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A Benefit-Risk Assessment of Medical Treatment for Uterine Leiomyomas

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Contents

Abstract

The growth of a uterine leiomyoma stops and regresses after the menopause suggesting that leiomyoma growth is dependent on ovarian steroids. Therefore, estrogen has received much attention as the major factor responsible for the development of uterine leiomyomas, but progesterone also plays an important role in development of this disease.

Cytogenetic analyses of resected samples has revealed that about 40 to 50% of leiomyomas show karyotypically detectable chromosomal abnormalities.

Gonadotrophin releasing hormone (GnRH) agonists exert their action through the suppression of endogenous gonadotrophins and gonadal steroid secretion. Significant reductions of uterine/leiomyoma volume under GnRH agonist therapy has been reported in several studies. However, the leiomyoma generally returns to its pretreatment volume within a few months after discontinuation of the GnRH agonist. To minimise the adverse effects of hypoestrogenism during GnRH agonist treatment, add back therapy can be used (estrogen-progestin, progestin alone and recently tibolone).

Antiprogestins have a potential clinical utility in uterine leiomyomas. Mifepristone is a synthetic steroid with both antiprogesterone and antiglucocorticoid activities, that may have an inhibitory effect on growth of leiomyoma. Danazol is an isoxazole of 17β-ethinyl testosterone, a synthetic steroid, which has a suppressive effect on sex hormone binding globulin concentrations, resulting in efficacy in the short-term treatment of uterine leiomyomas. Gestrinone is a tri-enic steroid with antiestrogen and antiprogesterone properties and has been shown to reduce uterine volume and stop bleeding.

Growth factors play a relevant role on the pathophysiology of uterine leiomyoma and probably the inhibition of the action of growth factors on the myometrium will be the basis for future therapy. A number of agents are under investigation for treating uterine leiomyoma. Agents developed from increasing genetic knowledge of this condition could represent, in the next few years, new trends in the medical treatment of uterine leiomyomas.

Uterine leiomyoma is the most common benign smooth muscle cell tumour of the myometrium. It occurs with an incidence of about 20 to 40% in women of reproductive age (30 to 40 years old).[1] Most affected women have multiple tumours, with the average number of tumours per uterus estimated to be 6.5.[2] Leiomyomas will shrink after menopause with regression of ovarian sex hormone production.

Studies of incidence show that Black women have over a 3-fold greater frequency of leiomyomas and a relative risk for leiomyomas of two or three times that of White women.[3] Black women have more severe disease in terms of higher uterine weights and greater likelihood of anaemia. They also tend to be younger at the time of diagnosis and at the time of hysterectomy. The risk of developing leiomyomas is higher in obese women and is lower in women who smoke.[3] Many studies have shown that being parous decreases risk of leiomyoma formation.[4] The majority of patients have multiple leiomyomas, and each leiomyoma is thought to be clonal, arising independently from a single smooth muscle cell.

Uterine leiomyomas are classified by their location in the uterus. Subserosal leiomyomas are located just under the uterine serosa and may be pedunculated (attached to the corpus by a narrow stalk) or sessile (broad-based). Intramural leiomyomas are found predominantly within the thick myometrium but may distort the uterine cavity or cause an irregular external uterine contour. Sub-

mucous leiomyomas are located just under the uterine mucosa (endometrium) and, like subserosal leiomyomas, may be either pedunculated or sessile. Tumours in subserosal and intramural locations comprise the majority (95%) of all leiomyomas; submucous leiomyomas make up the remaining 5% (figure 1).

Uterine leiomyomas cause a range of symptoms. Excessive menorrhagia represents a significant medical and social problem for many women. Other symptoms are severe abdominal pain, urinary incontinence and constipation, and voiding alterations where leiomyomas develop as subclinical pelvic masses. Reproductive issues are also a concern, as fibroids are associated with infertility and, if present during a pregnancy, may contribute to spontaneous abortion, premature labour or dystocia.

The presence of a uterine leiomyoma is suspected on the basis of a bimanual examination that reveals an enlarged, firm, nontender and irregular contoured uterus. In most cases, the ultrasound confirms the physical findings. There is a statistically significant correlation between bimanual examination findings and uterine size determined by ultrasonography in leiomyomatous uteri up to 20 weeks size.[5]

The progression of uterine leiomyomas to malignant leiomyosarcoma is rare; it is estimated at a frequency of less than 0.1%.

Although there was little change in conservative management for over a century after the first laparotomic myomectomy was described by Atlee at the end of the 1970s, several new techniques have been proposed as alternatives to myomectomy by laparotomy: surgical and medical alternatives.[6]

A new surgical approach to uterine leiomyomas is represented by laparoscopy. With this technique it is possible to obtain the same surgical result of laparotomy, myomectomy or hysterectomy, but with less hospitalisation and a rapid return to normal life. Intracavitary and submucous leiomyomas can be removed by hysteroscopic resection. The vaginal route, useful when leiomyomas are not larger than a 16-week pregnancy, has the same surgical results as the abdominal route with the same cost. Nonextirpative approaches such as myolysis and uterine artery embolisation are being evaluated, and may provide more options if they prove to be safe and efficacious in long-term follow-up.

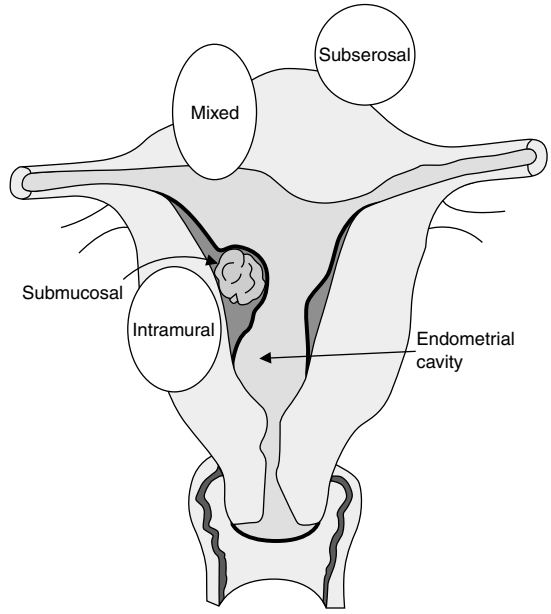

Fig. 1. Types of uterine leiomyomas: submucosal, intramural, subserosal and mixed.

Medical therapy is less expensive than a surgical approach, but the final result is not always the same: it is possible for there to be the regrowth of leiomyomas with medical therapy.

Uterine leiomyomas are the benign tumour with which the female population is most familiar. Indeed, because it is extremely frequent and has such an effect on women's reproductive health, it is a subject of importance for public health. There are various treatments for uterine leiomyomas but the only effective long-term therapy for treatment of these tumours is hysterectomy or myomectomy. Uterine artery embolisation and laparoscopic occlusion of uterine vessels are the new frontiers of

minimally invasive surgery for treatment of uterine leiomyomas. It seems to be effective long-term, but further studies are needed. In addition, a new generation of medical treatments is being investigated based on a better understanding how leiomyomas grow and develop.

1. Pathophysiology

The pathophysiology of uterine leiomyomas is not well understood. Steroid hormone concentrations as well as genetic predisposition play a role in formation and growth of uterine leiomyomas, as do growth factors relevant in fibrotic processes and angiogenesis.

The uterine leiomyoma growth stops and regresses after the menopause, when sex steroid plasma levels fall, suggesting that the growth of leiomyoma is dependent on ovarian steroids, but their mechanism of action is not completely clear.

Estrogen has received much attention as the major factor responsible for the development of uterine leiomyoma. Estrogen receptors (ER) α and β are present in fibroid and normal tissue of uteri. ERα expression is increased in leiomyoma tissue compared with that in the adjacent normal myometrium throughout the menstrual cycle. ERβ expression is the same or even lower in leiomyoma than in the adjacent normal myometrium.[7,8] Both the ER have DNA sequences that are very similar and share same functions; however, in many cases ERα and ERβ play very different roles.

Furthermore leiomyoma express aromatase activity, which converts androgen in estrogen, and its expression is higher in leiomyoma than in normal surrounding myometrium[9] thereby suggesting that leiomyoma cells synthesise estrogen *in situ* and this may contribute to the growth advantage of leiomyomas through paracrine/autocrine mechanism.[10]

The stimulatory role of progesterone on the growth of uterine leiomyomas has not been completely defined. The immunohistochemical analysis with a monoclonal antibody to proliferating cell nuclear antigen (PCNA) demonstrates the prevalence of proliferative activity of uterine leiomyoma cells during the secretory, progesterone dominated, phase of the menstrual cycle.[11]

Table I. Chromosomal rearrangements observed in uterine leiomyoma

Chromosomal region	Type of rearrangement	Genes mapped to region
6p21	Translocations, inversions	HMGIY
7q22q32	Deletions, translocations	CUTLI, PCOLCE, ORLC5L
12q14-15	Translocations, inversions	HMGIC
14q23-24	Translocations	RAD51B/HREC2

Several studies have focused on identifying a genetic factors in leiomyoma and recently an inherited component in their aetiology has been proposed.[12-16] The results of studies performed on twins, as well as analysis of individuals with multiple hereditary uterocutaneous leiomyoma, support a role for genetic factors in the development of these tumours.[12] Further attempts to categorise leiomyoma have been advanced by cytogenetic analyses of resected samples. About 40 to 50% of leiomyomas show karyotypically detectable chromosomal abnormalities that are both non-random and tumour-specific. These samples have been classified into several cytogenetic categories based upon the chromosome aberration present (table I).

A recent study showed a positive correlation between the presence of a cytogenetic abnormality and the anatomic location of the uterine leiomyoma.[13] The submucous leiomyomas were consistently shown to have fewer cytogenetic abnormalities when compared with intramural or subserous leiomyomas.

Cytogenetic analyses of multiple leiomyomas from a single uterus have demonstrated that the tumours can harbour different chromosomal changes, and have suggested that each leiomyoma develops independently. X-inactivation studies, which exploit the phenomenon of Lyonisation, have clearly demonstrated that leiomyomas develop as clonal lesions.[14-16]

2. Gonadotrophin-Releasing Hormone (GnRH) Agonists

2.1 Pharmacology

It is now more than 30 years since the seminal studies that allowed basic strategies for the preparation of superactive gonadotrophin-releasing hormone (GnRH) agonists were conducted.[17,18] The two fundamental modifications that permitted synthesis of these compounds are the replacement of the tenth amino acid (glycine) of the native GnRH sequence with an ethylamide (Net) residue and the substitution of the sixth amino acid (glycine) with other more lipophilic D-amino acids such as D-Phe, D-Leu or D-Trp. Other structural modifications that permit enhanced potency and that were incorporated in the design of clinically available GnRH agonists include the use of more complex amino acid molecules in position 6 [D-Ser (tBU), D-His (Bzl), D-Nal(2)] and/or in position 10 [aza-Gly], and the N-Me-Leu modification in position 7.[19]

Most of the modifications result in more hydrophobic compounds that are more stable than the native GnRH molecule because of greater conformational stability of a β II type bend in the analogue molecule. Receptor affinity and *in vitro* potency appear to be directly proportional to the hydrophobicity of each GnRH agonists. In addition, the more hydrophobic GnRH agonists are more resistant to enzyme degradation and bind more strongly to plasma proteins and body tissues, thus decreasing renal excretion and prolonging drug half-life.[20]

Greater receptor affinity, longer half-life and decreased degradation are all enhanced by increased hydrophobicity and act synergistically to increase GnRH agonist potency. Furthermore, enhanced hydrophobicity may not be the only factor contributing to agonist potency. In fact, when the more hydrophobic position 6 amino acid substitutions are employed, additional modifications such as Pro-Net do not appear to further enhance GnRH agonist potency. Thus, while [D-Leu6, Pro 9-Net] GnRH (leuprorelin) is more potent than [D-Leu 6] GnRH, [D-Trp 6, Pro 9-Net] GnRH (deslorelin) and [D-Trp 6] GnRH (triptorelin) appear to be roughly equipotent (table II).[21]

2.2 Mechanism of Action

GnRH agonists all exert their action through the down regulation of pituitary GnRH receptors located on gonadotrophin producing cells, with profound reductions of luteinising hormone (LH) and follicle-stimulating hormone (FSH) and as consequence of gonadal steroid secretion and gamete maturation. Therapeutically proven actions of GnRH agonists are exclusively related to the virtually complete elimination of gonadotrophin and/or gonadal steroid stimulatory effects on the reproductive system or on pathological tissues.

At the pituitary level, GnRH agonists binds GnRH receptors and block the postreceptor message that provides the normal input for gonadotrophin synthesis and secretion. This long-term inhibitory action is preceded by a transient (1 week) stimulatory phase associated with elevated

Table II. Structure and route of administration of gonadotrophin-releasing hormone agonists

Name	Structure	Route of administration
Triptorelin	PGlu-His-Trp-Ser-Tyr-DTrp-Leu-Arg-Pro-$GlyNH_2$	SC, IM
Leuprorelin	PGlu-His-Trp-Ser-Tyr-DLeu-Leu-Arg-Pro-NHE_t	SC, IM
Buserelin	PGlu-His-Trp-Ser-Tyr-DSer(0^tBu)-Leu-Arg-Pro-NHE_t	Nasal, SC, IM
Goserelin	PGlu-His-Trp-Ser-Tyr-DSer(0^tBu)-Leu-Arg-Pro-$AzaglyNH_2$	SC, IM
Histrelin	PGlu-His-Trp-Ser-Tyr-DHis(Bzl)-Leu-Arg-Pro-$AzaglyNH_2$	SC, IM
Nafarelin	PGlu-His-Trp-Ser-Tyr-D2Nal-Leu-Arg-Pro-$GlyNH_2$	Nasal, SC, IM

IM = intramuscularly; **SC** = subcutaneously.

serum gonadotrophin and gonadal steroid concentrations. This flare-up phase is usually clinically irrelevant. However, in specific conditions the flare-up phenomenon can cause dangerous complications (as in prostate cancer) or has been exploited to enhance therapeutic efficacy (as in ovulation induction).[22]

2.3 Route of Administration and Delivery Systems

All GnRH agonists now clinically available are highly potent and capable of inducing profound pituitary and gonadal suppression. Nevertheless, different administration routes affect drug absorption and may cause incomplete pituitary suppression. Different GnRH agonists have been formulated to be administered subcutaneously, intranasally, or as intramuscular or subcutaneous long-acting depot injections.

When choosing a GnRH agonist dosage, it should be remembered that complications or adverse effects from overdosage of these drugs have never been reported.

Conversely, inadequate pituitary/gonadal suppression may prevent full therapeutic efficacy of these compounds. Thus, when employing short-acting subcutaneous preparations, a daily GnRH agonist dosage in excess of that suggested by the manufacturer can be employed without concern if insufficient suppression is present or suspected. Partial pituitary suppression with borderline GnRH agonist dosages has been suggested to reduce adverse effects such as bone loss.[23] However, as it is virtually impossible to identify the precise GnRH agonist dose required for minimum suppression in each patient, this approach may result in a loss of therapeutic efficacy and should be avoided.

Several GnRH agonists are available in slow release forms (depot) that permit uninterrupted drug delivery for at least 4 weeks. New delivery systems permitting more prolonged drug administration (3 months) after a single injection are now available.[24] All GnRH agonists presently available are bound to d./-lactide, glycolide copolymers in the shape of microcapsules (leuprorelin, triptorelin) or rods (goserelin). The analogue-carrier complex is injected intramuscularly or subcutaneously. Relatively stable analogue concentrations are achieved thereafter, although differences have been reported for the presently available systems and on adequate pituitary desensitisation can be achieved.

Different regimens for therapy are: (i) a long-term protocol that consists of administration of the drug for at least 6 months using monthly injections; (ii) a short-term protocol that consists of monthly injections for at least 3 months (this is used as preparation for surgery); and (iii) intermittent administration that consists of an initial 6-month course of the GnRH agonist, after which the patient is observed for symptom recurrence. Symptom recurrence is managed by repeated 6-month courses of GnRH agonist therapy. It is necessary to consider the use of antiresorptive add back therapy when patients are given repeated courses of GnRH agonist therapy.

2.4 Efficacy of GnRH Agonist Treatment

The deep hypoestrogenism induced by GnRH agonist therapy rapidly decreases uterine and leiomyoma size. Significant reductions of uterine/leiomyoma volume have been reported in more than 300 patients in several large studies, some of which were conducted in a double-blind, placebo-controlled fashion.[25-29] GnRH agonist therapy produces a significant decrease in uterine leiomyoma size in 35 to 65% of cases. The most volumetric decrease occurs within 3 to 4 months from the initiation of treatment. Additional minor (usually not statistically significant) decrements continue up to the sixth month of therapy.[25-29] Efficacy of treatment is usually monitored with pelvic ultrasound and the myoma shrinkage during GnRH agonist therapy has been confirmed by nuclear magnetic resonance imaging.[30] However, the leiomyoma generally returns to its pretreatment volume within a few months after discontinuation of the GnRH agonist. In addition, leiomyomas may

recur even after conservative surgical removal. It was suggested that GnRH agonist treatment immediately before surgery may favour tumour recurrence. However, the relationship between GnRH agonist administration and postsurgical recurrence of leiomyomas was not confirmed.[31] The administration of low dose GnRH agonist therapy appears to be as effective as more standard dosages. Both the subcutaneous and intranasal routes of GnRH agonist administration are effective.[32]

Although GnRH binding sites were identified in leiomyoma tissue, the therapeutic affect of GnRH agonist therapy is likely related only to hypoestrogenism. The degree of leiomyoma shrinkage was found to be inversely related to estradiol concentrations at the twelfth week of GnRH agonist treatment. Leiomyomas obtained at surgery during GnRH agonist treatment show signs of decreased proliferative activity and of ischaemic injury and cellular atrophy.[33]

Some studies have suggested that GnRH agonists given in preparation for surgery may simplify the operative procedure, reduce bleeding and complications, or permit vaginal rather than abdominal hysterectomy.[34,35] However, the positive effect of GnRH agonist pre-treatment on classical surgical procedures is likely to be marginal if any.

Conversely, GnRH agonist pre-treatment could be more relevant in endoscopic procedures, such as laparoscopic and hysteroscopic myomectomy, for which reduced myoma size and diminished blood loss are critical parameters for optimal treatment outcome.[36]

Despite the limitations of this form of treatment, it is likely that the use of GnRH agonists for leiomyoma management will increase. In addition to endoscopic surgery, GnRH agonist use prior to traditional surgery permits the correction of the anaemia, which commonly presents in these patients and, thus, reduces the chances of blood transfusion being needed. Blockage of menometrorrhagia may also allow these patients to be scheduled for elective rather than emergency surgery.

2.5 Risks and Adverse Effects

GnRH agonists are widely used in therapeutic protocols for in vitro fertilisation (IVF). All data on embryo toxicity in humans have been obtained from studies on assisted reproductive technology. The possibility of embryo damage induced by GnRH agonists has been excluded by investigating the outcome of pregnancies exposed to GnRH agonists in very early pregnancy.[37]

The prevention of premature LH surges during ovarian stimulation is essential to rule out premature luteinisation leading to disrupted oocyte maturation and cycle cancellation. Current care for preventing premature LH surges is treatment with a combination of a GnRH agonist and gonadotrophins. Prospective and retrospective follow-up studies have been performed previously of children conceived by women who have undergone IVF and intracytoplasmic sperm injection (ICSI) and who were treated with GnRH agonist for ovarian stimulation.[38-46] The collection of such data is the only tool by which potential adverse health effects of drugs or assisted reproductive treatment procedures to the mother, fetus and/or live-born infant may be monitored. To date, the outcomes of these studies have indicated that pregnancies resulting from such treatment in combination with assisted reproductive treatment are exposed to a higher rate of perinatal adverse outcome, mainly related to a high prevalence of multiple pregnancies.[38,39,43,46] In contrast, the incidence of congenital abnormalities is not higher among IVF-embryo transfer pregnancies as compared with data obtained from the general population.[47]

All the adverse effects of GnRH agonists are dependent on the profound hyposecretion of gonadal steroids induced by these compounds. No adverse effects derive from a direct action of GnRH agonists. Other mechanisms responsible for the adverse effects of GnRH agonists have been suggested, but never demonstrated. In postpubertal women, vasomotor symptoms (hot flashes) are virtually inescapable. Other common subjective

adverse effects include insomnia, mood liability, headaches and vaginal dryness.[3] In male patients impotence is present during GnRH agonist administration, thus limiting the use of these medications to the area of prostate cancer.[48] Decreased libido also is often reported in women, but is less frequent and less severe than in men.[49]

Nevertheless, bone loss is the most clinically-significant adverse effect of long-term administration of these drugs,[50] since during a 3-month period, a bone loss of about 3% can be expected.

The addition of sex steroids to GnRH agonist therapy (add-back) has been tested as a way of minimising GnRH agonist-related adverse effects such as hot flashes and bone loss. Low dose of estrogens inhibit menopausal symptoms without stimulating the growth of uterine leiomyomas. The estrogens induce proliferative effects on myoma cells when plasma levels increase above 50 pg/ml.[51] The concomitant adjunction of medroxyprogesterone acetate (MPA) to GnRH agonist therapy appears to abolish the clinical efficacy of GnRH agonist therapy in reducing uterine volume, but the use of MPA after 3 months of GnRH agonist therapy does not block the effect on uterine volume reduction.[52] Conversely, the addition of conjugated estrogens and MPA beginning after 3 months of GnRH agonist therapy permitted the maintenance of uterine volume reductions while controlling adverse effects.[53] Greater efficacy of combined estrogen/progestogen versus progestogen alone supplementation was more recently confirmed by Friedman et al.[54]

Recently, the add back therapy with tibolone to GnRH agonist treatment reduces the bone loss and vasomotor symptoms that normally occur with GnRH agonist, thus making long-term treatment with GnRH agonists safer and more acceptable. It does not negate the therapeutic effect of GnRH agonist on uterine leiomyoma.[55]

2.6 Benefit-Risk Assessment

GnRH agonists are well tolerated drugs, whose efficacy in the treatment of leiomyomas is universally accepted. Furthermore, the availability of depot formulations makes their administration easy. The rate of success of GnRH agonists in the medical treatment of leiomyomas is considered by many authors to be the highest when compared with other drugs. However, the main problem with GnRH agonists is the severe induced hypoestrogenism which could exert unfavourable effects on bone density and lipid profile.

Clinicians need to have more information on efficacy and adverse effects of steroidal add-back therapy. GnRH agonists might be considered first choice treatment for uterine leiomyoma if the good results reported in preliminary studies investigating low dose estrogen-GnRH agonist combination therapy are confirmed in large randomised controlled trials.

3. GnRH Antagonists

Unlike the agonists, the structures of the antagonists differs substantially from that of GnRH. The structure of GnRH antagonists are different in positions 1, 2, 3, 6, 8 and 10. Their affinity for the GnRH receptor is 9 times higher than natural GnRH.[56] The GnRH antagonists bind to gonadotrope GnRH receptors and compete successfully with endogenous agonist GnRH molecules for receptor occupancy.[57]

The onset of action of GnRH antagonists is within a few hours with a competitive link with GnRH receptors, without any activation of these receptors and without any type of stimulation. GnRH antagonist may offer advantages over GnRH agonists when a rapid reduction in pituitary gonadotropins is required.

Both GnRH agonists and antagonists are administered to prevent the occurrence of LH rises and surges during ovarian stimulation.[58] From a clinical standpoint the major difference between Gn RH agonists and the antagonists is that a flare-up only occurs when the agonist is administered.

The advantage of administering a GnRH antagonist is the desensitisation of gonadotrophs, competitive luteinising hormone-releasing hormone

(LH-RH) receptor occupancy with an immediate decrease in the concentration of LH and FSH and the following reduction in estradiol levels that could lead to improvement in uterine bleeding and shrinkage in myoma dimensions, particularly in submucosal ones.[59]

The maximum reduction is achieved within 14 days of treatment, shorter time compared with the use of GnRH agonist. Ovarian function can be restored faster than following GnRH agonist treatment. The use of a GnRH antagonist could be used in preoperative treatment of uterine leiomyomas.[60]

3.1 Risks and Adverse Effects

Even though studies in animals exposed to therapeutic doses of GnRH antagonists did not demonstrate any adverse outcomes among the offspring, careful examination of pregnancy outcome obtained in humans is mandatory. Perinatal outcome and malformation rate are the first available elements of such follow-up, which is required for every new drug introduced into clinical practice.

Initial data on neonatal outcome and incidence of abnormalities are reassuring since they are within the same range as have been reported for IVF-embryo transfer pregnancies in much larger patient subsets.[61]

The local tolerance of ganirelix administered subcutaneously is generally good. The percentage of patients with at least one moderate or severe local intolerance reaction (skin redness, swelling, bruising, pain or itching) during ganirelix treatment is about 16%. Most frequently reported reactions were moderate or severe skin redness (9.5%) or swelling (9.5%) occurring 1 hour after injection, but by 4 hours after injection these reactions had mostly disappeared. At 24 hours after injection, bruising (moderate or severe) was most frequently reported (2.5%).[62]

3.2 Benefit-Risk Assessment

No additional benefits are expected using GnRH antagonists in comparison with GnRH agonists. Possibly the only advantage could be the faster shrinkage of uterine leiomyomas when the reduction of uterus is required before surgery. Unlike GnRH agonists, no depot formulations are available for antagonists. As 10% of patients report local intolerance reactions to GnRH antagonists, clinicians should prescribe agonists and not antagonists when planning a middle-term treatment of leiomyomas.

4. Steroid Antagonists

4.1 Antiprogestins

Antiprogestins have been shown to have potential clinical utility in uterine leiomyomas.[63] Mifepristone (RU486) is a synthetic steroid with both antiprogesterone and antiglucocorticoid activities. It is the first clinically available antiprogestin, and the majority of studies on this new class of drugs have been performed using mifepristone.

4.2 Pharmacology and Mechanism of Action

Mifepristone has a very long half life (about 20 hours) because of its ability to bind to plasma orosomucoid (an alfa 1-glyco-protein).[64] This binding is not found in primates, therefore studies involving primates should be interpreted in this light. Not all antiprogestins bind to orosomucoid, and RU40555 has a shorter half life because of this characteristic. These short acting compound are of interest in kinetic assessment of the hypothalamic-pituitary-adrenal-ovarian axis in clinical endocrinology.[65] Binding of agents, such as mifepristone and lilopristone (ZK98734), to orosomucoid may enhance their antisteroid effect since binding protects the drug against metabolic inactivation and provides a reservoir system for sustained delivery to target organs.[66]

It would be particularly helpful to have a pure antiprogestin for disease entities which require long-term administration, such as endometriosis and leiomyoma, since in these cases the antiglucocorticoid effect is probably neither necessary nor even useful. With higher doses (100 mg/day), it was also shown an effect on adrenal function.[67]

Mifepristone binds to the progesterone receptor and under certain circumstances may act as an antagonist or agonist. The 11 β-phenyl substitution is essential in determining the antagonist properties of most antisteroids, while an 11 β aliphatic chain may result in agonistic derivatives.[68]

Mifepristone binds to the progesterone receptor (PR) more avidly than it does to the glucocorticoid receptor. Similarly, glucocorticoid receptor binds cortisol with higher affinity than progesterone. These receptors are members of a superfamily, which includes not only the steroid receptors but also vitamin D, retinoic acid, and thyroid hormone.[69]

There is sufficient evidence to suggest that progesterone antagonists act through the progesterone receptor. Antagonists may act to block receptor function at multiple steps in the process which may include: (i) blocking binding of progesterone to the receptor; (ii) altering or blocking the conformational changes associated with binding; (iii) blocking dissociation of associated proteins; (iv) altering or blocking receptor dimerisation; (v) altering or blocking DNA binding; and (vi) altering interaction with other factors to produce transcriptionally active receptors.[70]

4.3 Efficacy of Mifepristone Treatment

That progesterone may play a role in leiomyoma growth is suggested by the finding of an higher mitotic count in leiomyoma obtained during the secretory phase than in the proliferative phase of the menstrual cycle.[71] Additionally, when a GnRH agonist and a progestin are coadministered, the expected regression of leiomyoma size seen with the GnRH alone is not achieved.[52]

Murphy et al.[72] attempted to reduce the growth of uterine leiomyomas by using low-dose (50 mg/day or approximately 1 mg/kg/day) mifepristone for 3 months in ten patients. A dose-response study was also carried out: ten patients were studied using a 25 mg/day dosage for 3 months and seven patients received 5 mg/day for the same length of time.[73]

Leiomyoma size decreased by 22% at 4 weeks, 39% at 8 weeks, and 49% at 12 weeks, respectively, for the 25 mg/day dosage.[72,73] These findings are at least equivalent to the decrease seen in leiomyoma size with the use of a GnRH agonist for 6 weeks.[74,75] The dose response data suggest that 25mg/day is effective in achieving regression of uterine leiomyomata.[73] At all doses studied, patients became amenorrheic. Adverse effects reported include mild atypical hot flashes in four out of ten patients receiving mifepristone 50 mg/day and in the three out of ten patients receiving 25 mg/day. No change was seen in bone mineral density of the spine and hips by dual photon absorptiometry after 3 months of therapy at 50 mg/day.[72,73]

The mechanism by which mifepristone produces a change in leiomyoma size is unknown. It is interesting to note that the decrease in size of the leiomyomas occurs along with symptoms of hypoestrogenism.[76] It may be that mifepristone alters the functional capacity of the estrogen receptor by acting as a 'non competitive' antiestrogen as proposed by both Wolf et al.[77] and Neulen et al.[78] Another theory is that mifepristone may have a direct effect on leiomyoma and myometrium. Clinical data suggest the dependence of leiomyoma growth on progestins. It is probable that antiprogesterone properties of mifepristone are responsible for the decrease in leiomyoma size. *In vitro* data suggest that mifepristone directly inhibits its growth of leiomyoma and myometrium and that addback of sex steroids (progesterone) re-establishes growth of leiomyoma or myometrium in culture.[79]

Recently, the effects of mifepristone 25 mg/day for 3 months or leuprolide acetate 3.75 mg/month for 3 months on uterine artery blood flow and uterine volume have been investigated in a randomised fashion. There were no significant differences between the two treatments in terms of resistive index or uterine volume.[80] The effect of mifepristone on blood flow may be mediated by its antiprogestin, antiglucocorticoid properties, or mediated by other undefined factors.

4.4 Risks and Adverse Effects

Data on tolerability of mifepristone have been obtained from studies investigating the abortive effect of the drug. Few women who receive single doses of mifepristone to interrupt pregnancy experience any adverse effects. When such effects do occur, they include nausea, vomiting, abdominal pain, and fatigue.[81-85] It is often difficult to dissociate many of these symptoms from those that result from the effects of normal pregnancy and spontaneous abortion.

The long-term administration of mifepristone in doses of 100 to 200 mg/day is generally well tolerated; the most common adverse effect is fatigue, which develops in the majority of patients. Nausea, anorexia, and vomiting may also occur.[76,86] Other adverse effects reported during long-term administration include a slight decrease in the serum potassium concentration, bodyweight loss, cessation of menses in premenopausal women, intermittent hot flashes, transient thinning of the hair, development of Hashimoto's thyroiditis, and an occasional decrease in libido and gynecomastia in men.[86] The latter is presumably caused by the binding of mifepristone to androgen receptors.

Because a few women do not abort and instead continue with their pregnancies after the administration of mifepristone and prostaglandin, it was important to determine whether these agents have any teratogenic effects. No such effects were observed in monkeys and rats receiving mifepristone.[87,88] Rabbits, however, had skull deformities that were attributed to mechanical effects due to uterine contractions that resulted from the decrease in progesterone activity. There are isolated case reports of normal pregnancies and neonates when women have taken mifepristone alone or in combination with a prostaglandin, have not aborted, and have elected to continue their pregnancies.[89,90] One woman's pregnancy was terminated at 18 weeks because ultrasonography revealed that the fetus had multiple severe congenital defects not thought to have been caused by mifepristone.[90] Nonetheless, at the current state of knowledge, women who do not abort after the administration of mifepristone plus a prostaglandin should be warned about possible teratogenic effects and should be offered surgical abortion.

4.5 Benefit-Risk Assessment

Mifepristone is a well tolerated drug with few and infrequent adverse effects. The drug is administered orally on a daily basis with a good compliance. In contrast to GnRH agonists, middle- and long-term administration does not lead to reduced bone density. Low-dose mifepristone treatment can be longer than 6 months and could be repeated when the leiomyoma rebounds. The few studies available on mifepristone treatment of leiomyomas report good efficacy and some studies found a similar reduction of uterus for mifepristone and GnRH agonists. However, at this moment mifepristone is not considered as a first choice drug for treatment of leiomyomas. Probably this is because the consolidated theory that pathogenesis of leiomyoma is strictly linked to local estrogen hyperresponsiveness and that progesterone antagonising-estrogenic effect has a protective role in the disease. However, we should underline that large randomised controlled trials comparing mifepristone with GnRH agonists are needed.

5. Danazol

5.1 Pharmacology and Mechanism of Action

Danazol is an isoxazole of 17 β-ethinyl testosterone (ethisterone), a synthetic steroid. Danazol is

chemically related to azastene and cyanoketone, two potent inhibitors of 3B-hydroxysteroid dehydrogenase.[91] It is absorbed well by the oral route, with a circulating half-life of about 15 hours in humans. Concentration of the drug is variable according to the target tissue; for example, 72% of the simultaneous serum concentration is found in the preovulatory dominant follicular fluid after 2 days of administration in humans.[92] At least 60 different metabolites have been identified (one of which is 17-ethinyl testosterone); their role in the biological effects of danazol is still controversial. Certain authors have stated that of the five metabolites of danazol which have been structurally identified, none is hormonally active.[93]

Danazol has been described as a 'selective androgen'.[94] However, many reports suggest that danazol binds to multiple classes of steroid receptors. Danazol binds to rat prostate, uterus, and brain androgen receptors, and the danazol-androgen receptors complex can translocate into the nucleus.[95,96]

Danazol binds to rat uterus and brain progesterone receptors.[95-97] The danazol-progesterone receptor complex translocates into the nucleus at a very slow rate and it is unable to stimulate ribonucleic acid (RNA) synthesis.[97] The effect of danazol in progesterone bioassays remains controversial. Potts and associates[98] have reported that danazol has no progestational activity in the Clauberg assay (test substance given to estrogen-primed immature rabbits and endometrial histology examined for progestational effects). In contrast, Dmowski et al.[99] observed atypical progestational effects in the endometrium of rabbits receiving danazol. In support of the findings of Dmowski's group, Wentz and associates[100] reported secretory changes in the endometrium of women receiving danazol. In discordance with all of the above, other investigators have reported that danazol is antiprogestational.[101] Danazol does not bind to estrogen receptors in human endometrium, rat uterus, or rat brain. These findings are consistent with the observation that danazol has no estrogenic effects in various bioassay systems.[91,92,94,95]

Of greater interest is the observation that danazol have a suppressive effect on sex hormone-binding globulin (SHBG) concentrations. This effect starts within 24 hours after drug administration and becomes significant after 48 hours at all doses (200 to 800 mg/day); with danazol 800 mg/day, the suppression reaches its maximum within a month.[102]

The mechanism of this suppression may involve an increased catabolic rate, a direct inhibition of the hepatic synthesis of SHBG, or an indirect inhibition, resulting from an increase in free testosterone; the suppression is independent of the serum estrogen concentration.[102]

Danazol binds with high affinity to SHBG. The binding capacity of SHBG is also reduced and seems to be related to the androgenic or antiprogesterone activities of danazol.[103] The possibility that some danazol metabolites may have such effects cannot be excluded.[104]

In vitro, danazol has been shown to inhibit multiple enzymes of steroidogenesis, including cholesterol cleavage enzyme, 3β-hydroxysteroid dehydrogenase, 17β-hydroxysteroid dehydrogenase, 17α-hydroxylase, 17,20-lyase, 11β-hydroxylase, and 21-hydroxylase.[105-107] Biochemical analysis suggests that danazol competitively inhibits the previously mentioned enzymes by binding to the active site for the steroid substrate.[106-109] In cell culture, danazol has been demonstrated to inhibit gonadotrophin-induced steroidogenesis in the rat, porcine, and hamster granulosa and luteal cell and in the rat Leydig cell.[96,106] In the rat luteal cell, danazol does not interfere with binding of human chorionic gonadotrophin (hCG) to the gonadotrophin receptor or with hCG stimulation of cyclic adenosine monophosphate. It is likely that danazol modifies ovarian steroidogenesis either by inhibiting the before mentioned enzymes or by binding to ovarian androgen receptors and blocking the synthesis of proteins essential to steroidogenesis.

5.2 Clinical Efficacy

In a recent study the efficacy of short-term danazol treatment in the management of uterine leiomyomas was investigated.[110] Twenty women, aged 34 to 42 years, with uterine leiomyomas were treated with danazol 400 mg/day for 4 months. After therapy, leiomyoma volume decreased significantly ($p < 0.01$) by an average of $23.6 \pm 5\%$. All patients experienced partial or complete relief of symptoms while using danazol. Three and 6 months after the end of treatment the leiomyoma volume had only increased slightly with respect to the volume at the end of therapy, but was still lower than the starting volume. This study showed the efficacy of danazol at a dose of 400 mg/day for 4 months in reducing the volume of leiomyomas and associated symptoms (figure 2).[110]

The use of danazol 100 mg/day for 6 months following a 3-month course of GnRH agonist therapy in women with leiomyoma was associated with a rebound of uterine volume of about 30% less than in controls by the end of danazol therapy (figure 3).[111] Furthermore, bone mineral content was substantially reduced during GnRH agonist treatment but improved significantly during danazol therapy, suggesting that low-dose danazol therapy could follow GnRH agonist therapy with the aim of avoiding leiomyoma rebound and increasing bone mineral density.[111]

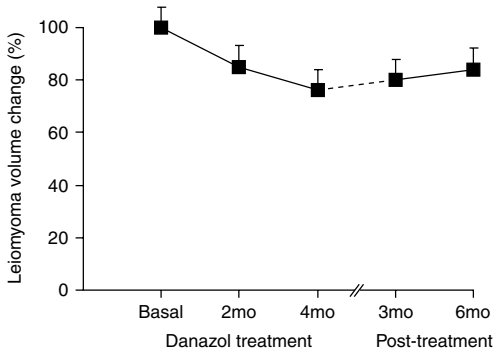

Fig. 2. Change in uterine leiomyoma volume after 2 and 4 months of therapy, and 3 and 6 months after the end of therapy. * $p < 0.01$ *vs* basal. Modified from De Leo et al.,[110] with permission.

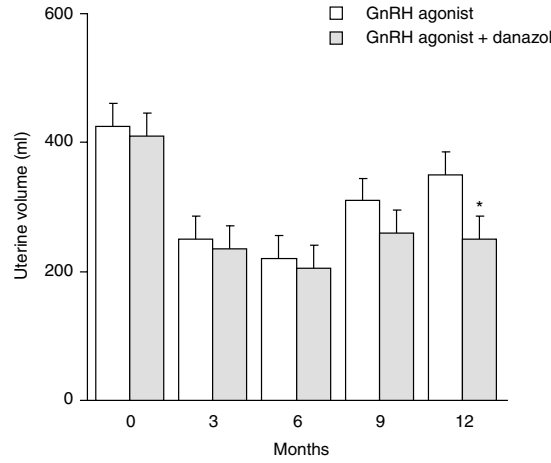

Fig. 3. Reduction in uterine leiomyoma volume 3 and 6 months after gonodotrophin-releasing hormone (GnRH) agonist therapy. Six months of danazol therapy following GnRH agonist therapy lead to a significantly lower increase in leiomyoma volume rebound. * $p < 0.01$ (from De Leo et al.,[111] with permission).

5.3 Risks and Adverse Effects

In the non-pregnant, non-breast feeding woman relatively few absolute contraindications to danazol therapy exist. Danazol is metabolised largely via hepatic mechanisms and has been reported to produce mild to moderate hepatocellular damage in some patients. Therefore, in patients with hepatic dysfunction danazol is relatively contraindicated. Since danazol can induce marked fluid retention, patients with severe hypertension, congestive heart failure or borderline renal function may experience deterioration of their medical condition after danazol is begun.[112]

Dmowski and Cohen[113] have reported a high number of second and third trimester intrauterine fetal deaths in patients who conceived within the first three cycles after discontinuation of danazol. They suggest that this degree of fetal wastage may be secondary to implantation in an atrophic endometrium and that following a course of danazol

one full menstrual cycle of normal flow and duration be observed prior to any attempts to conceive. Danazol administration during early pregnancy has been reported in 47 cases.[114,115] Of the 18 female fetuses exposed to danazol during the period of sensitivity to androgenic substances, 13 had virilisation that included clitoromegaly and partial labial fusion. In only two fetuses were the internal genitalia affected. Virilisation was not observed among any embryos exposed before the eighth week.[115]

The major adverse effects reported during danazol therapy are, in decreasing order of frequency: bodyweight gain, oedema, decreased breast size, acne, oily skin, hirsutism, deepening of voice, headache, hot flashes, changes in libido, and muscle cramps.[116] Significant bodyweight gain (2 to 10 kg) is not uncommon. In our experience more than 75% of patients receiving danazol will complain of one or more adverse effects; however, discontinuation of the drug because of adverse effects is uncommon.

5.4 Benefit-Risk Assessment

Few studies investigating danazol in the treatment of uterine leiomyoma are available. Results are good but moderate to severe adverse effects are reported. Danazol-induced uterine reduction is less or similar to that obtained with GnRH agonists or mifepristone so there is no reason to consider danazol as first choice drug.

Young women treated with danazol should be informed to not conceive in 3 months after the end of treatment. Danazol represents a good alternative to GnRH agonists for women at high risk for osteoporosis in whom a state of hypoestrogenism should be avoided. Furthermore, low-dose danazol could be prescribed after a 6-month course of GnRH agonist therapy to maintain the therapeutic effect as long as possible.

6. Gestrinone

Gestrinone is a tri-enic steroid with antiestrogen and antiprogesterone properties, synthetic derivative of ethynyl-nor-testosterone and has been shown to reduce uterine volume and stop bleeding. In addition, its benefits appear to persist.[117] In this study,[117] gestrinone was given at doses of 2.5 to 5mg (orally or by vaginal pessary), two or three times weekly. The treatment regimen depended upon tumour size. Gestrinone caused amenorrhoea in all patients and in most women it lasted throughout therapy. Most patients experienced at least some adverse effects associated with the mild androgenicity of gestrinone. These included bodyweight gain, seborrhoea and acne (which developed in most patients). Hirsutism, hoarseness and increase in libido are less common, affecting 10 to 20% of patients, depending on the dose and duration of treatment. Adverse effects of gestrinone include possibly the development of unhealthy cholesterol levels. All adverse effects were reversible.[118] Eighty-nine percent of the women treated with gestrinone for 1 year maintained a smaller uterine for at least 18 months after stopping the treatment. There were not adverse effects on bone density that even increased slightly.[119]

6.1 Benefit-Risk Assessment

Gestrinone has no advantage when compared to danazol. To date, its efficacy has been only been demonstrated in few studies limited to small number of women.

7. Future Strategies

7.1 Somatostatin

Forty years ago Grattarola and Li[120] demonstrated that growth hormone (GH) was synergistic with estradiol in the induction of increase in uterine weight in hypophysectomized-ovariectomised rats. GH receptor mRNA has been studied in the normal myometrium and myomas, suggesting a possible role of GH in the development of my-

oma.[121] Interestingly, it has been recently shown that acromegaly, a disorder characterised by high levels of GH, is associated with an high incidence of uterine leiomyoma.[122]

Growth hormone has various effects *in vitro*, *in vivo* and in different tissues. It promotes amino acid uptake by muscle and cartilage which is usually followed by increased protein synthesis. At first it was unclear whether protein synthesis was a direct result of GH or of other factors stimulated directly by GH, such as insulin-like growth factors (IGFs) and somatomedin. There is much evidence to suggest that most major anabolic effects of GH are mediated by these factors and that not only the liver, but most tissues, produce these substances. At least six proteins that bind these factors are produced by various tissues, and may either enhance or decrease IGF activity.[123]

IGF-I and its receptor have been identified in myometrium and leiomyoma. Increased IGF-1 expression has been demonstrated in leiomyoma compared with the adjacent myometrium.[124] IGF-I is a GH-dependent polypeptide with mitogenic properties which is been demonstrated to stimulate smooth muscle cell growth *in vitro*.[125] Hence, GH may exert an effect on the uterus directly interacting with GH receptor and indirectly increasing hepatic synthesis and secretion of IGF-1.

Lanreotide is a long-acting somatostatin analogue which, when administered as a 30mg depot injection, has been shown to reduce spontaneous GH secretion in healthy men. It has evaluated the effect of lanreotide depot, a somatostatin analogue, in seven women with uterine leiomyomas. Ultrasound examination showed a significant reduction in uterine and leiomyoma volume in all women after 3 months of therapy. Three months after the end of therapy, the reduction in uterine and leiomyoma volume was maintained.

Recently data have proved the presence of somatostatin receptors SST2 and SST5 in myometrium and myomas tissue (unpublished observations). These results showed that the GH-IGF system certainly plays a pathogenic role in maintaining uterine leiomyomas and that somatostatin analogue may be an effective new therapy for this condition.[126]

7.2 Antifibrotic Agents

Pirfenidone is an antifibrotic agent which is being investigated for use in patients with pulmonary fibrosis. It is an investigational drug whose structure is 5-methyl-1-1-phenyl-2-(1H)-pyridone. Pirfenidone has been shown to produce antifibrotic effects in a variety of animal models and to inhibit fibroblast proliferation *in vitro* in response to a number of growth factors.[127] Pirfenidone is an effective inhibitor of DNA synthesis, cell proliferation and collagen production for both normal myometrial and leiomyoma smooth muscle cells. Studies on human fibroblasts have shown that pirfenidone inhibits basic fibroblast growth factor, platelet derived growth factor, and transforming growth factor-β stimulated cell proliferation.[128] Leiomyomas contain large amounts of extracellular matrix consisting of collagen, proteoglycan, and fibronectin and show increased expression of collagen type I and type III mRNAs.[129] Pirfenidone effect was investigated in leiomyoma and myometrial tissue obtained from premenopausal women, without hormonal drug therapy, at time of hysterectomy. Pirfenidone significantly inhibited steady state levels of the mRNAs for both collagen type I and type III in myometrial cells at all concentrations tested. Collagen type I mRNA levels were also significantly inhibited in leiomyoma cells.

7.3 Selective Estrogen Receptor Modulators

A novel class of drugs, the selective estrogen receptor modulators (SERMs), have potential as viable alternatives to estrogen in hormone replacement therapy. SERMs bind to the estrogen receptor and exhibit tissue-specific agonist or antagonist activity.

Leiomyoma derived from Eker rat cell lines proliferated in response to estrogen, and estrogen-

induced cell proliferation could be inhibited by the estrogen antagonist fulvestrant and the SERMs raloxifene and tamoxifen. In addition to inhibiting cell growth, these antagonists also inhibited estrogen-induced increases in progesterone-receptor expression. These data indicate that SERMs such as raloxifene and tamoxifen act as estrogen antagonists in uterine myometrial cells and suggest that this class of compounds may be effective for treatment of this important gynecologic neoplasm.[130]

Tamoxifen, a triphenylethylene nonsteroid derivative of diethylstilbestrol, has been used in patients with leiomyoma. The rationale of use of tamoxifen was based on the expected antiestrogenic effect of this drug. After the preclinical use of SERMs in 12-month-old Eker rats there was evidence for therapeutic efficacy of tamoxifen and raloxifene for uterine leiomyoma.[131] The SERMs caused a significant reduction in incidence of uterine leiomyoma, by approximately 40 to 60%, and a reduction in the size of remaining tumours.[131] The use of tamoxifen in ten patients with leiomyoma complaining of abdominal pains and vaginal bleeding for 6 months demonstrated that uterine size was not affected.[132] There was a minimal decrease in the intensity of pain only after 4 months of treatment and the decrease of blood loss was not substantiated in terms of haemoglobin levels.[132] Other authors have reported no change in the size of the uterine leiomyoma[133] or sporadic cases in which growth of leiomyoma was observed in patients receiving tamoxifen.[134] Treatment with tamoxifen was often associated with the development of ovarian cysts, endometrial changes and symptoms like hot flashes and dizziness.

Raloxifene, a nonsteroid benzothiophene SERM, has beneficial estrogen agonist effects on bone and cardiovascular risk factors and estrogen antagonist effects on the breast and uterus.[135]

Recent data show a fast regression of estrogen-induced leiomyomas in guinea pigs treated with raloxifene.[136] Recently, a reduction in uterine and leiomyoma size in postmenopausal women was reported following raloxifene therapy (60 mg/day for 12 cycles of 28 days each). After 6, 9, and 12 cycles of raloxifene treatment, a significant ($p < 0.05$) reduction in mean uterine and leiomyoma sizes was observed in comparison with basal values. The maximum of reduction was 83.9% at 12 months. Adverse effects were hot flushes of various grades, occasionally the presence of leg cramps and nausea and gastralgia. These data show that raloxifene is well tolerated and effective in postmenopausal women affected by uterine leiomyomas. In particular a significant reduction in the mean uterine and uterine leiomyoma sizes, a high rate of amenorrhoea with a low number of spotting episodes and no significant length and severity of uterine bleeding.[137]

7.4 Interferon-α

A case report of a woman who was undergoing treatment with interferon-α for hepatitis C who had striking and sustained shrinkage of uterine myoma after 7 months of treatment has recently been reported.[138] Thus, interferon-α or similar compounds may be useful for the treatment of this condition. The mechanism by which interferon-α acts may be due to inhibition of proliferative effects of fibrotic-growth-factor on myoma cells as has been seen in *in vitro* culture.[139]

8. Conclusions

The recently acquired knowledge on the pathophysiology of uterine leiomyomas confirm the role of steroid hormones and growth factors on leiomyoma genesis and growth. There are new medical strategies to selectively modulate the actions of both estrogen and progesterone. The use of GnRH antagonists rather than the more common GnRH agonists could give the additional benefit of rapid onset of the action.[57,59] This aspect can be useful for preoperative management in women undergoing to surgery.

After pituitary down regulation, steroidal add-back therapy may lead to increase compliance with

Table III. Comparison of currently used medical therapies for uterine leiomyoma

	GnRH agonist	Danazol	Gestrinone	Mifepristone
Cost	Very expensive	Not expensive	Expensive	Not expensive
Efficacy	Very good	Good	Good	Good
Main route of administration	Intramuscular	Oral	Oral	Oral
Adverse effects	Menopausal symptoms	Bodyweight gain	Bodyweight gain	Mild hot flushes
	Dyslipidaemia	Mild hyperandrogenism	Mild hyperandrogenism	
	Reduced bone density			
Duration of therapy	Short-, middle-term	Long-term	Long-term	Long-term

GnRH = gonadotrophin-releasing hormone.

long-term therapy. Furthermore, low-dose estrogen can preserve bone density and reduce menopausal symptoms without reversing uterine shrinkage.[51] Use of steroid antagonists is another strategy to manipulate steroid hormone concentrations. Mifepristone acting as progesterone antagonist produces amenorrhoea and a reduction in uterine volume similar to that observed when GnRH agonist therapy is used.[72] Another steroid antagonist is danazol. The mechanism by which danazol reduces the volume of uterine myomas may be due to reduced estrogen plasma concentrations and to its antiprogesterone effects on uterine leiomyomas.[110] Moreover, danazol administration is useful to inhibit rebound after GnRH agonist therapy in women with uterine leiomyomas.[111] Recent studies have also demonstrated that in the guinea-pig, raloxifene, a SERM, also inhibits leiomyoma growth; this finding has been confirmed in humans.[137] A summary of the characteristics of current medical treatments for uterine leiomyoma is summarised in table III.

A new field of therapeutic drugs may develop from genetic investigations. The observation that specific genes are dysregulated in women with leiomyomas may indicate new possibilities for pharmaceutical intervention through the development of strategies for gene therapy and prevention of uterine leiomyomas. Inhibition of the action of growth factors on the myometrium is the basis for future therapy. Use of somatostatin analogues and interferon-α has been associated to a significant reduction in leiomyoma size; however, randomised studies on larger groups of women are needed.

These results suggests that future nonsurgical treatments for uterine leiomyomas may include compounds that block the actions of specific growth factors that regulate proliferation and collagen production by uterine smooth muscle cells.

If the genetic basis for fibroid development and/or the nuclear mechanism of myometrial proliferation are understood, additional nonsurgical therapeutic interventions may be forthcoming.

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