

The Role of GnRH Agonists in the Management of Large Myomas During a Pandemic

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This paper shall present a case of a 42-year-old nulligravid who complained of chronic pelvic pain, vaginal bleeding and palpable abdominal mass secondary to multiple large myomas. Due to the logistical and health restrictions in most hospitals during the peak of the COVID-19 pandemic, elective surgery was postponed and a temporizing medical management was instituted in the form of GnRH agonist, which afforded relief. This paper shall also discuss the mechanism of action of GnRH agonist, and its crucial role as an essential medical treatment option for patients with debilitating conditions such as myoma uteri.

Key words: myoma uteri, GnRH agonists, COVID-19

Introduction

The COVID-19 pandemic which affected the Philippines and the rest of the world starting first quarter of 2020, was a global health emergency which severely overwhelmed the local health system and restricted hospital operations, thereby affecting patients with serious gynecologic conditions. The surge of COVID-19 emergency cases caused most hospitals to stop or postpone all elective and “non-essential” surgeries due to unavailability of hospital beds, scarcity of hospital supplies and shortage of available medical staff. It was during this time when all international and local societies urgently recommended that non-operative conservative treatment including pharmacological therapies for hormone-sensitive pathologies should be implemented. Performing surgery on potential patients with COVID-19 posed a high risk challenge and experts have recommended a non-surgical approach when possible. All surgical procedures during the peak of the pandemic were generally considered high risk, because even asymptomatic patients may be possibly carrying the virus. The

presence of some patient comorbidity that results in greater morbidity due to laparotomic procedures, longer hospitalization period and higher risk of nosocomial infection was likewise highly considered during this time.

It was thus very important that during this crucial time, gynecologists should be highly knowledgeable about the medical alternatives that can be offered for patients who suffer from chronic pelvic pain, vaginal bleeding and abdominal mass due to benign, hormone-sensitive, gynecologic tumors to give them relief from their symptoms, and stave off an otherwise urgent surgical procedure until such time that it would be absolutely safe for them to undergo such necessary procedure.

Presented here is a case of a nulligravid patient who suffered from chronic pelvic pain and vaginal bleeding due to multiple large myomas, during the peak of the COVID-19 pandemic, and the temporizing medical treatment she received while waiting for the most safe and favorable time to undergo a definitive surgical procedure. This paper also discusses the mechanism of action of GnRH agonist, and its role as an essential medical

treatment option for women with large myoma uteri.

The Case

The patient is a 42-year old single nulligravid, admitted for the chief complaint of abdominal pain.

She was apparently well until 10 months prior to admission, when she palpated an abdominal mass which reached up to her umbilicus. No other accompanying symptoms were noted. She underwent a transrectal ultrasound which revealed multiple myoma uteri, with sizes ranging from 4 cm to 11 cm at the widest diameter, endometrium measured 1.06 cm thick, probably premenstrual endometrium; right ovary was not visualized, normal looking left ovary with small few follicles.

Nine months prior to admission, she started to complain of abdominal pain with VAS pain score 7/10, accompanied with vaginal bleeding. The pain was described as radiating to the back. A transrectal ultrasound showed a huge, irregularly shaped abdominopelvic mass, measuring 23.24 cm x 15.32 cm x 22.01 cm, with varying degrees of echogenicity, some structures with cystic and calcific changes probably representing a myoma uteri with cystic and calcific degeneration. A fundal subserous myoma was also noted, which measured 13cm x 14cm x 7cm; the right ovary was normal, while the left ovary was not visualized. An exploratory laparotomy, total abdominal hysterectomy was recommended, but because all hospitals were working at full capacity during the peak of the COVID-19 pandemic, the patient and her family decided to defer the surgery, upon the medical advise of her gynecologist. Medical management was started to possibly shrink the size of the myoma, control the vaginal bleeding, and decrease the pelvic pain and pressure. She was started on a monthly regimen of intramuscular injections of GnRH agonist (Leuprolide acetate 3.75mg). On her 1 month follow-up , patient reported that the pain has subsided and her menstruation has stopped.

Six months prior to admission, after 3 cycles of medical treatment, she noted recurrence of abdominal pain, but this time only at maximum VAS pain score of 4/10. During this time, patient still has not consented to undergo the surgical procedure. Additional 3 doses of GnRH agonist were given.

Few weeks prior to admission, as the number of cases of COVID-19 has dropped and stabilized, the patient finally agreed to undergo the contemplated surgical procedure.

Patient was a known diabetic and hypertensive, and was maintained on Metformin 500 mg BID, Amlodipine 10 mg OD and Telmisartan 100 mg OD. She has a family history of Diabetes Mellitus and hypertension on both sides of the family.

Social, menstrual, gynecologic and sexual histories were all non-contributory.

On physical examination, patient was awake, ambulatory, and not in cardiopulmonary distress. Vital signs were all stable. The pertinent physical examination findings include the following: a huge, doughy, slightly movable, and non-tender abdominopelvic mass measuring 28 cm x 26 cm. It was irregularly shaped, and inclined more to the right. Abdominal girth was 108 cms. On rectal examination, there was good sphincteric tone, no intraluminal masses palpated, with the inferior pole of the enlarged uterus palpable through the culdesac, the rectovaginal septum and parametria were smooth and pliable.

The admitting impression was Multiple Myoma Uteri, Diabetes Mellitus type 2, Hypertension stage 1, controlled, Obese Class 1, G0. The preoperative plan was for ureteral stenting by the urology service, exploratory laparotomy and total abdominal hysterectomy.

In the operating room, the Urology service had difficulty in identifying the ureteral orifice and after several attempts, decided to abandon the procedure. Cystoscopy showed that the lining of the bladder wall was thickened with a cobblestone surface. The clinical impression of the urologist was a possible Tuberculosis of the urinary bladder. With the patient in the supine position, the large myomas must have been pressing on the ureters, and thus the ureteral orifices could not be visualized.

Intraoperatively, there were a total of 11 myomas, with sizes ranging from 4 cm to 14 cm. Cut section of these myomas showed a typical whorled pattern; there was an intraligamentary myoma at the right adnexa, with the right ovary densely adherent to it. The cervix was small, smooth and measured 3 cms. Total hysterectomy with right salpingoophorectomy (right ovary densely adherent to the adnexa) and left salpingectomy was done. The whole specimen

weighed 11 kgs (Figures 1 & 2). Total blood loss was approximately 3 liters. A total of 4 units packed RBC and 1 unit fresh whole blood were transfused. Her postoperative course was uneventful. She was discharged on the 2nd post-op day.



Figure 1. Hysterectomy specimen showing multiple, large myomas



Figure 2. Cut section of the hysterectomy specimen.

Histopathology report showed Leiomyomata uteri, Multiple, subserosal, pedunculated, intraligamentary; Weakly proliferative endometrium; Chronic cervicitis; No diagnostic abnormality recognized in the right ovary, right and left fallopian tubes.

Discussion

In general OB-GYN practice, GnRH agonists are commonly used for the treatment of endometriosis, adenomyosis and uterine myoma. It is used mainly to control heavy menstrual bleeding, for the reduction of pain symptoms and regression of these diseases by causing a state of hypoestrogenemia.¹

The gonadotropin hormone-releasing hormone secreted by the hypothalamus, determines the pulsatile release of follicle stimulating hormone (FSH) and the luteinizing hormone (LH) from the pituitary gland which, in turn, regulates the release of the hormone estrogen and progesterone, and the gamete maturation.² In essence, GnRH is the driver of the hypothalamic-pituitary-ovarian axis.

GnRH agonists work by down-regulating the hypothalamic-pituitary-ovarian axis. This leads to suppression of the FSH and the LH from the pituitary gland which in turn suppresses the production of estrogen and progesterone, thereby creating a hypoestrogenic state.³

Myoma uteri: Review of Etiology and Epidemiology

Myoma uteri, or fibroids, are the most common benign, solid neoplasms of the reproductive tract, and are postulated to arise from monoclonal smooth muscle cells of the myometrium, under the influence of progesterone and estradiol. The presence of an aromatase enzyme in fibroid tissues allows for endogenous production of estradiol, and fibroid stem cells express estrogen and progesterone receptors that facilitate tumor growth in the presence of these hormones.⁴

Depending on the population of women involved, epidemiologic data on its prevalence would usually range between 20% and 80%, with the women of African or Black American descent noted to have the highest risk. Myoma uteri are rare before puberty, increase in prevalence during the reproductive years, and decrease in size after menopause.⁵ Other risk factors for the development of the disease include

increasing age, nulliparity, obesity, premenopausal status, personal history of hypertension, family history, and consumption of food additives and soybean milk. However, despite the high percentage of women affected by leiomyomata, it has been estimated that only 20%–30% will eventually become symptomatic.^{6,7}

Characteristic symptoms attributed to myoma uteri largely depend on the location of the tumor within the uterine corpus, that is, whether the tumor is submucosal, intramural, or subserosal, or a combination of any of the three. For example, submucous myoma (or a myoma with a submucous component) often manifest as abnormal uterine bleeding (AUB), and are often implicated in iron-deficiency anemia (secondary to AUB) and infertility. If a given patient is able to achieve pregnancy with a leiomyoma impacting the uterine cavity, they also are more likely to experience adverse pregnancy outcomes to include recurrent pregnancy loss (RPL), abnormal placentation (i.e., placenta previa), fetal malpresentation, preterm delivery, cesarean section, and postpartum hemorrhage. Large subserous or intramural myomas are more often associated with pelvic pressure, pelvic pain, dyspareunia, chronic constipation, and urinary incontinence.⁶ index patient experienced pelvic pain, pressure symptoms and increase in abdominal girth. The vaginal bleeding may have been due to the large intramural myomas that distort and partially impinge on the endometrial cavity.

Myoma uteri could have a negative impact on the reproductive system and can cause significant morbidity, and deterioration of quality of life.⁸ According to international literature, as much as 60% of all the hysterectomies performed in the United States are secondary to myomas.^{8,9} Here in the Philippines, hysterectomy secondary to myoma uteri consistently ranks among the top 3 most common gynecologic procedures in POGS-accredited hospitals.¹⁰

GnRH agonist as Medical Treatment for Myoma uteri

Gonadotropin-releasing hormone (GnRH) agonists are a popular medical treatment for myoma uteri because they decrease uterine blood loss due to myoma and the volume of the myoma as well, thereby

relieving most patients of their myoma-related symptoms and decreasing their need for hospital ER visits and admissions, and blood transfusions. In general, GnRH agonist therapy has been shown to decrease the size of the uterus and uterine myoma by 20% to 50%¹¹, and induce amenorrhea or a reduction in heavy menstrual bleeding within 4-8 weeks of treatment, in most women.¹² This property of GnRH agonist is beneficial most especially during the peak of the COVID-19 pandemic when almost all hospitals have been overwhelmed with the surge of COVID-19 emergency cases, and have severely restricted elective gynecological admissions due to inavailability of hospital beds and shortage of hospital supplies and medical staff, leading to postponement of almost all essential gynecologic surgical procedures. It was during this time when all international and local societies urgently recommended that non-operative conservative treatment including pharmacological therapies for hormone-sensitive pathologies should be implemented. Preoperative treatment with GnRH agonists leading to a decrease in myoma and uterine volume, as well as vascularity of myoma uteri, decreases the intraoperative blood loss and thereby reducing the need for massive intraoperative or postoperative blood transfusion. Blood products have been especially scarce during the peak of the pandemic due to low turn-out of donors, and the increased demand for blood components among the morbidly-affected COVID-19 patients. This temporizing measure using GnRH agonist would be most valuable, until a definitive surgical procedure could be done.

It is recommended that GnRH agonists be given at a maximum of six months. Longer than 6 months, patients would have symptoms of hot flashes, dryness of the skin and dryness of the vagina, fatigue, weight gain, fluid retention, and decreased libido. Long term therapy, may end in metabolic abnormalities, weight gain, worsening of the diabetes and osteoporosis.¹⁴

While GnRH agonist therapy may be very effective, rapid regrowth frequently occurs after the therapy is stopped.¹¹ This phenomenon is observed mostly among premenopausal women. It is thus very important for clinicians to inform and explain this phenomenon to patients, why GnRH agonist is not a permanent solution or the cure to their condition, and why most patients would still need

to eventually undergo definitive surgery. After the cessation of treatment, the myoma/s tend to recur in 2-3 months.¹³

GnRH Agonist: Mechanism of Action

The importance of estrogen in the pathogenesis of myomas is emphasized in the use of GnRH agonists as a necessary medical treatment. The reduction in the production of estrogen and progesterone is caused by the low gonadotropin levels secondary to negative feedback. Initially, there is an increased response to the GnRH agonists followed by downtrend of the receptor levels which desensitizes the pituitary to continued stimulation.

GnRH receptors are also found in the myoma. Through these receptors, GnRH agonists directly affect the myoma and reduce the proliferation of the tissues. This causes regression of the myoma and improvement in the clinical symptoms.¹⁵

A landmark study by Khan and his colleagues in 2010¹⁶ demonstrated that GnRH agonist may be an effective medical treatment for myoma uteri not only due to its classical pituitary endocrine effects, but may possibly be due to a direct tissue effect on myoma itself. The team of Professor Khan studied the tissue effect of GnRH agonists on the inflammatory response, angiogenic response and apoptosis in women with uterine myoma, and they found that, in addition to its hypo-estrogenic effect, GnRH agonist therapy retains multifunctional roles in the peripheral tissues of women with uterine myoma. GnRH agonist significantly reduces inflammatory reaction and angiogenic response and possibly induces apoptosis in uterine myoma tissues. The reduction in inflammatory reaction and angiogenic response was determined by a significant decrease in the amount of macrophage infiltration and micro-vessel density in the biopsy specimens derived from GnRH agonist-treated women, as compared with that of similar samples derived from women who were not treated with GnRH agonist. This could be due to the direct effect of GnRH agonist at the tissue level or an indirect effect of decreased estrogen level. It may somehow be reasonable to speculate that to a variable degree, the reduction of inflammatory reaction at the tissue level could be due to the decrease in endogenous estrogen levels among GnRH agonist users. GnRH agonist has also been

reported to decrease the expression of aromatase cytochrome P450 in the eutopic endometrium from women with myoma uteri.^{15,16}

The decrease in micro-vessel density after GnRH agonist treatment may indicate that reduction in the size of myoma tumor may be caused by reduction in blood flow in the pathologic lesions or in surrounding myometrial tissues. The capacity of GnRH agonist to reduce both inflammatory reaction and blood flow in pathologic lesions and corresponding myometrium may explain effective alleviation of pain symptoms of women suffering from these reproductive diseases. The possible apoptotic property of GnRH agonist treatment was also demonstrated by a marked increase in apoptotic index as measured by TUNEL assay as well as by increased Q-H scores of activated caspase-3 in the biopsy specimens derived from women with these diseases after GnRH agonist treatment.¹⁵

Conclusion

This is a case of a 42-year-old nulligravid who complained of chronic pelvic pain, vaginal bleeding and palpable abdominal mass secondary to multiple large myomas. Due to the severe restrictions brought about by the COVID-19 pandemic, elective surgery was deferred and medical management was instituted in the form of GnRH agonist, which afforded temporary relief. This paper discussed the mechanism of action of GnRH agonist, and its crucial role as a temporizing medical treatment for patients with debilitating condition such as a large myoma uteri.

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