patient acceptability is likely to be less than with depot goserelin, which is administered subcutaneously every 28 days. In 2 large comparative controlled trials, which included more than 600 women with all grades of endometriosis, goserelin was as effective as danazol in achieving a resolution of endometrial deposits and significant relief of symptoms.

Uterine leiomyomata are, like endometriosis, dependent on estrogen for their growth. These benign, often asymptomatic, tumours are reported to affect approximately 1 in 20 women of reproductive age.[3] Until the development of the GnRH analogues, symptomatic uterine leiomyomata were traditionally managed surgically (in the absence of satisfactory alternative pharmacological means of treatment). However, surgical myomectomy may be associated with adhesion formation and significant blood loss during the procedure.[2,3] During 3 to 4 months' treatment with goserelin, uterine volume and uterine leiomyoma volume decrease, although continued treatment does not usually result in further leiomyoma shrinkage. Furthermore, as observed with other GnRH analogues, rapid regrowth of these tumours occurs after goserelin is discontinued (when estrogen levels increase to baseline values, signalling the return of normal ovarian function).

The most useful therapeutic role for goserelin in the management of uterine leiomyomata appears, therefore, to be as a short term treatment prior to surgery. Indeed, as an adjunctive treatment goserelin has proved to be effective in facilitating surgery by reducing the size of leiomyomata and decreasing blood loss around the time of surgery. As an alternative to surgical management, goserelin may be a useful treatment for women approaching menopause, in whom uterine leiomyomata are likely to degenerate naturally. Moreover, goserelin may be of clinical benefit in the short term treatment of women unable to undergo surgery for the removal of uterine leiomyomata.

Dysfunctional uterine bleeding, is a cause of considerable morbidity in premenopausal women. This condition, presenting as excessive blood loss and abnormal endometrial growth, may warrant radical surgical management (hysterectomy), surgical ablation or resection. Goserelin has been shown to be an effective adjunctive surgical pretreatment in this clinical setting, facilitating surgical ablation or resection by suppressing endometrial growth and thinning the endometrium and reducing uterine size. Furthermore, fluid absorption, which may occur as a serious complication during ablative surgery, is significantly reduced following goserelin pretreatment. Other GnRH analogues (e.g. leuprorelin, buserelin and nafarelin) have also demonstrated therapeutic efficacy in treating some benign gynaecological disorders; however, data on the relative clinical efficacies of these agents and goserelin are limited. Moreover,

as other GnRH analogues are delivered via different delivery systems to goserelin,[104] it is difficult to draw meaningful conclusions from comparative studies.

In women undergoing ovarian stimulation in assisted reproduction programmes, goserelin is a useful adjunctive treatment. Several studies have shown that pituitary desensitisation with goserelin leads to increased oocyte recovery rates and to reduced numbers of cancelled cycles. In a prospective study, women who received goserelin prior to ovarian stimulation had a significantly higher pregnancy rate than clomifene recipients. Although the overall cost of the goserelin ovulation stimulation regimen was 40% higher than the clomifene stimulation regimen, formal pharmacoeconomic analysis is required to compare the cost-effectiveness of these treatments.

The tolerability profile of goserelin is characterised by adverse effects typical of a hypoestrogenic state, such as hot flushes, headache, vaginal dryness and loss of libido, all of which are reversible upon discontinuation of the drug. In addition, significant loss of bone mineral density has been observed during and after goserelin treatment. Whether bone mineral density losses are partially reversible after treatment has been discontinued is controversial. While there is some evidence of partial restoration of bone mineral density after discontinuation of goserelin, 1 placebo-controlled study reported sustained bone mineral density losses 6 months after goserelin had been discontinued. Given the therapeutic success of estrogen/progesterone HRT in the amelioration of hypoestrogenic symptoms in postmenopausal women, a number of clinical investigations have determined the efficacy of concomitant 'add-back' HRT in reducing the hypoestrogenic adverse effects of goserelin treatment. This treatment approach has been shown to be an effective means of reducing the incidence of hypoestrogenic adverse effects and of minimising the extent of bone mineral density loss without compromising therapeutic efficacy.

Although no published studies have compared the patient acceptability of long-acting depot GnRH analogues with that of short-acting GnRH analogues or danazol, treatment selection is likely to depend, at least in part, on the preference of the patient. A depot preparation of a GnRH analogue is likely to be an attractive option from a compliance perspective.

In conclusion, goserelin is well established in the treatment of endometriosis and is a useful alternative to danazol. In addition, goserelin is useful as an adjunctive treatment for women with uterine leiomyomata, dysfunctional uterine bleeding, and in assisted reproduction programmes. However, until there is more evidence that it can be combined with HRT as long term treatment in women with benign gynaecological disorders, goserelin treatment is limited to a maximum duration of 6 months due to bone mineral density loss during continuous administration. The availability of goserelin has broadened the range of options available for the management of the estrogen-dependent benign gynaecological disorders and, as it is administered as a depot injection on a monthly basis, it is a convenient and practical treatment choice.

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