

# Management of Adenomyosis in Subfertile Women and Pregnancy Outcome

Fathia E. Al Jama

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## Abstract

**Objectives:** To assess the outcome of treatment with only gonadotropin releasing hormone agonists (Gn-RHa) versus combined conservative surgery and Gn-RHa therapy in the management of sub-fertile patients with symptomatic uterine adenomyosis.

**Methods:** A retrospective study of the two treatment modalities allocated to 40 sub-fertile patients with pathology-proven adenomyosis over a period of eight years was undertaken at the Obstetrics and Gynecology department, King Fahad Hospital, Dammam University, Saudi Arabia. Twenty-two patients (Group A) were treated with Gn-RHa alone, and 18 patients (Group B) received combined conservative surgery with Gn-RHa therapy. After completion of six courses of Gn-RHa injections, there was a 3-year follow up period for all patients. Treatment outcome included relief of symptoms, pregnancy rate and successful deliveries, which were compared between the two groups.

**Results:** The patients in group A were younger in age, had lower CA-125 levels and shorter infertile years than Group B. Three (13.6%) spontaneous pregnancies resulted upto 18 months of stopping Gn-RHa in group A, while 8 (44.4%) pregnancies resulted upto 36 months in group B patients, which was statistically significant ( $p=0.0393$ ). Term delivery occurred normally in one (4.5%) Group A patient, while 6 (33.3%) patients in Group B had cesarean section at term ( $p=0.0328$ ).

**Conclusion:** Combined conservative surgery and Gn-RHa may provide effective symptom relief, better reproductive performance in subfertile patients with uterine adenomyosis and longer period of pregnancy prospects after treatment than patients who recieved Gn-RHa alone. Due to the nature of this study, a well conducted randomized trial is needed in the future to assess the benefits of the two treatment modalities.

**Keywords:** Adenomyosis; Infertility; Gn-RH analogues; Pregnancy outcome.

## Introduction

Uterine adenomyosis is known to affect multiparous women in their late 30-40 years with simple hysterectomy being the standard

treatment for patients with severe symptoms like dysmenorrhea and menorrhagia. Nonetheless, uterine adenomyosis can also occur in nulligravid women, although it is rare.<sup>1,2</sup> The association between adenomyosis and infertility still remains unclear.<sup>2</sup> Destruction of the normal architecture of the myometrium leading to impairment of the uterine mechanisms for rapid and sustained directed sperm transport has been proposed as the effect of adenomyosis causing infertility.<sup>3,4</sup>

Uterine adenomyosis can be classified as focal and diffuse; focal lesions being localized in the anterior and posterior uterine walls and diffuse ones involve the entire uterus.<sup>1</sup> Surgical excision of focal adenomyosis have been reported in the past,<sup>2,5-7</sup> but conservative surgical treatment, rather than hysterectomy, has been reported recently for diffuse adenomyosis.<sup>1</sup> Treatment of adenomyosis in subfertile patients is extremely challenging as preservation of the uterus for future childbearing is the aim and desire of all women.

To date, there is no agreement on the most appropriate therapeutic methods to manage infertile patients with adenomyosis.<sup>7</sup> Multiple treatment modalities including hormonal therapy with gonadotropin-releasing hormone agonists (Gn-RHa),<sup>8-11</sup> and conservative surgical procedures have been used to treat patients with unexplained infertility and adenomyosis with success.<sup>1,2,5,7,12,13</sup>

The aim of this report is to describe the outcome of management of uterine adenomyosis in subfertile patients over a period of 8 years in a teaching hospital with two treatment modalities.

## Methods

Between January 2000 and December 2007, a total of 40 patients with a history of dysmenorrhea, menorrhagia and unexplained infertility (6-15 years) were diagnosed to have uterine adenomyosis by clinical examination, transvaginal ultrasound (TV-USG) and magnetic resonance imaging (MRI). Adenomyosis in the study patients was suspected on TV-USG when the uterine size increased; asymmetrical thickening of the uterine body, with focal honeycomb, scattered, irregular non-encapsulated myometrial echoes with sub-endometrial linear striations. Diagnosis included uterine enlargement, hypertrophy of the anterior and posterior uterine walls, central uterine cavity and loss of the junctional zone on saggital MRI. The diagnosis of adenomyosis was confirmed by needle biopsy when the patients underwent laparoscopy for evaluation of their infertility. The patients who fulfilled the

Fathia E. Al Jama ✉

Department of Obstetrics and Gynecology, College of Medicine, Dammam University, and Consultant, King Fahad Hospital, Al Khobar, Saudi Arabia  
E-mail: fathiaaj@gmail.com

inclusion criteria for uterine adenomyosis were allocated to 2 groups for treatment solely on the patient preference and their consent along with physician counseling. Group A comprised of 22 patients treated with Gn-RHa injections alone, and Group B comprised of 18 patients who underwent conservative surgery followed by Gn-RHa injections.

Conservative "cytoreductive" surgery was performed in patients with uterine adenomyosis (Group B), using a microsurgical technique to avoid unnecessary injury to the uterus.<sup>12,13</sup> The focal adenomyotic lesions were meticulously dissected and excised. The surgical margins were electrocauterized to minimize bleeding. All dead spaces were carefully obliterated with horizontal and interlocking surgical sutures to close the residual myometrium. The serosa was closed with a continuous, inverting, interlocking suture of 3-0 poliglecaprone 25 (Monocryl; Ethicon, Sommerville, NJ) to minimize raw surfaces on the uterus. An adhesion-prevention barrier (oxidized regenerated cellulose, Interceed; Johnson and Johnson Medical Inc, UK) was applied to the sutured serosal coat. Histopathology of the excised adenoma varying in size from 2-4.5 cm, confirmed the diagnosis of adenomyosis. The lesions were mostly in the antero/lateral wall and, in two patients the adenoma was located in the postero-lateral uterine wall. There was no adenoma in the proximity of the tubal ostia.

Data retrieved from the patients' files included age, body mass index (BMI), period of infertility, menstrual cycles, uterine size on clinical and USG examinations and CA-125 (IU/mL). Severity of symptoms (a verbal, patient self-assessed expression as mild, moderate and severe) and reproductive performance of the patients were noted during the follow up period from 6-36 months after all treatment was completed. Group A (22 patients) with adenomyosis received Gn-RHa alone, subcutaneous (SC) depot injections (inj) of goserelin (Zoladex, Zeneca, Cheshire, UK), 3.5

mg, every month for 6 months, starting with the first injection just after the menses when treatment was decided. All the patients in Group B underwent conservative surgery followed by SC inj of 3.5 mg goserelin, every 4 weeks for 24 weeks with the first menses post-operation. The outcome treatment with regard to alleviation of symptoms and achievement of pregnancy in the two groups of patients were assessed. This study was approved by the ethical and research committees of the hospital.

Statistical analysis was performed using SPSS for Windows version 16. Categorical variables were assessed by two-tailed Fisher's exact tests. Descriptive statistics were analyzed as means,  $\pm$  standard deviation or percentages. A *p* value of <0.05 was considered significant.

## Results

Prior to treatment, majority of the patients in Group A had mild to moderate dysmenorrhea which was relieved with oral analgesics and the duration of periods ranged between 5-8 days with mild menorrhagia. While patients in group B complained of severe dysmenorrhea and menorrhagia, requiring injectable analgesics such as diclofenac (Voltaren, Novartis Pharma, Basel, Switzerland) 50 mg, intramuscular and regular oral hematinics. The demographic data of the two groups of patients and their characteristics are shown in Table 1. Age of the patients, baseline CA-125, and period of infertility as well as duration of menstruation were significantly higher in Group B patients. Other characteristics such as BMI, menstrual cycle, uterine size on USG measurements were similar in both groups. The CA-125 level performed one year post surgery in Group B patients was significantly reduced ( $43.3 \pm 13.7$  u/mL), (*p*=0.0009). (Table 2)

**Table 1:** Patient characteristics and findings from history and investigations

Observations	Group A (n = 22) (mean $\pm$ SD)	Group B (n = 18) (mean $\pm$ SD)	<i>p</i> value
Age (years)	34.3 $\pm$ 4.6	38.1 $\pm$ 0.9	0.0003*
BMI (kg/m <sup>2</sup> )	20.3 $\pm$ 6.6	23.4 $\pm$ 1.1	0.254
Period of infertility (yrs)	7.7 $\pm$ 2.3	11.4 $\pm$ 2.7	0.0197*
Menstrual cycle (days)	5-8/22-34	7-9/24-30	-
-Duration	6.3 $\pm$ 1.1	7.8 $\pm$ 0.9	0.0333*
-Cycle	26.8 $\pm$ 4.1	23.8 $\pm$ 8.9	0.3323
Age at menarche (yrs)	12.1 $\pm$ 1.4	12.2 $\pm$ 2.2	0.8770
Diagnostic tool	TV-USG + MRI	TV-USG + MRI	-
Uterine size (cm) (maximum diameter)	9.7 $\pm$ 4.4	10.4 $\pm$ 7.3	0.7686
Baseline CA-125 (U/ml)	43.3 $\pm$ 4.2	78.6 $\pm$ 24.5	0.004*

\* - statistically significant

**Table 2:** Outcome of treatment in the two groups of patients

Treatment Outcome	Group A (n = 22) Gn-RHa only, 6 courses	Group B (n = 18) Combined therapy
<b>Complications of treatment:</b>		
-Mild depression	1	-
-Blood transfusion (post-op)	-	4 (3-6 units of blood)
CA-125 (U/mL)	38.4 ± 4.6	43.6 ± 13.7* ( $p=0.0009$ )
Uterine size after one year	8.8 ± 3.5	8.6 ± 4.3 ( $p=0.3070$ )
Clinical pregnancy: 3-yr cumulative rate	3 (13.6%)	8 (44.4%)* ( $p=0.0393$ )
Time of conception after treatment (months)	5 - 20	4 - 30
<b>Outcome of pregnancy:</b>		
-Spontaneous abortion	1	2
-Ectopic pregnancy	1	-
-Term deliveries	1 (4.5%) vaginal deliveries (with retained placenta)	6 (33.3%)* cesarean deliveries ( $p = 0.0328$ )

\* - statistically significant

Three (13.6%) patients in group A became pregnant between 4-36 months after the completion of treatment, one patient had an early abortion, and another had ectopic pregnancy which required salpingectomy. One (4.5%) pregnancy in this group continued until term and had vaginal delivery complicated with retained placenta requiring manual removal under general anesthesia. On the other hand, there were 8 (44.4%) spontaneous pregnancies in Group B resulting in two abortions and 6 (33.3%) term deliveries by cesarean section. The clinical pregnancy and successful delivery rates were significantly higher in Group B ( $p=0.0393$ ) and ( $p=0.0328$ ) respectively, compared with group A. All the pregnancies in group A occurred within 18 months after treatment, while in group B, spontaneous pregnancy was noted up to 3 years of follow up.

An improvement of dysmenorrhea and menorrhagia were noted at the 6 and 12 month follow-up visits in both groups; except three patients (age range: 42-44 years) in Group B whose symptoms worsened and had total abdominal hysterectomy 3 years later upon request.

## Discussion

At present, the therapeutic methods of management of symptomatic uterine adenomyosis in subfertile patients is not agreed upon, mainly because the condition affects multiparous women in whom preservation of the uterus is not an issue. Besides, the relationship between infertility and adenomyosis remains uncertain and the incidence of subfertile women having uterine adenomyosis has not been reported in the literature. Serial immune responses are activated in patients with adenomyosis causing alterations in both cellular and humoral immunity.<sup>14</sup> The immune changes may hamper sperm function and embryonic development that may cause infertility in patients with adenomyosis. The immune mechanism of action and possible treatment of adenomyosis is purely hypothetical and at present not proven.

Treatment of adenomyosis with hypoestrogenic agents or surgical removal of the adenoma lesions may restore normal

immunity in patients. Currently, the accepted treatment of adenomyosis in infertile patients is with Gn-RHa. Many case reports in the literature of successful pregnancy and delivery have resulted from this therapy.<sup>8-10</sup> Why this occurs is unclear, but it may be due to the transient suppression of the hypothalamic-pituitary-ovarian axis by Gn-RH agonists with resultant shrinkage of the lesions in the uterus thereby reducing its size and relief of symptoms. It probably promotes uterine and endometrial receptivity.<sup>8</sup> However, its effect is often transient and is used mainly along with an operative therapy. Once the treatment with Gn-RHa has been stopped, recurrence of adenomyosis occurs as has been documented in the management of uterine leiomyomas.<sup>15,16</sup>

In group A (patients with adenomyosis treated in this study with Gn-RHa alone); the pregnancies occurred up to 18 months of completion of the medication and resumption of the first menstruation. Similar results have been reported where pregnancy occurred within the first 12 months of therapy,<sup>7,9,17</sup> indicating that the prospect of pregnancy in infertile women treated with Gn-RHa is good, but with a short effective period for pregnancy to be achieved.

Recent reports have discussed the role of surgical methods to excise focal and diffuse adenomyotic lesions, and the benefits of this approach in patients with extensive uterine adenomyosis.<sup>1,2,5,12,18</sup> The problems facing the management of adenomyosis surgically are selection of appropriate patients and the postoperative complications such as pelvic and intrauterine adhesions, future uterine deformities and reduced uterine capacity. Subsequent uterine scars may grow adenomyotic tissue and result in the reduction of its tensile strength predisposing it to uterine rupture during a pregnancy. Hence, a cautious decision needs to be undertaken in managing women with extensive adenomyosis by conservative surgery. One report in the literature described conservative surgical excision of diffuse uterine adenomyosis in infertile and symptomatic women with questionable safety of the procedure and a poor pregnancy rate, but good relief of symptoms.<sup>1</sup> The higher baseline CA-125 in group B with significant reduction

post operation along with the size of the uterus, may suggest that operative excision of the uterine "adenoma" could reduce the size of the uterus as well as the levels of CA-125 patients with adenomyosis, besides a 3-year period of symptom control, although it was a subjective evaluation of the patients.

In this study, conservative excision surgery was performed in 18 patients without extensive damage of the uterine walls and maintaining an intact uterine cavity. Gn-RHa was given to all the patients post-operation (Group B). Pregnancy occurred in a patient in this group up to the 3 years follow up period after treatment, which resulted in a live infant. It could therefore be inferred that the combined method of treatment seems to have resulted in better relief of symptoms of adenomyosis, improved pregnancy rate and a prolonged and sustained ability to achieve a pregnancy post treatment. Similar findings were also reported in other studies.<sup>7,12</sup> Patients who were treated with hormones alone, seemed to benefit for a shorter period of improved reproductive performance. The number of patients and pregnancies were small in this study to make a definite inference.

Preoperative diagnosis and the extent of adenomyosis with TV-USG and MRI have made it possible to select patients for treatment with conservative surgery with minimal disturbance of the uterine wall architecture. Patients most suitable for surgery are those with focal adenomyosis, where the adenoma is better to operate and excise than in patients with diffuse adenomyosis. Combination of medical and surgical methods of treatment may be appropriate in patients with failing Gn-RHa treatment alone and who have severe adenomyosis causing an enlarged and firm uterus with severe symptoms of dysmenorrhea and menorrhagia. Elderly patients who do not benefit from treatment are better off having hysterectomy with conservation of the ovaries to relieve their symptoms. No one particular method of treatment is wholly satisfactory to achieve pregnancy in the nulliparous infertile patient with adenomyosis, and patients should be made to understand this before any treatment is commenced. With advances in TV-USG, imaging and surgical techniques, more and more patients with unexplained infertility and adenomyosis are being diagnosed.<sup>19,20</sup> Clinicians will face the challenging task to treat this group of women with infertility and preserve the uterus.

## Conclusion

Although the patient number in the study was small, it showed that the combined surgical and hormonal treatment had significant benefits in giving women more effective symptom control compared with Gn-RHa alone. Furthermore, subfertile women treated by the combined surgical/hormonal approach, resulted in higher cumulative 3-year clinical pregnancy and successful delivery rates. Definite conclusions from the results of this non-randomized study cannot be drawn regarding the effectiveness of combined surgery and Gn-RHa over Gn-RHa alone in symptom relief and better reproductive performance. Due to the nature of this study, a well conducted randomized trial is needed in the future.

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