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Fertility sparing endometriosis surgery: A review

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ABSTRACT

Background: Endometriosis is a chronic inflammatory condition involving endometrial-like tissue outside of the uterus. There are no medical management options available to improve fertility in patients with known endometriosis prior to conception. Specifically, the fertility sparing surgical techniques used to manage endometriomas and colorectal endometriosis are controversial prior to natural conception and implementing assisted reproductive technology.

Methods: A literature search, including PubMed and the Cochrane Library, was performed from November 2020 to February 2021 and articles in English that addressed endometriosis associated infertility and surgical treatments were included. Our review provides a comprehensive evidence-based evaluation of fertility sparing endometriosis surgery.

Results: The pathogenesis of endometriosis and its role in infertility is poorly understood and complex. The management of patients with painful endometriomas continues to be excision, whereas small asymptomatic endometriomas require an individualized approach. Colorectal endometriosis excision improves pregnancy rates in retrospective and prospective cohort studies. However, randomized control trials are still needed to confirm these findings and their functional risks must be carefully discussed with the patient.

Conclusions: Surgical excision of endometriosis improves fertility in patients with symptomatic disease. Further research with randomized controlled trials is needed to determine if surgery is mandatory prior to implementing assisted reproductive technologies in those patients with asymptomatic endometriosis and infertility.

1. Background

Endometriosis is a chronic inflammatory condition involving endometrial-like glands at extrauterine sites that was first described by Rokitansky and Cullen in the late 19th century.[1] It is associated with early menarche, late menopause, and Mullerian anomalies.[2] It carries a hereditary component with a 6-fold increased risk in women with an affected first degree relative.[3] A multiple hit hypothesis has been proposed to account for the etiology of endometriosis. It notes that the pathological manifestations of this disease are attributable to the culmination of repetitive genetic and epigenetic insults accumulated throughout a woman's lifetime.[1] Cyclic retrograde menstruation has been proposed as the initiating spark that sets a cascade in motion. Further propagating factors involve a hostile environment that repetitively induce epigenetic changes that transforms a single cell into a clonal, collective group of ectopic endometrial glands.[1] These clonal cells exhibit erratic, self-propagating hormonal behavior that includes increases in aromatase, estrogen production, and in progesterone resistance all of which sustain the growth of these lesions.[4] Modern theories negate old paradigms as new research unravels the roles of uterine and bone marrow circulating adult stem cells, the immune system, and the microbiome's manipulation of the terroir necessary for endometriosis to thrive.[5]

Endometriosis has a significant impact on women's health and health care costs. Endometriosis affects 6–10 % of reproductive aged women and greater than 175 million women worldwide.[6,7] It was estimated in 2012 that the economic burden of endometriosis in the U.S alone was

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more than $49 billion.[8] Early diagnosis is key and research suggests that a misdiagnosis with inflammatory bowel syndrome (IBS) and pelvic inflammatory disease (PID) is common.[9] Clinical symptoms include severe dysmenorrhea, dyspareunia, sub-fertility, abdominopelvic pain, heavy menstrual bleeding, and postcoital bleeding.[9] Most women with endometriosis suffer physically and emotionally in their day-to-day function as a result of these painful symptoms. These symptoms are oftentimes improved with surgery. Alarmingly, studies have reported a long delay in the diagnosis of endometriosis of up to 10 years.[10]

Delayed diagnosis is not the only issue that complicates therapeutic management of this disease. A contentious topic within endometriosis studies continues to be establishing a reliable staging system. It has been suggested that superficial, ovarian, and deep infiltrative endometriosis lesions are different manifestations of the disease and data from Saavalainen et al. suggests that the distribution of occurrence is 51 %, 44 %, and 5 %, respectively.[11] The revised American Society for Reproductive Medicine (rASRM) classification is frequently used in research to communicate standardized findings among researchers at the time of surgery. However, the rASRM classification does not correlate well with pain or fertility outcomes and does not consider deeply infiltrating endometriosis (DIE) in all locations.[12,13] Recently, the #ENZIAN classification has been proposed to describe deep infiltrative endometriosis, ovarian, and superficial endometriosis and may be a more comprehensive, correlative, and practical tool to study the disease and the intraoperative findings.[14] Regardless of the staging system used, both systems point to a need to correlate surgical findings with clinical manifestations of this disease. This is needed to foster novel approaches that. improve therapeutic management of infertility, pain, and endometriosis.

2. Infertility and endometriosis

Endometriosis is associated with infertility in patients with rASRM stages I–IV. The cause of infertility in early stages is unclear but is proposed to result from the inflammatory milieu in the pelvic peritoneal fluid, which affects ovarian reserve and function of the egg and sperm.[5.] Fecundity, a woman's biological capacity to reproduce, is 2–10 % per month in patients with endometriosis. This is 10-times less than in a woman without the disease.[15] Moreover, up to 50 % of infertile women and 87 % of women with chronic pelvic pain are affected by endometriosis.[16–18] In addition to infertility, studies have shown an association with some adverse pregnancy outcomes in women with endometriosis. A study of 1267 patients who underwent endometriosis surgery (67 % with stage III or stage IV) showed a higher rate of small lesions for gestational age (SGA) infants at 15.9 %, preterm birth (PTB) at 12.7 %, and placenta previa at 1.6 % risk.[19] Of note, the authors stated artificial reproductive technology (ART), often used in women with endometriosis-related infertility, was an independent risk factor for PTB and placenta previa.[19] These studies indicate that endometriosis is a direct and significant cause of infertility and it may lead to adverse pregnancy outcomes once a woman becomes pregnant.

There exist three options for the management of endometriosis: medical, surgical, and expectant. Medical management alone of endometriosis has not been proven to cause regression of disease and hormonal medications block the ability to conceive during their administration,[20] leaving surgical and expectant management as the remaining interventions for women desiring to conceive. Multiple reviews of randomized controlled trials (RCTs) of operative laparoscopy have shown a benefit with respect to pain and fertility in women with endometriosis. A systematic review and a meta-analysis that included three randomized control trials examined laparoscopic treatment in women with stage I, II, and III endometriosis with results favoring excision over ablation for notable reduction in dysmenorrhea, dyschezia, and chronic pelvic pain at 12 months.[21] Moreover, laparoscopic resection of endometriosis has been shown to result in higher rates of spontaneous conception when compared to laparotomy.[22] Bafort et al. reviewed data representative of 1563 women with endometriosis and likewise showed an improvement in pain in the operative laparoscopic excision group versus the diagnostic laparoscopy group with a mean difference (MD) of 1.65 at 1 year. The same article found an improvement in viable pregnancy rate (PR) with an odds ratio (OR) of 1.89.[23] The improvement of PR is supported elsewhere in the literature. For example, prospective cohort studies have shown spontaneous pregnancy rates of 57 %–69 % and 52 %–68 % after laparoscopic surgery for stage III and IV disease, respectively.[10]

Even though there are surgical benefits to surgical intervention, this procedure has inherent risks. The reduction in pain and improvement in pregnancy rates would need to outweigh those risks to be considered a reasonable alternative to medical or expectant management. A systematic review by Leonardi et al. showed that operative laparoscopy improves overall pain at 6 months with a risk ratio (RR) of 2.65 without any clinically significant adverse outcomes indicating that the benefits to surgical management may outweigh the risks.[24]

Conversely, expectant management of stage III and stage IV disease has been shown to have a dismal PR as low as of 33 % and 0 %, respectively.[10] Cobo et al. have reported significantly lower oocyte survival, implantation, pregnancy, and cumulative live birth rates in endometriosis patients younger than 35 years old undergoing fertility preservation with oocyte vitrification.[25] These studies indicate that for stage III and IV endometriosis expectant management is associated with poor pregnancy rates. This association is well enough established although no RCT studies exist, the European Society of Human Reproduction and Embryology (ESHRE) recommends that women with stage III and IV endometriosis associated infertility should consider operative laparoscopy to increase spontaneous pregnancy.[10]

With medical management incompatible with fertility and expectant management shown to have poor pregnancy rates, further investigation is necessary to quantify the improvement in pregnancy rates and identify the optimal timing of spontaneous and ART after surgical intervention. Vercillini et al. prospectively reviewed 729 women undergoing laparoscopic endometriosis surgery and found a cumulative spontaneous PR of 47 % (51 % at stage I, 45 % at stage II, 46 % at stage III and 44 % at stage IV). Prospective and retrospective series have shown PR of up to 86.2 %, 81.5 %, 76.5 %, and 73.3 % for stages I-IV respectively after surgery over a 36 week follow up[26–28] with 93.7% of pregnancies occurring within 24 weeks after surgery.[27] A retrospective analysis conducted by Fuchs followed patients with moderate to severe endometriosis (73 % with stage III/IV disease and 53 % with endometrioma) and a history of infertility/poor pregnancy outcomes.[29] Those treated with operative laparoscopy showed a natural conception rate of 60 % of which 56 % gave birth at term. Among the 21 % of women in the study that had pregnancy failure before surgery, 71 % subsequently became pregnant and 80 % achieved pregnancy spontaneously.[28] Comparing fertility sparing endometriosis surgery with IVF for management of infertility, there was a spontaneous PR of 47 % after surgery compared with a PR of 29 % after IVF.[30,31] In addition, numerous studies also show a faster rate of conception in patients who proceed with natural conception versus ART.[28,32] One study showed a significant median time to pregnancy of 2 months for spontaneous pregnancy after surgery vs. 20.5 months in the ART after surgery group in Stage I and II.[28] The same study found an 8 and 12 month median delay to pregnancy that did not reach statistical significance for spontaneous vs. ART, respectively, in stages III and IV.[28] Although natural conception rates improved after fertility sparing endometriosis surgery, expectantly awaiting natural conception may not be appropriate for all patients and the need for ART must be determined on an individual basis. The endometriosis fertility index (EFI) is one useful tool for counseling patients with regards to natural conception or IVF postoperatively.[33] The EFI considers historical and surgical findings at the conclusion of endometriosis surgery and suggests pregnancy rates based on the scoring system[33] which may be helpful in determining whether to refer for ART. However, the EFI does not have clear data on live birth rates (LBR) which is important in counseling patients.[34]

Benoit et al. designed a nomogram to predict the LBR among women

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with endometriosis associated infertility after surgery followed by a median of 2 cycles of IVF.[34.] The women included did not have colorectal disease, and 34.7 % had stage III or stage IV disease. The area under the curve (AUC) was 0.77, which is supportive of good quality evidence. Overall, the pregnancy rate (PR) and – more importantly – the LBR was 73.4 % and 57.6 % (171/297), respectively, over 36 months. The authors suggested that the nomogram may be a useful tool in counseling patients considering donor egg ART.[34] To date, there are no RCTs proving that surgery before IVF improves LBR compared to IVF alone and the data we do have is mixed with both spontaneous and ART conceived pregnancy rates.[30]

Repeat endometriosis surgery is controversial with pregnancy rates after repeat surgery ranging between 28.6 % and 54 % for both spontaneous and ART conceptions.[35,36] Indeed, for patients in whom fertility is the aim, there is evidence that repeat surgery yields diminishing returns. A review by Berlanda et al. showed PR 20 %–26 % with repeat surgery versus 30 % with assisted reproductive technology versus 41% PR after primary surgery.[37,38]

3. Endometrioma

Another controversial topic involves management of the ovarian endometrioma. The surgical technique to optimize success rates regarding fertility and reducing recurrence. Endometriomas comprise 17 %–44 % of endometriosis cases.[39] In a study by Coccia et al. of 307 patients that underwent laparoscopic endometriosis surgery 27.8 % had bilateral ovarian endometriomas.[40] Chapron et al. showed that ovarian endometriomas are associated with histologically proven DIE nodules in 40.3 % of patients and severe pelvic pain in patients with an ovarian endometrioma is significantly associated with deeply infiltrating lesions, specifically with intestinal involvement.[41] Isolated ovarian endometriosis was found in 1.06 % of women according to observations by Redwine.[42] While the vast majority of endometriotic cysts are benign, a meta-analysis showed that endometriosis was associated with a 1.9-fold greater risk of ovarian cancer compared with women without endometriosis, with clear cell and endometrioid malignancy being the predominant histologic type.[11] Nonetheless, preservation of the ovary is usually recommended given the overall low absolute risk of malignancy. Medical therapy is not an effective treatment for endometriomas and the treatment for painful and large endometriomas remains surgical.[30]

Various studies have compared excisional versus non-excisional and surgical versus expectant management in the treatment of endometriomas. A Cochrane review by Hart et al. 2008, showed a significant decrease in recurrence, a longer time to recurrence, and an increased spontaneous pregnancy frequency in cystectomy versus drainage techniques in women with endometriomas >3 cm.[43] Both Beretta et al. and Alborzi et al., confirmed a substantial benefit of endometrioma excision, citing a pregnancy frequency of 60.9 % for excisional versus 23.4 % for non-excisional techniques, with an OR of pregnancy of 5.11 and a number needed to treat (NNT) of 2.7.[44,45]

When considering ovarian surgery, especially when performed with the goal of improving pregnancy outcomes, the benefit of removing the endometrioma must be weighed against the potential damage to the ovarian tissue. The ovaries house a woman's reproductive potential and anti-Mullerian hormone (AMH) is commonly used as a marker to assess chances of successful IVF.[46] Evidence is lacking to support the use of AMH to predict spontaneous conception, so caution is recommended when counseling patients in this regard. Kasapoglu et al. demonstrated that having an endometrioma alone decreases the AMH by a factor greater than 3 compared to normal ovarian decline.[47] The lower AMH levels associated with endometriomas combined with a risk for further compromise of functional ovarian tissue during surgery, results in a need to carefully consider the utility of surgical management and its impact on pregnancy rates. Counseling on egg preservation is recommended prior to surgical management of endometriomas.

Furthermore, studies suggest that excision may have an adverse effect. A more recent Cochrane review found no difference in clinical pregnancy rates in excision versus expectant management of endometriomas <6 cm in women undergoing ART.[48] Matsuzaki et al. found that the amount of normal ovarian tissue excised during endometrioma surgery was 10 times more than with other benign cyst types.[49] This aligns with data showing damage to ovarian reserve after laparoscopic excision of ovarian endometriomas with a mean diameter of 4.6 cm, as demonstrated by a 38 % decrease in AMH after surgery.[50,51] The decline was most evident in women undergoing bilateral endometrioma surgery with one study finding a risk of premature menopause in 2.4 % of women younger than 40 years old.[52] The European Society for Gynaecological Endoscopy (ESGE) and the European Society of Human Reproduction and Embryology (ESHRE) agree that small asymptomatic endometriomas < 3 cm may be left alone without surgery.[39.] For endometriomas of all sizes, prevention strategies to preserve maximal ovarian reserve at time of excision are strongly advised, including suturing, using hemostatic sealants, and avoiding crush injury and bipolar desiccation.[53,54]

Alternatives to endometrioma excision have been reviewed in the hopes of minimizing its impact on ovarian reserve as well as preventing recurrence such as: CO_2 ablation, laparoscopic sclerotherapy with alcohol agents, plasma energy ablation, and a combination of CO_2 ablation and stripping with or without the use of GnRH analogs with outcomes comparable to cystectomy.[39,55,56,.57] Candiani et al. saw a significant decrease in AMH in the cystectomy group at 3 months vs. no change in the CO_2 ablation group.[2] Many authors suggest that removing superficial endometriosis and DIE without concomitant ovarian endometrioma cystectomy is not detrimental to pregnancy rates. Namely, Roman et al. showed that surgical management of colorectal endometriosis does not negatively impact PR in patients with ovarian endometriomas treated by endometrioma plasma energy ablation.[58] Therefore, excision may not be mandatory for all endometriomas, especially in the case of a woman greater than 35 years old, with a low AMH, low suspicion for malignancy, and prior ovarian surgery.[30]

The review of the literature shows that the best surgical management of endometriomas is dependent on individual patient characteristics. Likewise, the goals and desires of the patient should be taken into consideration when counseling patients post-operatively on options for further management. Patients not desiring to conceive right away after endometrioma excision should be encouraged to pursue postoperative medical suppression with continuous combination oral contraceptives, as this has been shown to have the greatest impact on decreasing the chance of recurrence compared to other hormonal therapies.[59]

4. Deep infiltrative endometriosis (DIE)

Deep infiltrative endometriosis(DIE) is a surgical definition that describes an infiltration of endometrial glands and stroma into the peritoneum of >5 mm.[1] DIE is most often associated with rectovaginal and rectal involvement, but involves the ureters, intestines, uterine supportive ligaments, the pelvic side walls, bladder, vagina, and other extra-pelvic, distal locations. DIE has a prevalence of 0.2 %–0.5 % of the population.[1] In women with pain and infertility, the prevalence is estimated to be between 3 % and 10 % – based on a prospective study of 643 women by Koninckx et al.[60] The true prevalence of asymptomatic DIE is not known, but has been estimated to be around 5 %.[60]

The presentation of DIE in these locations is diverse. Intestinal involvement by deep endometriotic nodules has been estimated to occur in 5–25 % of women with endometriosis.[61] Colorectal DIE may present with sub-occlusive and occlusive prodromes sometimes leading to a surprising diagnosis of endometriosis by general surgeons, which undoubtedly go unreported in the gynecologic literature.[62] A population-based study using data from the Healthcare Cost and Utilization Project-Nationwide Inpatient Sample (HCUP–NIS) found that women with pelvic endometriosis had a significant OR of 2.6 for bowel obstruction and that intestinal endometriosis was associated with a 14.6-fold increased risk of bowel obstruction with rectovaginal

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endometriosis associated with a 2-fold increased risk.[63] The overall prevalence of bowel obstruction in this study was 1 %. The author's findings were independent of the presence of intra-abdominal adhesions. Although most DIE colorectal nodules are not progressive, Netter et al. showed that 27.9% of women with colorectal DIE had progression as seen by MRI over a 3 year period.[88]

DIE may also present with silent unilateral kidney failure secondary to obstruction; therefore, evaluation of the genitourinary system is recommended in women with endometriosis. As the majority of patients with DIE have severely painful symptoms, surgical intervention is usually indicated.[1] Indeed, a history of a previous surgery is a marker for severity of the disease with 78.3% of patients with DIE having prior surgery for endometriosis, which may allude to a possible activation of the disease by incomplete surgery.[64]

As surgery is usually indicated in patients with DIE and fertility sparing endometriosis surgery generally shows improvement in PR, there are several prospective cohort studies that show high PR after DIE surgery. In a recent study of 124 patients managed for ovarian endometrioma ablation using plasma energy, 52 patients had associated colorectal DIE managed by either conservative surgery or colorectal resection.[58] The colorectal conservative surgery arm comprised 73.1 % of the surgeries performed and employed discoid resection or rectal shaving as surgical techniques. Of the 38 patients with colorectal DIE desiring to conceive postoperatively, 65.8 % became pregnant, with 60 % of patients achieving spontaneous pregnancies.[58] Of note, the only independent risk factor decreasing PR was patient age over 35. As a result of the increased PR observed after surgical management of colorectal DIE, the authors suggest that ART is not necessarily compulsory for every patient desiring pregnancy. Another study by Vercellini et al. reviewed outcomes of women after surgical management of rectovaginal DIE and found that infertile patients had a spontaneous PR of 24 % (range 10 %–41 %).[65] The authors argued that the spontaneous postoperative PR was 37.5 % in the subgroup of women with colorectal DIE and preoperative infertility and the authors suggest that approximately 1 in 3 patients do not mandatorily require ART after a complete intraoperative and fertility assessment.[58,66] Moreover, >85 % of women with DIE showed complete improvement of painful symptoms with recurrence rates under 5 % after surgical excision[65]

To further investigate the effect of surgery on fertility in patients with colorectal DIE, some studies have examined fertility outcomes in patients undergoing ART alone with those undergoing ART after surgery for colorectal DIE. In 2012, Ballester et al. demonstrated that in 75 patients with colorectal endometriosis that had not undergone colorectal surgery, the cumulative pregnancy rates after undergoing 1, 2, and 3 IVF cycles with intracytoplasmic sperm injection (ICSI) were 29.3 %, 52.9 %, and 68.6 %, respectively.[67,66] A prospective nonrandomized trial by Bianchi et al., showed a significant difference in pregnancy rates between the IVF group (24 %) and the IVF with surgery group (41 %), with an OR of achieving a pregnancy of 2.45 in the surgery group.[68] Bianchi and his group did not report on the spontaneous conception of this cohort. Cohen et al. also compared IVF PR in those that had undergone surgery (46.9 %) and those that had not (29 %).[66,69] The authors further analyzed the cumulative live birth (CLB). After the first ICSI-IVF cycle in the first-line surgery group, the CLB was 32.7 % versus 13.0 % in the no surgery group. After the second cycle, the CLB was 58.9 % in the surgery group versus 24.8 % in the no surgery group. After the third cycle, a CLB of 70.6 % in the surgery group versus 54.9 % in the no surgery group, indicating that PR improved in IVF patients that had undergone surgery for colorectal DIE.[66,70] More recently, the ENDORE RCT had an PR of 81 % at 5 years among women who had colorectal endometriosis resection. In those women that became pregnant, 65 % were spontaneous with a LBR of 78 %.[32] Time to spontaneous conception was achieved significantly earlier in the surgery group compared to patients referred for ART. In the 63 % of women in this trial that were clinically infertile, the postoperative pregnancy rate was 74 %, with over half of the PR by natural conception.[32,66] These results, the authors argue, suggests that surgical management enables natural conception in women with deep endometriosis of the rectum, for whom the likelihood of preoperative conception is low.[32]

A review of cohort, case–control, and observational studies with an appropriate control group by Casals et al. showed that surgery for DIE prior to ART demonstrated a pregnancy rateper cycle of 1.84 (95 % CI 1.26–2.70) and a live birth frequency per patient that was 2.22 (95 % CI 1.42–3.46) times more likely for operated patients compared to non-operated ones.[71] Results favor surgery in DIE with bowel involvement (OR 2.43, 95 % CI 1.13–5.22) and also in DIE without colorectal involvement (OR 1.55, 95 % CI 0.61–3.95).[71] It is important to note that no RCTs were included in this review and there was paucity of data on complications, therefore conclusions must be carefully weighed with the information that is known.

The surgical management of DIE ranges from bowel shaving to bowel resection, and the risks of surgery vary based on surgical approach. Conservative bowel surgery should be attempted whenever possible. It is clear in nonrandomized controlled trials that the data favors rectal shaving whenever possible given its low bowel complication rate and recurrence rate of <10 %.[72] This is compared to radical bowel surgery such as segmental bowel resection, which may lead to long term bowel, bladder, sexual dysfunction, and anastomotic leak. A review of the leakage rate and functional problems after sigmoid resection by Ret Dávalos et al. found that for sigmoid resection, leaks occur in <1 % of cases with remote long-term problems.[73] Consistently, lesions of the low rectum (<5–8 cm from the anal verge) appear to be the greatest culprit of anastomotic leaks.[74] For low rectal resections, risk of leaks increases to 15 % or more and carry a disturbingly high lifelong risk of bowel, bladder, and of sexual/anorgasmia problems, cited at 30 %, 30 %, and 40 %, respectively.[73,75] Other complications include hemorrhage (1 %–11 %) infections (1 %–3%) and laparotomy conversion (up to 12 %).[74]

Even after weighing these risks with previously discussed benefits of increase in PR, not all authors agree that bowel surgery should be done systematically as part of “fertility enhancing” endometriosis surgery.[76] Bendifallah et al. argue that the impact of colorectal endometriosis alone on fertility remains unclear.[76] Indeed, the efficacy of colorectal surgery as a measure to improve fertility are mostly derived from non-RCTs and the strength of this type of evidence is limited.[76] Vercellini and his group argue that the overall postoperative PR after colorectal endometriosis resection seen in the systematic review by Daraï et al. increased by a mere 5%.[76] In asymptomatic patients, most authors suggest that bowel surgery should be considered only after two IVF failures. [76] Although, this seems a moot point since 95% of patients with DIE are symptomatic. Vercelleni et al. suggests that disc excision and segmental bowel resection performed solely for the purpose of improving the reproductive performance of infertile women should be considered an experimental procedure to be performed exclusively in high-volume hospitals by experienced surgeons with the objective of limiting complications.[76] Moreover, while awaiting data and standardizations of practice, women must be informed that the outcomes published may not be generalizable, as the research we do have is a product of highly skilled expert endometriosis surgeons from around the globe.[76]

5. Adenomyosis

An under-appreciated aspect of research funding and women's health is the subject of adenomyosis. Adenomyosis is defined as endometrial glands and stroma within the myometrium.[77] Its parallel pathogenesis to endometriosis is evident by its very definition. Related pathogenic mechanisms underlying endometriosis and adenomyosis have been suggested by multiple authors.[77] The prevalence of adenomyosis is wide ranging and is cited between 5 % and 70 %.[77] The prevalence of endometriosis in women with adenomyosis may be as high as 96.3% and the prevalence of adenomyosis in patients with endometriosis was 91.1% in one study.[75,78] Focal adenomyosis has been found to be the most common type associated with endometriosis.[75] Adenomyosis is frequently

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associated with DIE and colorectal endometriosis – most notably with the classic "question mark" sign on ultrasound which is highly associated with posterior compartment DIE.[84,85] In a surgical series of 292 women, focal adenomyosis on MRI was detected in 7.5 % of patients with superficial peritoneal endometriosis, in 19.3 % of those with ovarian endometriomas, and in 66.3 % of those with DIE. The prevalence of adenomyosis in women without endometriosis was 5.3 %.[79] The diagnosis of adenomyosis itself continues to evolve. Adenomyosis is no longer just associated with older multiparous women and has moved from a pathologic diagnosis to a radiologic one for obvious fertility sparing reasons. Similar to the staging of endometriosis, the radiologic diagnosis of adenomyosis is complicated as a result of heterogeneity in the diagnostic criteria.[77]

As adenomyosis is now commonly recognized in younger reproductive aged women and adolescents and its co-occurrence with endometriosis, its relationship to infertility is undergoing investigation. Adenomyosis may impact reproductive outcomes, reducing the likelihood of implantation and increasing the risk of miscarriage.[80–83] A meta-analysis by Vercellini et al., showed that DIE and adenomyosis decreased the chance of pregnancy by 68 %.[80]

Most experts agree that older patients with adenomyosis, low AMH, and asymptomatic small endometriomas will benefit from IVF.[80–82] According to a systematic review among patients who underwent surgical treatment for rectovaginal and colorectal endometriosis including bowel resection, only 11.9 % of those who had a preoperative imaging diagnosis of adenomyosis achieved a natural pregnancy compared with 43.0 % of those without adenomyosis.[80] Furthermore, a recent systematic review by Mikos et al. found that fertility sparing surgical treatment of adenomyosis results in high success rates for control of pain and menorrhagia, both >70 % at 12 months.[86] Furthermore, conservative surgical management facilitates conception with an acceptable rate of pregnancy complications.[86] Additional studies on adenomyosis and infertility are needed to further delineate adenomyosis' role in infertility and optimal surgical management in infertile patients with adenomyosis.

6. Conclusion

Endometriosis and infertility are two related diagnoses that impair a woman's daily functioning and reproductive goals, which can cause great physical, emotional, and psychological distress. Unfortunately, expectant management and medical management have either limited effects or shrinking effects on conception with surgical management showing modest improvements in PR. IVF is commonly recommended to women with endometriosis, but it is not optimal in holistically treating the patient in moderate and sometimes debilitating severe pain who is attempting pregnancy. With half of the women with endometriosis suffering difficulty in conceiving, expert surgeons around the world have accumulated data showing the impact of surgery in all stages of endometriosis. Radicality of endometriosis surgery has decreased over the decades in expert referral centers with pathogenesis of this benign yet chronic disease better understood. Surgeons have evolved their techniques based on their experience yet continue to be challenged by the complexity of this elusive disease process.

Most surgeons agree that asymptomatic patients whose lesions are diagnosed incidentally on clinical exam and/or radiologic findings do not systematically warrant surgery. Abrão et al., suggest that surgery for DIE of the recto-sigmoid is indicated only in the following situations:

(i) Patients who present with significant pain such as dyspareunia and dyschezia (VAS > 7) that results in major impairment of quality of life[74]
(ii) Patients who present with signs of bowel obstruction[74]
(iii) Patients who have failed previous in vitro fertilization (IVF) cycles.[74]

The authors recommend ART first for asymptomatic or mild painful symptoms if pregnancy is the priority.[74]

However, there remain major advantages to laparoscopy with the goal of fertility compared to ART including pain relief, faster time to spontaneous conception, avoiding the high cost of ART in the U.S., avoiding multi-fetal gestations, and avoiding further ART procedures for future pregnancies.[30] In addition, surgery has the added benefit of avoiding progression of occlusive bowel or ureteral pathology, avoiding endometrioma rupture and/or abscess, and confirming benign pathology in the case of suspicious endometriomas.[30,66,87–89] Limitations of surgery when compared to ART for endometriosis include a dearth of expert surgeons compared to the rising number of women afflicted with the disease, potential harm to ovarian reserve in patients with bilateral endometriomas and older age, immediate and long-term complications of radical bowel surgery, and the limitations in treating other causes of infertility such as male factor.[30,48,50,90] Further research with randomized controlled trials is needed to answer the question of whether surgery is obligatory prior to ART in patients with asymptomatic endometriosis and infertility. Until then, expert surgeons will continue to strive in improving pain and quality of life through surgery.

The science is clear that further RCTs are required to ultimately answer questions left on the table and to better care for patients with endometriosis who present with desires for future fertility. It is also clear that the research needs to prioritize earlier diagnosis, new treatment modalities that do not inhibit pregnancy, adenomyosis, and prevention of chronic debilitating symptoms. Awareness, continued research, and early referral to multidisciplinary endometriosis expert centers is critical to timely, correct management.

Declaration of competing interest

There are no financial conflicts of interest to disclose.

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