GnRH agonists and uterine leiomyomas

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Gonadotrophin-releasing hormone (GnRH) agonists are widely used in the treatment of women with symptomatic leiomyomas. The effectiveness of this treatment, as far as symptoms are concerned, is well established, and in recent years many studies have contributed to defining the optimal role for GnRH agonists. Side-effects and health risks prohibit the long-term use of these compounds. The combined use of high-dose agonists and steroids in the so-called 'add back' schedules reduces many of the disadvantages of the monotherapy. However, it is still an expensive alternative when compared with definitive surgery, and therefore should only be used in women who insist on preservation of the uterus. Low-dose agonist therapy ('draw back') has not yet been proven to be suitable for clinical application. The use of GnRH agonists and steroids in sequential schedules seems to result in a loss of both the volume reduction as well as the reduction in clinical symptoms. The use of GnRH agonists prior to myoma surgery should not become a routine measure and should be limited to cases where the size of the uterus is >600 ml. Hysterectomy should only be preceded by GnRH agonist treatment if uterine volume decrease is expected to facilitate either the abdominal or vaginal procedure. For both operative procedures the presence of myoma-related anaemia is an indication for pretreatment. The use of GnRH agonists before endoscopic surgery is widely accepted on the basis of assumptive advantages; however, definite proof of these advantages is not yet available.

Key words: GnRH agonists/leiomyoma treatment/pre-treatment/surgery

Introduction

Uterine leiomyomas are very common benign tumours in women of reproductive age. It is estimated that 20–30% of women have a myoma (Buttram and Reiter, 1981). In clinical pathology studies the frequency of myomas is often much higher, especially when careful sectioning is applied to hysterectomy specimens (Cramer and Patel, 1990). The myomas can either be single or multiple, may vary considerably in size and can be found anywhere in the uterine or cervical...
wall. Size and location of the myomas will determine the symptomatology. If symptoms occur they will fall into one of the following categories: pressure signs (pain, urinary frequency, constipation), abnormal uterine bleeding (menorrhagia) and/or reproductive dysfunction (infertility, early pregnancy loss, premature birth, dystocia). Hysterectomy is the classical treatment strategy and the only definitive cure for myomas. Uterine preservation by abdominal or endoscopic myomectomy is an alternative, but bears the risk of a repeat surgical approach in case of recurrent myoma growth (Donnez et al., 1989; Candiani et al., 1991; Dubuisson et al., 1991; Verkauf, 1992).

Hormonal therapy aims at reducing symptoms and/or size of the myomas and may be used either as a long-term treatment or as an adjuvant prior to surgery. Long-term treatment of leiomyomas may be indicated in patients with absolute contra-indications to surgery or in patients who wish to avoid surgery for emotional reasons or until the menopause takes place. Presurgery uterine and myoma volume reduction may facilitate both hysterectomy and myomectomy procedures (Friedman et al., 1989a; Stovall et al., 1991; Falsetti et al., 1992; D'Addato et al., 1992; Vercellini et al., 1993; Lumsden et al., 1994). Gonadotrophin-releasing hormone (GnRH) agonists are increasingly being used to achieve the aforementioned aims of hormonal treatment.

**Mechanism of action of GnRH agonists**

Ever since the elucidation of the structure of native GnRH by Schally and Guillemin (see Arimura, 1991), a large number of GnRH analogues have been synthesized. The agonistic analogues have a higher biological potency than endogenous GnRH. After binding to the GnRH receptor at the gonadotrophin cell surface, an intense release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) is produced. However, prolonged exposure of the pituitary to the GnRH agonist results in a desensitization of the gonadotrophin cells within several hours and a rapid decrease in the release and synthesis of gonadotrophins, especially of LH. The gonadotrophin cell will be left unresponsive and depleted as long as the pituitary is continuously exposed to high dosages of the agonist.

In the hormonal treatment of uterine fibroids, the use of i.m. or s.c. GnRH agonist depot formulations has become widespread. In most depots the agonist is dispersed into biodegradable polymer microspheres [poly(DL-lactide-co-glycolide)] (Beck et al., 1979). Plasma concentrations of the agonist during the delivery period of the depot are related to the total dose of the agonist dispersed in the polymer (Beck et al., 1979; Zorn et al., 1988). Dose studies where the optimal load of the GnRH agonist is evaluated are almost absent. The single administration of a half-dose triptorelin depot (1.87 mg) appears to create an initial endocrine response which is similar to the one obtained by the full-dose depot (Balasch et al., 1992). Moreover, the duration of pituitary and ovarian suppression seems to be unaltered by the dose reduction. This may imply that
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the amount of agonist present in the standard triptorelin depot is too high to achieve the endocrine and clinical aims.

Most of the depots seem to be designed to release the drug for a 4 week period. However, pharmacokinetic studies after single depot injections are scarce. In two studies the release of triptorelin from the depot in women and men was studied (Gonzalez-Barcena et al., 1989; Broekmans et al., 1993). Triptorelin remained detectable until the 7th week after the depot administration. This indicates that the interval between depot administrations may well be prolonged to 6 weeks (Broekmans et al., 1993).

Directly after a single GnRH agonist depot administration, a sharp rise is observed in LH and FSH concentrations. Maximum concentrations are reached after 4 h, followed by a gradual decline to subnormal concentrations after 2 weeks. LH concentrations remain suppressed below the detection limit of the assays for a period of 7 weeks (Broekmans et al., 1992). FSH concentrations generally show a tendency to be restored to early follicular values. Bioactivity of the circulating FSH appears to be unaltered (Huhtaniemi et al., 1988).

Ovarian function shows an initial response to the gonadotrophin burst, where oestradiol concentrations become raised to the mid- and sometimes late follicular range. After 1–2 weeks oestradiol concentrations have fallen to post-menopausal values and remain so until the sixth week after the single depot administration. In addition, inhibin concentrations after a single administration of buserelin depot are continuously decreased until ovarian function is restored. Endocrine patterns after a single administration of goserelin (3.6 mg) or buserelin (3.3 and 6.6 mg) depot show the same short-term effects as after triptorelin depot (Fraser et al., 1992). The duration of pituitary and ovarian suppression, however, seems to be 2 weeks shorter for goserelin (Matta et al., 1988a) and to be highly variable for buserelin (Fraser et al., 1992).

Repeated administrations of a GnRH agonist depot formulation will create a solid state of pituitary suppression as evidenced by extremely low LH concentrations and absent LH and FSH response to exogenous GnRH bolus injection (Filicori et al., 1993). In addition, repeated administrations will result in a continued state of hypo-oestrogenism. The degree of ovarian suppression may show some slight variation between the different agonist depots (Filicori et al., 1993). This may be explained by presumed differences in the degree of suppression of FSH and/or LH release by the various depot formulations.

Long-term GnRH agonist treatment in uterine leiomyomas

The first use of a GnRH agonist in the treatment of women with symptomatic leiomyomas was published by Filicori et al. (1983). The pituitary desensitization and ovarian suppression led to a 50% reduction in the volume of the uterus and myomas and a control of uterine bleeding by creating amenorrhoea. Since then, many studies have been published on the beneficial effects of long-term GnRH agonist treatment in uterine leiomyomas (Maheux et al., 1984, 1987; Healy et al.,
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1984, 1986; Coddington et al., 1986; Perl et al., 1987; West et al., 1987; van Leusden and Dogterom, 1988; Andreyko et al., 1988; Friedman, 1989c; Friedman et al., 1989b; Golan et al., 1989; Matta et al., 1989; Letterie et al., 1989; Nakamura et al., 1991). Most of the studies in recent years have used depot formulations that release the agonist for several weeks from biodegradable polymers. Only two studies (Friedman et al., 1989b; Schlaff et al., 1989) have really proved the efficacy of this treatment in randomized, placebo-controlled trials.

After GnRH agonist treatment for 6 months the mean reduction in uterine and myoma size appears to be 50%, while the response of separate myomas ranges from 0-100% (Stewart and Friedman, 1992). The percentage reduction in uterine volume is negatively correlated with the serum oestradiol concentration during treatment and with the patient’s body weight (Friedman et al., 1992b). Some authors have found a positive correlation between the initial fibroid size and the subsequent regression on therapy (Coddington et al., 1986; Vollenhoven et al., 1990). The age of the patient has no predictive value (Vollenhoven et al., 1990; Friedman et al., 1992b). Approximately 85% of the final volume reduction will be established within the first 2-3 months of treatment (Friedman et al., 1988; Hackenberg et al., 1992; Stewart and Friedman, 1992). Some authors have claimed that a poor response to treatment (reduction <50%) can be predicted as early as after 1 month of treatment (Hackenberg et al., 1992). Related to the reduction in uterine and myoma size, relief in pain and pressure symptoms will become clear in the first 2 months (Friedman et al., 1991). By suppression of the menstrual cycle, bleeding problems and related anaemia will in most cases be controlled after the first month of treatment, especially if treatment has been started in the mid-luteal phase of the cycle (Candiani et al., 1990).

When GnRH agonist treatment by monthly depots is discontinued, menses return after an interval of 8-12 weeks. With the return of normal menses, a rapid increase of the uterine and myoma size is observed towards pretreatment values (Letterie et al., 1989). Even if normal cyclic ovarian function remains suppressed by changing from a monthly agonist depot to a low-dose oestrogen/progesterone contraceptive pill, a rapid regrowth of the fibroids was observed (Balasch et al., 1995).

Mechanism of GnRH agonist-induced uterine and myoma volume reduction

Continuous exposure of the pituitary creates a state of gonadotrophin desensitization and ovarian suppression. The subsequent hypo-oestrogenic state is well correlated with the uterine and myoma volume response. If ovarian suppression is incomplete and oestadiol concentrations do not reach post-menopausal concentrations initially or the agonist is combined with an oestrogenic substance, reduction in myoma and uterine volume is either absent or minimal (Friedman et al., 1987; Lumsden et al., 1989b; Uemura et al., 1990). If the hypo-oestrogenic
state becomes reversed and normal midcycle oestradiol concentrations are produced, rapid regrowth of the uterine fibroids is the result (Letterie et al., 1989). Apparently, the role of hypo-oestrogenism is crucial. The mechanism by which suppression of oestradiol production leads to uterine and myoma volume reduction, however, is still obscure.

Oestradiol receptor studies have shown that the concentration of this receptor is higher in fibroids treated with a GnRH agonist than in those not treated (Lumsden et al., 1989a; Rein et al., 1990). This paradoxical finding may be explained by the absence of progesterone, which is known to suppress oestradiol receptor synthesis (Sherman et al., 1979; Rein et al., 1995). On the other hand, in women exposed for 3 months to tamoxifen, an oestradiol receptor-blocking agent, oestradiol binding in fibroids was significantly lower when compared with normally-cycling women (Lumsden et al., 1989a). This may indicate that, during agonist exposure, hypo-oestrogenism leads to a high degree of unoccupied oestrogen receptors, while up-regulation of receptor numbers by the absence of progesterone may be an additional factor. However, receptor studies do not provide a solid explanation for the fibroid-reducing effects of hypo-oestrogenism. Moreover, the insight into the role of oestradiol and progesterone receptors is further blurred by the finding that the combined use of a GnRH agonist and medroxyprogesterone failed to produce uterine or fibroid volume reduction (Friedman et al., 1988; West et al., 1992).

The role of progesterone suppression by the use of GnRH agonists has recently been reviewed by Rein et al. (1995). Several clinical and biochemical observations support the assumption that progesterone may enhance the incidence of somatic mutations in myometrium cells and thereby contribute to myoma formation. Once a myoma has emerged, growth stimulation by progesterone is exerted in the luteal phase (Harrison-Woolrych and Robinson, 1996). Moreover, progesterone antagonists have been shown to induce amenorrhoea and significant uterine volume reduction, while oestradiol concentrations remained at those of the early follicular phase (Murphy et al., 1993). Therefore, the blockade of progesterone production by pituitary suppression may play an important role in addition to the hypo-oestrogenic state created by the agonist.

Recently, evidence has emerged for the role of local growth factors, including epidermal growth factor (EGF), that act as mediators of oestrogenic effects on the myometrium and myoma cells. In a study by Lumsden et al. (1988), the specific binding of EGF to myoma tissue homogenates was lower after treatment with GnRH agonists in comparison with untreated controls.

Oestrogens are known to cause vasodilation of the uterine vasculature, in animal studies (Resnik et al., 1974; Leiberman et al., 1993) as well as in studies in the human female (de Ziegler et al., 1991). Doppler assessment of blood flow velocity wave forms demonstrated a reduction in the blood supply to the uterus during long-term GnRH agonist treatment (Matta et al., 1988b). Possibly, a hypo-oestrogenism-mediated reduction in the blood flow is the main mechanism of uterine and myoma volume reduction (Schlaff et al., 1989).

Histologically, fibroids show a high degree of structural variety. They consist
of elongated smooth muscle fibres and collagenous fibrous tissue. The relative proportion of these two components is highly variable. Degenerative changes such as hyalinization, myxoid and cystic changes and calcification further contribute to the variability of the histological picture. Therefore, histological comparison of fibroids after long-term GnRH agonist treatment with untreated fibroids has been difficult. Reports on histology are conflicting. In leuprolide-treated patients, either a reduction in cellularity and proliferative activity (Upadhya et al., 1990; Barbieri et al., 1993) or no change at all was observed (Gutmann et al., 1994). In contrast, Rein et al. (1993) found significant changes in the extracellular collagen matrix and an increase in the cellularity. They concluded that the reduction in myoma volume could well be the result of a reduction in the water content of the cells or the extracellular matrix. Yet another report suggests that tissue necrosis, as a result of ischaemia, is more frequently encountered in GnRH agonist pre-treated myomas (Colgan et al., 1993).

Finally, direct effects of the agonist through specific binding sites in leiomyomas may play an additional role (Wiznitzer et al., 1988), although this has been doubted by Neuman et al. (1991). Moreover, the use of a GnRH antagonist, which binds to the receptor without intrinsic agonistic effects, has the same effect on ovarian oestrogen production and myoma size (Kettel et al., 1993). Recently, a direct effect of GnRH agonists at the level of the granulosa cell has been suggested (Furger et al., 1996), leading to a decrease in the FSH sensitivity of antral follicles and thereby hampering follicular development and oestrogen production.

Dose assessment of GnRH agonists in leiomyoma treatment

A few studies have been published indicating that the hypo-oestrogenic state and myoma volume reduction may well be accomplished by adjustments in the dose schedule. For instance, the use of half-dose leuprolide depot with intervals of 4 weeks appeared to have the same effectiveness as the use of full-dose depot (Watanebe et al., 1992). Pharmaco-kinetic and dynamic studies after a single triptorelin depot administration (Gonzalez-Barcena et al., 1989; Balasch et al., 1992) have shown that the depot is capable of suppressing the pituitary and gonad for a period of 6 weeks. Changing the interval between subsequent full-dose depot administrations to 6 weeks may prove to produce the same state of ovarian suppression as with injections at 4 week intervals.

A dose-finding study by Uemura et al. (1990) suggested that the use of 900 µg of buserelin intranasally may be optimal for adequate reduction in uterine and myoma volume. The use of 600 µg had a similar clinical effect but, due to higher oestradiol concentrations, reduction in myoma volume was almost absent (Smitz et al., 1990). These findings indicate that in the use of GnRH agonists for symptomatic or preoperative treatment of women with fibroids data on the optimal dose are still scarce.
Side-effects of long-term GnRH agonist treatment

The severe hypo-oestrogenic state induced by the GnRH agonist gives rise to annoying side-effects. Hot flushes are the most prominent side-effect, occurring in >80% of patients. Headaches, depressive mood changes, sleeping disturbances, joint and muscle stiffness, decreased libido, vaginal dryness and dyspareunia and hair loss are reported in 5–15% of cases. In spite of the full pituitary and ovarian suppression, not all women will experience amenorrhoea. Slight, intermittent vaginal bleeding may occur in some 15% of patients and may be explained by endometrial atrophy in an enlarged uterine cavity or by the presence of submucous myomas. In 2% of all women treated with a GnRH agonist severe haemorrhage due to necrosis and degeneration of a submucous myoma will appear (Friedman, 1989a). Rarely, anaphylactic reactions during the use of the agonist have been reported (Letterie et al., 1991).

Health risks with regard to cardiovascular changes and accelerated bone loss are additional problems related to long-term GnRH agonist therapy. Studies on plasma lipid profiles have suggested a lipid neutral effect of GnRH agonist treatment for 6 months (Adashi, 1994). However, continuation of the hypo-oestrogenic state has to result in diminished cardioprotection as has been shown for the natural menopause (Adashi, 1994). Bone loss at the lumbar vertebrae during GnRH agonist therapy has been well documented by the use of quantitative computer tomography (QCT) and dual energy X-ray absorption (DEXA) and varies between 2.9–7.4% after 6 months of treatment (Waibel Treber et al., 1989; Whitehouse et al., 1990; Surrey and Judd, 1992; Fogelman, 1992; Dawood, 1993; Leather et al., 1993; Scialli et al., 1993; Gallagher, 1993; Uemura et al., 1994). The hypo-oestrogenic state is believed to be responsible for the bone loss (Adashi, 1994). Oestrogens have direct effects on bone tissue, presumably by antagonizing osteoclast-mediated bone resorption and stimulating development of osteoblastic cells from precursors (Turner et al., 1994). In addition, oestrogens may directly increase calcium transport by the bowel and kidney (Prince, 1994). After cessation of therapy, recovery of bone density has been claimed to be incomplete (Whitehouse et al., 1990; Surrey and Judd, 1992; Dawood, 1993). A recent report on long-term effects after a 6 month GnRH agonist treatment period documented a complete recovery of the loss in lumbar bone mineral density 2 years later (Paoletti et al., 1996).

Last, but not least, medical treatment of symptomatic leiomyomas may delay the tissue diagnosis of the rare leiomyosarcoma (Shek et al., 1987; Hitti et al., 1991; Murphy and Wallace, 1993; Schwartz et al., 1993). Therefore, an absence of response to the GnRH agonist therapy must lead to prompt surgical removal of the myomas.

Oestrogenic state correction

Health risks and side-effects make continuation of GnRH agonist treatment for >6 months unattractive. Cessation of therapy leads to restoration of the normal
Figure 1. Oestradiol threshold hypothesis. Gonadotrophin-releasing hormone (GnRH) agonist treatment will reduce oestradiol concentrations into the post-menopausal range (zone C). By oestrogen and progesterone 'add back', oestradiol concentrations are corrected into a threshold area (zone B), in which regrowth of the uterus does not occur and side-effects and bone resorption are limited or prevented (adapted from Friedman *et al.*, 1990).

Continuing the GnRH agonist treatment for longer periods only seems possible if some correction in the gonadal steroid environment is achieved. Friedman *et al.* (1990) and Maheux *et al.* (1991) have postulated that partial restoration of the oestrogenic state in addition to the continued use of the agonist is a possible strategy for long-term medical treatment. Oestradiol concentrations within a certain threshold concentration zone would reduce or minimize side effects and prevent ongoing bone loss, without producing regrowth of the myomas (Figure 1). In addition, it has been doubted as to whether a severe hypo-oestrogenic condition is really necessary to achieve or maintain uterine or myoma volume reduction (Uemura *et al.*, 1990; Maheux *et al.*, 1991).

Partial restoration of the oestrogenic state may be accomplished by administration of small quantities of oestrogen and progesterone in addition to the agonist, after a 3 month period of single agonist therapy (Friedman, 1989b, 1993; Maheux and Lemay, 1992; Friedman *et al.*, 1993, 1994) (Figure 2). In these so-called 'add back' regimens, treatment can be continued for a period of at least 2 years, without regrowth of the uterus. It must be noted, however, that the drop out rate was rather high in these studies. Furthermore, bone density decreased significantly...
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GnRH agonist

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Figure 2. Schematic representation of the sequential ‘add back’ treatment schedule. Initial gonadotrophin-releasing hormone (GnRH) agonist monotherapy is followed by combined treatment with oestrogen-progesterone (after Stewart and Friedman, 1992).

during the initial steroid-free treatment period, but showed no change during the ‘add back’ period. Sugimoto et al. (1993) demonstrated that the dose of the oestrogen used in the ‘add back’ scheme may well be crucial in the bone protecting effects of such regimen, while others showed ongoing bone loss in spite of the steroid ‘add back’ (Sugimoto et al., 1993; Mezrow et al., 1994).

Periodical complete restoration of endogenous oestrogen production is another possible strategy. Intermittent therapy, where a 3 month treatment period is alternated with a 3 month agonist-free interval, may show minimal increase in uterine size during the drug-free interval (Blumenfeld et al., 1990). Increasing the interval between subsequent dosages of triptorelin depot from 4 to 10/12 weeks seems to create an adequate reduction in uterine volume, while side-effects decreased to such an extent that treatment could be continued for up to 2 years (Golan, 1993).

The use of sequential treatment schedules, where GnRH agonist therapy is interrupted after 3–6 months and is followed by the use of combined oestrogen/progesterone preparations or progesterone alone, has shown that reduction in uterine size is almost completely reversed during the steroid treatment period (Benagiano et al., 1990; Balasch et al., 1995). Apparently, the use of these steroid compounds without the concomitant use of GnRH agonists creates a myoma growth promoting situation. This is presumably caused by the lack of suppression of endogenous oestradiol production and the use of potent synthetic steroids, possessing contraceptive properties. It must be noted however, that this finding is in contradiction to earlier reports on the reduced risk of myoma growth in women using oral contraceptives (Ross et al., 1986).

Finally, reduction of the agonist dose to a concentration at which endogenous production of oestradiol is partially restored without the appearance of high preovulatory oestradiol concentrations and with continued inhibition of ovulation may prove to be an adequate treatment modality. Several studies have shown that the state of pituitary suppression by the agonist is dose-dependent (Monroe et al., 1986; Maheux et al., 1988; Scheele et al., 1996). The degree of pituitary suppression, induced by a certain dose, appears to remain constant during long-term agonist treatment (Monroe et al., 1986; Maheux et al., 1988; Uemura et al., 1992). Ovarian suppression by low-dose agonist treatment has been studied in
Figure 3. Schematic representation of the 'draw back' treatment schedule. High-dose agonist therapy for 8 weeks is followed by reduced dose treatment in comparison with a continued high-dose regimen.

contraception studies, mainly by Bergquist et al. (Nillius, 1985; Bergquist and Lindgren, 1983; Lundkvist and Bergquist, 1986; Gudmundsson et al., 1986, 1987). Fluctuating oestradiol concentrations were found without adverse effects on the endometrium, despite lack of progesterone opposition. Treatment was well tolerated by the patients for long periods of time. These findings indicate that long-term treatment with low-dose agonist may be an alternative route for oestrogenic state correction.

'Draw back' GnRH agonist treatment of uterine leiomyomas

The possibility of inducing partial correction of endogenous oestradiol production by reducing the GnRH agonist dose in the long-term treatment of uterine leiomyomas has been investigated in a so-called two-step regimen (Broekmans et al., 1996). Standard, high-dose treatment was followed by reduced dose therapy. The treatment schedule is depicted in Figure 3. A total of 24 women with a uterine size of >300 ml initiated daily s.c. self-administration on the second day of the menstrual cycle. A daily dose of 500 µg triptorelin was used for 1 week, followed by a dose of 100 µg for 7 weeks. From weeks 9–26, treatment was continued by either 100, 20 or 5 µg triptorelin per day.

During triptorelin treatment the median uterine size was reduced to 57.8% of baseline (Figure 4). There were no differences in volume reduction between the dose groups. LH and oestradiol concentrations were restored in a dose-dependent way. However, oestradiol concentrations showed considerable variation in the lowest dose group (Figure 4).

From the results in the study it can be assumed that reduction of the agonist load in the triptorelin depot from 3.75 to 1.5 mg may well prove to be adequate in the long-term treatment of women with uterine fibroids, as it will deliver a
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![Graphs showing uterine volume, steady state LH, and steady state E2 concentrations with time and dose effects.](image)

**Figure 4.** Median (range, middle two quartiles) proportional change in uterine volume (upper panel) and median (range, middle two quartiles) steady state lutemizing hormone (LH) and oestradiol concentrations (E2) (middle and lower panel) during standard and randomized dose triptorelin treatment. Steady state LH and oestradiol concentrations were calculated from weekly measurements. *P* values relate to repeated measurements, analysis of variance with time and dose contrast for linear trends.

A daily dose of ~20 µg of triptorelin. As the delivery from a depot is more constant, compared to the saw-toothed concentrations generated by s.c. injections, even further dose reduction may prove to be possible.

In a study by Gudmundsson et al. (1984), using intranasal, low-dose agonist regimens for contraception, the oestradiol concentrations and bleeding patterns showed a considerable individual variation, while even in amenorrhoeic women oestradiol concentrations were in the early follicular range. This implies that both the ovarian and endometrium response in the low-dose agonist treatment is hard to predict in an individual patient. The use of a ‘draw back’ treatment schedule, where uterine volume reduction is maintained by a low-dose depot formulation and control on the proliferation state of the endometrium is carried.
out by intermittent courses of progesterone is a management strategy that is worth further investigation (Lemay et al., 1985; Geisthoeval et al., 1987).

**GnRH agonists and progesterone**

The use of progesterone in the treatment of leiomyomas has never been clearly demonstrated to be successful (Goodman, 1946; Segaloff et al., 1959; Goldzieher et al., 1966). Progesterone, administered in high doses, suppresses the pituitary release of gonadotrophins and thereby blocks the production of oestrogens from the ovary. The degree of ovarian suppression, however, appears to be less severe when compared with GnRH agonist-induced gonadal suppression (Benagiano et al., 1990).

It has become increasingly clear that progesterone has growth stimulating effects on leiomyomas (Goldzieher et al., 1966; Rein et al., 1995; Harrison-Woollych and Robinson, 1996), even in the absence of oestrogens. The combined use of progesterone and GnRH agonists fails to produce uterine and myoma volume reduction (Friedman et al., 1988; West et al., 1992). When single GnRH agonist treatment for 3 or 6 months is followed by either combined agonist–progesterone therapy (Friedman et al., 1993) or by progesterone alone (Benagiano et al., 1990; Scialli and Jestila, 1996), regrowth of the uterus and myomas is observed to a considerable extent. Furthermore, the use of progesterone antagonists as a single therapy has shown to establish a clear volume reduction in women with fibroids (Kettel et al., 1994).

Mitotic activity in leiomyomas during the luteal phase often is higher than in the follicular phase (Kawaguchi et al., 1989). A recent report by Brandon et al. (1993) showed increased expression of progesterone receptor mRNA and protein in leiomyomas, in comparison with adjacent myometrium. Combined oestrogen and progesterone replacement therapy in post-menopausal women leads to an increased proliferative index in myomas, whereas oestrogen-only therapy creates proliferation indices comparable to untreated post-menopausal controls (Lamminen et al., 1992).

GnRH agonist–progesterone therapy may prove to be beneficial with regard to bleeding problems, bone resorption and agonist-related side-effects (Scialli and Jestila, 1996). However, the disadvantages of progesterone-related side-effects, induction of uterine regrowth and less favourable lipid profiles, raise doubts over whether progesterone will become an acceptable adjunct to the GnRH agonist treatment of leiomyomas.

**Pre-surgery GnRH agonist treatment**

With the use of GnRH agonists the volume of the uterus can be reduced by 35–50%. The size reduction of myomas seems to be of a lesser magnitude, although a wide range (15–90%) is reported. With the use of magnetic resonance imaging,
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Volume response of myomas is reported to be 30–35%. In addition to size reduction, blood flow through the uterine vessels is decreased (Matta et al., 1988b), presumably caused by the lack of normal oestrogen stimuli on the uterine vasculature (Resnik et al., 1974).

The use of GnRH agonists prior to uterine surgery has been promoted for several reasons. A reduction was expected in intraoperative blood loss and in the need for pre-, per- and postoperative blood transfusions on the basis of size reduction alone (Ginsburg et al., 1993). Selective removal of fibroids was thought to become technically easier, thereby reducing the risk of postoperative formation of adhesions and increasing the fertility potential after preserving surgery. Total removal of the enlarged uterus in cases of symptomatic myomas was expected to become easier, for instance by changing the route of operation from abdominal to vaginal. Finally, application of GnRH agonists before endoscopic fibroid surgery is promoted for reduction of fluid loss in hysteroscopy and enabling the endoscopic removal of larger fibroids in general. Studies addressing these expectations and questions are far from numerous. Comparative studies often lack randomization and in the endoscopic field comparison to other hormonal or no pretreatment is absent.

GnRH agonist treatment before abdominal myomectomy

Abdominal myomectomy is indicated in myoma-related menorrhagia and otherwise unexplained infertility of long duration. The means by which myomas hamper fertility has been a matter of debate. Impaired gamete transport has often been suggested but never proven. Cavity distortion by submucous or intramural myomas leading to implantation problems is another explanation. Recently, the presence of cavity deformation has been found to reduce the implantation rate in in-vitro fertilization (IVF) cycles when compared with cases where a normal cavity was seen at hysteroscopy (Fahri et al., 1995). These findings are the first to really support the assumption that myomas actually impair fertility.

Although the beneficial effects of myomectomy in bleeding problems are well established (Buttram and Reiter, 1981), the role of myomectomy upon fertility treatment is still somewhat obscure. A success rate of ~50% within 1 year after surgery is achieved in patients with longstanding infertility and no other factor than uterine myomas (Babkia et al., 1978; Garcia and Tureck, 1984; Rosenfeld, 1986; Verkauf, 1992). However, comparative studies providing some definite proof of benefit are lacking. Finally, conservative surgery on the uterus for fibroids may always be frustrated by an overall recurrence rate of up to 40% (Friedman et al., 1992a; Fedele et al., 1995) and the chance of reducing the fertility potential by postoperative adhesion formation (Tulandi et al., 1993).

The benefits of pretreatment with GnRH agonists for a period of 2–3 months before myomectomy have been studied by six different authors. Study results concerning blood loss are summarized in Table I. In the placebo-controlled study by Friedman et al. (1989a), blood loss was assessed by measuring aspirated
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Table I. Comparative studies on the effect of pre-myomectomy gonadotrophin-releasing hormone (GnRH) agonist (Ag) treatment on intra-operative blood loss and transfusion rate

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</tr>
<tr>
<td>Fedele et al., 1990</td>
<td>8/16</td>
<td>235/275</td>
<td>NS</td>
</tr>
<tr>
<td>Golan et al., 1993</td>
<td>12/9</td>
<td>320/476</td>
<td>0.03</td>
</tr>
<tr>
<td>Non-randomized studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Falsetti et al., 1992</td>
<td>30/35</td>
<td>205/310</td>
<td>0.001</td>
</tr>
<tr>
<td>Gardner and Shaw, 1992</td>
<td>13/9</td>
<td>304/502</td>
<td>0.01</td>
</tr>
<tr>
<td>Kiltz et al., 1994</td>
<td>19/9</td>
<td>650/750</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant.

blood volume and sponge weight gain divided by 1.06 gm/ml. Myomectomy was performed using a lower uterine segment tourniquet and vascular clamps on the ovarian vessels. Especially if the preoperative uterine size was >600 ml, blood loss during the actual uterine surgery could be reduced by 50%. The number of patients was, however, small. Fedele et al. (1990) performed an asymmetrical randomized study. The mean pretreatment uterine size was rather small (450 ml). No difference in blood loss was reported. This finding may be in line with those of Friedman et al. (1989a), where only the large-sized uterus seemed to benefit from pretreatment. Golan et al. (1993) carried out a randomized study on patients undergoing hysterectomy or myomectomy. Stratification to the type of surgery was done post hoc. Although the method of assessment of blood loss was based on estimations of aspirated blood and the number of soaked pads, a clear difference was found in favour of the agonist-treated group. In addition, a significant difference in the need for blood transfusions was reported (Table I).

In the three non-randomized studies historical or matched controls were used. Mean pre-treatment uterine volume was 700 ml in the study by Gardner and Shaw (1992), 550 ml in that of Falsetti et al. (1992) and 1000 ml in the study by Kiltz et al. (1994). In the two former studies the difference in blood loss was significant. In Gardner’s study the very reliable alkaline haematine method was used for intraoperative blood loss estimation. In the study by Kiltz the use of the agonist appeared to have no benefit when compared to the historical control group.

From the studies presented the benefits of GnRH agonist pretreatment prior to abdominal preserving surgery seem to be confined to cases where the uterine size exceeds a certain value, for instance 600 ml. Whether these benefits will include a reduction in the formation of postoperative adhesions remains to be investigated. Finally, there has been some discussion regarding whether pretreatment of myomas by GnRH agonists may prevent the identification and removal
GnRH agonists and uterine leiomyomas

Table II. Comparative studies on the effect of pre-hysterectomy gonadotrophin-releasing hormone (GnRH) agonist treatment on intra-operative blood loss and transfusion rate

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Mean blood loss (ml) (perop)</th>
<th>Transfusion rate (per/postop)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ag/no Ag</td>
<td>Ag/no Ag</td>
<td>P</td>
</tr>
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<td><strong>Randomized, controlled studies</strong></td>
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<tr>
<td>Stovall et al., 1991</td>
<td>25/25</td>
<td>527/614</td>
<td>0.042</td>
</tr>
<tr>
<td>Lumsden et al., 1994</td>
<td>35/35</td>
<td>187/308</td>
<td>0.003</td>
</tr>
<tr>
<td>Golan et al., 1993</td>
<td>17/15</td>
<td>208/309</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Non-randomized studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vercellini et al., 1993</td>
<td>41/92</td>
<td>159/333</td>
<td>0.01</td>
</tr>
<tr>
<td>Gardner and Shaw, 1992</td>
<td>9/11</td>
<td>182/350</td>
<td>0.01</td>
</tr>
</tbody>
</table>

perop = peroperative; postop = postoperative; NS = not significant.

of smaller myomas. In the study by Fedele et al. (1990), some support for this hypothesis was found from an increased incidence of myoma recurrence in the agonist pretreated group. Friedman et al. (1992a), however, in a study with a much longer follow-up period, could not confirm these findings.

**GnRH agonist treatment before hysterectomy**

Hysterectomy for the treatment of symptomatic women with uterine leiomyomas offers a definite solution. Due to the size of the uterus abdominal surgery is often mandatory and even with the abdominal approach surgery may not always be easy. Size reduction of the uterus and reduction in the blood flow in the uterine vasculature by the use of GnRH agonists may improve the handling of the uterus and limit the amount of peroperative blood loss and the rate of blood transfusions. Preoperative correction of myoma-related anaemia without the need for blood transfusions may be an additional advantage, although this aim may in itself be achieved by other hormonal treatments.

Five studies have been published concerning the possible benefits of GnRH agonist pretreatment. Data concerning blood loss are summarized in Table II. Stovall et al. (1991) compared two groups of women in whom the uterine size was between 14–18 weeks’ gestation. Patients in the group pretreated with leuprolide acetate for 2 months were much more likely to undergo a vaginal hysterectomy (76 versus 16%). The small difference in the peroperative blood loss in favour of the pretreated group may be explained by the difference between the groups in the route of operation. In the very detailed study by Lumsden et al. (1994), a clear difference was found in the amount of peroperative blood loss, while hysterectomy in the agonist-treated group was technically easier. In addition, pretreatment with the agonist allowed a transverse incision in 69% of cases compared with 44% in the placebo treated group. In the study by Golan et al. (1993), in addition to the reduction in blood loss during surgery, operating
time was significantly reduced. This finding, however, is not confirmed in the other studies.

In a non-randomized trial, Vercellini et al. (1993) analysed the effects of pretreatment in patients with myoma-associated menorrhagia. It was shown that in the pretreated group the vaginal route of operation could be chosen three times as often as in the nontreated group, while the pretreatment uterine size was not different between the groups. In the control group the need for preoperative blood transfusions was ~35%, compared with zero for the agonist-treated group. Finally, the study by Gardner and Shaw (1992) showed a difference in the amount of blood loss in favour of the agonist-treated group. However, the initial uterine size was clearly greater in the control group, which may account for the observed differences.

In two additional reports the possible benefits of agonist pretreatment were studied in mixed groups of patients, comprising myomectomy and hysterectomy cases (Audebert et al., 1994), or patients with either myomas or a normal uterus (Ylikorkala et al., 1995). These studies, therefore, could not be included in one of the tables. In the study by Audebert, the main benefit from pretreatment was in a reduction of the need for blood transfusions and a possible faster and safer surgical procedure. Ylikorkala concluded that GnRH agonist pretreatment is indicated if preoperative anaemia needs correction.

The advantages of GnRH agonist pretreatment in hysterectomy procedures seem to be more clearly defined than in abdominal myomectomy. However, the benefits may not outweigh the costs related to the use of these hormones and therefore preoperative treatment should not be recommended as a routine measure. The use of these compounds may be indicated in cases where the uterine size reduction is expected to enable the use of a transverse incision or vaginal route of operation. For preoperative correction of myoma-associated anaemia, a GnRH agonist should only be used if there is an indication for uterine size reduction as such. In any other case, suppression of the pituitary–ovarian axis can be achieved by much cheaper hormone preparations.

GnRH agonist treatment before endoscopic myomectomy

The use of GnRH agonists prior to endoscopic surgery results in a reduction of the blood flow in the uterine vasculature (Matta et al., 1988b), a decrease in size of the myomas, and a reduction in size of the uterine cavity (Watanabe and Nakamura, 1995). Furthermore, the ovarian suppression leads to endometrial atrophy. These changes induced by the agonist are believed to reduce the amount of blood loss during endoscopic surgery, facilitate surgery on larger myomas, and diminish the risk of distension fluid loss into the circulation. The use of agonists is widely advocated (Donnez et al., 1989; Dubuisson et al., 1991), in spite of the fact that proper comparative studies are lacking. The preoperative treatment with progesterone preparations in order to induce endometrial atrophy may be an alternative and cheaper strategy, which deserves comparison to GnRH
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agonists with regard to intraoperative blood loss, technical ease and fluid balance. As stated earlier, the possibility of gestagen-induced increase in myoma volume has recently been stressed by several authors (Rein et al., 1995; Harrison-Woolrych and Robinson, 1996).

References


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