

The Efficacy of Excision Surgery as Treatment for Endometriosis

Deborah Seymour

University of Connecticut

Advanced Pathophysiology

NURS-5060

Kyle Baumbauer

December 16, 2015

The Efficacy of Excision Surgery as Treatment for Endometriosis

"Endometriosis is one of the most treatable, but least treated of women's health problems"

Padma Lakshmi, international supermodel, TV show host, and co-founder of the Endometriosis Foundation of America.

Introduction

Endometriosis is a common but enigmatic disease, affecting only women, and appearing within the reproductive years. For such a widespread disease it is frustratingly misunderstood and causes immense pain and suffering to the women who are misfortunate enough to be diagnosed with it. Treatments are disappointingly ineffective and few, and the treatments that are available are uncomfortable, fraught with side effects and largely unsuccessful. The symptoms that lead to diagnosis are vague and varied, and this contributes to either a delay in diagnosis or a complete failure of diagnosis altogether. Because the disease is so misunderstood despite the size of the affected population, education about the disease is extremely lacking or non-existent. Years and years of my own suffering, diagnosis, surgeries and subsequent research, has led to my deep understanding of this disease, and because of this I hope to use this knowledge to educate and help other women who suffer from it. I started my website, angryuterus.com, in 2007 in order to address the lack of good and reliable information available to newly diagnosed women, or even women who just suspected they had the disease. My experiences showed me that the advice and treatment coming from medical professionals and providers was inadequate, and I wanted to encourage women to educate themselves in order to be able to make better choices that preserved their health.

“If you are a gynecologist dealing with endometriosis, you know the trite drill dictated by conventional wisdom: in the office diagnose pelvic pain as a sexually transmitted pelvic inflammatory disease (PID) and treat with antibiotics; diagnose recurrent pelvic pain as recurrent PID in a woman with loose morals and treat again with antibiotics;...what is wrong with this picture? Modern therapy of endometriosis has become unimaginative, rigid and dogmatic” (David Redwine, 2015).

Dr. David Redwine, the founder of the Oregon Institute of Endometriosis at St. Charles Medical Center, Bend, Oregon, is the leading pioneer of the gold standard of excision surgery for endometriosis, and after his retirement in 2012 he has continued to advise patients and share his knowledge and experience through his website endopaedia.com. It was his vision that led to the only effective treatment for endometriosis, and his research drives the content of this paper.

Pathophysiology

Endometriosis is defined as ectopic hormonally-responsive endometrial implants in the pelvic/extra-uterine cavity that affects 6-10% of women of reproductive age (Burney, et al., 2012), an estimated 176 million women worldwide (Adamson, 2011). The American Society for Reproductive Medicine states that endometriosis can be found in 24 to 50 percent of women who experience infertility (ASRM, 2015). It causes severe pelvic pain, menorrhagia, dysmenorrhea, infertility, GI issues, fatigue, dyspareunia, back pain and abdominal bloating. It is a benign disease but shares similar features with malignancies, in that cells migrate to other areas and implant themselves and grow ectopically. This can cause significant distortion and disfigurement of internal organs and structures.

The lesions seen in endometriosis are comprised of endometrial cells. They are hormone-responsive and so despite whichever structure they adhere to they continue to respond to hormonal signals during the menstrual cycle. When a woman starts her menses these implants can also bleed wherever they are, causing pain, scarring and adhesions through the pelvic cavity. Lesions may travel to the entire pelvic wall, uterine ligaments, lining of the uterus (adenomyosis), ovaries, bladder, bowel and even the lungs and brain. Lesions on the ovaries can form endometriomas, cysts filled with blood, that may rupture causing significant pain when the dark, old and sticky contents are spewed throughout the pelvic cavity.

The reason that endometriotic lesions seem to be so pervasive is because of neoangiogenesis at the site of the lesions and that they appear to proliferate in an inflammatory environment. Experiments in mice given antiangiogenic drugs showed a decrease in size of lesions (Ahn, et al., 2015). Pro-inflammatory cytokines such as TNF- α , IL-6, and IL-8 are increased in the peritoneal fluid in women with endometriosis, and now IL-17A has also been shown to have a role in the pathogenesis of autoimmune diseases and in tumor formation and could be present in peritoneal fluid of women with endometriosis as well (Ahn, et al., 2015).

Interestingly, research has shown to suggest that eutopic endometrium behaves differently in women with endometriosis at a molecular level, and then when endometrial cells escape into the pelvic cavity, and become ectopic infiltrates, the immune system does not recognize them as foreign, allowing them to grow unhindered in aberrant areas (Ahn, et al., 2015). These lesions are not just adaptive, as a malignancy might be, but also create their own blood and hormone supply and are often innervated (Johnson, 2013). This allows the lesions to proliferate and make them harder to detect and treat.

The mesothelium is a protective membrane inside the pelvic cavity, and it would normally be impenetrable to infiltrative cells, but in endometriosis it has been shown that endometriotic lesions are able to infiltrate the mesothelium at sites that show signs of damage. It has not been proven that these lesions occur as a result of injury, or if they indeed cause the injury due to the irritation of the menstrual contents (Burney et al., 2012).

Endometriosis does not just cause physical or structural problems, but also more vague and systemic problems such as fatigue and flu-like symptoms, suggesting that there is indeed an immune response. Studies show that abnormal immune processes and responses to female hormones are altered in women who go on to develop endometriotic lesions in the peritoneal membrane (Ahn, et al., 2014).

Etiology

Endometriosis was originally described by Sampson as being due to “retrograde menstruation”, a term coined for the theory that uterine cells were forced back along the fallopian tubes into the reproductive system during menses producing endometrial implants that caused pain and infertility. This theory, however, assumed that endometriosis was merely an autotransplant of tissue that behaved normally in places where it shouldn’t be, and did not account for what we now know as autoimmune dysfunction. An autotransplant is the relocation of tissue from one part of the body to another, either by a disease process or from surgical means (Redwine, 2002). Retrograde blood flow cannot be assumed to be the cause of endometriosis as this phenomenon can be seen during laparoscopy in 90% of women that are experiencing menses (Dmowski, 1991).

Another leading excision specialist, Dr. Camran Nezhat, describes endometriosis as an ancient disease, with examples of endometriosis-like symptoms being reported 4,000 years ago, and these symptoms were described in the middle ages as hysterical outpourings from women with “mad and immoral” imaginations (Nezhat et al., 2012). It appears not much has changed in this perception. The invisibility and cyclical nature of these symptoms make it an elusive and difficult concept to understand, and women were often described as being “hysterical”, a word which has connotations with the Greek word for uterus: hystera. Today, women report that their symptoms are often dismissed or described by their physicians as “in their heads” and it is common for women to be prescribed anti-depressants as an answer to their pain.

The true and definitive cause of endometriosis is not known, and new theories that it is an autoimmune disease are changing the way in which this disease is viewed and treated. Women with endometriosis show fundamental differences in genetic, immunological, or biochemical factors that may contribute to the development of the disease, (Ahn, et al., 2014).

There are also genetic influences involved in the development of endometriosis and studies show that women who have a first degree relative with the disease are six times more likely to develop it themselves (Ahn, et al., 2014). A recent discovery at Yale University has identified an inherited mutation located in part of the KRAS gene that leads to abnormal endometrial growth and an increased risk of developing the disease (Peart, 2012).

Environmental factors may also influence the development of endometriosis. Chemical compounds such as dioxins, found in pesticides and plastics, have been linked to the development of endometriosis. A study on primates in Madison, WI showed that when the

monkeys were exposed to increasing levels of dioxins, the severity of endometriosis increased also (Gibbons, 1993).

Endometriosis increases the risk of ovarian cancer and appears in 3.4 - 52.6% of women who are diagnosed with endometriosis (Heidemann, 2014). One third of endometriosis patients showed an inflammation profile similar to those with cancer, suggesting that cancer-like immune similarities may develop early in women with endometriosis (Suryawanshi et al., 2014). This highlights the importance of removing endometriotic lesions in totality, rather than leaving them to grow and possibly progress into malignancy.

Clinical Presentation

Women frequently present with painful periods, chronic pelvic pain and infertility, and are frequently accompanied with associated back/hip/leg pain, fatigue, and bowel and bladder problems. Misdiagnoses are common, with many women being told they have interstitial cystitis, irritable bowel disease, or just that they have “normal” period pain. It is not uncommon to have women having several presentations to several different doctors over many years complaining of non-specific symptoms. Diagnosis is often delayed because of the difficulty of diagnosing the disease which is only done with direct visualization and biopsies of the lesions during a diagnostic laparoscopy. A study from the UK showed that average delay in diagnosis was 9.41 years (Hadfield, et al., 1996). Using only visualization without histological specimen can lead to a false-positive rate of around 50%, especially in women with more mild disease (Wykes et al., 2004).

Diagnosis

Endometriosis is classified into four stages by The American Society for Reproductive Medicine. Stage I is described as minimal lesions through to Stage IV which signifies deep infiltrating disease with severe adhesions and anatomic distortion. The gold-standard method for diagnosis of endometriosis is a diagnostic laparoscopy, where a camera is inserted into the pelvic cavity where lesions may be visualized and biopsied. Endometriosis can be definitely diagnosed by histological specimens removed at surgery as well as visual grading of obvious and microscopic lesions. Initial lesions may be identified as white peritoneal plaques. Other lesions may appear as brownish specks, termed powder burn. Scarring, fibrosis and hemorrhaging with adhesions may accompany these.

Magnetic resonance imaging scans (MRI), Computed Tomography (CT) and x-ray are unable to detect endometriosis lesions and so are ineffective as a diagnostic tool.

Ultrasonography may be useful in diagnosis of endometriomas and adenomyosis (endometriosis in the lining and walls of the uterus) but the gold-standard is pathology specimen following biopsy during surgery.

Inflammation is also a key influence in the disease. It has not been proven whether inflammation is a cause or an effect in affected women. Often the C - reactive protein marker (CRP) is elevated but this is non-specific to endometriosis and is only a generalized indication of inflammation and so cannot be definitely used as a diagnostic result. A CA-125 may also be indicative of inflammation but can also be a marker of ovarian cancer. It may be useful in differentiating between endometriomas and ovarian tumors but again is not specific. A CA-125

may also be elevated in women with endometriosis, leading to further investigations and procedures to rule out malignancy.

Treatment

Many women with endometriosis are offered synthetic hormones as a first-line treatment in the form of birth control in an attempt to suppress ovulation. Unfortunately, these do not have a good record of success and have severe side effects that can leave a woman feeling sicker than she did before. If the birth control offered contains estrogen, it can compound the problem and exacerbate the symptoms because endometriosis is an estrogen-fed disease. Symptoms of these side effects can include increased pain, bleeding and mood changes. Synthetic progestins may also be offered as treatment but they too have side effects, such as bleeding, weight gain, water retention and mood changes as well as having an adverse effect on fertility. Progestins mimic progesterone but are not bio-identical and so the side effects cannot be mitigated.

Some good anecdotal results have been reported using natural bio-identical progesterone, but the best results have occurred in tandem with removal of all xeno-estrogenic compounds from the environment simultaneously, although the literature reveals very little in the way of organized trials. Xeno-estrogens are compounds that imitate estrogen and have been found in many modern environmental items such as food containers, pesticides, household chemicals and plastics. Further good results have been shown to occur with radical changes in diet, with removal of inflammatory foods such as animal proteins and processed foods, and in particular, wheat. Despite the fact that there have been no randomized trials into the connection between diet and disease, the work of leading nutritionist Dian Shepperson-Mills in the UK has shown great promise and warrants further investigation.

Other hormonal treatments, such as Danazol, an androgen that suppresses the production of gonadotropins are offered as second-line medical treatments, but can cause unfortunate masculinization such as hair growth and lowering of the voice which are irreversible. Perhaps the most notorious of all hormonal treatments offered to endometriosis patients is Lupron (leuprolide acetate for depot suspension - a pituitary GnRH receptor agonist), that inhibits the secretion of gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and plunges women into a medical menopause. Although some women do find temporary relief, the side effects are severe and are often irreversible. Bone loss can occur, along with depression, bone pain, fatigue, hot flashes, memory loss and insomnia. Another negative effect of Lupron is its transient action. Because of the bone loss potential it can only be prescribed for short periods of up to 6 months, and when the cycle ends the disease returns, while the side effects remain. There is currently a petition to the US Congress to investigate Lupron and its wake of injured and disabled women. A review of Lupron by the FDA in 1999 failed to take action and so women continue to unwittingly take a treatment that is not only transient in its effectiveness, but has the potential to harm them. “No medicine eradicates endometriosis, and medicine treats only the symptoms, not the disease” (Redwine, 2000).

Hysterectomy is the surgical removal of the uterus. There are different types of hysterectomy that have different approaches or remove varying amounts of the reproductive organs. Partial hysterectomy is the removal of the uterus above the cervix. Total hysterectomy is removal of the uterus and cervix, and can be done either laparoscopically through the vagina (laparoscopically assisted vaginal hysterectomy, or LAVH), or via an abdominal incision. Hysterectomy with bilateral salpingo-oophorectomy is the removal of the uterus, cervix,

fallopian tubes, and ovaries. Radical hysterectomy is the removal of the uterus, cervix, ovaries, fallopian tubes, part of the upper vagina and surrounding lymph nodes.

Hysterectomy is commonly offered to women with endometriosis due the misconception that endometriosis symptoms are of uterine origin and that if menstruation is stopped, then the disease process will also be stopped. While it is true that endometriosis lesions are comprised of endometrial cells, the disease is actually extra-uterine: outside of the uterus. Endometriosis within the uterus itself is known as adenomyosis, a rarer variation of endometriosis. While adenomyosis sufferers may benefit from hysterectomy, endometriosis sufferers may not. Lesions can continue to reappear and grow in the pelvic cavity and scarring and adhesions may continue. Unless the microscopic lesions are removed in totality they will continue to proliferate unhindered. Lesions that are left behind are most likely the cause of recurrent symptoms post-surgery, if they have not been excised deeply enough (Rizk, et al., 2014).

Part of the reason for this is that lesions left behind will continue to responsive to estrogen from ovaries that are retained. Although oophrectomy can assist in reducing the effect of the lesions, the side effects of surgically induced menopause can be severe and disabling for women. Any estrogenic hormone replacement therapy given to reduce those side effects can once again feed the disease and so the woman is left to deal with the side effects unopposed, making her feel worse than before. Removal of the ovaries (oophrectomy) may still not reduce the activity of the lesions and so the outcome can be hard to predict. This would suggest that complete excision of endometriosis is a more reliable way of removing the disease, rather than the ovaries themselves, and would prevent the unpleasant effects of surgically induced menopause. Dr. David Redwine noted in a study that invasive disease on the uterosacral

ligaments or the GI tract may remain symptomatic if the lesions are not removed deeply or completely enough, even after oophrectomy (Redwine, 1994).

Laparoscopic excision is heralded as the gold-standard of treatment for endometriosis (Endometriosis.org). There are two types of surgical laparoscopic treatments for endometriosis: ablation and excision. Prior methods of surgically treating endometriosis included thermal ablation with laser vaporization or electrocoagulation which do not penetrate the lesions deeply enough. Using ablation either fails to remove disease completely, or only partially removes it causing scarring and further adhesions because it only superficially burns off the top layer of the lesions, rather than penetrating deeply. However, importance of early intervention is key, as the risk of repeat surgeries in women under the age of 30 at time of diagnosis is high (Shakiba et al., 2008).

Deeply invasive disease is indicative of more painful and established lesions, and often contributes to a poorer outcome if not removed in entirety during surgery. These deeper lesions strongly correlate with more pelvic pain and complaints of dyspareunia than superficial lesions (Garry, 1997). Old, hard, fibrotic lesions may be overlooked by a less experienced surgeon but in fact contain active endometriotic glandular tissue and are more clinically significant than more easily visible superficial lesions. In order to remove them effectively, deep excision techniques must be used. Deep excision may be done using sharp scissors, monopolar or bipolar electrosurgery, and laser by an experienced endometriosis excision specialist, of which there are significantly few in the United States. Excision surgery is a time-consuming specialist surgery that may require the presence of other specialist surgeons (such as GI) in the operating room as an adjunct, and so is less cost-effective than hysterectomy (You, 2006). Peritoneal excision has

also been shown to be a faster method of surgery and leave behind no necrotic areas which have a risk of encouraging fibrin deposits (Wood, et al., 1996).

Currently, there is not enough evidence to support or refute claims that excision is more or less effective than ablation (Healey, 2010). A study in Australia, one of the few trials that compared the efficacy of the two treatments, was inconclusive in its results. The study participants (N=178) presented with various forms of dysmenorrhea and dyspareunia and were divided into two groups; one underwent excision and one ablation (N=89). All were diagnosed intraoperatively and staged at the time of surgery. None of the women were taking any kind of hormone therapy at the time of the study. The outcome was evaluated by comparing their visual analogue scale (VAS) scores before and after surgery (at 1 year) by *t-test*. The study was unable to reject the null hypothesis that excision surgery would not show a greater improvement, although there were some statistically non-significant improvements in overall pain ($p=0.17$). Healey suggested that this was due to flaws in the study, particularly that the participant group was too small and should comprise of at least 220 subjects per group. Also, the exclusion criteria excluded women who had obvious disease involving the muscle levels of bowel, bladder, or ureter, and these are the very patients that might prove to benefit most from excision surgery.

However, another Australian trial by Abbott showed that women who received immediate excision at time of diagnosis, versus women who received only a diagnostic laparoscopy initially followed by excision after 6 months, had a much better outcome 12 months post-surgery ($P=.0001$). Out of the women in the delayed treatment group, 45% had worsening of their disease in the interim period between diagnosis and excision. This might signify that early excision at time of diagnosis would be a more effective way of stopping disease

progression. However, that would require a larger amount of excision specialist surgeons to be available in every area, and this has not proved to be forthcoming.

A further study that investigated the usefulness of using infliximab, a TNF- α inhibitor, in conjunction with excision surgery noted that while infliximab was not significant in reducing pain, excision surgery was confirmed by the study as being efficacious. (Koninckx et al., 2012).

It has been shown that excision of endometriomas is more effective than mere ablation and can minimize occurrence, but only if the excision used is precise and minimizes destruction of the ovary and its surrounding tissue (Hart et al., 2008).

Conclusion

Unfortunately, there is little in the way of randomized trials to support evidence of the efficacy of excision surgery being more effective than other treatments due to the lack of specific studies, however there is enough evidence to support that there is a large potential for it to be effective and that more studies are needed. There appears to be many small, unconnected studies that all point to excision being the most effective treatment, but what is needed is a large randomized trial that is inclusive of many types of endometriosis patients with varying levels of disease. Meta-analysis does indeed support the finding that excision is successful in providing good outcomes, especially in terms of restoring and preserving fertility (Jacobson et al., 2010).

There is a small subsection of surgeons who truly believe that their work and specialization help more women, more effectively, and for longer periods, and this has created an underground of endometriosis sufferers worldwide who seek the help of such a specialist. This has resulted in a large internet presence that proliferates the notion that in order to find relief one must travel far from home to seek help.

I believe that the initial diagnosing gynecologist should limit surgery on those women who are seen to have deep infiltrating disease and refer them on to a specialist for further examination to reduce the amount of harmful or ineffective surgeries that may have poor outcomes due to poor excision techniques, as it has been shown that first definitive surgical intervention has the best outcomes (Abbott et al., 2004).

It is obvious that a multi-faceted approach is needed to treat endometriosis, and that one single treatment is not enough on its own, but excision surgery is the most effective way to remove the deep, invasive lesions that are associated with the most pain. I believe the literature does support the efficacy of excision based on independent surgeons' research and data, and so I think that this work warrants further investigation into the efficacy of excision. "Symptom relief is excellent and fertility is not compromised by excision" (Redwine, 2000).

References

- Abbott, J. A., Hawe, J., Clayton, R. D., & Garry, R. (2003). The effects and effectiveness of laparoscopic excision of endometriosis: a prospective study with 2–5 year follow-up. *Human Reproduction*, *18*(9), 1922-1927.
- Abbott, J., Hawe, J., Hunter, D., Holmes, M., Finn, P., & Garry, R. (2004). Laparoscopic excision of endometriosis: a randomized, placebo-controlled trial. *Fertility and sterility*, *82*(4), 878-884.
- Adamson, G. D. (2011). Endometriosis classification: an update. *Current Opinion in Obstetrics and Gynecology*, *23*(4), 213-220.
- Ahn, S. H., Edwards, A. K., Singh, S. S., Young, S. L., Lessey, B. A., & Tayade, C. (2015). IL-17A contributes to the pathogenesis of endometriosis by triggering proinflammatory cytokines and angiogenic growth factors. *The Journal of Immunology*, *195*(6), 2591-2600.
- Ahn, S. H., Monsanto, S. P., Miller, C., Singh, S. S., Thomas, R., & Tayade, C. (2014). Pathophysiology and Immune Dysfunction in Endometriosis. *BioMed Research International*.
- Brown, J., & Farquhar, C. (2015). An Overview of Treatments for Endometriosis. *JAMA*, *313*(3), 296-297.
- Burney, R. O., & Giudice, L. C. (2012). Pathogenesis and pathophysiology of endometriosis. *Fertility and sterility*, *98*(3), 511-519.
- Dmowski, W. (1991). Etiology and histogenesis of endometriosis. *Annals of the New York Academy of Sciences*, *622*(1), 236-241.

- Garry, R. (2004). The effectiveness of laparoscopic excision of endometriosis. *Current Opinion in Obstetrics and Gynecology*, 16(4), 299-303.
- Garry, R. (1997). Laparoscopic excision of endometriosis: the treatment of choice? *BJOG: An International Journal of Obstetrics & Gynaecology*, 104(5), 513-515.
- Gibbons, A. (1993). Dioxin tied to endometriosis. *Science*, 262(5138), 1373-1373.
- Hadfield, R., Mardon, H., Barlow, D., & Kennedy, S. (1996). Delay in the diagnosis of endometriosis: a survey of women from the USA and the UK. *Human Reproduction*, 11(4), 878-880.
- Hart, R. J., Hickey, M., Maouris, P., & Buckett, W. (2008). Excisional surgery versus ablative surgery for ovarian endometriomata. *The Cochrane Library*.
- Healey, M., Ang, W. C., & Cheng, C. (2010). Surgical treatment of endometriosis: a prospective randomized double-blinded trial comparing excision and ablation. *Fertility and sterility*, 94(7), 2536-2540.
- Heidemann, L. N., Hartwell, D., Heidemann, C. H., & Jochumsen, K. M. (2014). The relation between endometriosis and ovarian cancer—a review. *Acta obstetrica et gynecologica Scandinavica*, 93(1), 20-31.
- Jacobson, T. Z., Duffy, J., Barlow, D. H., Farquhar, C., Koninckx, P. R., & Olive, D. (2010). Laparoscopic surgery for subfertility associated with endometriosis. *The Cochrane Library*.
- Johnson, N. P., Hummelshoj, L., Abrao, M. S., Adamson, G. D., Allaire, C., Amelung, V., ... & de Bie, B. (2013). Consensus on current management of endometriosis. *Human Reproduction*, 28(6), 1552-1568.

- Koninckx, P. R., Craessaerts, M., Timmerman, D., Cornillie, F., & Kennedy, S. (2008). Anti-TNF- α treatment for deep endometriosis-associated pain: a randomized placebo-controlled trial. *Human Reproduction*, 23(9), 2017-2023.
- Laufer, M. R., & Missmer, S. A. (2011). Does complete laparoscopic excision of endometriosis in teenagers really occur?. *Fertility and sterility*, 96(3), e145.
- Ness, R. B. (2003). Endometriosis and ovarian cancer: thoughts on shared pathophysiology. *American journal of obstetrics and gynecology*, 189(1), 280-294.
- Nezhat, C., Nezhat, F., & Nezhat, C. (2012). Endometriosis: ancient disease, ancient treatments. *Fertility and sterility*, 98(6), S1-S62.
- Peart, K. (2012). Gene mutation discovery sparks hope for effective endometriosis screening. Retrieved December 16, 2015, from <http://news.yale.edu/2012/02/06/gene-mutation-discovery-sparks-hope-effective-endometriosis-screening>
- Redwine, D. (2012). Embracing the challenge of complete excision surgery, the gold standard of endometriosis treatment. Retrieved December 15, 2015, from <http://endopaedia.info/treatment25.html>
- Redwine, D. B. (1994). Endometriosis persisting after castration: clinical characteristics and results of surgical management. *Obstetrics & Gynecology*, 83(3), 405-413.
- Redwine, D. B. (2000). Excision of pelvic endometriosis. *International Journal of Gynecology & Obstetrics*, 70, C5.
- Redwine, D. B. (2002). Was Sampson wrong?. *Fertility and sterility*, 78(4), 686-693.

- Rizk, B., Fischer, A. S., Lotfy, H. A., Turki, R., Zahed, H. A., Malik, R., ... & Herrera, D. (2014). Recurrence of endometriosis after hysterectomy. *Facts, views & vision in ObGyn*, 6(4), 219.
- Shakiba, K., Bena, J. F., McGill, K. M., Minger, J., & Falcone, T. (2008). Surgical treatment of endometriosis: a 7-year follow-up on the requirement for further surgery. *Obstetrics & Gynecology*, 111(6), 1285-1292.
- Soares, S. R., Martínez-Varea, A., Hidalgo-Mora, J. J., & Pellicer, A. (2012). Pharmacologic therapies in endometriosis: a systematic review. *Fertility and sterility*, 98(3), 529-555.
- Surgery : Endometriosis.org: Global information and news. (2015). Retrieved December 18, 2015, from <http://endometriosis.org/treatments/endometriosis-surgery/>
- Suryawanshi, S., Huang, X., Elishaev, E., Budiu, R. A., Zhang, L., Kim, S., ... & Lee, T. (2014). Complement pathway is frequently altered in endometriosis and endometriosis-associated ovarian cancer. *Clinical Cancer Research*, 20(23), 6163-6174.
- The American Society for Reproductive Medicine. *Endometriosis*. (2015). Retrieved December 15, 2015, from https://www.asrm.org/BOOKLET_Endometriosis/
- Wood C, Maher P. Peritoneal surgery in the treatment of endometriosis—excision or thermal ablation? *Aust NZ J Obstet Gynaecol* 1996;36:190–7.
- Wykes, C. B., Clark, T. J., & Khan, K. S. (2004). REVIEW: Accuracy of laparoscopy in the diagnosis of endometriosis: a systematic quantitative review. *BJOG: An International Journal of Obstetrics & Gynaecology*, 111(11), 1204-1212.
- You, J. H., Sahota, D. S., & MoYuen, P. (2006). A cost-utility analysis of hysterectomy, endometrial resection and ablation and medical therapy for menorrhagia. *Human Reproduction*, 21(7), 1878-1883.