

Is Endometriosis a Surgical Disease?

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Endometriosis affects one in ten reproductive-aged women, is a cause of pelvic pain and infertility, and accounts for \$22 billion and \$1.8 billion in total annual costs to American and Canadian society, respectively [1-3]. Endometriosis is defined as uterine endometrial glands/stroma being ectopically present outside of the uterus, usually elsewhere in the pelvis (e.g. the ovaries or pelvic peritoneum). The formal diagnosis of endometriosis requires surgical excision or biopsy followed by histological confirmation. However it is controversial whether endometriosis is truly a surgical disease.

One argument against endometriosis as a surgical disease is that formal diagnosis requires surgery and thus invasive and not without risk, and therefore national guidelines support initial empiric medical treatment of symptomatic women [1]. Nonetheless, such symptomatic women are likely to have a spectrum of underlying conditions such as endometriosis, primary dysmenorrhea, or even non-gynecologic problems. If empiric medical treatment (e.g. hormonal suppression) is unsuccessful, or if the patient chooses to discontinue medical treatment (e.g. due to side-effects or desire for pregnancy), then conservative surgery can be offered to diagnose and treat endometriosis, if present. Conservative surgery for endometriosis involves laparoscopic ablation or excision of the endometriosis lesions. In addition to its therapeutic aspect, laparoscopic surgery provides women additional information about their reproductive health. For example, if endometriosis is present then women can be counseled about implications for fertility [4], new research showing a relationship between endometriosis and ovarian cancer [5,6], and the increased risk of endometriosis for family members [7]. Correspondingly, women diagnosed with endometriosis may alter the timing of their reproductive decision making, choose long-term hormonal contraception for prevention of ovarian cancer, and their young family members may seek treatment earlier and thus possibly prevent development of chronic pelvic pain. Alternatively, if no endometriosis is found, then women can be reassured. This difference in prognosis highlights the importance of laparoscopic recognition of not only classic lesions of endometriosis (e.g. powder-burn), but also its atypical and subtle appearances (e.g. vascular or white) [8].

Another argument against endometriosis as a surgical disease is the importance of the uterus in endometriosis. The uterine endometrium is known to be abnormal in endometriosis, and retrograde menstruation of uterine endometrial glands/stroma through the fallopian tubes and into the pelvis is the major etiologic mechanism for the development of endometriosis [9-11]. Therefore, one wonders how conservative surgery alone could have any long-lasting efficacy, as it involves ablation or excision of endometriosis lesions but does not treat the uterus. However, conservative surgery can be accompanied by other procedures such as pre-sacral neurectomy (division of the nervous supply to the uterus) or intra-operative insertion of the levonorgestrel-releasing intrauterine device (IUD), which have been found to improve pelvic pain when added to conservative surgery for endometriosis [12,13]. Alternatively, definitive surgery involving removal of the uterus (hysterectomy), with or without bilateral salpingo-oophorectomy, can be offered as it has low recurrence rates with a 10-15% risk of re-operation at 5 years [11]. Definitive surgery can be performed laparoscopically in most cases, and remains a choice for women once childbearing has been completed.

Studies on the effectiveness of conservative surgery for endometriosis-related pain are controversial. There is a significant rate of symptom recurrence after conservative surgery for endometriosis,

with one study reporting a 50% risk of re-operation at 5 years [11]. In a Canadian RCT (n=29) with 1 year outcome data on 15 patients, where conservative surgery for endometriosis was compared to placebo laparoscopy (with diagnostic biopsy only), pain reduction was 45% in the surgery group and 33% in the placebo group which was not significantly different [14]. However, in the Cochrane review, meta-analysis of another three RCTs comparing conservative surgery to placebo laparoscopy clearly demonstrated that surgical treatment did significantly improve pain at 6 months [15]. This cannot be overlooked, as these were blinded placebo-controlled trials, and such trials for other pelvic pain procedures are either not available (e.g. for uterine suspension) or have shown no impact (e.g. for laparoscopic uterosacral nerve ablation (LUNA) [16]). Notably, the Canadian trial was not combined with the other three RCTs in the meta-analysis [15], seemingly due to differences in how pain outcomes were measured. Based on this Cochrane analysis, the weight of randomized trial evidence appears to support a benefit of conservative surgery for endometriosis pain.

There is also evidence that conservative surgery for endometriosis can increase pregnancy rates in women with infertility; however, assisted reproductive technology (ART) such as in vitro fertilization (IVF) also improves pregnancy rates in endometriosis-associated infertility [17] and some prefer empiric ART to surgical treatment of endometriosis. As well, surgical excision of ovarian endometriosis cysts may reduce ovarian reserve and negatively affect ovarian stimulation, although the impact on ART pregnancy rates is less clear [17,18]. On the other hand, a Cochrane review of two RCTs for conservative surgical treatment of minimal-mild endometriosis for infertility did show a fertility benefit for surgery [19] (although on their own, only one study showed a difference [20]). The results of the meta-analysis are modest (NNT=12), but again cannot be overlooked as surgical treatment was compared to placebo laparoscopy. In addition, larger endometriosis cysts are unlikely to resolve on their own and can present technical challenges for IVF [21], with the most recent committee opinion for the American Society for Reproductive Medicine stating that surgery should be considered for endometriosis cysts >4cm in women planning IVF [22]. Furthermore, surgical excision of endometriosis cysts is known to increase the odds of spontaneous pregnancy in randomized trials [23]. Therefore, surgery for endometriosis and endometriosis ovarian cysts remains a viable option for selected women who prefer a surgical approach to infertility.

Perhaps some of the controversy is that the outcomes of interest, pain and infertility, are outcomes where it can be difficult to achieve an absolute "success". Patients with endometriosis can have a multifactorial

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origin of their pain (e.g. painful bladder, irritable bowel, musculoskeletal dysfunction, neuropathic pain, or psychological comorbidity) [24,25], and such patients are unlikely to be completely pain-free with conservative surgery alone. Infertility is also multifactorial, and no treatment for infertility will ever be 100% successful in achieving pregnancy, with even IVF having limits for per-cycle pregnancy rates [26]. Thus, perhaps expectations for endometriosis surgery need to be more realistic.

Moreover, there is debate on the best method for conservative surgery, with RCTs showing no significant differences between excision and ablation of endometriosis (possibly due to insufficient power) [27,28]. But perhaps the focus should be less on the method of conservative surgery, and more on the degree to which the endometriosis was completely treated. For example, one observational study found that complete conservative surgical treatment of endometriosis resulted in higher pregnancy rates, compared to incomplete surgical treatment that left visible residual disease [29]. Thus, the key factor may be the surgeon completely treating all visible endometriosis (regardless of method). Hence, one would expect that ablation and excision of minimal-mild superficial endometriosis would be equivalent, since both methods can completely treat such lesions. In contrast, excision is likely to be superior for the complete treatment of moderate-to-severe deeply infiltrating endometriosis. More studies are needed to confirm whether the concept of complete treatment (“optimal debulking”) applies to endometriosis as it does to gynecologic cancers.

In conclusion, we propose that endometriosis remains a surgical disease but with many subtleties and controversies. More research is needed to refine the role of surgery in endometriosis. In the future, endometriosis may be diagnosed by non-invasive means, and novel disease-modifying drugs may become available, but until then, surgery remains indispensable to the diagnosis and management of endometriosis.

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