

## Ultrasound Guided Injection of GnRH $\alpha$ in the Treatment of Leiomyoma

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**Abstract:** The most common Medical treatment used nowadays is GnRH agonists which relies upon hypoestrogenic state. The treatment however is often associated with hypoestrogenemia and significant bone loss, that preclude the long term use of GnRH  $\alpha$ . GnRH<sub>2</sub> and GnRHR<sub>2</sub> were expressed in fibroid at the mRNA level and GnRH<sub>2</sub> at the protein level. Activation of GnRH<sub>2</sub> receptor pathway may have a very distinct functions compared with activation of GnRH receptor, so it was speculated another mechanism of action of GnRH agonist by direct effect which resulted in anti proliferative effect via GnRHR<sub>2</sub> expressed by leiomyoma. Based on a previous work that a second form of GnRH and corresponding receptors exist in fibroid and that an autocrine loop exist GnRH could potentially exert a direct anti proliferative action on fibroid via GnRHR<sub>2</sub>. Aim of the work Is to test this hypothesis that a second form of GnRH and corresponding receptor exists in the fibroid and that GnRH agonists interact directly with GnRH receptors present in fibroids, and produce a new modality of treatment of fibroid avoiding hpoestrogenic state and bone loss by ultrasound guided injection of GnRH in the fibroid. Ten women had uterine myoma were enrolled in the study, the inclusion criteria were Age between 20 to 35 years mean age is ( 32 $\pm$ 5.22), single, myoma interstitial or subserous myoma (5 cases for each), mean diameter at 3D transvaginal ultrasound >56mm. As an outpatient using sedation in the form of 15 mg pethidine and 10 mg pentazocain intravenously, GnRH $\alpha$  is given directly into the center of the myoma by 3D transvaginal ultrasound guided injection, we developed a new equation in order to calculate the dose of GnRH (Leuprolide acetate 3.75mg). The results of this work shows statistically significant decrease in uterine volume and myoma volume after the treatment and statistically significant increase in the Hemoglobin concentration. In Conclusion Ultrasound Guided Injection Of GnRH $\alpha$  In The Treatment Of Leiomyoma is a new modality and new delivery system, reducing the cost of treatment, no effect on bone metabolism, no hypoestrogenic symptoms, but and very big but we needed more cases and more randomization before testing the efficacy of this new line of treatment.

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**Key word:** Ultrasound, GnRH  $\alpha$ , Leiomyoma

### 1. Introduction:

Uterine fibroid are the most common benign tumors in the reproductive age and are source of morbidity for the 20 to 50% of affected reproductive aged women <sup>[6]</sup>

Therapeutic interventions for Leiomyomas can be surgical (myomectomy, hysterectomy) or medical.

Its well established that myomas are hormonally responsive to ovarian steroid hormones: estrogen and progesterone.

The most common Medical treatment used nowadays is GnRH agonists which relies upon hypoestrogenic state. The treatment however is often associated with hypoestrogenemia and significant bone loss, that preclude the long term use of GnRH  $\alpha$ . GnRH<sub>2</sub> and GnRHR<sub>2</sub> were expressed in fibroid at the mRNA level and GnRH<sub>2</sub> at the protein level<sup>[5]</sup>

Activation of GnRH<sub>2</sub> receptor pathway may have a very distinct functions compared with activation of GnRH receptor, so it was speculated another mechanism of action of GnRH agonist by direct effect which resulted in anti proliferative effect via GnRHR<sub>2</sub>

expressed by leiomyoma<sup>[5]</sup>. Based on a previous work <sup>[5]</sup> that a second form of GnRH and corresponding receptors exist in fibroid and that an autocrine loop exist GnRH could potentially exert a direct anti proliferative action on fibroid via GnRHR<sub>2</sub>.

### Aim of the work

Is to test this hypothesis that a second form of GnRH and corresponding receptor exists in the fibroid and that GnRH agonists interact directly with GnRH receptors present in fibroids, and produce a new modality of treatment of fibroid avoiding hpoestrogenic state and bone loss by ultrasound guided injection of GnRH in the fibroid.

### 2. Material and Method:

Ten women had uterine myoma were enrolled in the study, the inclusion criteria were Age between 20 to 35 years mean age is ( 32 $\pm$ 5.22), single, myoma interstitial or subserous myoma (5 cases for each), mean diameter at 3D transvaginal ultrasound >56mm.

The exclusion criteria were metabolic, infectious diseases, previous hormonal therapy over the previous

9 months and history of previous surgical operation, previous myomectomy, combined adenomyosis and fibroid, history of aspirin intake, anticoagulant therapy, antihypertensive.

As an outpatient using sedation in the form of 15 mg pethidine and 10 mg pentazocain intravenously, GnRH $\alpha$  is given directly into the center of the myoma by 3D transvaginal ultrasound guided injection, we developed a new equation in order to calculate the dose of GnRH (Leuprolide acetate 3.75mg). ABOIT Laboratories:

$$\text{Farid equation ( 2008 ) }^{[15]} = \frac{\text{uterine volume}}{\text{Myoma volume}}$$

If more than 2 (2 ampoules)

Less than 2 (1 ampoule)

#### Follow up:

3D ultrasound was done after 3 months to measure uterine volume, myoma volume, Hemoglobin concentration before and after the treatment.

**Table (1): Effect of ultrasound guided direct fibroid injection of GnRH agonists (Leupron 3.75mg) in 10 patients:**

Characteristics	Before treatment	After treatment ( 2 months)	<i>p</i>
Uterine volume	414.2± 44.3	201±33.1	< 0.001
Myoma volume	169.8± 13.7	18.7 ±2.3	< 0.001
Hb concentration	7.3 ± 1.6	13.2 ±2.1	< 0.001

Value is expressed as mean ± SD

#### 4. Discussion:

Uterine fibroid are the most common benign smooth muscle cells tumors of the myometrium occurring in at least 25% of women of reproductive age<sup>[1]</sup> and it is the main cause of health expense in the field of gynecology<sup>[1]</sup>.

Fibroids are hormone dependent containing highest levels of receptors for both estrogen and progesterone than for regular myometrium<sup>[3]</sup>.

Gonadotrophin releasing hormones (GnRH) agonists induce temporary amenorrhea and shrinkage of fibroids secondary to suppression of ovaries<sup>[4]</sup>. However fibroid regrowth occurs as soon as treatment is stopped and adverse effect such as reduction in bone density, limit long term treatment. Thus, the role of GnRH agonist is currently limited to preoperative shrinkage of fibroid<sup>[2]</sup>. A second form of GnRH and corresponding receptor in fibroid and myometrium was found<sup>[5]</sup>, it was speculated that an autocrine loop exists and that GnRH agonists may interact directly with GnRH receptors present in the uterine fibroid<sup>[5]</sup> this speculation was the scientific basis of our work.

GnRH and GnRHR are located peripherally in addition to its production in basal forebrain, the peripheral site of production including reproductive and immune tissue throughout the body<sup>[7-9]</sup>, it was speculated an autocrine and paracrine function to

#### Ethics:

Informed Consent and explaining all the details of the procedure to the patients, and all procedures involving human subjects complied with the declaration of Helsinki 1975 and revised in 2000, again all the procedures accepted from the ethical committee of Heliopolis research center and Heliopolis Hospital.

#### 3. Result:

As an outpatient procedure using sedation in the form of 15 mg pethidine and 10 mg pentazocain intravenously, GnRH is given directly into the center of the myoma by 3D transvaginal ultrasound guided injection in 10 women with mean age 32± 5.22, single myoma interstitial or subserous.

The results are summarized in the following table 1 which shows statistically significant decrease in uterine volume and myoma volume after the treatment and statistically significant increase in the Hemoglobin concentration.

GnRH1, and GnRHR1<sup>[10]</sup>, The autocrine and paracrine function of GnRH can explain the antiproliferative effects through GnRHR<sub>2</sub> receptors<sup>[9]</sup>, so it was first to be demonstrated both the expression of GnRH1 and GnRHR1 expression in cultured leiomyoma cells<sup>[8]</sup> and it has been demonstrated that concentrations as low as 10<sup>(-7)</sup> M of GnRH agonists can alter gene expression in tissue culture<sup>[11-13]</sup>

Also on the other side mRNA and protein expression of GnRH receptors in cultured leiomyoma cells was increased by GnRH antagonist treatment (*Cetrotide acetate*)<sup>[14]</sup>.

It was demonstrated that GnRH $\alpha$  rapid regrowth of myoma to their original size and recurrence of the symptoms<sup>[17]</sup>, also GnRH $\alpha$  can obliterate the myoma myometrial interface and as a result inoculation of myoma becomes more difficult<sup>[18]</sup>

We put another theoretical explanation is based upon the "by standard effect" which means the tumor regression occurred when a fraction of tumor mass is genetically modified, so direct injection of GnRH $\alpha$  will lead to genetic modification of fibroid and hence regression of the tumor<sup>[16]</sup>

A great advantage of local injection of GnRH $\alpha$  the reduced dose in our work, the maximum dose was 2 vials (and hence reduced the expense of the treatment) in contrary to intramuscular rout, again one

single injection not repeated injection the great advantage of this method that it is a single injection, no effect on bone, no manifestation of hypoestrogenemia which need addback therapy.

##### 5. Conclusion:

Ultrasound Guided Injection Of GnRH $\alpha$  In The Treatment Of Leiomyoma is a new modality and new delivery system, reducing the cost of treatment, no effect on bone metabolism, no hypoestrogenic symptoms, but and very big but we needed more cases and more randomization before testing the efficacy of this new line of treatment.

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