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REVIEW ARTICLE

GnRH Agonists: Do They Have a Place in the Modern Management of Fibroid Disease?

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Abstract In the management of women with fibroid disease, GnRH agonists (GnRHa) are frequently used to reduce volume and vascularity before myomectomy, apparently to render the operation easier and reduce operative blood loss, and to enable a transverse supra-pubic incision instead of a midline vertical one. They induce amenorrhoea and thus aid in the correction of pre-operative anaemia. Other gynaecologists use GnRHa to shrink sub mucous fibroids greater than 5 cm in diameter to facilitate access and reduce blood loss and operating time at transcervical resection. GnRHa are also occasionally used as a temporizing measure in women with symptomatic fibroids within the climacteric. We argue against the use of GnRHa in the management of fibroid disease because they are not cost effective, render myomectomy more difficult to apply because they destroy tissue planes, the more difficult enucleation in fact increasing rather than reducing perioperative blood loss and operating time. When used before myomectomy, they increase the risk of 'recurrence' because they obscure smaller fibroids that 'recur' when the effects of the GnRHa wear off, and are associated with side effects in situations where they confer no benefits, or where alternative cheaper drugs with fewer side effects are available.

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Introduction

Gonadotrophin-releasing hormone agonists (GnRHa) are synthetic derivatives of the natural hypothalamic neuropeptide gonadotrophin-releasing hormone (GnRH) that is released in a pulsatile fashion and stimulates the pituitary gland to release the hormones FSH and LH that in turn regulate the production of oestrogen and progesterone by the ovary. Their advent has revolutionized the management of many conditions in gynaecology and other areas of medicine, based on the discovery that when administered in a non-pulsatile fashion, they down regulate pituitary GnRH receptors, and therefore the production of FSH and LH. Several GnRHa are available for clinical use, and their potential for use in fibroid disease became apparent when it was realized that ovarian steroids, particularly oestrogen, accelerate the growth of fibroids. They were first tested as therapeutic treatments for fibroids in the late 1980s when Filicori et al. [1] and Maheux et al. [2] demonstrated a reduction in the size of fibroids. These findings were corroborated by many subsequent reports, and there is no argument about the fact that GnRHa reduce uterine and fibroid volume by as much as 30–40 %. However, it soon became apparent that GnRHa were not the medical Holy Grail for the treatment of symptomatic fibroids. The fibroids did indeed regress during GnRHa treatment but

immediately grew back to their original size or beyond upon cessation of the therapy. The menopausal side effects and bone demineralization caused by GnRHa also meant that they were unsuitable for the long-term treatment of fibroids.

The focus of interest shifted to the potential short-term use of GnRHa preoperatively to optimize surgical outcomes. Summarizing data from 21 randomized controlled trials a Cochrane review concluded that the use of GnRHa for 3–4 months before fibroid surgery reduced both uterine volume and fibroid size. They were beneficial in the correction of pre-operative iron deficiency anaemia, as well as apparently in reducing intra-operative blood loss, avoidance of midline incisions at laparotomy and rendering vaginal hysterectomy more likely [3]. It came as no surprise then, when a recent survey of a group of the UK consultant gynaecologists showed that 87 % use preoperative GnRH agonists to reduce operative blood loss at myomectomy in contrast to a smaller percentage who use other methods (35 % use myomectomy clamps, 23 % tourniquets and 19 % use vasoconstrictors) [4].

We argue below that the routine use of GnRHa in the management of fibroid disease is misguided and should be abandoned.

The Side Effects of GnRHa Therapy May Outweigh Their Benefits

The use of GnRH agonist is associated with significant adverse effects. The hypoestrogenic state induced by GnRHa therapy results in the acceleration of loss of bone mineral density (BMD). Studies [5, 6] have reported significant decreases in the mineral content of vertebrae after 6 months of GnRHa treatment although there have been other studies with contradictory findings. A report on use of intranasal GnRHa for 6 months for endometriosis suggested that this loss of bone density might be reversible within 6 months after cessation of the treatment [7]. A Cochrane review in 2003 which included 15 randomized controlled trials also suggested that there was a significantly bigger BMD loss in the GnRHa-only group and that both Danazol and Progesterone + Estrogen add-back therapies were shown to be protective of BMD, while on treatment and up to 6 and 12 months later. After 24 months of follow up, there was no difference in BMD in those women who had hormone replacement add-back therapy [8]. Another major side effect of GnRHa is menopausal symptoms such as hot flushes and night sweats which can have a major impact on women's quality of life. Other minor adverse effects include vaginitis, arthralgia, myalgia, peripheral oedema, insomnia, nausea and nervousness. There is some evidence that add-back therapy either with Progstogen, Tibolone, combined Estrogen and Progestogen, or Raloxifene, can reduce these menopausal side effects, but there is a lack of good quality research data to derive definite conclusions [9]. It is worth raising the question—do the perceived benefits of GnRHa therapy truly outweigh the significant risks of adverse effects and exposure to the add-back therapy? We believe this is not the case.

The Use of GnRHa for the Correction of Anaemia is an Unnecessary Expense

When used pre-operatively to reduce uterine and fibroid volume, or to correct anaemia, the common practice is to administer three injections of a GnRHa over 3 months. The British National Formulary (BNF) [10] gives an approximate cost of £195.00 for this course of treatment (Zoladex, Astra Zeneca). Should the woman develop significant menopausal symptoms, add-back hormone replacement therapy in the form of Tibolone (Livial, Organon) 2.5 mg once a day might be prescribed, at a cost of £20.72 for a 2 months' treatment course. To aid in the correction of anaemia, amenorrhoea can be successfully induced with a progestogen such as Norethisterone (non proprietary) 5 mg three times a day continuously. If given over 3 months, the BNF gives a total cost of £19.62 for the treatment course. Side effects, mainly premenstrual-like syndrome (including bloating, fluid retention and breast tenderness), weight change, nausea, headache, drowsiness and mood swings are minimal, and are tolerated by most women. No bone demineralization occurs with Norethisterone. It is true that no reduction in uterine or fibroid volume occurs, but we question the value of any such reduction as discussed below.

The Reduction in Uterine and Fibroid Volume Confers no Advantages in Myoma Surgery

There can be no argument that GnRHa cause fibroid regression, but we argue against any perceived advantage. The vast majority of surgeons contemplating myomectomy do not consider the vaginal route. Therefore, when GnRHa are used to reduce volume to facilitate the vaginal rather than abdominal route, this is usually in women where hysterectomy is the intended treatment rather than myomectomy. When treating massive fibroids (extending to the level of umbilicus and beyond), the reduction in volume following a course of three injections of a GnRHa administered over 3 months is minimal or negligible [11]. With regard to the issue of abdominal incision, even for these massive fibroids, it is exceptionally rare to need to use a vertical incision for first-time myomectomy [12]. While for repeat myomectomy it would indeed be imprudent to use a transverse supra-pubic incision because of the frequent presence of bowel adhesions, it is rare to encounter this problem with first-time myomectomy. Even

if it is not possible to immediately 'deliver' the fibroid uterus via a transverse incision, initial debulking via the transverse incision will allow eventual delivery.

GnRHa Destroy Tissue Planes and Render Fibroid Enucleation Difficult

A problem frequently encountered in clinical practice, but poorly researched, is that GnRH agonists render surgical planes less distinct, perhaps due to softening of the fibroids, which makes enucleation more difficult. It is teleologically sound to suppose that the difficulty encountered with enucleation of fibroids would not only increase operating time, but would tend to increase rather than reduce blood loss. In a series of 426 women who underwent laparoscopic myomectomy, Dubuisson et al. [13] reported that 11.3 % were converted to open procedures, and analysis suggested that the pre-operative use of GnRHa was one of four factors identified which were independently related to the risk of conversion, presumably at least in part due to the indistinct tissue planes. This might also account for the significantly longer operative time for laparoscopic myomectomy associated with pre-operative GnRH agonist use [14]. Most gynaecologists who perform open myomectomy on a regular basis will attest to the difficulties encountered at surgery following a pre-operative course of GnRHa. Interventional radiologists too avoid the use of GnRHa before uterine artery embolization as they appear to narrow the uterine arteries, rendering them more difficult to catheterize [15].

GnRHa are Associated with an Increased Risk of Recurrence of Fibroids After Myomectomy

Reported recurrence rates after myomectomy vary widely, and have been quoted between 40 and 50 % [16]. In reality, the issue of risk of recurrence is probably more complex than the studies that have so far addressed this issue might imply. The use of GnRHa pre-operatively is highly likely to influence 'recurrence' rates. Smaller fibroids would tend to shrink and not be seen, or be ignored as too small to remove, at the time of surgery, only to re-appear and grow even more rapidly after withdrawal of the GnRH agonist. No wonder then that pre-operative use of GnRH agonists has been reported as a risk factor for recurrence of fibroids [17–19].

There is Conflicting Evidence for the Benefits of GnRHa Used Pre-Operatively in the Hysteroscopic Resection of Sub Mucous Fibroids

Sub mucous fibroids may not only cause menstrual disturbance, but they could also be associated with sub fertility and miscarriage [20]. They can be readily removed by hysteroscopic transcervical resection (of fibroid, TCRF), and it has been suggested that pre-operative GnRHa could facilitate resection. It has been postulated that by reducing fibroid volume the operating time is reduced, thereby lowering the risk of excessive fluid absorption and overload [21]. Interestingly, it has been suggested that reduction in fibroid size induced by pre-operative GnRHa also results in a higher proportion of the tumour protruding into the endometrial cavity, increasing the chance of complete resection of the sub mucous fibroid [21–23]. Despite these theoretical advantages, until recently there had been no randomized clinical trials comparing TCRF with or without GnRHa pre-treatment. One non-randomized trial [24] reported that operating time is reduced, but another [25] suggested that the operations may actually take longer to complete. The year 2010 saw the publication of two randomized clinical trials of GnRHa pre-treatment, one from the United Kingdom [26] and the other from Italy [27]. The latter found in favour of GnRHa, reporting that GnRHa treatment before hysteroscopic resection of G0–G1 10–35-mm sub mucous myomas was effective in reducing operative times, fluid absorption and difficulty of the procedure. The UK study did not support the routine administration of GnRHa before TCRF, as they did not identify any benefit from such treatment. These two studies are not entirely comparable. The UK study was arguably more rigorous, being double blinded and placebo-controlled in which the participants were given three injections of a GnRHa or placebo. On the other hand, in the Italian study, women were randomized to either direct surgery or 2 months (two injections) of GnRHa. If GnRHa pre-treatment really does have benefits, then one would have expected to see it in the UK study, and perhaps not so in the Italian study. The issue therefore remains largely unresolved, although we are persuaded by the rigour of the UK trial. Our own alternative approach suggests that infiltration of the myometrium with vasopressin (20U diluted in 50 ml normal saline, injected into the myometrium transvaginally using a spinal needle, 5–10 min before TCRF) renders the operating field virtually bloodless, providing excellent views and therefore allowing for a rapid operation with minimal risk of excessive fluid absorption. For sub mucous fibroids greater than 5 cm in diameter, where access into the uterine cavity is often compromised, such fibroids are rarely, if ever, found in isolation, more often than not being accompanied by several intramural fibroids. In such circumstances, the abdominal approach may be appropriate to remove all fibroids, including the sub mucous one which can be removed deliberately by breaching the uterine cavity and then taking measures to minimize the risk of formation of intrauterine adhesions.

It is not Appropriate to Use GnRHa as Temporizing Therapy in Women within the Climacteric

Undoubtedly, GnRHa can render women amenorrhoeic, but how long should these women be treated? There is no easy way of predicting the timing of the menopause, and one is giving a drug with the potential to cause osteoporosis in women who, unlike their younger counterparts, do not have the window to restore the bone loss they suffer even from the treatment of 3 months. There are certainly more effective and safer treatment approaches to women with symptomatic fibroids within the climacteric. Uterine artery embolization (UAE) is now a recognized alternative to hysterectomy [28]. UAE may be particularly advantageous in women within the climacteric as the risk of precipitating earlier onset of the menopause is higher and the risk of symptomatic recurrence of fibroids is lower [29]. Progestogens are once again cheaper and effective alternatives to GnRHa. The Mirena IUS could alleviate symptoms in carefully selected women, especially those in whom there are no sub mucous fibroids or distortion of the uterine cavity by intramural fibroids.

Concluding Remarks

We argue against the widespread use of GnRHa in the modern management of fibroid disease for the following reasons: The large and multiple fibroids show minimal regression in response to GnRHa therapy. The use of GnRHa has not been shown to be cost-effective. GnRH agonists have a significant side effect profile and render fibroid surgery difficult due to destruction of tissue planes. It is teleologically sound to suppose that the use of GnRHa increases the risk of recurrence since the smaller fibroids regress and are left behind at the time of myomectomy, only to re-grow aggressively when the GnRHa is withdrawn after surgery. We find no evidence for reduction in intra-operative blood loss as a result of the use of GnRH agonists and there are cheap yet effective alternative treatments available for preoperative correction of anaemia. For hysteroscopic resections, intra-myometrial vasopressin renders the surgical field dry at a fraction of the cost of GnRHa, and without the side effects.

Fibroids are common, and are symptomatic in 50 % of women who have them. It is highly likely that there will be a progressive increase in the number of women requiring myomectomy, not only as an expression of choice, but also because women are delaying childbirth to their thirties and forties, when fibroids are most symptomatic. Poor practices in myoma management would do a disservice to those women wishing to preserve or improve their fertility potential. GnRHa are invaluable tools in some areas such as sub fertility, but they are costly and have significant side effects: They should be administered only when there is proven clinical benefit because of their use.

Conflicts of interest None of the authors have any conflicts of interest to declare.

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