Preoperative Gonadotropin Releasing Hormone Agonist Treatment for Giant Endometrial Polyp: A Case Report and Review of Literature

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Endometrial polyps are localized outgrowths of glands and stroma within the endometrium primarily caused by hyperestrogenism. They are common causes of abnormal uterine bleeding and infertility by altering the endometrial surface. Polyps may be small, large (measuring more than one centimeter), or giant (more than 4 centimeters in size). Large and giant polyps are very rare and prone to oncologic malformation, thus biopsy is recommended. Endometrial resection with biopsy is the gold standard of treatment, but could be difficult since giant endometrial polyps occupy the entire endometrial cavity resulting to morbidity and failure on hysteroscopy. Limited case reports and studies have used gonadotropin releasing hormone (GnRH) agonist as preoperative therapy to decrease polyp size prior to hysteroscopic resection. The aim of this case report is to discuss a rare case of giant endometrial polyp treated with neoadjuvant GnRH agonist prior to hysteroscopic resection, and to present the recent literature regarding giant endometrial polyps.

Introduction

Endometrial polyps are localized overgrowths of glands and stroma that project beyond the surface of the endometrium.[1] They arise from high estrogen states and over expression of estrogen and progesterone receptors in the endometrial stroma.[2] Polyps could be asymptomatic or could present with abnormal uterine bleeding and cause infertility by rendering an unfavorable environment for the growth of the embryo.[3] The prevalence increases with age especially during menopause wherein malignant degeneration is common.[4] Endometrial polyps are treated either by curettage, which is a blind procedure, or through hysteroscopy, which is the gold standard of treatment. The latter has been proven to improve fertility and pregnancy rates among women with endometrial polyps regardless of size and number.[5] Endometrial polyps greater than 1 centimeter are considered large and those greater than 4 centimeters are giant. Giant endometrial polyps are extremely rare especially in the reproductive age group.[6] Endometrial resection with biopsy is the gold standard treatment, but could be difficult since giant endometrial polyps occupy the entire endometrial cavity resulting to morbidity and failure of hysteroscopy. Very few case reports and studies have used GnRH agonist as neoadjuvant therapy to decrease polyp size prior to hysteroscopic resection based on the premise that it causes a hypoestrogenic state.

The aim of this case report is to discuss a rare case of giant endometrial polyp treated with neoadjuvant GnRH agonist prior to hysteroscopic resection, and to present the recent literature regarding giant endometrial polyps.

The Case

This is the case of a 27-year-old, nulligravid, who presented with abnormal uterine bleeding. The patient had her menarche at 14 years-old. Subsequent menses occurred at regular intervals, lasting

for 3 to 4 days, consuming 1 to 3 moderately soaked pads a day with associated dysmenorrhea relieved by pain relievers.

Patient had no gynecologic diseases in the past nor contraceptive use. She had her coitarche at the age of 22 and is in a monogamous sexual relationship with her boyfriend for 5 years. She is desirous of pregnancy.

The past medical and family history were unremarkable. She is a non-smoker and a non-alcoholic beverage drinker.

Patient's condition started 9 months prior when she had vaginal bleeding lasting for 2 weeks to one month per cycle, using up 1 to 2 moderately soaked sanitary pads a day. She also noted post-coital bleeding and abdominal enlargement. She consulted a local hospital wherein an ultrasound revealed an enlarged uterus with heterogenous and bulky posterior wall, suggestive of adenomyosis. The endometrium was heterogenous and thickened to 5 centimeters. The sonologic impression was to consider endometrial hyperplasia (Figure 1). She was advised surgical intervention, but decided to seek a second opinion at a tertiary government institution.

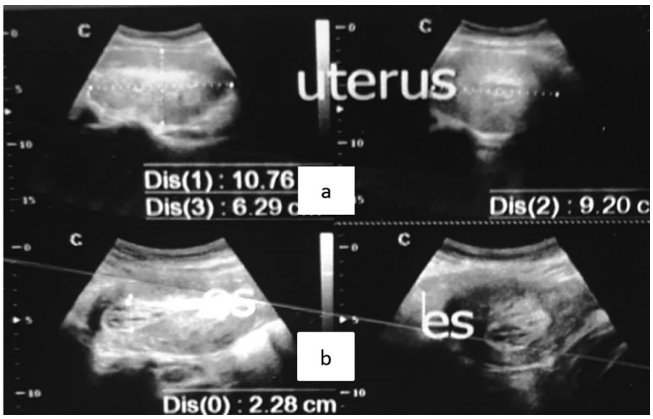

Figure 1. Preliminary transvaginal ultrasound of the patient which revealed an enlarged uterus (a) and thickened endometrium (b). Sonologic impression was adenomyosis and thickened endometrium with areas to consider endometrial hyperplasia.

At the Outpatient Department, speculum examination was done and a pinkish polypoid fleshy mass protruding from the cervical os was noted (Figure 2). On internal examination, the fleshy mass measured about 2cm x 2cm with a non-palpable base. The uterus was enlarged to 17 weeks size with no palpable adnexal masses. Complete blood count revealed anemia (Hemoglobin 63 mg/dL). A repeat ultrasound revealed an enlarged uterus measuring 16.96cm x 13.16cm x 10.48cm. There was a mass within and dilating the endometrial cavity measuring 12.35cm x 12.02cm x 7.27cm (volume of 584.77cc) with multiple anechoic cystic structures within and posterior acoustic shadows. The sonologic impression was endometrial mass consider endometrial polyp extending into the endocervix (Figure 3). The clinical impression was abnormal uterine bleeding secondary to a giant endometrial polyp. Plan was to do punch biopsy of the mass and correction of anemia.

Patient was admitted and punch biopsy of the endocervical mass was done. Anemia was corrected by transfusion of 2 units of packed red blood cells. Histopathologic examination of the mass revealed sections with polypoid tissue fragments composed of tubular or tortuous glands lined by simple columnar epithelium. These are surrounded by fibrotic stroma with scattered thick-walled vessel which was consistent with an endometrial polyp (Figure 4).

Patient was discharged and advised treatment with 3 doses of GnRH agonist (3.75 mg) intramuscular every 28 days. This is to possibly reduce the polyp size since hysteroscopic resection is technically difficult at that time. She had her first GnRH injection 1 month post biopsy. Patient noticed gradual decrease in abdominal size over the next 3 months with associated decrease in uterine bleeding and eventual amenorrhea. An add-back treatment of Tibolone (2.5 mg tablet daily) and Calcium with

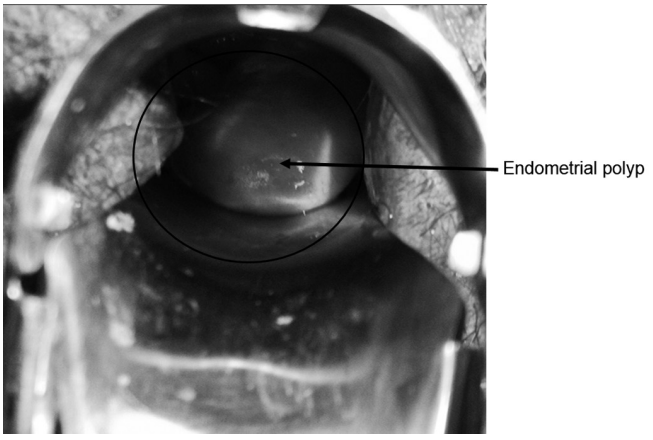

Figure 2. Speculum examination on initial consultation showing a 2cm x 2cm fleshy polypoid mass protruding through the cervical os.

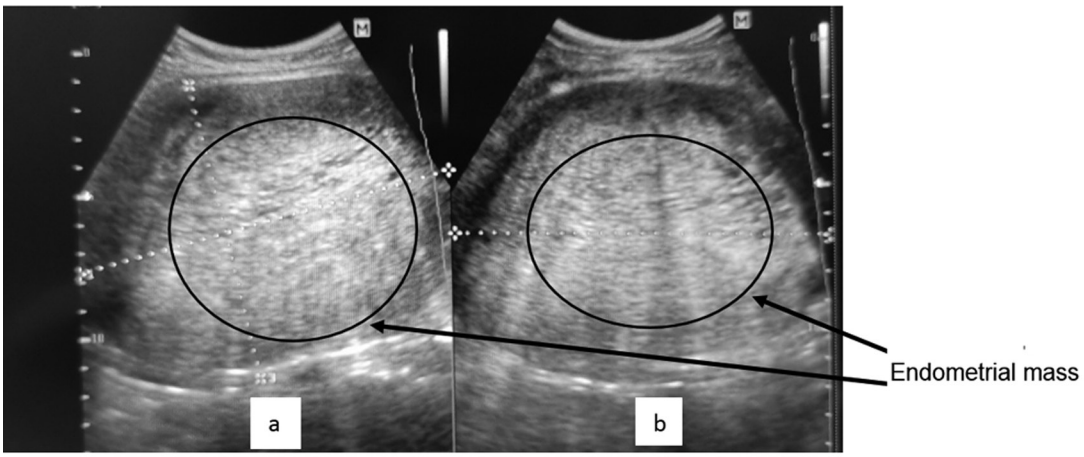

Figure 3. Transvaginal ultrasound on initial admission which revealed an enlarged uterus and a giant endometrial polyp measuring 12.35cm x 12.02cm x 7.27cm occupying the entire endometrial cavity. (a) Uterus on longitudinal view; (b) Uterus on transverse view.

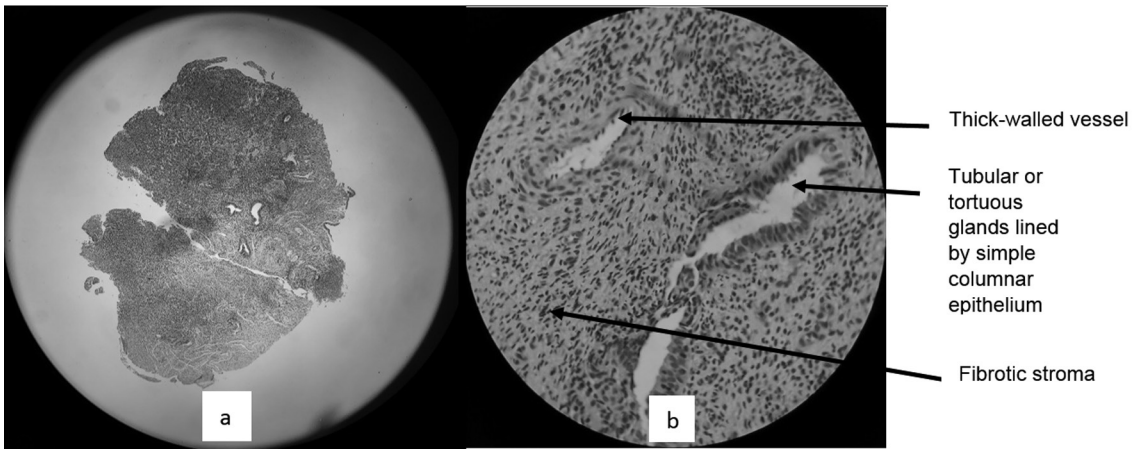

Figure 4. Punch biopsy of the prolapsing endometrial mass, which showed sections with polypoid tissue fragments composed of tubular or tortuous glands lined by simple columnar epithelium. These are surrounded by fibrotic stroma with scattered thick-walled vessel which was consistent with an endometrial polyp. (a) Low power objective view; (b) High power objective view.

Vitamin D (1 tablet twice daily) were given to prevent vasomotor symptoms and bone loss.

Repeat ultrasound was done after 3 doses of GnRH agonist revealing decrease in uterine size from a previous of 16.96cm x 13.16cm x 10.48cm to 10.76cm x 9.20cm x 6.29cm or a 73.38% decrease in uterine volume. The endometrium was still thick at 2.3 cm with heterogeneous appearance and cystic spaces in the fundal area. Sonologic impression was an interval decrease in the size of the enlarged uterus and a decrease in endometrial thickness to consider endometrial pathology.

Since hysteroscopy will still be difficult, she was advised another 3 doses of GnRH agonist injection given intramuscular every 28 days. Add-back therapy consisting of Tibolone and Calcium with Vitamin D was continued. A repeat transvaginal ultrasound was done after a total of 6 doses of GnRH agonist with findings of 10.82cm x 9.39cm x 8.0cm uterine size. The endometrial stripe was 2.76 centimeters with multiple cystic structures within. Sonologic impression was thickened endometrium consider endometrial pathology (Figure 5).

Hysteroscopic resection of endometrial polyp was done after a total of 6 doses of GnRH agonist. Intraoperatively, the previously prolapsing endocervical mass was no longer seen on vaginoscopy (Figure 6). The uterine depth was 8 centimeters.

On hysteroscopy, bilateral fallopian tube ostia were visualized (Figure 7). Within the endometrium was a fleshy polypoid mass measuring 2.7cm x 2cm x 2 cm with a base measuring 2 centimeters attached at the posterofundal area. There were areas of increased vascularity both on the mass and midcorpus area with intrauterine adhesions surrounding the polyp at the fundal area (Figures 8 & 9).

On microscopic examination, histopathologic sections showed irregular and polypoid endometrial tissues with vari-sized glands lined by simple columnar epithelium. It is supported by mostly fibrotic stroma with scattered prominent thick-walled vessels consistent with an endometrial polyp (Figure 10). Final diagnosis was abnormal uterine bleeding secondary to giant endometrial polyp; status post hysteroscopic (transcervical) resection of endometrial polyp; status post 6 doses of GnRH agonist. Patient was advised continuous treatment with low dose estradiol valerate (2mg) daily with overlap of medroxyprogesterone acetate (10mg) for the last 5 days of each month for 3 months to prevent intrauterine adhesions.

Three months post treatment, a repeat transvaginal ultrasound revealed a thin endometrial stripe of 0.69cm with no appreciable endometrial mass

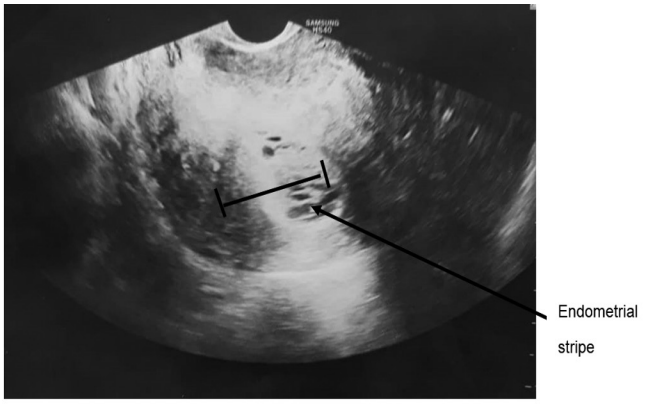

Figure 5. Transvaginal ultrasound after 6 doses of GnRH agonists which revealed a uterine size of 10.82cm x 9.39cm x 8cm from a previous 16.96cm x 13.16cm x 10.48cm. The endometrial stripe was 2.76 cm with cystic spaces within from a previous 12.35cm x 12.02cm x 7.27cm polyp size.

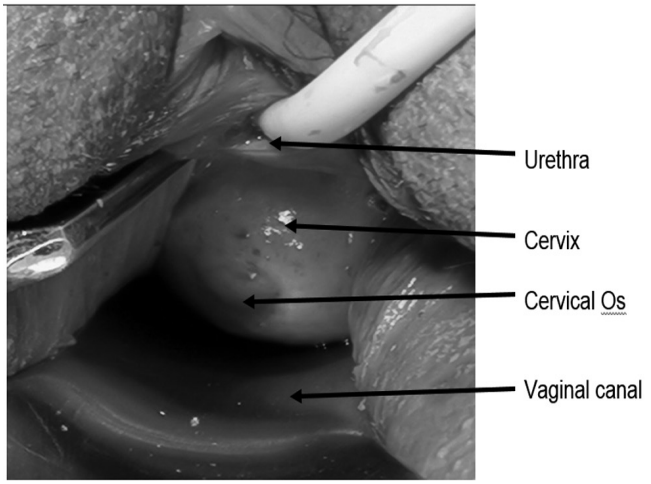

Figure 6. Vaginoscopy showed absence of the previous prolapsing endometrial mass after adjuvant GnRH agonist treatment.

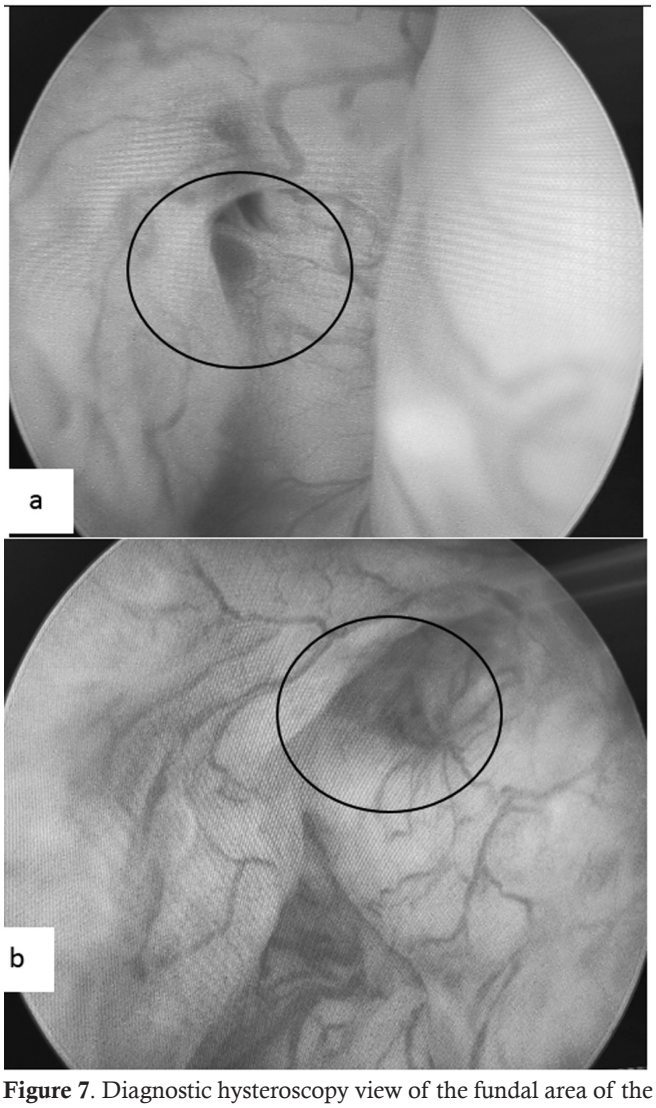

Figure 7. Diagnostic hysteroscopy view of the fundal area of the uterus showing ostia of the bilateral fallopian tubes. (a) Right fallopian tube ostium; (b) Left fallopian tube ostium.

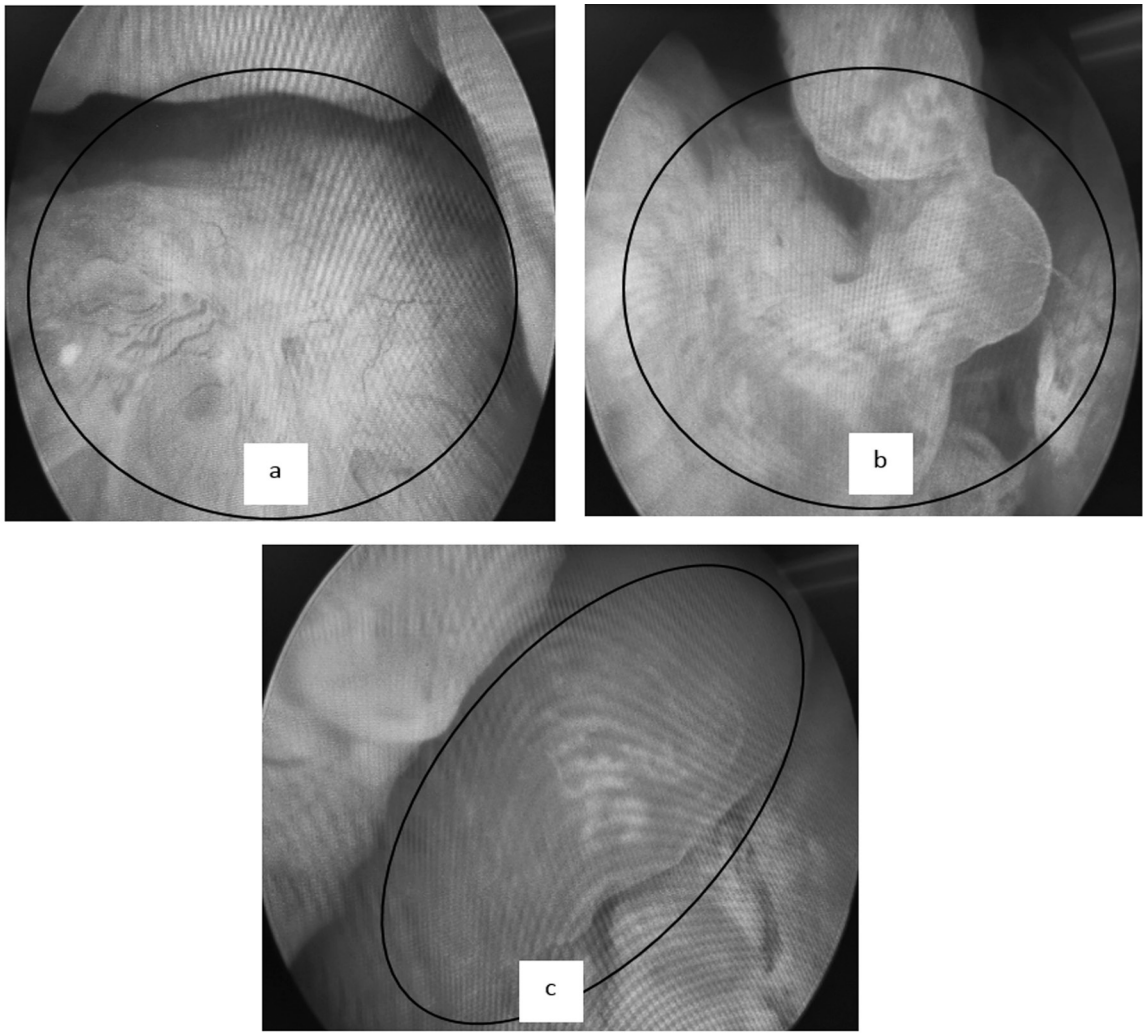

Figure 8. Diagnostic hysteroscopy view of the midcorpus and fundal area of the uterus showing an endometrial mass measuring 2.7cm x 2 x 2cm with a base of 2cm attached at the posterofundal area. The endometrial mass and the midcorpus area are hypervascular. (a) Superior view of the mass; (b) Lateral view of the mass; (c) Inferior view of the mass..

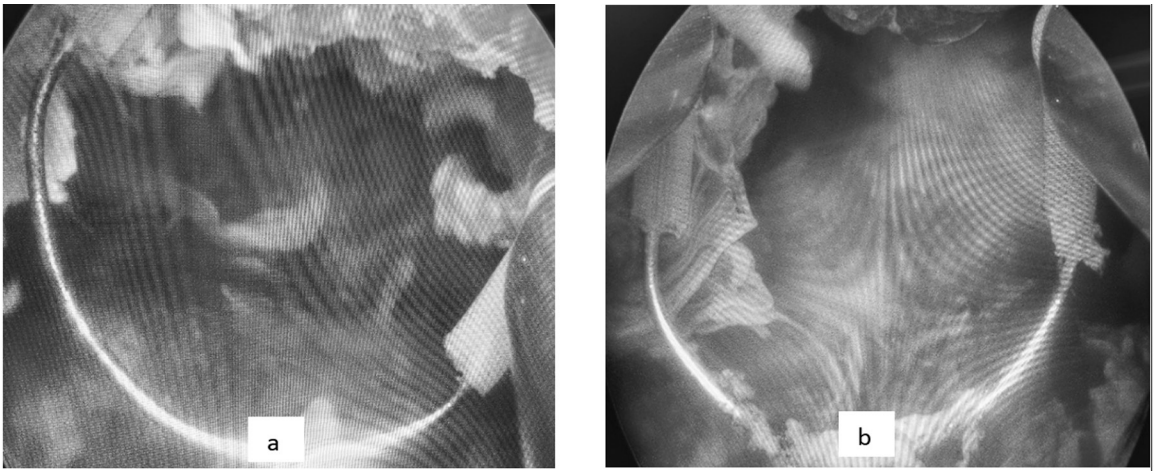

Figure 9. Hysteroscopic view of the midcorpus (a) and fundal area (b) of the uterus after the resection of the giant endometrial polyp.

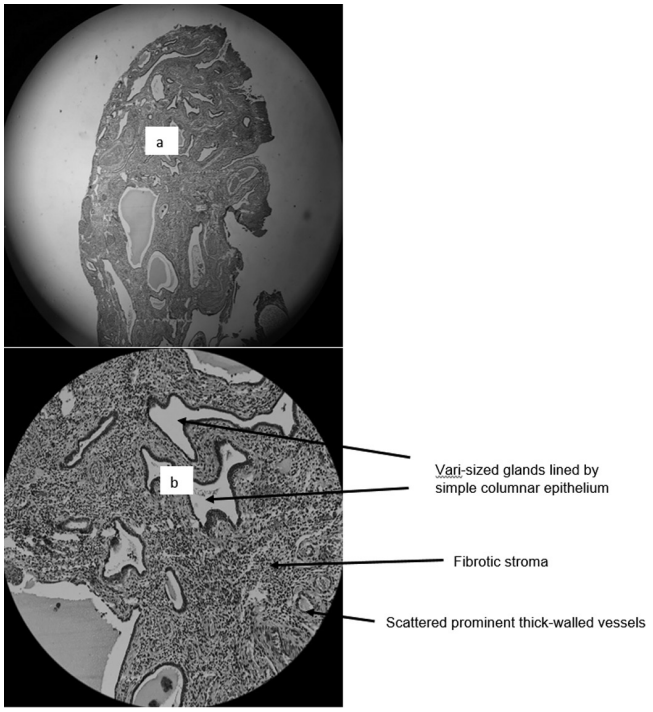

Figure 10. Histopathologic sections showed irregular and polypoid endometrial tissues with vari-sized glands lined by simple columnar epithelium, supported by mostly fibrotic stroma with scattered prominent thick-walled vessels. Findings were consistent with an endometrial polyp. (a) Low power objective view; (b) High power objective view.

(Figure 11). Second look hysteroscopy was done where the endometrial surface was thin. Bilateral fallopian tube ostia were visualized. No remnant of endometrial polyp and intrauterine adhesions were noted (Figure 12).

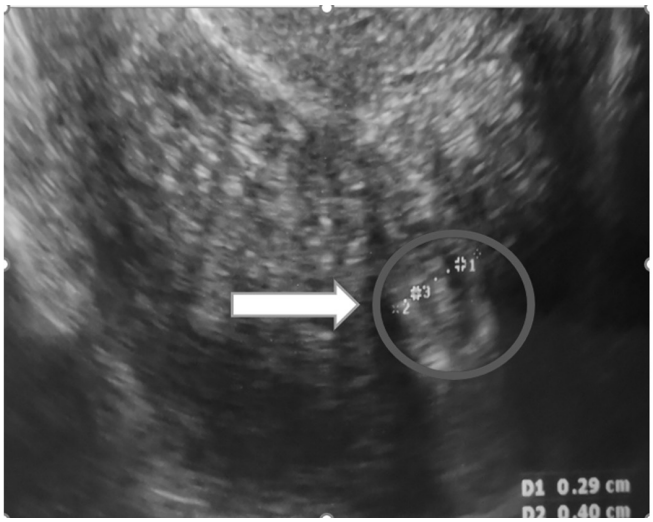

Figure 11. Repeat transvaginal ultrasound 3 months post hysteroscopy revealed a thin endometrial stripe of 0.69cm with no appreciable endometrial mass.

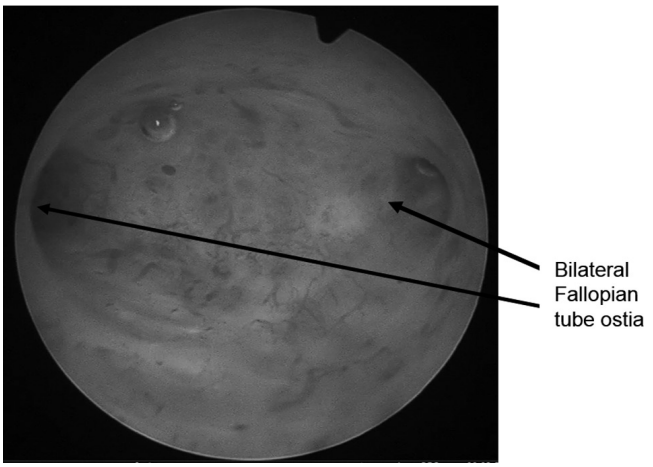

Figure 12. On second look hysteroscopy, the endometrial surface was thin. Bilateral fallopian tube ostia were visualized. No remnant of endometrial polyp and intrauterine adhesions were noted.

Discussion

Endometrial polyps are common in all groups of women with higher prevalence in patients with increasing age.[6,7] These are common lesions and mostly are benign. Polyps could be small, or large enough to fill the entire endometrial cavity. Majority are found in the fundus and often in the cornua providing difficulty in removal by curettage.[8] They are gland overgrowths admixed with stroma, blood vessels and epithelium that are highly reactive to estrogen stimulation.

Theories such as monoclonal hyperplasia, endometrial aromatase over-expression, genetic mutations of BcL-2, which is a regulator of apoptosis, and tamoxifen use are implicated in the development of endometrial polyps.[9] Estrogen and progesterone receptors are present in the glandular epithelium of polyps. Higher concentration of these receptors promote enlargement and prevents shedding off due to its higher number inside glandular epithelium promoting its increase in size and preventing the sloughing off of endometrial stroma. Enlarged glandular epithelium promoted by these receptors do not usually undergo apoptosis which could be attributed to the presence of BcL-2 genes. These are anti-apoptotic genes that promote the growth and

proliferation of endometrial polyps synergistically with that of estrogen and progesterone receptors in glandular epithelium.[2]

Endometrial polyps could be asymptomatic but sometimes are responsible in causing abnormal uterine bleeding and a non-favorable environment for the implantation of the embryo leading to infertility.[10] As seen in the case, the patient presented with chronic abnormal uterine bleeding leading to anemia. In addition, despite regular unprotected sexual intercourse for 5 years, patient has not been pregnant although a complete fertility work-up has not been done.

Polyps may enlarge, but are typically less than 1 centimeter in size. Those that are larger than 1 centimeter are termed "large polyps" and have higher risk of oncologic malformation.[11] Rarely, polyps grow larger than 4 centimeters and are called "giant polyps".[5] In the case of the patient, she had a rare giant endometrial polyp which measured 12.35cm x 12.02cm x 7.27cm extending into the endocervix. Biopsy is indicated in these cases to rule out the presence of malignancy, which was initially done in the patient confirming a result of endometrial polyp.

Ultrasonography has been a common modality in the diagnosis of endometrial polyps and with its easy accessibility, more patients are being diagnosed easily. Saline infusion sonography improves diagnostic accuracy. On ultrasound, endometrial polyps may be sessile or pedunculated, with a hyperechogenic area within the endometrial cavity, with or without cystic structures within, and surrounded by a hyperechoic edge.[7] Transvaginal ultrasound done in the case revealed a 12.35cm x 12.02cm x 7.27cm endometrial mass with multiple anechoic cystic structures within, which was consistent with an endometrial polyp. Saline infusion sonography was not attempted due to possible difficulty of inserting a catheter in the endometrial cavity and difficulty in uterine distention due to the large size of the mass.

Hysteroscopic resection is the gold standard for diagnosis and treatment of endometrial polyps. However, in cases of giant endometrial polyps, hysteroscopy could be technically difficult because a large polyp would cause difficulty in visualization and scope entry for both diagnostic and operative hysteroscopy.[5] In addition, uterine distention will be difficult to maintain in the presence of a very large endometrial mass. Complications such as fluid overload and uterine perforation could also be encountered.

In limited case reports and studies, preoperative use of GnRH agonist was used to decrease endometrial polyp size prior to hysteroscopic resection to facilitate visibility of the mass, ease of resection and reduce potential complications of uterine perforation and fluid overload.

Gonadotropin releasing hormone agonists work by binding to gonadotroph receptors in the hypothalamus resulting to oversaturation leading to desensitization, which would promote production of low follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels in the pituitary. This in turn results to low estrogen production of the ovaries causing a pseudo-menopause state. It is currently used in the treatment of prostate cancer, endometriosis and leiomyoma uteri. It has been used in medical castration as an alternative treatment in prostate cancer wherein long term use of this treatment renders luteinizing hormone biologically inactive.[12] In cases of endometriosis, GnRH agonists provide a state of medical oophorectomy by inducing a pseudo-menopause state decreasing inflammation and reducing size of endometriotic cysts. Marked pain relief has been observed among patients who had GnRH agonist treatment.[13] In leiomyoma uteri, GnRH agonists are known to reduce volume as well as clinical symptoms prior to surgical intervention; however, menopausal side effects prohibit its long term use. The use of an add back therapy or "draw back" (low dose agonist therapy), as was given in the index case, is thereby recommended to relieve vasomotor symptoms and other symptoms related to psudomenopause.[14]

Limited case reports and studies have used GnRH agonist as preoperative treatment prior to hysteroscopic resection of large or giant endometrial polyps. All showed effectiveness of the drug in decreasing polyp size to facilitate resection by hysteroscopy. In a case series by Cupino-Arcinue and Tan-Espiritu (2018), it was adopted as a neoadjuvant therapy prior to hysteroscopic resection of 3 cases of giant endometrial polyps, proving it an effective adjunct in debulking polyp size.[15] Gonadotropin releasing hormone agonist was also used in a case report by Yu-Hung Lin, et al., (2012) to reduce the size of

an adenomyomatous polyp presenting as a large hypervascular tumor.[16] A study by Vercelleni, et al. (1996) used goserelin acetate, a type of GnRH agonist, to reduce polyp size before endometrial resection.[17]

Gonadotropin releasing hormone agonist, which is a proven treatment to decrease leiomyoma uteri and pelvic endometriotic cysts size, provide a hypoestrogenic environment; hence can possibly decrease endometrial polyp size. The mechanism of action is the same for the treatment of each of the pathologies previously mentioned. GnRH agonists initially stimulate the pituitary gland to produce FSH and LH which in turn is downregulated by the pituitary gonadal axis by negative feedback inhibition thus providing a low estrogen state.[18] After 6 doses of GnRH agonist treatment, the patient had significantly decreased uterine and polyp size. Hysteroscopic resection of the entire endometrial mass was then done without difficulty due to the polyp's smaller size. There was good visualization due to adequate maintenance of uterine distention. In addition, there were no complications encountered like fluid retention and uterine perforation. Hence, reduction in polyp size by using GnRH agonist prior to hysteroscopic resection, may not only reduce morbidity, but also improve operative outcomes for it facilitates complete resection of mass and lessens operative time and fluid infusion.

Conclusion

The presence of giant endometrial polyps that occupy the whole endometrial cavity hinder adequate uterine distention and visualization making hysteroscopic resection impossible. GnRH agonists provide a hypoestrogenic state which could decrease both polyp and uterine size, thereby facilitating better intrauterine distention and visualization, easier polypectomy, and lesser incidence of hysteroscopic complications such as perforation and fluid overload.

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