

# Hysteroscopic Myomectomy: Is There a Place for Pretreatment with GnRH Agonist?

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## Abstract

Uterine fibroids (also known as myomas or leiomyomas) are the commonest benign solid tumours found in the female genital tract. Hysteroscopic myomectomy presently represents the standard minimally invasive surgical procedure for treating submucous fibroids. Whether treatment with GnRH agonist before hysteroscopic myomectomy offers significant advantages is still a matter of debate.

A literature search was performed using Medline and the Google search engine, Springerlink and Highwire Press. A total of 11 articles were selected for review.

GnRH agonist use prior to hysteroscopic myomectomy probably has potential benefits in terms of reduction in size of the fibroid and improvement of hemoglobin level, especially in patients with underlying secondary anemia. However, universally acceptable guidelines on the indications and duration of pretreatment whether administered monthly or as daily injections are lacking. Large randomized controlled trials are urgently needed to clarify the gray areas.

**Keywords:** Hysteroscopy, myomectomy, GnRH agonist, submucous fibroids.

## INTRODUCTION

Uterine fibroids (also known as myomas or leiomyomas) are the commonest benign solid tumors found in the female genital tract, with an incidence of 20-25% amongst women in the reproductive age group.<sup>1,2</sup> The incidence is increased in women of Afro-Caribbean origin.<sup>3</sup>

Uterine fibroids arise from the muscular part of the uterus. As they grow, they usually migrate to a place of lower resistance. This can be towards the peritoneal cavity in which case the subserous variety develops or towards the uterine cavity giving rise to submucous fibroids, which constitutes 5-10% of uterine fibroids.<sup>4</sup> The pathogenesis of uterine fibroids is not well understood. It is however known that multiple tumors in the same uterus are derived from individual myometrial cells and not through a metastatic process.<sup>5</sup> Fibroids are hormone dependent and are rarely present prior to menarche while typically regressing after menopause when sex steroids are low. Studies have found that estrogen and progesterone receptors are over expressed in fibroid tissues compared with normal myometrium.<sup>6</sup> Submucous fibroids are classified based on the degree of myometrial penetration. G0 represents a fibroid that is completely within the uterine cavity and appears only connected

to the cavity wall by a thin pedicle; G1 has its larger part (>50%) in the uterine cavity while G2 has its larger part (>50%) in the myometrium.<sup>7,8</sup>

Submucous fibroids may induce severe clinical symptoms such as excessive uterine bleeding usually during menses, colicky dysmenorrhea and are thought to predispose patients to reproductive failure.<sup>2,9</sup> They also have been associated with preterm delivery, abnormal presentation, postpartum hemorrhage and puerperal infection.<sup>10</sup>

Hysterectomy and laparotomic excision have long been considered the two standard routes of surgical treatment for symptomatic submucous fibroids.<sup>11,12</sup> While hysterectomy is usually proposed to those patients who have completed their family size, abdominal myomectomy was reserved for younger patients still desirous of a pregnancy. Abdominal myomectomy however comes with complications such as increased need for cesarean section and increased risk of postoperative pelvic adhesions.<sup>4</sup> Hysteroscopic myomectomy presently represents the standard minimally invasive surgical procedure for treating submucous fibroids.<sup>13,14</sup> The first reported hysteroscopic myomectomy was performed by Neuwirth and Amin in 1976.<sup>15</sup>

Because of the dependence of fibroids on steroid hormones, it follows that medications to reduce the levels of gonadal steroids are options for the treatment of uterine fibroids. The use of gonadotropin releasing hormone agonist (GnRH agonist) in a woman with uterine fibroids was first reported by Filicori in 1983.<sup>16</sup> The patient had a 77% reduction in the size of the fibroid, cessation of excessive bleeding and an increase in hemoglobin concentration from 7.4 to 12.8 g/dl. Although a recent review by Gutmann and Corson<sup>17</sup> reported that "the most clinically relevant indication for preoperative GnRH agonist use appears to be in patients with submucous fibroids", whether treatment with GnRH agonist before hysteroscopic myomectomy offers significant advantages is still a matter of debate.<sup>18,19</sup>

The aim of this study is to review the available literature on the use of GnRH agonist before hysteroscopic myomectomy with a view to determining its role if any.

## MATERIAL AND METHODS

A literature search was performed using Medline and the Google search engine, Springerlink and Highwire Press. The following

search leads were used: Hysteroscopy, myomectomy, GnRH agonist, submucous fibroids, resectoscope. Criteria for selection of articles were: Title; this must be relevant to the review, Methodology; should be a comparative analysis of the benefits or otherwise of GnRH agonist as pretreatment before hysteroscopic myomectomy, preferably randomized controlled trials with standard statistical analysis. Review articles were equally considered.

Karaq'ozov<sup>23</sup> showed a significant increase in hemoglobin levels from  $8.9 \pm 0.9$  g/l to  $11.7 \pm 1.2$  g/l after three months of treatment with GnRH agonist. In addition, total uterine volume decreased by 30% before surgery while the fibroid volume decreased by 39%. After three months of treatment, the patients in Mencaglia and Tantini's study<sup>24</sup> had  $61 \pm 10\%$  reductions in fibroid size with an associated reduction in vascularization. Similar findings were reported by Arcaini et al.<sup>25</sup> Perino et al.<sup>26</sup> in a prospective

## RESULTS

Article (Year)	Method -ology	N	Duration (Months)	Amenorrhoea	Intra Op Bleedn	Fibroid size	Op Time	Fluid Abs	Recurr-ence
Crosignani et al 1996	Review		2-3	Yes		↓	↓	↓	
Moghissi 1991	Review				↓	↓			
Hart et al 1999	Prospective observe	122							No
Nikelov and Kara-q'ozov	Randomised	34	3	Yes		↓			
Mencaglia andTantini 1993	NR	25	3		↓	↓			
Perino et al 1993	Randomised	58			↓		↓		
Romer et al 2000	Review			Yes	↓	↓			
Parazzini et al 1998	Comparative Review			Yes			↓	↓	
Fedele et al 1990	Randomised	24	3		No diff	↓			Yes
Campo et al 2005	NR	80	2				↑		
Arcaini et al 1994	NR	17	2-3	Yes	↓	↓		↓	Yes

N = Number of subjects  
 Intraop bleedn = Intraoperative bleeding  
 Op time = Operative time (Duration)  
 Fluid Abs = Fluid absorption  
 NR = Not randomized  
 No diff = No difference

A total of 11 articles were selected for review. Crosignani et al in 1996<sup>20</sup> reviewed data from the English language literature and found that inducing amenorrhoea in patients with menorrhagia and severe anemia before both conservative and definitive surgeries for uterine fibroids raises hemoglobin and hematocrit values to within normal range, limits homologous blood transfusion and enables surgeries to be scheduled with the patients in better condition. It was also shown that GnRH agonist use before hysteroscopic myomectomy induced endometrial thinning, reduced bleeding and mucous debris and also decreased the diameter of submucous fibroids improving visibility and limiting operating time. Administration of GnRH agonist for two to three months was therefore recommended. Moghissi<sup>21</sup> in an earlier article had also suggested that GnRH agonist therapy reduces the risk of surgical complications and excessive blood loss. Hart<sup>22</sup> in a prospective observational study showed that pretreatment with hormonal agents did not significantly influence the need for submucous fibroid reintervention. In a small prospective study, Nikolov and

randomized study showed a decreased volume of distention fluid, reduced surgical time and bleeding in those patients (n=33) preoperatively treated with GnRH agonist in comparison with controls (n=25).

Romer et al<sup>27</sup> in 2000 suggested preoperative treatment with GnRH agonist prior to hysteroscopic myomectomy for submucous fibroids greater than 3 cm in diameter and/or with an intramural portion or if the patient suffers from secondary anemia. Donnez et al<sup>28</sup> had earlier suggested a diameter of > 4 cm as cut off for pretreatment with GnRH agonist. Parazzini et al<sup>29</sup> in a literature review found that pretreatment with GnRH agonist was associated with a reduction in operating time (between 2 and 25 minutes) and a further reduction in fluid absorption during hysteroscopic myomectomy.

On the other hand, in a small randomized study by Fedele et al,<sup>30</sup> induction of a period of hypoestrogenism with GnRH agonist before myomectomy was associated with an increase in recurrence rate. Indman<sup>31</sup> considers a large sized uterine fibroid as a contraindication for GnRH agonist therapy because of the

risk of severe hemorrhage. Bradley<sup>32</sup> in 2002 showed an increase in uterine perforation during hysteroscopic myomectomy due to reduced myometrial thickness in those patients pretreated with GnRH agonist while Lin et al<sup>33</sup> described an increase risk of the “sinking” phenomenon due to a decreased elasticity of myometrial tissue caused by estrogen deficiency. Furthermore, in a retrospective study by Campo et al<sup>12</sup> it was suggested that preoperative treatment with GnRH agonist did not seem to offer advantage in terms of long and short-term outcomes. Patients who had GnRH agonist had significantly longer surgical times compared with untreated patients. Hallez<sup>34</sup> in his published reports did not recommend any preoperative hormonal treatment before myomectomy.

## DISCUSSION

Abnormal uterine bleeding was a common indication for hysteroscopic myomectomy in most of the studies reviewed with a percentage range of 60-84.1%.<sup>12,15,20,22,31,34</sup> Carlson et al<sup>35</sup> found that symptomatic fibroids accounted for 27% of all hysterectomies performed in the United States with more than 100,000 cases performed for fibroids that caused abnormal uterine bleeding. While the studies reviewed did not agree on all the parameters assessed, most however agree on certain outcomes. There is a resolution of preoperative anemia as GnRH agonist creates a state of amenorrhea<sup>20,21</sup> enabling the patients suffering from menorrhagia to build-up their blood counts thus reducing the need for blood transfusion.<sup>25,36</sup> There is equally a reduction in endometrial thickness as well as the size and vascularity of the fibroids.<sup>24,25</sup> This apparently leads to reduced fluid absorption (through a reduction of uterine blood flow) and possibly operating time. The few minutes reduction in operating time were however of questionable clinical significance while also the 100-150 ml reduction in intravasation may not influence the risk of severe complications which ensues only when the fluid deficit is greater than 1 liter.<sup>29</sup> Campo et al<sup>12</sup> however believes there is an increase in cervical resistance in patients pretreated with GnRH agonist leading to an increase in operating time. Another possible inference that can be drawn is that there is a possibility of surgical scheduling. Indeed, as patients do not necessarily have to be operated upon in the early proliferative phase, preoperative treatment also has a practical benefit in that it allows surgery to be performed at any time<sup>29</sup> which could be beneficial to the Surgeon as well as the patients. The potential risk of GnRH agonist therapy resulting in a delay of the surgical treatment of an unsuspected leiomyosarcoma should however be borne in mind.<sup>37</sup>

There is still a debate with respect to the cut off in terms of fibroid size at which point GnRH agonist should be commenced. Donnez et al<sup>28</sup> suggested that fibroids up to 2 cm do not require any preoperative treatment, while 2-4 cm should be treated for 3

weeks with a progestogen or danazol and GnRH agonist only reserved for those fibroids > 4 cm. However Indman<sup>31</sup> considers a large sized fibroid as contraindication for the fear of severe hemorrhage. Larger randomized controlled trials are still needed to resolve this.

In terms of duration of therapy, most of the studies used three months of treatment. There seems to be an agreement that a 6-8 weeks course will be sufficient to shrink the fibroid by 30-50%.<sup>24,26</sup> In a recent study Stamatellos and Bontis<sup>38</sup> suggested a prolongation of therapy for 2-4 months in patients presenting with anemia with the addition of iron supplements to correct for the anemia.

It must be appreciated that GnRH agonist is not without some well known disadvantages. These would include the high cost of the drug as well as problems with storage especially in temperate countries. In addition side effects such as hot flushes could occur.<sup>1</sup>

Majority of the publications were nonrandomized small studies and therefore lack enough statistical power. Another limitation is that of publication bias; positive studies tend to be over presented in the literature, as the decision to publish data is often based on informal observation of favorable outcomes.<sup>29,39</sup>

## CONCLUSION

GnRH agonist use prior to hysteroscopic myomectomy probably has potential benefits in terms of reduction in size of the fibroid and improvement of hemoglobin level, especially in patients with underlying secondary anemia. However, universally acceptable guidelines on the indications and duration of pretreatment whether administered monthly or as daily injections are lacking. Large randomized controlled trials are urgently needed to clarify the gray areas.

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