Novel Diagnostic Methods for Endometriosis

Anushka Tejeswi

Gifted Gabber

ABSTRACT

Endometriosis is a detrimental disease that affects millions of women globally often resulting in symptoms as serious as infertility. While this disease is so prevalent, limited research and funding in search of diagnostic methods exists to this day. Currently, the gold standard for diagnosing endometriosis is through an extremely invasive surgery called a laparoscopy. As many women do not want to go through with this surgery it leads to countless women around the world unaware of the fact that they possess this disease. This paper intends to evaluate the accuracy and effectiveness of emerging diagnostic techniques such as biomarkers, imaging modalities, and additional tests for the early detection and diagnosis of endometriosis. Through a comprehensive literature review and examining existing studies, this paper aims to highlight the positives and negatives of various diagnostic methods in order to replace the gold standard invasive laparoscopy surgery. By evaluating these various diagnostic techniques, the use of biomarkers and targeting miRNA cells proved to be more promising for future diagnosis of endometriosis. They were cost-effective, reliable, and non-invasive. The other diagnostic methods were somewhat favourable however they lacked enough research and reliability. Through these evaluations, it is able to be seen that there are additional methods for diagnosing endometriosis which are far less invasive. More money and research is required in the field of endometriosis and women's health, in general, to acquire FDA funding for these methods and allow for fewer women globally to suffer from the painful side effects of this harmful disease.

Introduction

Endometriosis is a fairly common disease, affecting around 10% of women in their reproductive age. Despite the percentage of people affected by this disease, many people are unaware of its symptoms and severity. 33 percent of women do not know what endometriosis is. Similarly, 74 percent of men don't know what endometriosis is either. Endometriosis is a disease where tissue which is similar to the lining of the uterus grows outside of the uterus, often resulting in pelvic pain and infertility. It can additionally lead to extremely painful menstrual cramps and pain during or after sex. Endometriosis causes an inflammatory reaction in the pelvis resulting in various types of lesions within the pelvis and other parts of the body. These lesions can be identified as superficial endometriosis, cystic ovarian endometriosis, deep endometriosis, or endometriosis found outside of the pelvis.

There have been very limited advancements in the diagnosis and cure of endometriosis. Currently, there is no cure for endometriosis but rather early treatments. These can include non-steroidal anti-inflammatory drugs, analgesics, hormonal medicines, and contraceptives. Additionally, in terms of diagnosing endometriosis, the only way is through a very invasive method. This is through a surgery called a Laparoscopy. There have been no further options for diagnosing this disease; other screening tools have been proposed but none of been validated yet. There have been very limited advancements in terms of diagnosing and treating this disease historically due to limited funds for its research. This paper will focus on emerging non-invasive diagnostic techniques for endometriosis including biomarkers, imaging modalities, and other tests. As a result of the usage of these less invasive techniques, treatment in endometriosis would improve and become more accessible. Overall this paper hopes to evaluate and compare non-invasive diagnostic methods for endometriosis, with the goal of enhancing early diagnosis and treatment accessibility.

Current Diagnostic Techniques

Many people dismiss the possibility of endometriosis, disguising it as merely painful period cramps. Due to this reason "the diagnosis of endometriosis is typically delayed by 8-10 years" (Ahn et al., 2017). Additionally, it can take many years to diagnose due to the particularly invasive method of diagnosing it. This is through a surgery called a Laparoscopy however it is less used due to the fact that it is so invasive, and many women would rather dismiss the pain as period pain. This causes many women to live with severe pain and other harmful side effects such as infertility, simply due to the lack of research into better methods of diagnosing this disease. Therefore, endometriosis often goes undetected for years in women.

Biomarker Diagnostics

One emerging technique for diagnosing endometriosis is through biomarkers. Currently, reliable biomarkers for this disease are elusive with no proven validation regarding this technique. Biomarkers allow for faster diagnosis and therefore faster treatment of this debilitating disease. Biomarkers can be "objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention." My research provides emphasis on the development of biomarkers based on existing scientific literature. Currently, there are no FDA-approved endometriosis biomarkers due to the complexity of the ongoing endometriosis metabolic process.

Biomarkers have already tested the serum of women with endometriosis, identifying increased levels of monocyte chemoattractant protein-1, IL-6, IL-8, normal T cells, and C-reactive proteins. Additionally in the peritoneal fluid of endometriotic women, high levels of macrophage migration inhibitory factor, cytokines such as interleukins, tumor necrosis factor-alpha, and activated macrophages have been detected. Biomarkers are being further proven to help with the actual diagnosis of endometriosis currently (Anastasiu et al., 2020).

Several types of biomarkers for the diagnosis of endometriosis include blood biomarkers, endometrial biomarkers and urinary biomarkers. Out of these tests, urinary biomarkers prove to be the most successful with the most research published regarding it. Two additional noninvasive biomarkers include circulating miRNAs and lncRNAs. For circulating miRNA, it has been proven that "the circulating level of let-7b can be used as a reliable biomarker with 83.3% sensitivity and 100% specificity" (Ahn et al., 2017) regarding the diagnosis of endometriosis. Other types of circulating miRNA have been further proven beneficial for the diagnosis of endometriosis such as miR-17-5p, miR-20a, and miR-22. The only limitation of the miRNA biomarker diagnostic technique is the lack of research supporting it. It has not been tested in all stages of endometriosis, making it difficult to tell the sheer benefits of this biomarker. Additionally, there is a discrepancy regarding its levels in tissue and blood, further validating the need for additional research and exploration in the usage of miRNA biomarkers as a potential diagnostic of endometriosis. A more recently relevant biomarker for diagnosing endometriosis are lncRNAs. These are "a class of molecules with nucleotides>200 in length involved in the regulation of gene expression." lncRNAs are used to investigate tissue-specific from specifically eutopic endometriosis in patients. Circulating lncRNA proves useful in endometriotic tissue and serum, helping to detect how critical the progression of endometriosis is within a patient. One study (Wang et al., 2016) proved that by combining five lncRNAs, endometriotic patients were able to be differentiated from control subjects with 89.7% sensitivity and 73.2% specificity. This further validates the advantageous nature of the emerging lncRNA biomarker (Ahn et al., 2017).

Some biomarkers however prove to be not as useful in their results. One example of this is seen with inflammatory cytokines. Inflammatory cytokines promote inflammation and are secreted from immune cells while mainly produced by T helper cells and macrophages. Inflammatory cytokines were tested as a method of diagnosing endometriosis, however, the results proved not favorable. Differences lacking between the control group and the group of

endometriotic patients made the results nonconclusive, proving no benefits of using inflammatory cytokines as a bi-omarker (Ahn et al., 2017).

Overall, biomarkers prove to be useful for the diagnosis of endometriosis. Several biomarkers as opposed to one singular is more advantageous in a diagnosing aspect allowing for a higher sensitivity and specificity rating. Further research and exploration of this technique are necessary for a painless and quick diagnosis of endometriosis.

Imaging Modalities Diagnostics

In order for a more reliable diagnostic technique regarding endometriosis to occur, more advanced imaging systems are required. One of the emerging and popular techniques is transvaginal sonography. This is due to cheaper costs and wider availability of it. Operators can use transvaginal sonography for imaging within "the sonographic description of DE lesions", "the peritoneum for superficial implants", "the uterus for adenomyosis", and "the ovaries for endo-metriomas."

Another potential imaging modality includes magnetic resonance imaging(MRI). MRI is recommended as a secondary technique for the diagnosis of endometriosis, not optimal for being the only diagnostic technique. MRI images identify implants or tissue masses in "the torus uterinum, USLs, vagina, RVS, rectosigmoid, POD, para-metrium, bladder, and round ligaments" in order to diagnose endometriosis. MRI's save time in the diagnosis of endometriosis; however, the imaging quality is not as precise as other imaging modalities.

Table 1: Illustrates the differing protocol required for magnetic resonance imaging and what is most optimal for diagnosis of pelvic endometriosis. Adapted from "Diagnosis of deep endometriosis: clinical examination, ultrasonog-raphy, magnetic resonance imaging, and other techniques" (Bazot & Daraï, 2017)

MRI protocol	Recommendation(grade)
Technical requirements	
Device 1.5 or 3.0 T	No recommendation
Phased-array coil	Standard (C)
Timing of MRI examination	No recommendation
Fasting	Standard (B)
Moderately full bladder	Standard (C)
Bowel enema	"Best practice" (GPP)
Supine position	Standard (B)
Abdominal strapping	Standard (C)
Anti-peristaltic agent	Standard (C)
Vaginal opacification (gel)	Option (GPP)
Rectal opacification (water, gel)	Option (GPP)
MR sequences	
2DT2-weighted MRI (sagittal, axial, Oblique)	Standard (B)
3DT2-weighted MRI	Option (C)
T1-weighted MRI without/with fat-suppression	Standard (B)
Dixon technique (alternative to T1W)	Standard (C)
Intravenous contrast-enhanced MRI	No recommendation
Diffusion weighted MRI	No recommendation
Susceptibility-weighted MRI	No recommendation
Half-Fourier acquisition single shot turbo spin echo	Standard (C)

Studies have shown that MRI has a higher accuracy in diagnosing uterosacral ligaments than transvaginal sonography. Both MRI and transvaginal sonographies have strengths and weaknesses for differing types of endometrioses and can be used synonymously for accurate diagnosis of endometriosis. Challenges for these types of imaging modalities include that neither of them is particularly accurate for all types of endometriosis and can take additional types with varying types of imaging modalities to properly assess and diagnose the disease. Additionally, due to the high costs and the fact that these tests are not always readily available, this method of diagnosing endometriosis may not be accessible to all. An MRI can cost up to 4000 dollars and a transvaginal sonography often costs a couple hundred dollars. Due to this, patients may feel less inclined to spend money on these imaging modalities without the promise of reliable results. However, this technique is far less invasive than the gold standard diagnostic technique utilizing a laparoscopy (Bazot & Daraï, 2017).

Other non-invasive tests

Besides biomarkers and imaging modalities, there are other noninvasive methods to diagnose endometriosis. These noninvasive tests are still undergoing research and tests to ensure they are a safe and reliable method for diagnosing endometriosis. These tests include targeting miRNAs and through statistical methods.

Targeting miRNAs

MiRNAs are micro-RNA structures. They are particularly used in gene expression by controlling this process by binding with mRNA in the cytoplasm of the cell. Current studies are evaluating the effectiveness of targeting miRNAs. They have discovered the "miRNA endometriosis signature" which are many miRNAs that are regulated when a person has endometriosis. Two methods where miRNAs are used are through blood-based miRNA structures and through salivary-based miRNA structures. Blood-based has been proven to be unreliable due to study and control group issues. The results have not been particularly consistent, making blood-based not a promising diagnostic method of endometriosis. However, saliva-based miRNA studies are being conducted more frequently, especially the ENDO-miRNA study. It's said to be valuable due to "the combination of the intrinsic quality of miRNA to condense endometriosis phenotypes(and its heterogeneity) and the modeling power of AI." (Bendifallah et al., 2022) One particular study (Bendifallah et al., 2022) revealed how "97.3% of all miRNAs are detectable in the saliva" allowing for an inexpensive and quicker method of diagnosis. The most promising signature in the model reveals a sensitivity of 96.7%, a specificity of 100%, and an AUC of 98.3%. Overall, saliva-based miRNA structures are a promising method of diagnosing endometriosis as it is non-invasive, reliable, and inexpensive.

Statistical Analysis Methods

An additional non-invasive test to diagnose endometriosis is through statistical methods. One current method is through the Lasso analysis. The Lasso analysis is known as a regression analysis method which uses shrinkage. The data values shrink towards the mean value, meant for the selection of the subset of variables. It is often used in machine learning, combined with a specific algorithm, to allow for better prediction accuracy, in this case, would be for the prediction of the presence of endometriosis. In one particular study (Szubert et al., 2023), Lasso analysis "identified the combination of painful menses, BMI levels, and CA125" in order to predict whether or not the subject has endometriosis. There was a sensitivity of 0.88 and a specificity of 0.80 with these methods. The study found that CA125 was the most promising in diagnosing endometriosis. Through this noninvasive algorithm, it provides another option for cheap and readily available diagnosis of endometriosis rather than the gold standard of the laparoscopy diagnosis.

Best Diagnosis Technique

Out of the endometriosis diagnostic techniques outlined in this paper, some methods are more promising than others. The two more promising methods seem to lie within the use of biomarkers and targeting miRNAs. The research surrounding these methods results in favorable odds of these techniques being reliable and noninvasive. Due to their objectivity, non-invasiveness, speed, and high specificity, they prove to be reliable and realistic methods of diagnosing endometriosis. However, the diagnostic methods of imaging modalities and statistical methods are not as promising. While they are cheap alternatives, there has been limited research regarding these topics. Specifically with imaging modalities, no singular imaging modality can reliably capture the presence of endometriosis within the uterus, and it must be supported with other evidence. For the statistical methods, there is not enough evidence to use that method as a reliable technique. Overall, through this research, it can be seen that alternative, non-invasive methods of diagnosing endometriosis are most reliable with biomarkers and targeting miRNAs.

Conclusion

Endometriosis is a harmful and debilitating disease, often resulting in infertility and period pain for the reproductive years of a woman's life. The current gold standard for diagnosing endometriosis through laparoscopy surgery is far too invasive and expensive, simply not living up to the medical advancements seen in other fields. Through evaluating alternative methods of diagnosis such as urinary biomarkers, circulating miRNAs, lncRNAs, inflammatory cytokines, MRI and transvaginal sonography imaging modalities, targeting miRNAs, and the Lasso analysis, it is clear that there are many other methods for diagnosing endometriosis. The biomarker and miRNA methods proved to be more promising. More research is necessary in this field to get these diagnosing methods through FDA approval in order for fewer women around the world to be severely affected by this detrimental disease.

Acknowledgments

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