HIGH SCHOOL EDITION
Journal of Student Research
Volume 12 Issue 4 (2023)

Biomarker Development for Endometriosis

Sahasra Saravan[1], Dr. Rajagopal Appavu[#] and Jothsna Kethar[#]

[1]Frisco Centennial High School
[#]Advisor

ABSTRACT

Endometriosis debilitates many women in the U.S. and around the world which is characterized by lesions either localized on the uterus or attached to other organs. These lesions act as endometrial tissue which means that during the monthly menstrual cycle, this tissue sheds which results in blood being stuck in body cavities. The only definitive way to diagnose endometriosis is to go through a laparoscopic procedure which is invasive and expensive. Patients may avoid their endometriosis and rely on pain medications to get relief from their symptoms. Biomarkers can be the next method of diagnosis which is noninvasive. Biomarkers can be taken from proteins during angiogenesis, blood, urine, saliva, and genomics. Blood and saliva have a common biomarker of miRNA. CA-125 in the blood is the most common biomarker used to detect endometriosis but it isn't always accurate. Saliva can remain stable without extra precautions, which makes it an ideal method of gaining and testing biomarkers. However, a panel of biomarkers may also be beneficial. Additionally, there may be specific genes in DNA that can show that a patient has endometriosis. An efficient, non-invasive diagnosis method is needed to reduce the amount of time taken to get a diagnosis and get treatment for symptoms closer to the onset of the disease.

Introduction

Endometriosis is a gynecological disease characterized by lesions on various organs that emulates the uterine lining. These lesions shed blood which gets stuck in the abdominal cavity, and the scar tissue and inflammation associated with endometriosis can cause infertility. One out of ten women have endometriosis, but this common disease doesn't get diagnosed until 8-10 years after the onset. Symptoms include heavy, painful cramps, so when women visit gynecologists, they often label them as menstrual cramps associated with the regular menstrual cycle. As endometriosis gets diagnosed at a later time, it gets increasingly more difficult to treat this disease and manage the unbearable cramps that debilitate women from participating in society and putting their best foot forward. Biomarkers are proving to shed some light on a new method of noninvasive diagnosis, especially in saliva, blood, or urine which would be less expensive and more accessible than a laparoscopic invasive procedure. This would lead more women to get diagnosed closer to the onset of the disease which means that doctors can treat their patients with this condition at an earlier stage. There are so many different types of endometriosis, different phenotypes, and various stages where different biomarkers may be needed to properly diagnose endometriosis. Additionally, multiple biomarkers may need to be detected to confidently diagnose endometriosis rather than one biomarker, so research on noninvasive diagnosis methods is still underway.

Clinical Diagnosis Method

Currently, laparoscopy is the standard and the most accurate way to diagnose endometriosis, but it consists of invasive surgery with heavy costs which leads women to postpone this diagnostic procedure and rely on pain medication to relieve the symptoms of endometriosis. A camera is placed through the body to visualize the structures and any lesions

that may be attached to the uterus or other surrounding structures. Lesions are usually large and can vary in color (Hsu et al., 2010).

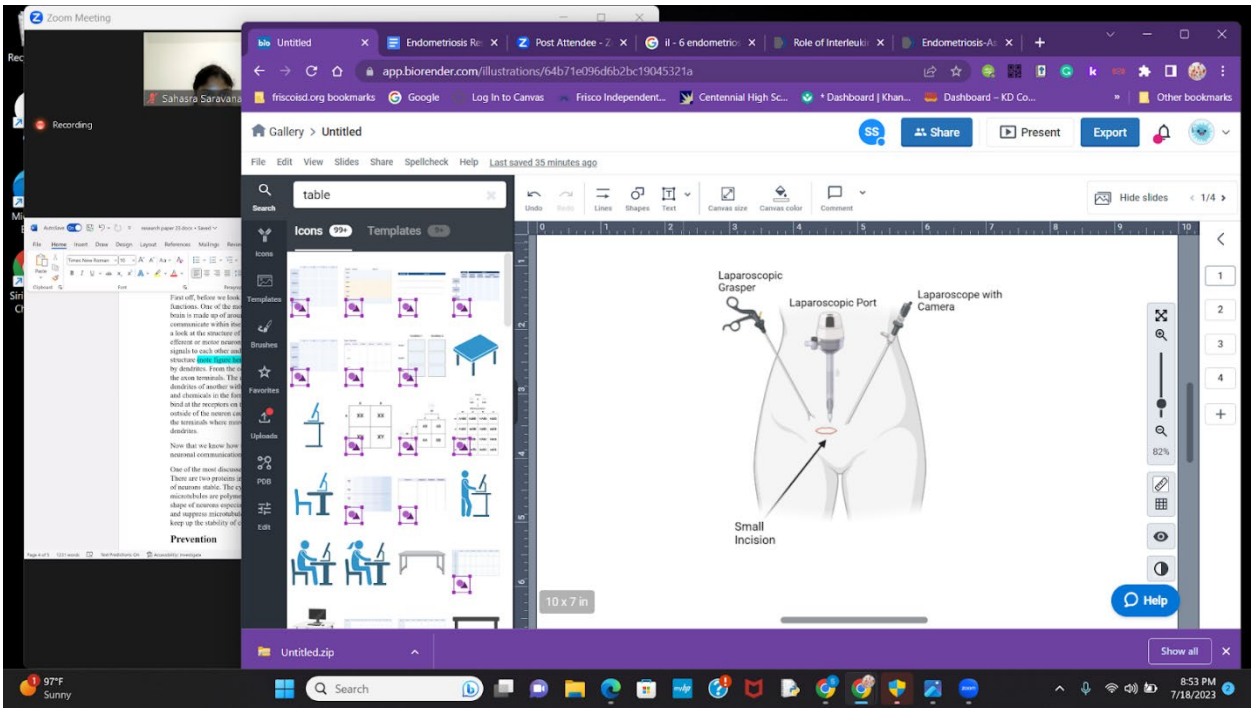

Figure 1: Laparoscopy is an invasive procedure that consists of a laparoscopic grasper, a laparoscopic port, and a camera. Image inspired by (Jacobson 2018).

Symptoms include heavy, painful cramps, so when women go visit gynecologists, they often label it as just menstrual cramps associated with the regular menstrual cycle. But sometimes the case isn't that doctors aren't taking patients' concerns seriously but it's that endometriosis doesn't have extensive research done on it. This can also be due to the gender gap in research where male bodies are researched extensively, and those findings are then applied to female bodies which doesn't always work out due to different structures and hormones.

Additionally, endometriosis can also present itself as asymptomatic which makes it even more difficult to diagnose, or even appear in men which is a whole different perspective. Transvaginal ultrasounds and regular ultrasounds are sometimes used to try to diagnose endometriosis, but often the lesions can be hidden or the results can be inconclusive. Most imaging techniques to diagnose endometriosis do not have the best resolution to detect the lesions (Hsu et al., 2010). Additionally, the medication that people take lowers estrogen levels since estrogen is the driving force behind endometriosis which can then lead to infertility. Endometriosis can be found in the abdominopelvic cavity, thoracic cavity, and nasal mucosa is an example that retrograde menstruation is not the only process affecting the progression of endometriosis. Having different phenotypes of endometriosis increases the chance of false-negative laparoscopic surgery in women presenting symptoms which increases the need to find other techniques to help with the diagnosis process (Soo Hyun Ahn et al., 2017).

Role of Pathogenesis and Angiogenesis

Angiogenesis has an important role in the pathogenesis of endometriosis since the growth of new blood vessels is necessary for lesions to persist in patients with endometriosis (Chung & Sang Jun Han, 2022).

The formation of veins includes molecules such as vascular endothelial growth factor. IL-17A is associated with being an important angiogenic factor and increases levels of VEGF and IL-8 which increase ectopic foci in endometriosis patients. IL-17A is further noted as an integral part of endometriosis, as levels of this biomarker decreased after patients went through surgery to treat their endometriosis. High levels of IL-17A are present in peritoneal fluid, serum, and lesions. IL-17A is present in the promotion of the progression of a disease, infection, pathogenesis of autoimmune diseases, injury, and chronic inflammatory disorders (Shi et al., 2022).

Blood Biomarkers

CA - 125 is the most common biomarker to diagnose endometriosis, but the specificity and sensitivity tend to be higher when combined with other biomarkers such as TNF-α and IL - 8. Another panel of biomarkers includes chemokine receptor type 1, mRNA, and MCP1. This panel has a sensitivity of 92.2% and a specificity of 81.6%. CA-125 presents itself in higher levels in patients with endometriosis, but decreases after surgery takes place and lesions are removed (Costin Vlad Anastasiu et al., 2020). CA-125 is an important predictor for patients with endometriosis and should be considered when there are signs of surgical need, especially if the stage of disease, lesion size, and adhesion score are taken into consideration (Karimi-Zarchi et al., 2016).

CA - 19-9 is another tumor marker like CA-125, CA - 19-9 also has elevated levels in the blood, but the sensitivity of this molecule is lower than that of CA - 125 (Costin Vlad Anastasiu et al., 2020).

Interleukin 6 has been known to have increased serum levels in people with endometriosis, and it is a proinflammatory cytokine. Specifically, stages I-II in endometriosis had increased levels of this molecule. It has a sensitivity of approximately 75% and a specificity of 83.3% (Costin Vlad Anastasiu et al., 2020).

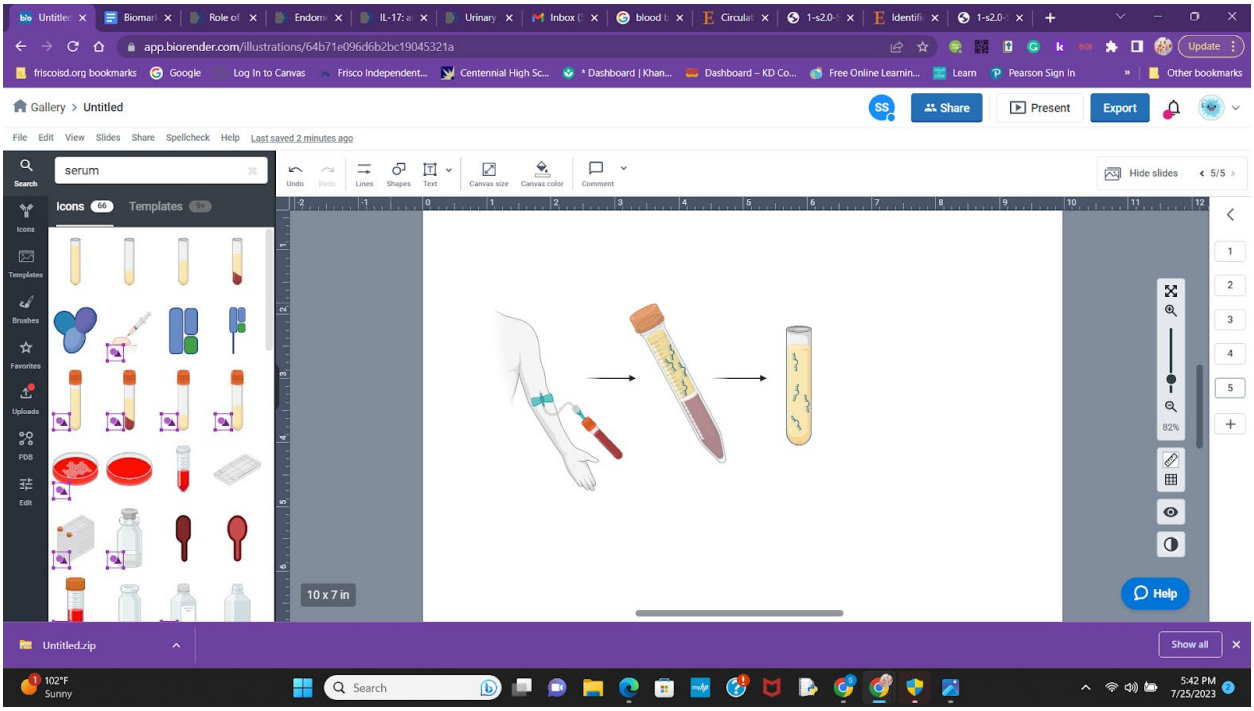

Figure 2: miRNA can be collected from a blood sample to help diagnose endometriosis. Image inspired by (Misir et al., 2021).

Urine Biomarkers

Enolase is a urine biomarker and may be increased during tissue inflammation or inflammatory disease states. Enolase-1 can be found in various tissues, including several tumors associated with chronic inflammatory change. Enolase -1 is not commonly used as a biomarker to detect endometriosis as levels of this molecule are relatively the same in both people with and without endometriosis. This biomarker has a less powerful detection ability but has the potential to be used in a panel of biomarkers (Chen et al., 2022).

A panel of three combined biomarkers (serum CA125, urinary VDBP, and A1AT creatinine ratio) had a sensitivity of 90.9% and a specificity of 76.5%. Double urine markers used in along with VDBP and A1AT creatinine ratio also presented good chances of being potential valid biomarkers (sensitivity 81.8% and specificity 76.5%). VDBP is a protein that is a key factor in the immune system, as it activates macrophages, neutrophils, and monocytes during inflammation. VDBP has increased expression in patients with endometriosis like the blood biomarkers covered previously. There was increased expression of VDBP in urine from people with endometriosis compared to people without the disease. However, the diagnostic performance was less than that for serum CA125. Although the AUC value for the urinary VDBP-creatinine ratio was not higher than that of serum CA125 (0.841 vs. 0.888), it still has potential as a non-invasive detection biomarker (Chen et al., 2022).

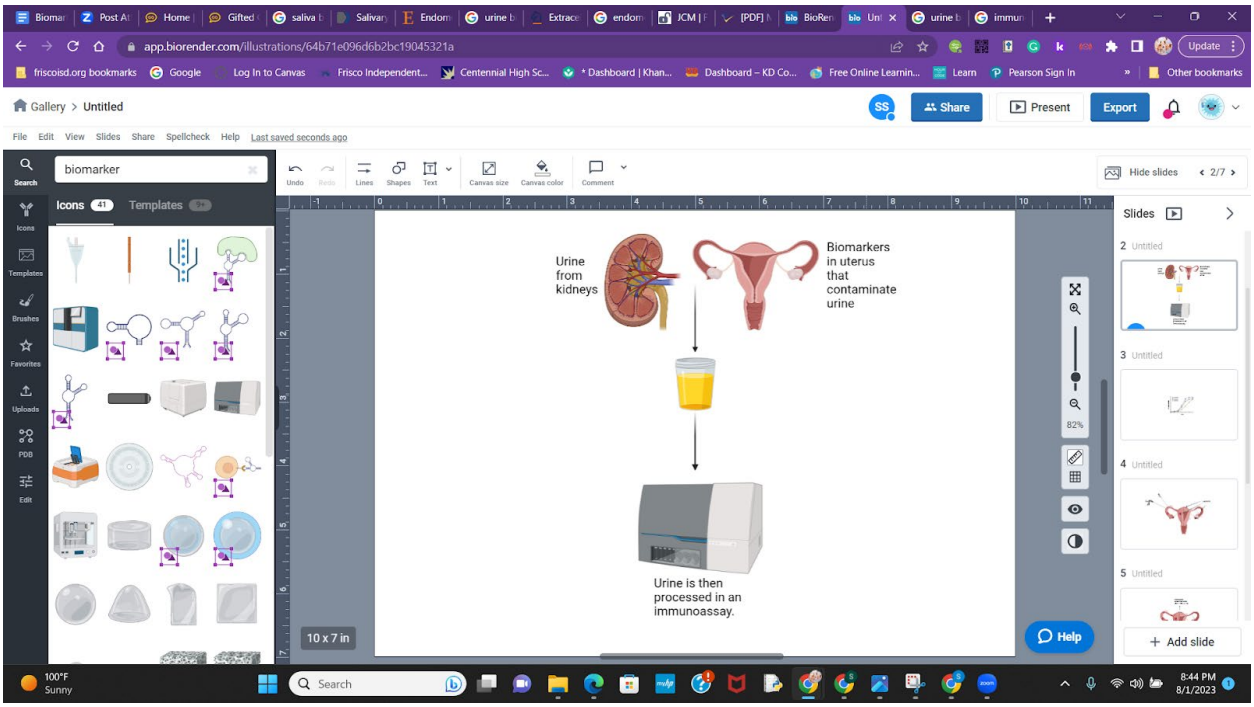

Figure 3: Urine biomarkers can be derived from the kidneys or uterus and then can be processed to detect biomarkers. Image inspired by (Njoku et al., 2020).

Saliva Biomarkers

Hsa-mir-16-5p and hsa-mir-191-5p are present in samples of the saliva of patients with endometriosis. However, hsa-mir-145-3p was less common. Hsa-mir-135a had a greater presence in the saliva of women with endometriosis in comparison with women without endometriosis (Perricos et al., 2022).

In a study, 109 mi RNAs were tested with their sensitivity, specificity, and AUC ranging from 80% to 96.8%, 80% to 100%, and 79.9% to 98.4%. 84 of the miRNAs were tied to malignant and benign disorders. However, miR-34c-5p and miR-19b-1-5p have specifically been associated with the disease of endometriosis. Additionally, 29 of the miRNAs were correlated to the signaling pathways of the disease. These included PTEN, PI3K/Akt, YAP/TAZ/EGFR, HIF1α/NF κB, and Wnt/β-catenin. Saliva is an increasingly attractive body fluid in the search for disease biomarkers since it has great stability in severe conditions, can be stored for extended periods, and is more accessible for menstruators in third-world countries as there is less risk of infection and doesn't require a procedure to obtain (Sofiane Bendifallah et al., 2022).

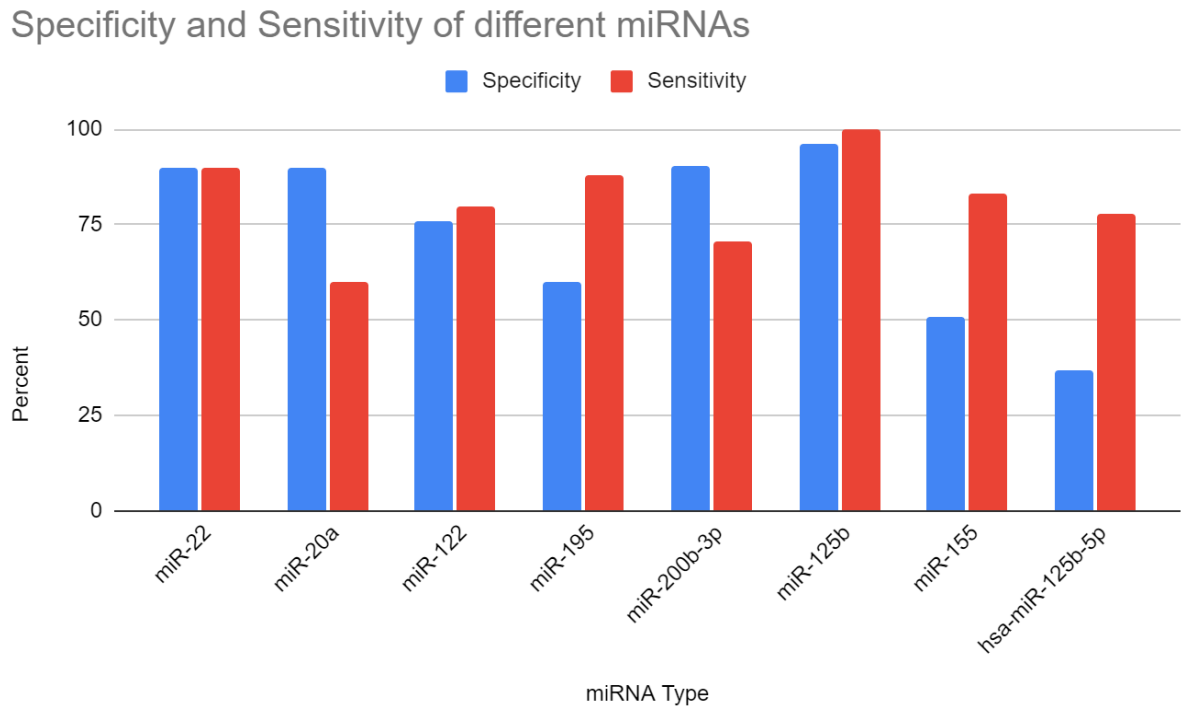

Figure 4: This graph displays the potential of different miRNAs to be biomarkers for endometriosis. Data derived from (Costin Vlad Anastasiu et al., 2020).

Genomics/Proteomics

Genomics may be a potential way of diagnosing endometriosis, especially in the earlier stages of the disease. Some gene-based technologies include cDNA hybridization and cDNA microarray techniques. Studies show that women with endometriosis have higher plasma concentrations of cDNA than those without the disease. Mitochondrial DNA also has the potential to be a biomarker for endometriosis, but further research needs to be conducted (Costin Vlad Anastasiu, 2020).

Using SELDI-TOF MS, a study examined different patterns of serum proteins in 90 women with endometriosis. The researchers concluded that a panel of proteins, with molecular weights ranging between 2000 and 20,000 Da differentiated affect women and women without endometriosis. The panel had a sensitivity of 81.3% and a specificity of 60.3%. Using, ELISA, AXIN1 and ST1A1 were examined in endometriotic women and women without the disease. These molecules are presented at higher levels in women with endometriosis than women without. AXIN1 seems to have great potential to be a non-invasive diagnosis protein for endometriosis (Costin Vlad Anastasiu et al., 2020).

Drawbacks of Biomarkers

Instead of relying on blood or even urine for potential biomarkers, which may contain other information and molecules than to indicate the presence of endometriosis in women, using the direct source of the disease-like tissue might be more beneficial to study, but this is still invasive. Additionally, physicians may have to have a panel of biomarkers which could be hard to get all the samples if they are from different substances (Soo Hyun Ahn et al., 2017).

Conclusion

A couple of blood biomarkers have been the most commonly used to help diagnose endometriosis, but there are so many other biomarkers that have the potential to help the diagnosis process, especially in a panel. Genomics also has a promising outlook and could be the next reliable step to diagnose endometriosis. MirNA also has a high potential to be a biomarker, especially considering the accessibility to acquiring this molecule through saliva. Biomarkers can be the new diagnostic tool due to the ease of getting these molecules which is mostly noninvasive. MiRNA can be obtained through blood and saliva which is easier to get a sample of than going through surgery which can lead to complications that the woman may not be able to afford. Endometriosis is a disease that negatively affects the way many women lead their lives and also impacts the progress of a country due to its debilitating effects. A noninvasive diagnosis is a priority to getting treatment in the earlier stages of endometriosis to reduce the risk of infertility.

Acknowledgments

Thank you to Dr. Rajagopal Appavu and Coach Jo for mentoring me through the research and writing process.

References

Agrawal, S., Tapmeier, T. T., Rahmioglu, N., Kirtley, S., Zondervan, K. T., & Becker, C. M. (2018). The miRNA Mirage: How Close Are We to Finding a Non-Invasive Diagnostic Biomarker in Endometriosis? A Systematic Review. *International Journal of Molecular Sciences*, *19*(2), 599. https://doi.org/10.3390/ijms19020599

Ahn, S. H., Singh, V., & Tayade, C. (2017). Biomarkers in endometriosis: challenges and opportunities. *Fertility and Sterility*, *107*(3), 523–532. https://doi.org/10.1016/j.fertnstert.2017.01.009

Alborzi, S., Madadi, G., Samsami, A., Soheil, P., Azizi, M., Alborzi, M., & Bakhshaie, P. (2015). Decreased ovarian reserve: any new hope? *Minerva Ginecologica*, *67*(2), 149–167. https://pubmed.ncbi.nlm.nih.gov/25668507/

Amini, L., Chekini, R., Nateghi, M. R., Haghani, H., Jamialahmadi, T., Sathyapalan, T., & Sahebkar, A. (2021). The Effect of Combined Vitamin C and Vitamin E Supplementation on Oxidative Stress Markers in Women with Endometriosis: A Randomized, Triple-Blind Placebo-Controlled Clinical Trial. *Pain Research and Management*, *2021*, 1–6. https://doi.org/10.1155/2021/5529741

Anastasiu, C. V., Moga, M. A., Elena Neculau, A., Bălan, A., Scârneciu, I., Dragomir, R. M., Dull, A.-M., & Chicea, L.-M. (2020). Biomarkers for the Noninvasive Diagnosis of Endometriosis: State of the Art and Future Perspectives. *International Journal of Molecular Sciences*, *21*(5), 1750. https://doi.org/10.3390/ijms21051750

Bartiromo, L., Schimberni, M., Villanacci, R., Mangili, G., Ferrari, S., Ottolina, J., Salmeri, N., Dolci, C., Tandoi, I., & Candiani, M. (2022). A Systematic Review of Atypical Endometriosis-Associated Biomarkers. *International Journal of Molecular Sciences*, *23*(8), 4425. https://doi.org/10.3390/ijms23084425

Bazot, M., & Daraï, E. (2017). Diagnosis of deep endometriosis: clinical examination, ultrasonography, magnetic resonance imaging, and other techniques. *Fertility and Sterility*, *108*(6), 886–894. https://doi.org/10.1016/j.fertnstert.2017.10.026

Bendifallah, S., Suisse, S., Puchar, A., Delbos, L., Poilblanc, M., Descamps, P., Golfier, F., Jornea, L., Bouteiller, D., Touboul, C., Dabi, Y., & Daraï, E. (2022). Salivary MicroRNA Signature for Diagnosis of Endometriosis. *Journal of Clinical Medicine*, *11*(3), 612. https://doi.org/10.3390/jcm11030612

Brosens, I., Puttemans, P., Campo, R., Gordts, S., & Kinkel, K. (2004). Diagnosis of endometriosis: pelvic endoscopy and imaging techniques. *Best Practice & Research Clinical Obstetrics*

Burney, R. O., & Giudice, L. C. (2012). Pathogenesis and pathophysiology of endometriosis. *Fertility and Sterility*, *98*(3), 511–519. https://doi.org/10.1016/j.fertnstert.2012.06.029

Chapron, C., Lafay-Pillet, M.-C., Santulli, P., Bourdon, M., Maignien, C., Gaudet-Chardonnet, A., Maitrot-Mantelet, L., Borghese, B., & Marcellin, L. (2022). A new validated screening method for endometriosis diagnosis based on patient questionnaires. *EClinicalMedicine*, *44*. https://doi.org/10.1016/j.eclinm.2021.101263

Chapron, C., Marcellin, L., Borghese, B., & Santulli, P. (2019). Rethinking mechanisms, diagnosis, and management of endometriosis. *Nature Reviews Endocrinology*, *15*(11), 666–682. https://doi.org/10.1038/s41574-019-0245-z

Chen, W.-C., Cheng, C.-M., Liao, W.-T., & Chang, T.-C. (2022). Urinary Biomarkers for Detection of Clinical Endometriosis or Adenomyosis. *Biomedicines*, *10*(4), 833–833. https://doi.org/10.3390/biomedicines10040833

Chung, M. S., & Han, S. J. (2022). Endometriosis-Associated Angiogenesis and Anti-angiogenic Therapy for Endometriosis. *Frontiers in Global Women's Health*, *3*. https://doi.org/10.3389/fgwh.2022.856316

Coutinho, L. M., Ferreira, M. C., Rocha, A. L. L., Carneiro, M. M., & Reis, F. M. (2019). New biomarkers in endometriosis. *Advances in Clinical Chemistry*, 59–77. https://doi.org/10.1016/bs.acc.2018.12.002

Czyzyk, A., Podfigurna, A., Szeliga, A., & Meczekalski, B. (2017). Update on endometriosis pathogenesis. *Minerva Ginecologica*, *69*(5), 447–461. https://doi.org/10.23736/S0026-4784.17.04048-5

Encalada Soto, D., Rassier, S., Green, I. C., Burnett, T., Khan, Z., & Cope, A. (2022). Endometriosis biomarkers of the disease: an update. *Current Opinion in Obstetrics & Gynecology*, *Publish Ahead of Print*. https://doi.org/10.1097/gco.0000000000000798

Evrim Ebru Kovalak, Tolga Karacan, Oğuzhan Zengi, Özlem Karabay Akgül, Eser Sefik Ozyurek, & Hakan Güraslan. (2023). Evaluation of new biomarkers in stage III and IV endometriosis. *Gynecological Endocrinology*, *39*(1). https://doi.org/10.1080/09513590.2023.2217290

Fassbender, A., Vodolazkaia, A., Saunders, P., Lebovic, D., Waelkens, E., De Moor, B., & D'Hooghe, T. (2013). Biomarkers of endometriosis. *Fertility and Sterility*, *99*(4), 1135–1145. https://doi.org/10.1016/j.fertnstert.2013.01.097

Ferrier, C., Bendifallah, S., Suisse, S., Dabi, Y., Touboul, C., Puchar, A., Zarca, K., & Durand Zaleski, I. (2022). Saliva microRNA signature to diagnose endometriosis: A cost-effectiveness evaluation of the Endotest®. *BJOG: An International Journal of Obstetrics & Gynaecology*, *130*(4), 396–406. https://doi.org/10.1111/1471-0528.17348

Fitting, D., Krenzer, A., Troya, J., Banck, M., Sudarevic, B., Brand, M., Böck, W., Zoller, W. G., Rösch, T., Puppe, F., Meining, A., & Hann, A. (2022). A video-based benchmark data set (ENDOTEST) to evaluate computer-aided polyp detection systems. *Scandinavian Journal of Gastroenterology*, *57*(11), 1397–1403. https://doi.org/10.1080/00365521.2022.2085059

Gynaecology, *18*(2), 285–303. https://doi.org/10.1016/j.bpobgyn.2004.03.002

He, Y., Li, J., Qu, Y., Sun, L., Zhao, X., Wu, H., & Zhang, G. (2023). Identification and Analysis of Potential Immune-Related Biomarkers in Endometriosis. *Journal of Immunology Research*, *2023*, 2975581. https://doi.org/10.1155/2023/2975581

Horne, A. W., & Missmer, S. A. (2022). Pathophysiology, diagnosis, and management of endometriosis. *BMJ*, *379*, e070750. https://doi.org/10.1136/bmj-2022-070750

Hsu, A. L., Khachikyan, I., & Stratton, P. (2010). Invasive and non-invasive methods for the diagnosis of endometriosis. *Clinical Obstetrics and Gynecology*, *53*(2), 413–419. https://doi.org/10.1097/GRF.0b013e3181db7ce8

Huang, L., Liu, B., Liu, Z., Feng, W., Liu, M., Wang, Y., Peng, D., Fu, X., Zhu, H., Cui, Z., Xie, L., & Ma, Y. (2021). Gut Microbiota Exceeds Cervical Microbiota for Early Diagnosis of Endometriosis. *Frontiers in Cellular and Infection Microbiology*, *11*, 788836. https://doi.org/10.3389/fcimb.2021.788836

Jacobson, J. D. (2018). *Pelvic laparoscopy: MedlinePlus Medical Encyclopedia Image*. Medlineplus.gov. https://medlineplus.gov/ency/imagepages/1109.htm

Jiang, H., Zhang, X., Wu, Y., Zhang, B., Wei, J., Li, J., Huang, Y., Chen, L., & He, X. (2022). Bioinformatics identification and validation of biomarkers and infiltrating immune cells in endometriosis. *Frontiers in Immunology*, *13*. https://doi.org/10.3389/fimmu.2022.944683

Karimi-Zarchi, M., Dehshiri-Zadeh, N., Sekhavat, L., & Nosouhi, F. (2016). Correlation of CA-125 serum level and clinico-pathological characteristic of patients with endometriosis. *International Journal of Reproductive Biomedicine*, *14*(11), 713–718. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5153578/

Kavoussi, S. K., Lim, C. S., Skinner, B. D., Lebovic, D. I., & As-Sanie, S. (2016). New paradigms in the diagnosis and management of endometriosis. *Current Opinion in Obstetrics & Gynecology*, *28*(4), 267–276. https://doi.org/10.1097/gco.0000000000000288

Kiesel, L., & Sourouni, M. (2019). Diagnosis of endometriosis in the 21st century. *Climacteric*, *22*(3), 296–302. https://doi.org/10.1080/13697137.2019.1578743

Kimber-Trojnar, Ż., Pilszyk, A., Niebrzydowska, M., Pilszyk, Z., Ruszała, M., & Leszczyńska-Gorzelak, B. (2021). The Potential of Non-Invasive Biomarkers for Early Diagnosis of Asymptomatic Patients with Endometriosis. *Journal of Clinical Medicine*, *10*(13), 2762. https://doi.org/10.3390/jcm10132762

Koninckx, P. R., Fernandes, R., Ussia, A., Schindler, L., Wattiez, A., Al-Suwaidi, S., Amro, B., Al-Maamari, B., Hakim, Z., & Tahlak, M. (2021). Pathogenesis Based Diagnosis and Treatment of Endometriosis. *Frontiers in Endocrinology*, *12*(12), 745548. https://doi.org/10.3389/fendo.2021.745548

Lalami, I., Abo, C., Borghese, B., Chapron, C., & Vaiman, D. (2021). Genomics of Endometriosis: From Genome Wide Association Studies to Exome Sequencing. *International Journal of Molecular Sciences*, *22*(14), 7297. https://doi.org/10.3390/ijms22147297

Leone Roberti Maggiore, U., Ferrero, S., Mangili, G., Bergamini, A., Inversetti, A., Giorgione, V., Viganò, P., & Candiani, M. (2015). A systematic review on endometriosis during pregnancy: diagnosis, misdiagnosis, complications and outcomes. *Human Reproduction Update*, *22*(1), 70–103. https://doi.org/10.1093/humupd/dmv045

Li, J., He, Y., Liang, T., Wang, J., Jiang, X., & Zhang, G. (2022). Identification of potential differentially methylated gene-related biomarkers in endometriosis. *Epigenomics*, *14*(19), 1157–1179. https://doi.org/10.2217/epi-2022-0249

Li, S., Fu, X., Wu, T., Yang, L., Hu, C., & Wu, R. (2017). Role of Interleukin-6 and Its Receptor in Endometriosis. *Medical Science Monitor*, *23*, 3801–3807. https://doi.org/10.12659/msm.90522

Lukac, S., Schmid, M., Pfister, K., Janni, W., Schäffler, H., & Dayan, D. (2022). Extragenital Endometriosis in the Differential Diagnosis of Non- Gynecological Diseases. *Deutsches Arzteblatt International*, *119*(20), 361–367. https://doi.org/10.3238/arztebl.m2022.0176

M D'Hooghe, T., Fassbender, A., F O, D., & Vanhie, A. (2019). Endometriosis biomarkers: Will codevelopment in academia–industry partnerships result in new and robust noninvasive diagnostic tests? *Biology of Reproduction*, *101*(6), 1140–1145. https://doi.org/10.1093/biolre/ioz016

Macer, M. L., & Taylor, H. S. (2012). Endometriosis and Infertility. *Obstetrics and Gynecology Clinics of North America*, *39*(4), 535–549. https://doi.org/10.1016/j.ogc.2012.10.002

Mehedintu, C., Plotogea, M. N., Ionescu, S., & Antonovici, M. (2014). Endometriosis still a challenge. *Journal of Medicine and Life*, *7*(3), 349–357. https://pubmed.ncbi.nlm.nih.gov/25408753/

Misir, S., Hepokur, C., Oksasoglu, B., Yildiz, C., Yanik, A., & Aliyazicioglu, Y. (2021). Circulating serum miR-200c and miR-34a-5p as diagnostic biomarkers for endometriosis. *Journal of Gynecology Obstetrics and Human Reproduction*, *50*(4), 102092. https://doi.org/10.1016/j.jogoh.2021.102092

Murji, A., Biberoğlu, K., Leng, J., Mueller, M. D., Römer, T., Vignali, M., & Yarmolinskaya, M. (2020). Use of dienogest in endometriosis: a narrative literature review and expert commentary. *Current Medical Research and Opinion*, *36*(5), 895–907. https://doi.org/10.1080/03007995.2020.1744120

Njoku, K., Davide Chiasserini, Jones, E. M., Barr, C. E., O'Flynn, H., Whetton, A. D., & Crosbie, E. (2020). Urinary Biomarkers and Their Potential for the Non-Invasive Detection of Endometrial Cancer. *Frontiers in Oncology*, *10*. https://doi.org/10.3389/fonc.2020.559016

Perricos, A., Proestling, K., Husslein, H., Lorenz Kuessel, Hudson, Q. J., Wenzl, R., & Iveta Yotova. (2022). Hsa-mir-135a Shows Potential as A Putative Diagnostic Biomarker in Saliva and Plasma for Endometriosis. *Biomolecules*, *12*(8), 1144–1144. https://doi.org/10.3390/biom12081144

Reis, F., Monteiro, C., & Carneiro, M. (2017). Biomarkers of Pelvic Endometriosis. *Revista Brasileira de Ginecologia E Obstetrícia / RBGO Gynecology and Obstetrics*, *39*(03), 091–093. https://doi.org/10.1055/s-0037-1601398

Rolla, E. (2019). Endometriosis: advances and controversies in classification, pathogenesis, diagnosis, and treatment. *F1000Research*, *8*. https://doi.org/10.12688/f1000research.14817.1

Shamsa, A., Gilchrist, R. B., Robertson, D. M., Rodgers, R. J., Donoghoe, M. W., Ledger, W. L., Abbott, J. A., & Riepsamen, A. H. (2023). Oocyte-Secreted Serum Biomarkers GDF9 and BMP15 in Women with Endometriosis. *Reproductive Sciences (Thousand Oaks, Calif.)*, *30*(5), 1521–1527. https://doi.org/10.1007/s43032-022-01107-6

Shi, J.-L., Zheng, Z.-M., Chen, M., Shen, H.-H., Li, M.-Q., & Shao, J. (2022). IL-17: an important pathogenic factor in endometriosis. *International Journal of Medical Sciences*, *19*(4), 769–778. https://doi.org/10.7150/ijms.71972

Starodubtseva, N. L., Vitaliy Chagovets, Borisova, A. V., Dinara Salimova, Aleksandrova, N. V., Konstantin Chingin, Chen, H., & Vladimir Frankevich. (2019). Identification of potential endometriosis biomarkers in peritoneal fluid and blood plasma via shotgun lipidomics. *Clinical Mass Spectrometry*, *13*, 21–26. https://doi.org/10.1016/j.clinms.2019.05.007

Taylor, H. S., Kotlyar, A. M., & Flores, V. A. (2021). Endometriosis is a chronic systemic disease: clinical challenges and novel innovations. *The Lancet*, *397*(10276), 839–852. https://doi.org/10.1016/s0140-6736(21)00389-5

Udwadia, T. E. (2004). Diagnostic laparoscopy. *Surgical Endoscopy*, *18*(1), 6–10. https://doi.org/10.1007/s00464-002-8872-0

Vercellini, P., Viganò, P., Somigliana, E., & Fedele, L. (2013). Endometriosis: pathogenesis and treatment. *Nature Reviews Endocrinology*, *10*(5), 261–275. https://doi.org/10.1038/nrendo.2013.255

Višnić, A., Čanadi Jurešić, G., Domitrović, R., Klarić, M., Šepić, T. S., & Barišić, D. (2023). Proteins in urine – Possible biomarkers of endometriosis. *Journal of Reproductive Immunology*, *157*, 103941. https://doi.org/10.1016/j.jri.2023.103941

Wang, M., Zheng, L., Lin, R., Ma, S., Li, J., & Yang, S. (2023). A comprehensive overview of exosome lncRNAs: emerging biomarkers and potential therapeutics in endometriosis. *Frontiers in Endocrinology*, *14*, 1199569. https://doi.org/10.3389/fendo.2023.1199569

Wang, X., & Yu, Q. (2019). Endometriosis-related ceRNA network to identify predictive biomarkers of endometrial receptivity. *Epigenomics*, *11*(2), 147–167. https://doi.org/10.2217/epi-2018-0190

Warzecha, D., Załęcka, J., Mańka, G., Kiecka, M., Lipa, M., Spaczyński, R., Piekarski, P., Banaszewska, B., Jakimiuk, A., Issat, T., Rokita, W., Młodawski, J., Szubert, M., Sieroszewski, P., Raba, G., Szczupak, K., Kluz, T., Kluza, M., Wielgoś, M., & Ołdak, Ł. (2022). Plasma and Peritoneal Fluid Fibronectin and Collagen IV Levels as Potential Biomarkers of Endometriosis. *International Journal of Molecular Sciences*, *23*(24), 15669. https://doi.org/10.3390/ijms232415669

Yilmaz, B. D., & Bulun, S. E. (2019). Endometriosis and nuclear receptors. *Human Reproduction Update*, *25*(4), 473–485. https://doi.org/10.1093/humupd/dmz005

Zhang, N., Hu, G., Myers, T. G., & Williamson, P. R. (2019). Protocols for the Analysis of microRNA Expression, Biogenesis, and Function in Immune Cells. *Current Protocols in Immunology*, *126*(1). https://doi.org/10.1002/cpim.78