INFERTILITY MANAGEMENT

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INFERTILITY MANAGEMENT SERIES

ABNORMALITIES OF THE PELVIS

Foreword
Anil Gudi

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Science. Pregnancy. Happiness

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Chapter 2

Management Options for Endometrioma Associated with Infertility

Parul Katiyar

INTRODUCTION

Endometriosis is a benign, estrogen-dependent gynecological condition characterized by presence of endometrial tissue outside the uterus. Endometriosis affects approximately 5–10% of women of reproductive age group and symptoms include chronic pelvic pain, dysmenorrhea, dyspareunia, and/or infertility.[1] Endometrioma is a distinct presentation of endometriosis and may manifest in isolation or in association with other features of endometriosis and its association with infertility or reduced ovarian reserve remains controversial. Ovarian endometrioma is seen in approximately 17–44% of women with endometriosis and over 40% of women having ovarian endometrioma have accompanying deeply infiltrating endometriosis.[2]

PATHOGENESIS

The exact pathogenesis of formation of ovarian endometrioma is not yet known. The three main theories to explain formation of endometrioma are:

1. Invagination of ovarian cortex secondary to bleeding of a superficial implant
2. Invagination of ovarian cortex secondary to metaplasia of coelomic epithelium in cortical inclusion cyst
3. Endometriotic transformation of functional cyst.

EFFECTS OF OVARIAN ENDOMETRIOSIS ON FERTILITY

Endometrioma has been found to be present in approximately 17% of cases with clinical infertility and approximately 20–40% women who undergo assisted reproductive technology (ART) have endometriosis. Visualization of endometrioma may be an isolated finding or may be a manifestation of underlying endometriosis. Endometriosis has been associated with pain and

infertility. Although the relationship between endometriosis and pain is well proven, the link between endometriosis and infertility is less well defined.

The exact mechanism by which endometrioma causes infertility is also not known, though a number of mechanisms have been suggested. The probable mechanisms for endometriosis-related infertility include distorted pelvic anatomy, inflammation, endocrine and immunologic abnormalities, poor ovarian reserve and ovulatory dysfunction.

DIAGNOSIS OF ENDOMETRIOMA

Endometriosis often presents with pain in abdomen and pelvis, which is associated with dyspareunia, dysmenorrhea, menorrhagia, and other nonspecific IBS/PID-like symptoms. Endometrioma is a distinctly visualized cyst in the ovary. The diagnosis of endometriosis is traditionally based on laparoscopy, which is also the gold standard for diagnosis.

However, endometrioma can be easily diagnosed using a traditional transvaginal ultrasound (TVS) also because of its characteristic ultrasonographic appearance—unilocular cyst with homogeneous ground-glass echoes and thick walls resulting from hemorrhagic debris. This appearance occurs in 50% of cases. In some cases, the endometrioma may be multiloculated with presence of hyperechoic wall foci.[3]

TREATMENT OF INFERTILE WOMEN WITH ENDOMETRIOMA

Objective of Treatment

The ultimate goal of treatment in these patients is to achieve pregnancy, either spontaneously or using IVF.

Surgical Options for Management of Endometrioma

Effective and lasting treatment of endometriosis is a big challenge for gynecologists. Laparoscopy is generally considered an effective and proven treatment option for endometriosis due to its good tolerance and low morbidity.[4] However, there is limited clinical evidence and consensus to support its direct role in treating endometrioma. The high recurrence rate of ovarian endometrioma and its concurrent symptoms represents one of the less satisfactory aspects of the surgical treatment of endometriosis.[5]

Options for Surgical Management

- *Laparoscopic cystectomy*: It is a surgical procedure, which strips the entire cyst wall from the ovary and removes the entire endometrioma from

the ovary. The procedure was initially considered a standard treatment care for women with endometriomas because of a reduced recurrence rate. The advantages of cystectomy are an increase in spontaneous pregnancy rates (ranging from 14% up to 54%), reduced pelvic pain and also reduced recurrence rates. In an observational study, Barri et al. compared the pregnancy outcome in patients with endometriosis who underwent surgical intervention with the ones who underwent expectant management. They found that up to 54% women in the surgical intervention group became pregnant over a 7-year follow-up, whereas only about 12% women from the expectant management group conceived.[6]

However, laparoscopic cystectomy has its own disadvantages. Since the cyst does not have an actual cyst wall, cystectomy leads to removal of healthy ovarian cortex and follicles leading to reduced ovarian reserve and, even, ovarian failure in some cases. There is also a potential risk of scarring of the ovaries as well as inflammation which may lead to even poor outcomes. Therefore, in view of potential complications, laparoscopic cystectomy should be performed by experienced surgeons only. Laparoscopic cystectomy has been found to have a recurrence rate of 45%.[7]

- *Laparoscopic cyst aspiration and ablation of the cyst wall*: In this procedure, the cyst is first drained and then followed by ablation of the cyst wall using either electrosurgical current or laser energy. Ablating the cyst wall reduces the chances of recurrence, and spares the removal of healthy ovarian tissue that is associated with cystectomy. While both electrocautery and laser have been used for ablation, laser ablation (CO_2 or KTP) is considered to be better due to its tissue sparing effect. Laser ablation does not have the adverse effect on ovarian reserve, which could result from use of electrocautery.

  A Cochrane review that compared the clinical outcomes of cystectomy and ablative surgery in women with endometrioma concluded that excisional surgery for endometrioma had more favorable clinical outcome than drainage and ablation in form of lesser cyst recurrence rate, lesser recurrence of pain symptoms, and better subsequent spontaneous pregnancy rate in previously subfertile women. However, women planning subsequent IVF should avoid surgical intervention.[8]
- *Cyst aspiration*: This is a procedure in which the endometriotic fluid is aspirated from the transvaginal route with a needle under ultrasound visualization. This is a simple procedure yet is not popular because of a high chance of recurrence with a recurrence rate of up to 91% after a single aspiration; therefore, the patient may need to undergo multiple aspirations, with up to six aspirations reported to have a 5.4% recurrence

rates.[9] The other potential risks are infection leading to ovarian abscess formation and adhesion formation. Cyst aspiration has also been tried in conjunction with sclerotherapy using 95% ethanol or methotrexate, in order to reduce the risk of recurrence after aspiration. The sclerosing agent chemically destroys the cyst wall, thereby preventing recurrence. This method, however, is not routinely practiced.

- *Other options*: Other surgical options for the management of an endometrioma include cystectomy with vasopressin injection into the cyst wall, cystectomy with ablation, cystectomy with gelatin matrix seal, and a three staged technique combining laparoscopic cyst drainage followed by gonadotropin-releasing hormone (GnRH) agonist treatment for 3 months followed by a second laparoscopic surgery for vaporization of the cyst wall using CO_2 laser. These methods also attempt to reduce the recurrence rates of endometrioma without adversely affecting the ovarian reserve.

Surgical management of endometriosis has been under considerable investigation due to high incidence of recurrence and because of the potential damage to the ovary. Many studies have analyzed the recurrence rate of endometriomas after laparoscopic surgery, and found it to be between 11.0% and 30% after more than or equal to 2 years of observation.[10-15]

Medical Management of Patients with Endometrioma

There is minimal role of medical management of endometrioma in improving pregnancy rates, as most of the medications like birth control pills are counterproductive to pregnancy. In one of the early studies on this subject, Donnez et al. compared effectiveness of GnRH with that of placebo in reducing size of the cyst and found that GnRH group had 25% higher reduction in diameter of the cyst as compared to the placebo group.[16] GnRH analogs have also been tried in conjunction with surgery in which GnRH analog is given for 3–6 months following either a laparoscopic cyst drainage or partial cystectomy to reduce the cyst size. This approach could have an advantage for selected group of patients, as this approach minimizes the loss of ovarian volume during surgery and preserves maximum ovarian reserve. However, it is a time taking approach and, therefore, is not suitable for many women.

A recent meta-analysis showed that using GnRH analogs for a 3–6 months period prior to an IVF cycle improved the odds of clinical pregnancy in women with endometriosis by four times. However, we need to be careful while extrapolating the results from this analysis to wider patient population

as the study population was rather short, and also the study included three studies on patients with endometriosis and not specifically endometrioma.[7]

Medical management, however, is moderately effective in alleviating pain associated with endometriosis.

Expectant Management of Patients with Endometrioma

This entails no surgical or medical intervention in women presenting with endometrioma. The disadvantages of expectant management include:

- Missing out on an early stage malignancy (very low probability)
- Progression of endometriosis
- Rupture of the endometrioma
- Worsening of associated symptoms like pain
- Further decline in ovarian reserve, thereby further reduction in fertility potential.

While prescribing expectant management to these patients, one should counsel them for the potential pitfalls of nonintervention and recommend a repeat consultation in case the symptoms deteriorate.

In Vitro Fertilization

A significant number of women with moderate to severe endometriosis seeking treatment for infertility need ART. Intrauterine insemination (IUI) may be useful only for women with mild endometriosis. Therefore, IVF or ICSI (intracytoplasmic sperm injection) is the preferred treatment for women with endometrioma. Long and ultra-long GnRH agonist protocols are considered the most effective stimulation protocols for such patients. However, a prospective randomized trial on women with minimal to mild endometriosis and endometrioma comparing the results of GnRH antagonist and GnRH agonist protocols for IVF concluded that the implantation rate and clinical pregnancy rate with antagonist protocol were not any inferior to those for the agonist protocol.[17]

A recent meta-analysis of impact of endometrioma on outcome of IVF concluded that women with endometrioma had similar reproductive outcomes as women without the disease, although cycle cancellation rate was significantly higher in the affected women. Also prior surgical intervention had no beneficial effect on the IVF outcome.[18] Women with endometrioma undergoing IVF have higher cancellation rate, higher total gonadotropin requirement, and lower oocyte yield as compared to women undergoing IVF for other indications. However, these women have similar fertilization rate, implantation rate, and pregnancy rate to those without endometrioma.

Impact of Ovarian Endometrioma on IVF Outcome

Endometriosis and specially endometrioma has been implicated to adversely impact oocyte quality and ovarian reserve, which lead to reduced ovarian responsiveness and poor pregnancy rate.[19]

- *Impact of an ovarian endometrioma on oocyte quality*: The effect of endometrioma on oocyte quality is controversial. Early histological studies by Maneschi et al., Muzii et al., and Schubert et al. indicated toward a significant detrimental effect of presence of ovarian endometrioma on the ovary.[20-22] Matsuzaki S attributed this detrimental effect on affected ovaries to the oxidative stress resulting from presence of the ovarian endometrioma.[23] They found that the amount of oxidative stress and ROS production in the ovarian cortex surrounding ovarian endometrioma was much higher than in other kinds of ovarian cysts. However, more recent clinical studies have found that the endometrioma has less dramatic impact on the clinical outcome of IVF and pregnancy. Kumbak et al. found that the number of oocytes retrieved in women with endometrioma was significantly lesser in comparison to women with simple ovarian cysts.[24] However, the number of mature oocytes and fertilization rates were not significantly different between the two groups, though the implantation rates were lower for women with endometriomas. Fillipi et al. compared ovarian responsiveness and oocyte quality between the affected and contralateral intact ovary in women with unoperated unilateral endometrioma who underwent IVF.[25] They did not find any statistically significant difference between ovarian responsiveness and oocyte quality between the two sides. They also did not find any significant difference in fertilization rate, cleavage rate, and the percentage good quality embryos on two sides, thereby concluding that the presence of ovarian endometrioma does not affect oocyte developmental competence. Bongioanni et al. compared the outcome of IVF in women with previous or present diagnosis of ovarian endometriosis with that in patients with tubal factor infertility in a retrospective analysis.[26] While women with ovarian endometriosis were found to have significantly higher cycle cancellation rate and women with history of laparoscopic ovarian cystectomy prior to IVF had reduced ovarian responsiveness to gonadotropins, the authors found similar pregnancy, implantation, and delivery rate across the two groups.
- *Impact of an ovarian endometrioma on ovarian reserve*: Ovarian reserve, defined as a woman's total ovarian follicle pool which includes both primordial and growing follicles, is most commonly measured using the antral follicular count (AFC) on ultrasound, serum AMH (anti-Müllerian hormone) levels, and day 3 FSH (follicle-stimulating hormone)

levels. Barri et al. compared AFC in women undergoing IVF for ovarian endometrioma with those undergoing IVF for male factor infertility and found that women in the endometrioma group has significantly lower AFC than the other group.[6] Almog et al. found that in women with unilateral endometrioma, the AFC was significantly lower in the affected ovary than in the unaffected contralateral ovary. However, the difference in AFC count between two ovaries was not found to be significant in cases with unilateral benign cysts.[27]

- *Impact of an ovarian endometrioma on ovarian responsiveness*: The evidence on this point is contradictory. Filippi et al. in a prospective cohort study did not find any significant difference between ovarian responsiveness and oocyte quality between the affected (ovary with endometrioma) and the intact ovary.[25] They also did not find any statistically significant difference in the number of viable embryos and number of high quality embryos between the two groups. Thus, they concluded that in women undergoing IVF, the presence of ovarian endometriomas does not affect the oocyte development. These findings are in line with similar studies conducted by Almog B et al. and Benaglia L et al.[27,28] However, findings from most studies on this subject are not in agreement with the above-mentioned findings. In a meta-analysis of five studies by Gupta et al., fewer oocytes were retrieved from women with endometriomas as compared to women without endometriomas.[29] Several other researchers have verified that endometrioma does have a negative effect on the ovarian responsiveness.[24,30,31] This result is also supported by a recent histological study by Kuroda M et al. They studied the ovarian tissue adjacent to the ovarian endometrioma cysts in women under the age of 35 years and found that these women had 33% to 66% fewer follicles as compared to the ovarian tissue adjacent to other benign ovarian cysts.[32] The difference in number of follicles in the ovarian tissue adjacent to the endometrioma is most likely an outcome of oxidative stress led inflammatory response, which causes fibrosis of the surrounding normal ovarian cortex.[23,33,34]

Practical Approach to Management of Infertility Associated with Endometrioma

Following should serve as the guiding principles for treatment in this group of patients:

- Points to consider while evaluating patient for treatment:
  - *Age of the patient*: Age is a major determinant in selection of treatment for an infertile woman with endometrioma. Ovarian reserve and the chance of conception falls with age. Presence of

ovarian endometrioma further reduces the ovarian reserve. The result of laparoscopic cystectomy is also related to patient's age.[35] Barri et al. in an observational study concluded that women over 35 years of age had significantly lower chance of spontaneous pregnancy as compared to younger women after undergoing laparoscopic cystectomy for endometrioma. The older women were also found to be at a higher risk of ovarian failure, although loss of ovarian reserve was observed in all women.[6]

- *Duration of infertility*: Young women with short duration infertility associated with endometrioma have close to 30% probability of spontaneous pregnancy. On the other hand, women with longer duration infertility achieve better pregnancy rates with IVF treatment. There is no added advantage of doing a surgery prior to IVF in such women.
- *Ovarian reserve*: Since women with endometrioma are at higher risk of reduced ovarian reserve and responsiveness, these women are not recommended for expectant management for prolonged periods. They should proceed to IVF early enough in order to maximize their chances of conception.
- *Nature of endometriotic cyst*:
  - *Number and size of endometrioma*: There is no correlation between size of the endometrioma and its effect on the ovarian reserve or outcome of IVF. Similarly, the number of endometriotic cysts in the affected ovary also does not impact the number of oocytes retrieved, and hence has no effect on outcome of treatment. So, the clinician should not get worried on finding large or multiple cysts in women with unilateral endometrioma.[27]
  - *Location of cyst within ovary*: Endometriomas can technically hinder oocyte retrieval because of their location, and can also cause oocyte contamination, if they get punctured. This is often cited as one of the major indications for surgical intervention prior to IVF.[27] However, there is not enough evidence to support that IVF outcome actually improves after cystectomy in such patients.
  - *Laterality of cyst*: As previously mentioned, the ovarian reserve is often found to be reduced in the ovary affected by the endometriotic cyst. This problem gets further aggravated in women with bilateral endometriomas. Therefore, operative procedures like cystectomy are not suitable for such women, as the surgery could further reduce the already reduced ovarian reserve, potentially even causing ovarian failure. This is in line with conclusions from retrospective study by Busacca et al. who

found that two out of six patients with bilateral endometrioma who underwent cystectomy eventually had ovarian failure.[36]

- *Prior surgical treatment*: Since the recurrence rate of endometrioma after laparoscopic cystectomy is rather high, IVF is a more plausible treatment option in patients with recurrent cysts, as compared to repeated cystectomy.[37]

CONCLUSION

- Surgical treatment for endometrioma in infertile patients should be reserved for a small section of young women only, as it improves spontaneous pregnancy rate among young women. However, surgical treatment has no definitive advantage over expectant management in majority of women with endometrioma.
- Many different surgical methods have been described and tried for improving fertility among women with endometrioma. However, none of these is conclusively superior to the others.
- Some of the other indications of surgical intervention in infertile women with endometrioma include cysts blocking access to ovary for egg retrieval, to treat concomitant pain symptoms, or in cases where malignancy cannot otherwise be ruled out with reasonable accuracy.
- Women with endometrioma generally have lower ovarian reserve than their age matched control group. Therefore, we recommend proceeding directly to IVF in order to reduce time to pregnancy.
- Despite of a negative impact on ovarian reserve and ovarian responsiveness, the results of IVF treatment in women with infertility associated with endometrioma are comparable to overall results of IVF in women with tubal factor infertility.

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