

2018

# Among Patients with Endometriosis, Does the Use of Serum Biomarkers, Versus Laparoscopic Surgery For Diagnosis and Staging of the Disease Decrease the Incidence of Disease Related Negative Outcomes

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Among Patients with Endometriosis,  
Does the Use of Serum Biomarkers, Versus Laparoscopic Surgery  
For Diagnosis and Staging of the Disease  
Decrease the Incidence of Disease Related Negative Outcomes

By

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Paper Submitted in Partial Fulfillment

Of the Requirements for the Degree

Of Master of Science Physician Assistant Studies

Augsburg University

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## Abstract

*Objective:* To determine the ability and efficacy of non-invasive serum biomarker testing as a replacement for laparoscopic surgery in the diagnosis and staging of endometriosis to decrease the incidence of negative disease outcomes, leading to improvement in the accuracy of diagnoses and patient tailored treatment protocols.

*Background:* Endometriosis is a debilitating inflammatory disease of the reproductive tract. Currently, the gold standard for the diagnosis and staging of endometriosis is exploratory laparoscopic surgery. The use of surgery as the source of achieving a definitive diagnosis holds the potential to increase the incidence of negative disease outcomes. Because of this, the use of peripheral serum biomarkers for the initial diagnosis of endometriosis is being explored as a non-invasive diagnostic option to decrease the incidence of negative disease outcomes.

*Methods:* Articles used were retrieved from PubMed, Google Scholar, Cochrane, Science Direct and UpToDate. Additionally, two individuals who had been surgically diagnosed with endometriosis were interviewed via email.

*Conclusion:* The potential of serum biomarkers as an alternative to laparoscopy to diagnose and stage endometriosis in order to decrease the incidence of negative disease outcomes cannot be ignored. When weighed against the potential risks of surgery, as well as the high incidence of disease recurrence after conservative ablative procedures, peripheral serum biomarkers should be considered the forefront of endometriosis research in order to improve patient outcomes. To achieve this, the scientific community must work in close collaboration with each other, as well as become proficient in the clinical findings of endometriosis in order to achieve adequate and tailored patient centered care.

## Introduction

Endometriosis is an exquisitely painful disease that does not discriminate; it is known to affect females of all ages, races and lifestyles. The migration of endometrial glands and stroma outside of the uterine cavity has the potential to cause a broad range of symptoms and degrees of debilitation including, but not limited to, chronic pelvic pain, dysmenorrhea, dyspareunia and infertility.<sup>1</sup> Endometrial lesions have been discovered in the pelvis, bowel, diaphragm and the pleural cavities of patients affected, providing greater support to the insidious nature of this disease.<sup>1</sup>

The American Society for Reproductive Medicine Practices Committee, which was cited by Schenken R.S. et al, states that “endometriosis should be viewed as a chronic disease that requires a lifelong management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgeries.”<sup>2</sup> However, the current diagnostic, staging, and therapeutic gold standard treatment protocol for endometriosis is carried out primarily by exploratory laparoscopic surgery, which often carries the weight of multiple surgical procedures throughout a patient's lifetime.

It is well known that surgery does not come without risks to the patient, and endometriosis patients are forced to take these risks over and over again. This is to both achieve the documented diagnosis of endometriosis so that their treatment costs can be covered by insurance, and to attempt to remove the endometrial tissue and associated adhesions to decrease their daily burden of chronic pain and infertility.

The repeated surgical procedures being performed on these patients, along with the associated experienced risks by said patients including scarring, adhesions, subsequent bowel

resection and colostomy and an increased risk of infertility, above the level of infertility presented by the endometriosis itself, begs the question, is there any other way to diagnose and treat these women that is less invasive and potentially more accurate in order to decrease their surgical burden?

New research being conducted related to the presence of specific biomarkers may prove to resolve this question. Biomarkers only require simple, serial blood draws or urine samples to detect and measure the presence of elements of specific diseases. Not only are these biomarkers able to detect the presence of endometriosis, but they are also likely to provide insight into the pathogenesis of endometriosis itself; a mechanism of disease that has only been minimally identified and understood. Furthermore, these biomarkers have the potential to identify the stage of each individual patient's level of disease. Current research has specifically honed in to microRNA (miRNA) and interleukins due to their rolls in gene expression, immune responses to inflammation, stability and specificity to their translated disease and disease outcomes. With these findings, the possibility of non-invasive gold standard protocols being implemented in the diagnosis and treatment of endometriosis grows increasingly more likely and the risk to patients affected by this debilitating disease can begin to improve.

## Background

### Associated Prevalence & Risk

Although endometriosis has been a known and widespread cause of pelvic pain in patients, its degree of permeation is relatively undervalued in the clinical setting. However, through analysis of its diagnosis, it is made clear that endometriosis is a highly pervasive disease which

deserves more attention both clinically and surgically. An analysis of endometriosis as a whole revealed the following findings: in a cohort study of greater than 9500 women, 15 percent were diagnosed with endometriosis during benign hysterectomy procedures; 57 percent were diagnosed with endometriosis associated with pelvic pain, in which probable endometriosis was an exploratory surgical indication; 21 percent were diagnosed with endometriosis upon laparoscopic exploration with perioperative pelvic pain, non-specific, as the surgical indication; 8 percent were diagnosed with endometriosis as an incidental finding upon laparoscopic surgery without pelvic pain or endometriosis as a presumed differential diagnosis.<sup>1</sup>

Furthermore, as a result of this analysis, the prevalence of endometriosis in symptomatic patient referrals is vastly higher and was diagnosed in: 40 percent of adolescents with genital tract abnormalities; 50 percent of women experiencing clinically diagnosed infertility; 70 percent of adolescents and women presenting with pelvic pain.<sup>1</sup>

Through this analysis it can also be deduced that the ubiquity of endometriosis has historically been greatly underestimated. The occurrence of the disease that was found to be affecting the participants in this cohort study stands as a testament that endometriosis is a disease that deserves the greater attention of the scientific and medical communities to further support and treat patients – and a great amount of this attention is beginning to hone in on the idea that repetitive surgeries may not be the most beneficial option.

#### The Drawbacks of the Current Gold Standard

While laparoscopic surgery is the current gold standard, its treatment efficacy remains rather low. This low efficacy can be attributed to several aspects of the disease, along with the reality that the accuracy of diagnosis is strongly correlated with the type and position of each

endometriosis lesion, along with the skill and experience of the surgical team. Endometriosis implantation contains fibrous tissue, blood and cysts, unlike the endometrial tissue occurring in the uterus.<sup>1</sup> The red blood cells contained in these implantations are broken down by the body's inflammatory cells – this results in the formation of pigmented histocytes and hemosiderin-laden macrophages at the areas of implantation.<sup>1</sup> Therefore, the more advanced the lesion is, the darker its pigment appears when visualized via laparoscopic surgery. The actual appearance of the endometrial lesions is extremely variable at any point in surgery, often leading to the retention of multiple implantations after therapeutic surgical intervention (i.e. multiple surgeries can be diagnostic, but do not lead to maximum therapeutic outcomes).<sup>1,3</sup>

Problems with the laparoscopic method also translate to the staging of excised endometrial lesions. The glandular components of the lesions are often absent, sparse, or have been transformed by hormonal and metaplastic changes or cellular atypia.<sup>1</sup> The stromal component is often masked by infiltrates of foamy and pigmented histocytes, fibrosis, or other immune modulated processes.<sup>1</sup> Inflammatory processes do not only occur in the adhesions themselves, but can also occur in the surrounding tissues, causing diagnosis and staging of lesions to be very difficult via laparoscopic visualization.<sup>1</sup>

Although exploratory laparoscopic surgery exists as the current gold standard for the diagnosis and staging of endometriosis, it is not uncommon for it to take years for a patient to reach the point of being offered a surgical procedure for diagnostic and therapeutic indications. This is primarily due to the need for concrete surgical indications, as endometriosis is still painfully underrecognized clinically. In an interview with a patient, referred to as D.D., currently being treated for endometriosis, she stated “It took about 2 years to finally diagnose that I had endometriosis [via laparoscopic surgery]”, “They removed my appendix, gall bladder, had me



eat gluten free until they finally referred me to a gynecologist who did the laparoscopic surgery to see if it was endometriosis.” In another patient interview, referred to as R.S., she stated that she had been struggling with severely painful menstrual cycles since she was 14 years old. After struggling with fertility and continued chronic pelvic pain, she decided to undergo a uterine ablation and tubal ligation, per her gynecologist’s recommendations. It was during this surgery that her endometriosis was discovered at the age of 49. RS had suffered with this debilitating disease without a true diagnosis for 35 years. Through further analysis of the literature of endometriosis including personal accounts, this is unfortunately not uncommon. The surgical indications for endometriosis include persistent pain despite medical therapy, contraindications to, or refusal of, medical therapies including hormonal contraceptives, the need for exclusion of malignancy based of symptoms and/or family history, or signs and symptoms of an obstruction of the bowel or urinary tract.<sup>3</sup>

The road to a diagnosis of endometriosis can be clearly seen to lead to an increase in the duration of suffering for patients, both physically and emotionally. Further along in the above-mentioned patient interview, D.D. stated “Someday, not being able to have kids. Also struggling to lose weight has been very difficult” when asked what troubles her the most in her struggle with endometriosis. She also expressed a great deal of frustration in the delay of her endometriosis diagnosis, leading to several unnecessary surgeries during her adolescent and young adult years.

Several common negative outcomes of laparoscopic surgery include bowel and bladder injury (which requires additional surgical management), reduction of ovarian reserve leading to an increase in infertility, and the formation of adhesions. While this list is not comprehensive, and will be discussed further in later paragraphs, it should be mentioned that there is a definite

place for therapeutic surgical interventions of endometriosis. A 2014 systematic review and meta-analysis for 10 laparoscopic surgical trials for endometriosis diagnosis and treatment compared conservative versus invasive surgical methods.<sup>3</sup> In this analysis, conservative surgery, or ablation, was defined as the “eradication of endometrial lesions through the use of laser vaporization, electrosurgical fulguration or ultrasonic cutting and coagulation, whereas invasive surgery, or excision, was defined as the “removal of lesions with laparoscopic scissors.”<sup>3</sup> This analysis revealed that conservative surgery decreased the overall pain experienced by patients by 73% (vs 21%) and increased live births or ongoing pregnancy rates by 30% (vs 18%) when compared to invasive diagnostic laparoscopic procedures.<sup>3</sup> Therefore, conservative surgical procedures are most often performed as both initial and follow up surgical measures for the diagnosis and treatment of endometriosis and they have been proven to be therapeutically beneficial. However, the same study also discovered that conservative surgery holds a higher rate of recurrence of endometriosis lesions and the rate of reoperation was found to increase over time. While therapeutic surgical treatment may decrease the pain of endometriosis in the short term for patients, it was found that close to 20 percent of these patients will require a repeat operation within two years of their initial surgical procedure due to the relapse of their endometriosis related symptoms.<sup>3</sup> This same risk of recurrence continues to hold fast at approximately 40 percent at 10 year follow up post-operatively.<sup>3</sup>

The risk factors involved in the recurrence rate of endometriosis in patients who have underwent laparoscopic surgery include the incomplete excision of the endometriosis lesions, the drainage of subsequent ovarian cysts, and elective ovarian conservation.<sup>3</sup> Furthermore, women with advanced disease have a decreased likelihood that their lesions would be completely excised during surgery. As an example of this, a multicenter prospective cohort study found that

women with stage III to stage IV endometriosis had higher rates of recurrence than women with disease stages of I to II at 2 years post operatively.<sup>3,4</sup> If it was possible for medical professionals to diagnose endometriosis earlier through the use of proposed serum biomarkers rather than exhausting all efforts to diagnose the cause of each patient's symptoms, only to eventually reach the conclusion years later through laparoscopic surgery once the disease was allowed to progress unchallenged, the doors open to the possibility of early diagnosis and subsequent earlier interventions, leading to the need to fewer necessary surgeries due to disease recurrence throughout a patient's lifetime.

The recurrence of endometriosis lesions is not the only draw back to laparoscopic surgery remaining the gold standard for the diagnosis of endometriosis. A vast number of women who undergo an initial laparoscopic surgery for diagnostic purposes, and later require additional surgeries, also suffer from negative surgical outcomes. In a systematic meta-analysis of randomized trials and cohort studies, it was found that approximately 20 to 40 percent of patients who have had laparoscopic surgery with a post-operative indication of pelvic pain, report chronic pain as a post-operative complication. This was found to be primarily due to the formation of adhesions.<sup>5</sup> These patients are subjected to an exploratory surgery due to persistent pelvic pain and a lack of a less invasive diagnostic option and are left with an increase in their pain due to another, and unfortunately iatrogenic, cause. This analysis goes further by stating "At present, there is little evidence to support routine use of adhesiolysis in treatment for chronic pain"<sup>5</sup> due to the risk of bowel injury and the number of negative laparoscopies, meaning that no signs of endometriosis were found, but that the patient was still left with post-operative complications including pelvic pain as a result of surgically induced adhesions.<sup>3,5</sup>

Another possible detrimental negative outcome to diagnostic laparoscopy is the risk of fenestrations, or inappropriate formed openings. One study which followed a 32 year old woman with debilitating symptoms of endometriosis throughout her surgical treatments discovered that initial exploratory laparoscopic surgery, which diagnosed endometriosis in her diaphragm, was the cause of the formation of fenestrations in her diaphragm. The formation of these fenestrations caused an increase in her already disabling symptoms.<sup>6</sup> The providers found that the use of ablative thermocoagulation techniques to remove the observed diaphragmatic endometrial lesions caused necrosis of tissue, leading to the need for a repeat surgery; an additional operation not to treat her endometriosis, but to treat a post-operative complication.<sup>6</sup> Another example of the need for a non-invasive method for the diagnosis of endometriosis.

Another inarguable aspect of endometriosis is the effect that it has on the quality of life of those living with the disease. Living with chronic pain, infertility, etc. elicits a great deal of emotional and physical fatigue. This decrease in quality of life due to the effects of endometriosis has been documented and studied and serves as an additional tool on the road to further research toward the finding of a non-invasive diagnostic tool for endometriosis. This is significant as it is not only the disease itself that causes these debilitating effects, but the current surgical gold standard contributions as well. A study which looked at women ages 18 to 49 years old from the year 2004 to 2013 who underwent either a laparoscopic therapeutic procedure or a hysterectomy as a result of their endometriosis specifically honed in on this decrease in quality of life.<sup>7</sup> The study found that of the 37,308 patients who underwent a therapeutic laparoscopy and the 24,915 patients who underwent a hysterectomy, all participants had an increase in both the number of hospitalizations and the duration of hospitalizations post operatively due to the inherent risks of these surgical procedures.<sup>7</sup> According to Surrey E.S. et al, “the endometriosis

patients in this analysis had a considerable risk of surgical complications, subsequent surgeries, and hospital admissions both during and after their initial therapeutic laparoscopy or hysterectomy.”<sup>7</sup> The described surgical complications included, but were not limited to, venous thromboembolism, neuropathy, infection, the need for additional vascular repair as a direct result of surgical damage, duodenitis and the need for bowel, bladder or ureter repair as a direct result of surgical damage.<sup>3,7</sup> Therapeutic laparoscopy alone elicited 13,590 documented patients who experienced post-operative complications.<sup>7</sup> Laparoscopy alone also carried an increased risk of subsequent surgeries and hospital readmissions during the studied one year post-operative time period.<sup>7</sup>

One of the most severe of these complications includes colorectal anastomotic stenosis.<sup>8</sup> In a study by Bertocchi et al, which looked at 1643 endometriosis patients who underwent laparoscopic surgery as a consequence of their pelvic pain between the years 2002 to 2016, it was found that 6.3% of these patients returned with symptomatic anastomotic stenosis as a result.<sup>8</sup> Many of these women then required a series of three endoscopic dilation procedures to correct the surgically induced complication.<sup>8</sup>

To further this point, one retrospective study performed in 2008 also found a correlation with initial diagnostic and therapeutic surgery for endometriosis and the incidence of reoperation.<sup>9</sup> In this study, 240 women who had underwent a surgical procedure for endometriosis were analyzed at 2, 5 and 7 year follow ups.<sup>9</sup> Of the 240 person sample population, 120 women were treated with hysterectomy with or without oophorectomy, and 120 women were treatment with laparoscopic excision.<sup>9</sup> Of these women, data showed that the incidence of reoperation increased as post-operative time increased.<sup>9</sup> It was found that in women in which laparoscopic excision was performed, the percentages that remained surgery free were

79.4% at 2 years, 53.3% at 5 years and 44.6% at 7 years post operatively.<sup>9</sup> In women in which a hysterectomy with ovarian preservation was performed, the percentages that remained surgery free were 95.7% at 2 years, 86.6% at 5 years and 77.0% at 7 years post operatively.<sup>9</sup> Finally, in those women in which a hysterectomy without ovarian preservation was performed, the percentages that remained surgery free were 96.0% at 2 years, 91.7% at 5 years and 91.7% at 7 years post-operatively.<sup>9</sup> While these results correlate with prior knowledge that endometriosis is hormonally mediated and thus, would required less repeat surgeries if the ovaries are removed, the younger population should arguably be the main focus in the push for an earlier non-invasive detection method. Shakiba et al also discovered that of the 240 women studied, those between the ages of 19 and 29 years old had between a 1.75 to 6.66 times increased risk of reoperation than those women greater than 30 years old.<sup>9</sup> Additionally, when the age group of 19 to 29 years old was specifically analyzed for the occurrence of reoperation at 2, 5 and 7 year follow ups, the percentages appear vastly different than those of the group as a whole. Shakiba et al found that the percentages of women between the ages of 19 and 29 years old who underwent a laparoscopic excision that remained surgery free were 63.9% at 2 years, 33.3% at 5 years and 27.8% at 7 years post operatively.<sup>9</sup> Through this retrospective research, it can be deduced that the younger the age of the first surgery, which is currently necessary for the diagnosis of endometriosis, the greater number of surgeries a patient will require in their lifetime.

Another commonly overlooked implication of surgery is the stress that is induced in the human body as a result. It is proposed that the physical and emotional stress of both initial and repeat surgeries should be considered in a thorough patient evaluation due to its potential to increase the severity of both the symptoms and the stage advancement of endometriosis in a given patient. Current research published in 2017 reveals that endometriosis symptoms become

more severe when the affected individual is subjected to stress.<sup>10</sup> Hernandez et al, through the use of an animal study in which endometriosis was induced in mice, discovered that stress causes an increase in colonic damage, mast cell infiltration and the severity of vesicles caused by the infiltration of endometriosis.<sup>10</sup> These findings give greater weight to the theory that surgical stress can itself cause endometriosis to worsen.<sup>10</sup>

These findings were also discovered to correlate with the decrease in physical activity which so often accompanies the post-operative time period. Hernandez et al also discovered that endometrial lesions were found to increase in size when the ability to perform physical activities was negated.<sup>11</sup> Therefore, it is possible to deduce that multiple surgeries and the need for reoperations, which was found to be more prevalent when the initial diagnostic surgery was performed at a younger age, may also hinder the healing process and induce disease proliferation and advancement.<sup>6,11</sup> This is because the lesions left behind after laparoscopic excision have now been found to have a greater likelihood of both increasing in size and causing an increase in symptom severity.<sup>11</sup>

If all of the risks of utilizing laparoscopic surgery for the initial diagnosis of endometriosis coincide with an increase in severity of endometriosis lesions that require repeat surgical procedures for both therapeutic and corrective reasons that inherently carry greater risks for the patient, the question must be asked, why does this remain the gold standard? Through the above literature analysis, it can be inferred that the use of laparoscopic surgery as the current diagnostic protocol inherently increases the prevalence of negative disease outcomes of those patients suffering from the debilitating symptoms of endometriosis.

## Emerging Research to Improve Diagnostic Standards

The answer to the improvement of these outcomes appears to be lying in the promising research and analysis of biomarkers as a non-invasive option for detecting the presence of endometriosis in a given patient. Fassbender et al goes on to state that a non-invasive diagnostic test for women with symptoms of endometriosis would be especially beneficial for women suffering from infertility as exploratory surgery further decreases the likelihood of natural conception as infertility is among the highest ranked troubling consequences of the disease.<sup>12</sup> This is also particularly advantageous for those women who have symptoms of endometriosis including chronic pelvic pain who have had normal transvaginal ultrasounds in an effort to defer surgery but still need to procure an accurate diagnosis.<sup>12</sup> These non-invasive diagnostic tests have the capability to identify the presence of endometriosis in women with both minimal to moderate symptom classifications, as well as those with moderate to severe symptom classifications.<sup>12, 13</sup> According to Fassbender et al, most research on diagnostic biomarkers of endometriosis is currently at the Phase I stage of exploration.<sup>12</sup> This includes “exploratory preclinical studies” with the goal of identifying viable biomarkers with high diagnostic specificity.<sup>12, 14</sup> This research is immensely important to continue to tailor to become daily protocol in clinical practice for many reasons; most notably, to decrease the prevalence of unsavory disease outcomes as a result of frequent surgical interventions, but also for the fact that endometriosis costs each affected women approximately \$11,250 annually to manage; which adds both a personal and economic burden to these patients and their providers.<sup>12, 13</sup>

One emerging area of research in the area of biomarker mediated diagnostics is the use of specific genetic materials to detect the presence of the disease. The theory that endometriosis is highly genetic in nature, as it has been seen to affect multiple generations of women in a single



family once the first case is recognized, is becoming an increasingly accepted theory in the pathogenesis of the disease. This theory has led to the utilization of specific microRNAs. MicroRNAs (or miRNAs) are described by Agrawal et al as “single-stranded, highly conserved, non-coding RNAs, approximately 21–25 nucleotides long, that bind to their complementary messenger RNA (mRNA), and through regulation of mRNA degradation, repress translation. Secreted within extracellular vesicles by cells, they can act as cell-to-cell messengers and carry information between cells.”<sup>13</sup> In short, miRNAs are specific and tightly regulated messenger substances that hold a high degree of potential to be used in the diagnosis of endometriosis. The study of miRNAs in the diagnosis of disease, although relatively new, has already resulted in the implication of approximately 2000 miRNAs known to be specific to, as well as to contribute to the pathogenesis of a variety of diseases.<sup>13, 14</sup> These miRNAs can be found in multiple forms of bodily fluids including blood, serum and urine, making them readily available for testing regardless of the specifications or challenges of each individual patient.<sup>13</sup> The use of miRNAs also has promise in the area of therapeutic interventions for chronic diseases.<sup>14</sup> It was discovered that small samples of miRNAs give more insight into the pathomechanics of a disease than studying the expression of larger quantities of messenger RNAs (mRNAs).<sup>13, 14</sup> In this way, the study and subsequent use of miRNAs in the diagnosis of endometriosis could also further the understanding of the disease, including the identification of risk factors in early disease and the staging of already formed lesions in later disease processes. This, in turn, holds the possibility of advancing therapeutic procedures to areas outside of surgical interventions in not only the diagnosis, but also in the treatment of endometriosis throughout the lifetime of an affected patient.

Agrawal et al explains through the use of a systematic review that there is evidence that a physiological dysregulation of miRNAs may be fundamental to the pathogenesis of endometriosis.<sup>13</sup> This was discovered to be due to the the regulation of mRNAs by miRNAs and the molecular pathways that are thought to contribute to the pathogenesis.<sup>13, 14</sup> These contributions include inflammation, angiogenesis, tissue repair and items of the extracellular matrices.<sup>13</sup> Women with endometriosis were found to have specific miRNA sequences present in circulation, however the roll of these substances and their specific source has yet to be identified.<sup>13, 14</sup> There are several hypothesis about the origin of these endometriosis specific miRNAs including the possibility of their active secretion by cells in order to communicate with their surroundings.<sup>13, 15</sup> Another hypothesis suggests that these miRNAs may be a product of diseased or damaged cells as a result of the disease process; this could potentially be implicated in identifying a specific disease stage in a patient through the use of biomarkers in order to formulate a therapeutic treatment plan.<sup>13, 16</sup> Surgery would become superfluous as a diagnostic and staging tool if these biomarkers were approved for clinical use. The number of surgeries necessary for the lifetime management of endometriosis would decrease, along with the associated surgical risks. Additionally, through the study of miRNAs in endometriosis, it was found that these molecules, when present in the endometrium, make chemical adjustments throughout the various phases of the menstrual cycle and therefore have the potential to be used in the identification of a patient's source of infertility, and the specific tailoring of patient-centered treatment options.<sup>13</sup>

Another potential marker of endometriosis that could be utilized in the diagnosis and staging of the disease is interleukins. Interleukins can be described as proteins within the body that are released by immune cells in response to regulation of inflammatory processes.

Therefore, since endometriosis is a disease of inflammation and dysregulation of immune function, it is reasonable to assume their role in the disease and begin careful analysis of their action. One study by Othman EE et al set out to investigate this assumption.<sup>17</sup> In a study that compared women who had been diagnosed with endometriosis vs women who had not undergone laparoscopy nor had been diagnosed with endometriosis as a control, they found that serum interleukin 6 (IL-6) provided an adequate distinction between the groups.<sup>17</sup> Furthermore, when compared to the regular menstrual cycles of both the control and the experimental groups, IL-6 did not fluctuate throughout the menstrual phases.<sup>17</sup> This further increases the efficacy of this test as it can be measured at any time, at any scheduled clinic appointment in women in whom endometriosis is expected. This also decreases the chance of inaccurate results as the levels of IL-6 remain constant and can be tracked on a standardized scale for each woman. This could also be potentially useful in the staging of endometriosis. It is possible that the higher the IL-6 level, the higher the stage of disease that could be expected. This has the potential to be vastly beneficial to patient outcomes as disease treatments can be planned more effectively. For example, Othman EE et al also states that “one-third of women who undergo diagnostic laparoscopy will have endometriosis, one-third will have no pelvic pathology, and the remaining one-third will have other gynecological conditions. This means that two-thirds of women who undergo laparoscopy for pelvic pain or infertility will be subjected to the potential risks as well as the cost associated with this procedure without actually having endometriosis.”<sup>17</sup> Additionally, this study included women suffering from infertility who had undergone exploratory laparoscopy that showed no pathologic findings.<sup>17</sup> The inclusion of this population proved invaluable as the presence of IL-6 identified allowed for the likely diagnosis of endometriosis in these patients without the employment of additional laparoscopies, which have the potential to worsen the

severity of their infertility and further decrease their ability to conceive in the future.<sup>17</sup> With the use of IL-6 for the diagnosis and ensuing staging of endometriosis, the number of unnecessary surgeries and the incidence of subsequent complications could presumably be decreased, leading to improved disease outcomes for patients.<sup>17, 18</sup>

Through the analysis of the previous literature on the potential detriments of utilizing laparoscopic surgery as the gold standard for the diagnosis of endometriosis, along with the examination of emerging research on the topic of biomarkers as a potential replacement it can be deduced that the disease outcomes of patients could be immensely improved with these newer, less invasive diagnostic methods.

## Methods

The journal databases of PubMed, Google Scholar, Cochrane, Science Direct and UpToDate were utilized in the location and organization of the research cited in this document. The key words, endometriosis, endometriosis pathogenesis, endometriosis diagnosis, endometriosis negative surgical outcomes, endometriosis laparoscopy, endometriosis biomarkers, and opioid use in endometriosis were utilized in the various performed searches. Each scholarly review and meta-analysis cited was thoroughly analyzed; the research articles analyzed in each review were included in this document and cited as they corresponded with the proposed research question.

Additionally, two individuals were interviewed via email about their personal experiences with the symptoms, diagnosis and treatment of endometriosis. The individuals elected to remain anonymous. Therefore, no identifying materials were used in this article, apart

from their personal statements, per their request. Each individual's answers were saved anonymously and the email conversations were destroyed to protect their privacy.

The questions sent to each participant are as follows:

- 1) At what age were you diagnosed with endometriosis?
- 2) How long since your first visit for endometriosis symptoms was it diagnosed?
- 3) How was the diagnosis made? (surgery, ultrasound, physical exam, etc.)
- 4) What were your symptoms before your diagnosis that caused you to seek treatment?
- 5) What treatments have you tried for your symptoms? (therapeutic surgery, physical therapy, birth control medications, opioid pain medications, etc.)
  - a. Which of these treatments have been most beneficial to you?
- 6) If you have had surgery to manage symptoms, have you had any negative effects of surgery/multiple surgeries? (scarring, adhesions, reactions to anesthesia, etc.)
- 7) If there was an option to reduce the number of surgeries necessary to manage your endometriosis symptoms, would you be interested in that option?
- 8) Have you ever heard of blood and urine testing to diagnose and track stages of endometriosis?
- 9) What troubles you the most about your diagnosis of endometriosis?
- 10) Do you feel that after your diagnosis, the treatments offered to you are adequately managing your symptoms?

## Discussion

Endometriosis can be considered one of the most debilitating, insidious diseases of the female genitourinary tract. It is a disorder that hijacks the body's own normal function of menstruation and carries its inflammation inappropriately throughout the body, often leaving women with chronic pelvic pain and infertility. Currently, the gold standard for its diagnosis is exploratory laparoscopic surgery; but is this really the best option?

It is reasonable to assume that the reason that the gold standard of diagnosis has remained laparoscopy simply because endometriosis has thrived relatively unrecognized for years in the clinical setting. Women suffering with nondescript pelvic pain, dyspareunia, dischezia, infertility, etc. are often offered treatment options that simply cover up the problem if all other non-surgical diagnostic procedures reveal no conclusive pathology. Furthermore, if a woman refuses surgery, cannot afford surgery, or simply does not have access to healthcare, their disease is allowed to continue to flourish and cause irreversible damage such as permanent infertility and bowel infiltration. This disconnect between patient and provider and the lack of recognition of such a pervasive disease has undoubtedly left many women confused and in chronic pain for years of their fertile lifetimes.

For these reasons, research is emerging to begin to uncover the disparities of the gold standard of laparoscopy, along with other currently utilized non-invasive imaging modalities to begin the move towards discovering the most beneficial methods of diagnosis and treatment for patients affected. The fact is that different modalities for diagnosis play a large role in the incidence of the correct diagnosis and staging of endometriosis. A matched cohort study found conclusively that the incidence of diagnosing endometriosis is vastly different when current techniques were compared to each other.<sup>20</sup> These methods included histology, MRI, and

visualization by a skilled surgeon through the use of laparoscopy.<sup>20</sup> Through this research, it was estimated, quite conservatively, that approximately 11% of women remain undiagnosed with progressing endometriosis and are therefore not receiving adequate treatment for their condition.<sup>18</sup> With this data, it is clearly seen that the current methods being utilized are not meeting the standards of disease prevalence within the population.

The underdiagnosis of endometriosis is not the only roadblock to patient centered proper treatment. The utilization of laparoscopic exploratory surgery as the gold standard diagnostic protocol is, in itself, a barrier for these patients. The first being the amount of time that it takes to reach the point of surgical intervention. The surgical indications for laparoscopy still remain persistent pain despite medical therapy, contraindications to, or refusal of, medical therapies including hormonal contraceptives, the need for exclusion of malignancy based of symptoms and/or family history, or signs and symptoms of an obstruction of the bowel or urinary tract.<sup>3</sup> As seen above in interviews with D.D. and R.S., it took them years of chronic pain to finally arrive at their diagnosis through surgery once it was finally deemed appropriate. This problem with a patient's time to surgery it undoubtedly also due to the fact that laparoscopy is invasive and carries risk to the patient. Surgeries performed for any reason on any area of the body are typically done so with a clear indication. Surgical exploration for the presence of endometriosis is performed without the promise of an answer to a patient's pain. This is both due in part to the level of skill of the surgeon and their team, along with the very nature of endometriosis. It is an evolving disease that transforms and thrives through various stages – stages of which look very different from each other and are often hard to visualize until they have been pigmented by histocytes, fibrosis, or other immune modulated processes.<sup>1</sup> However, this inflammatory

pigmentation not only occurs in the adhesions themselves, but also the surrounding tissues, making diagnosis by histological evaluation problematic.<sup>1,3</sup>

In addition to the sheer difficulty of patients to reach the surgical stage of the diagnosis of their endometriosis, many patients also face difficulties after their laparoscopic surgical exploration takes place. One of the major disadvantages to laparoscopic surgery is the incidence of the recurrence of endometriosis lesions and consequent return of pelvic pain. Primarily, when the initial laparoscopy is performed, it is considered conservative, meaning that an ablative procedure was performed with the use of laser vaporization, electrosurgical fulguration or ultrasonic cutting and coagulation techniques.<sup>3</sup> These techniques are utilized if endometrial lesions are identified to attempt to eradicate them while maintaining the underlying anatomy primarily in women who are not yet finished childbearing. While these conservative measures are the most common primary surgical intervention in the treatment of endometriosis, it also carries the highest rate of recurrence as close to 20 percent of these patients will require a repeat operation within two years of their initial surgical procedure due to the relapse of their endometriosis related symptoms.<sup>3</sup> Additionally, a 40 percent recurrence rate was also observed at 10 year follow up appointments after utilizing this surgical method for diagnosis.<sup>3</sup> For this very reason, it can be seen that by utilizing surgical methods for the diagnosis of endometriosis it likely increases the number of negative disease outcomes associated with endometriosis.

Many of the negative outcomes of endometriosis are due to the invasive nature of the disease itself, partnered with the fact that it is so often left undiagnosed. However, the risks and various complications of the multiple surgeries being performed throughout the lifetimes of each patient affected account for a large amount of these adverse outcomes.



Two of these undesirable outcomes include the affects of surgical procedures alone. As analyzed by Hernandez et al, physical and emotional stress, paired with the inability to remain physically active as a result of surgery are detrimental to those suffering with endometriosis.<sup>10</sup> Both the pre-surgical and post-surgical time periods have been shown to increase both physical and emotional stress in patients. This was seen both through the psychological analysis of patients as well as through an increase in serum stress markers as seen in the animal study performed by Hernandez et al.<sup>10</sup> This increase in bodily stress was found to increase colonic damage, mast cell infiltration and the severity of vesicles caused by the infiltration of endometriosis.<sup>10</sup> Since this finding was clearly seen though the study of animals paired with the findings of the harmful effects of stress on the body that have been extensively studied, this should be taken into consideration before beginning the cycle of laparoscopies throughout the lifetimes of patients with endometriosis. Moreover, the downtime associated with surgical procedures was similarly found to be detrimental to the disease outcomes of endometriosis patients. Hernandez et al also went on to describe that the downtime and subsequent decrease in physical activity which often accompanies the post-operative time period increases the severity of endometriosis both through the increase in the size of endometriosis lesions, as well as the pain experienced as a result.<sup>11</sup> Therefore, since the intrinsic nature of surgical intervention can be understood to worsen the disease outcomes of endometriosis, this should be used as evidence supporting the need to replace laparoscopic surgery as the gold standard for the diagnosis of endometriosis.

Apart from the intrinsic risks of surgery on the human body, the risks and possible severe complications of laparoscopic surgery specifically related to the diagnosis of endometriosis also prove unfavorable. These adverse outcomes appear to carry enough weight to propel current

research to discover a non-invasive and highly effective diagnostic test forward into fruition. Several of these documented complications include venous thromboembolism, neuropathy, infection, the need for additional vascular repair as a direct result of surgical damage, duodenitis and the need for bowel, bladder or ureter repair as a direct result of surgical damage and colorectal anastomotic stenosis.<sup>7,8</sup> One study that analyzed the incidence of post-operative complications in 568 women who had surgical treatment for their endometriosis associated symptoms came to the conclusion that surgical intervention, especially for endometrial lesions that are more deeply penetrating, is “feasible, but it is associated with major complications, especially when any type of rectal surgery must be performed.”<sup>20</sup> One important point to note in regard to this statement is to consider that women who undergo these surgical procedures do so without a clear diagnosis and expected outcome of their surgery. As so, they often return from surgery with multiple surgical interventions that they had not previously prepared for, commonly including bowel resection requiring additional surgeries to repair. As a proposition in regard to these adverse effects leading to more negative disease outcomes, surgery with all of its associated risks should be saved for the treatment of endometriosis related symptoms alone and should either not be initiated or should be initiated with extreme caution and preparation in those without a clear diagnosis.

At present, the most promising research available that has the potential to put this proposition into practice is the use of serum biomarkers to detect the presence of endometriosis in symptomatic individuals. By engaging the use of cohort studies, the biomarkers that have proved most promising are both miRNAs and interleukins. This is primarily due to their rolls in gene expression, immune responses to inflammation, stability and specificity to their translated disease and outcomes. The use of miRNAs appears to be specifically useful for their use in the

identification of endometriosis as the source of infertility in affected patients. It was found that these proteins tailor themselves to specifically correlate with the menstrual cycle and can therefore be determined to affect fertility.<sup>13</sup> This finding has the potential to increase the specificity of patient-centered treatment options in these women, and avoid the use of multiple, unnecessary laparoscopic surgical procedures to gain a diagnosis. This is especially important in this population since an additional complication of surgery in these women is the worsening of their infertility due to surgical damage to the reproductive organs and the potential for the formation of adhesions. The potential seen in interleukins for the diagnosis of endometriosis is similarly promising. In particular IL-6 has been shown to be the one of the most specific biomarkers seen in women with endometriosis. Contrary to miRNAs, IL-6 does not fluctuate nor does it change its chemical structure throughout the menstrual cycles of patients. For this reason, there is potential for universal standardized ranges for diagnostics and disease severity.<sup>17</sup> These two biomarkers appear to be two of the more promising findings in the quest for a non-invasive diagnosis for endometriosis and give confidence to the goal of decreasing the incidence of negative disease outcomes in patients with endometriosis by replacing laparoscopic surgery as the gold standard of diagnosis.

This research, however, is not without flaws. As endometriosis as a whole is still not completely understood, and its pathomechanics are still being studied, it is difficult to conduct research on an already misunderstood population and disease. For this reason, a vast majority of the research on diagnostic biomarkers remains at the Phase I stage of investigation.<sup>12</sup> Since no biomarkers have been proven in multiple studies to be definitively exclusive to the diagnosis of endometriosis, no test currently exists for clinical use. In order to remedy this deficiency, medical institutions must consider incentivizing research into the pathogenesis of endometriosis.

Only once the disease is more clearly understood can this extremely important research on biomarkers be definitively linked to the diagnosis and staging of endometriosis, leading to new diagnostic protocols.

Finally, it should be noted that although surgery is not without significant risks, there is a very importance place for laparoscopic intervention in the treatment of endometriosis. It was discovered that the use of conservative therapeutic surgical procedures in women with endometriosis decreased the overall pain experienced by patients by 73% (vs 21%) and increased live births or ongoing pregnancy rates by 30% (vs 18%) when compared to invasive diagnostic laparoscopic procedures.<sup>3</sup> Due to the infiltrative and chronic nature of this disease, it is difficult to dispute a patients eventual need for therapeutic surgical intervention and that should not be taken as the point of this analysis. Only the use of laparoscopic surgery as the gold standard for the initial diagnosis and staging of endometriosis is being argued due to the potential irreversible risks to the patient, along with the high incidence of negative disease outcomes and a decrease in a patient's quality of life associated with early and multiple pelvic surgeries.

## Conclusion

Endometriosis is a debilitating disease affecting women of all ethnic backgrounds throughout their reproductive years. These women suffer from chronic pelvic pain, dyspareunia, dischezia, dysuria and dysmenorrhea; all of which greatly impact their quality of life. Currently the protocol for the definitive diagnosis of endometriosis is exploratory laparoscopic surgery. This approach appears to have a negative impact both on the quality of life of these patients, as well as their expected disease outcomes.

The indications for laparoscopic surgery in patients in which endometriosis is suspected have been shown to cause a large delay in time to diagnosis, and subsequent time to appropriate treatment. This delay in diagnosis and treatment not only leads to an increase in negative disease outcomes due to the increased opportunity for the endometrial lesions to proliferate and more deeply infiltrate, but it also leads to an increase in physical and emotions stress on these patients as they are so often left without an answer for years as to the source of their severe and chronic pain. The additional fact that this increase in stress and fatigue has also been shown to worsen the disease provides further grounds to a need for change in diagnostic protocols.

Furthermore, once a number of these patients are approved for surgery in order to confirm their diagnosis of endometriosis, they are often left with the risk or presence of debilitating post-operative complications including adhesions, venous thromboembolism, neuropathy, infection, the need for additional vascular repair as a direct result of surgical damage, duodenitis and the need for bowel, bladder or ureter repair as a direct result of surgical damage and colorectal anastomotic stenosis.<sup>7, 8</sup>

Why does laparoscopic surgery remain the gold standard for diagnosis when the risks of surgery and the proven increase in the incidence of the need for reoperations as a result of laparoscopic exploratory interventions can be seen clearly in the literature? After careful analysis, it becomes difficult to argue that anything except non-invasive biomarker analysis of patients in which endometriosis is suspected could lead to an improvement in disease outcomes and the overall quality of life for these patients.

Through the thorough analysis of these risks and their impact on quality of life for patients affected by endometriosis, it is not surprising research is emerging in the area of peripheral serum biomarkers for the initial diagnosis of endometriosis [see Figure 1]; with most

notable findings today being found in the potentials of miRNAs and IL-6. Due to the known inflammatory pathomechanics of endometriosis, these proteins have the potential to be targeted and utilized in the non-invasive diagnosis of endometriosis [see Figure 2]. Through the use of non-invasive peripheral markers moving into their place as potential gold standards for diagnosis, it is possible to decrease the negative disease outcomes of endometriosis related to surgical delay as well as the potential for post-operative complications and the need for multiple reoperations as a result of continued lesion recurrence.

In order to see this carried out to completion, in the words of Fassbender A. et al. “More centers need to work together to include as many patient samples as possible from an established biobank with the same SOPs (standardized operating procedures) and the research approach should be discussed in a collaborative manner. Biostatisticians should be more involved in the design of future studies in order to transfer comprehensive biomarker knowledge into essential analytes to develop the diagnostic test.”<sup>22</sup> The field of endometriosis study is expanding. Researchers and clinicians are daily gaining an increased knowledge base as to how to better diagnose and treat patients suffering from the effects of endometriosis and its surgical aftermath. However, the scientific community must continue to work collaboratively to find suitable biomarkers for the initial diagnosis of endometriosis. Through this, the incidence of negative outcomes of this debilitating disease can be decreased and patients can be provided tailored treatment protocols that will thus increase their quality of life.

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Appendices

Figure 1. Potential Endometriosis Biomarkers 20

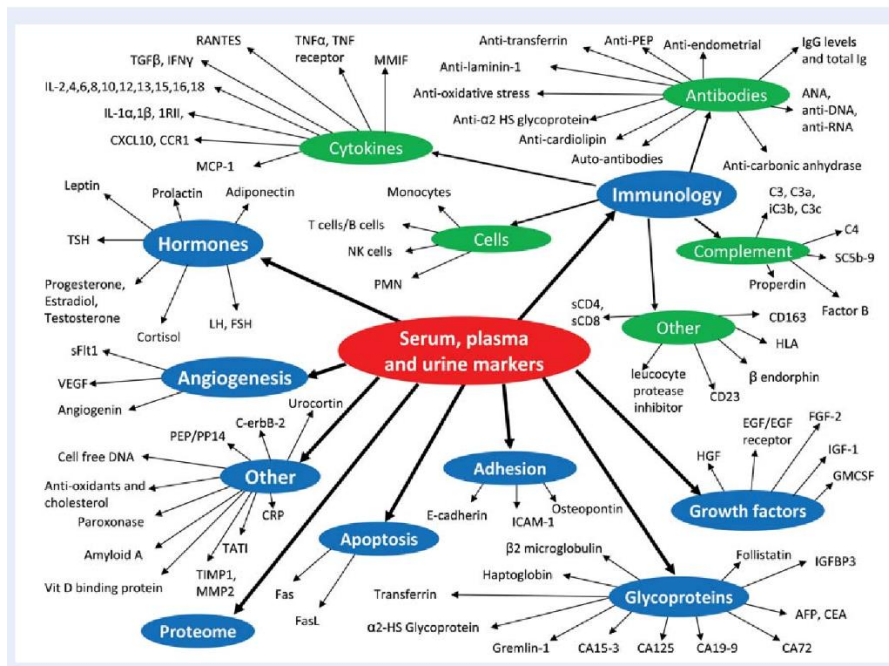
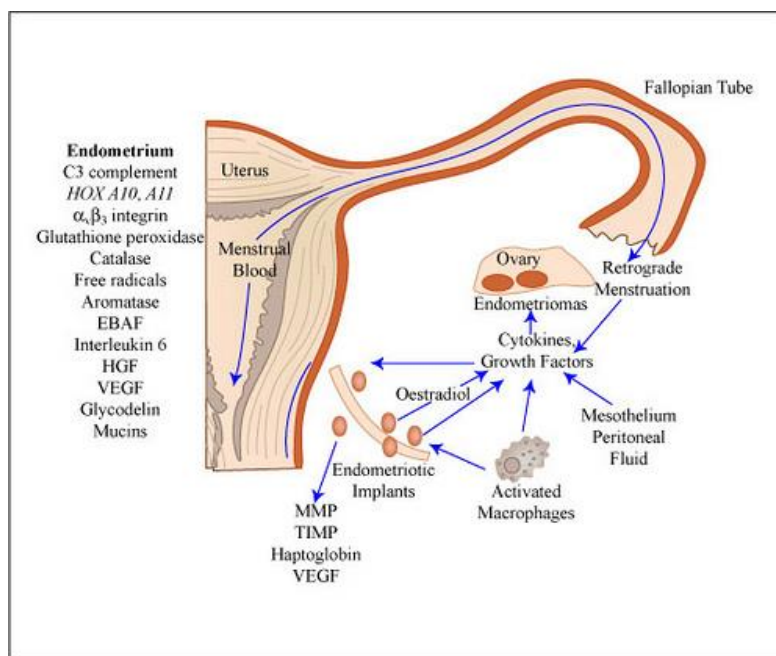


Figure 2. Pathogenesis of Endometriosis 21



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