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Endometriosis: Potential Biomarkers For Detection And Goal Of Highlighting Risk Factors That Could Be Used In Combination With Biomarkers

[1*]Goodluck Azuonwu (Ph.D) & [2]Akagbuo Rose Ngikanni

[1]Department of Nursing Science, University of Port Harcourt, Rivers State, Nigeria
***(goodator2002@yahoo.com)**

[2]Department of Human Kinetics, Health and Safety Education,
Ignatius Ajuru University of Education, Rivers State, Nigeria

ABSTRACT
Endometriosis is a disease of adolescents and reproductive-aged women characterized by the presence of endometrial tissue outside the uterine cavity and commonly associated with chronic pelvic pain and infertility. Here we review the epidemiology of endometriosis as well as potential biomarkers for detection and with the goal of highlighting risk factors that could be used in combination with biomarkers to identify and treat women with endometriosis earlier. Recent findings: Early age at menarche, shorter menstrual length, and taller height are associated with a higher risk of endometriosis while parity, higher body mass index (BMI) and smoking are associated with decreased risk. Endometriosis often presents as infertility or continued pelvic pain despite treatment with analgesics and cyclic oral contraceptive pills. Summary: Despite a range of symptoms, diagnosis of endometriosis is often delayed due to lack of non-invasive, definitive and consistent biomarkers for diagnosis of endometriosis. Hormone therapy and analgesics are used for treatment of symptomatic endometriosis. However, the efficacy of these treatments are limited as endometriosis often recurs. In this review, we describe potential diagnostic biomarkers and risk factors that may be used as early non-invasive in vitro tools for identification of endometriosis to minimize diagnostic delay and improve reproductive health of patients.
Keywords: Endometriosis, Biomarkers, Detection, Adolescent, Factors

INTRODUCTION

Endometriosis, described, as the presence of endometrial tissue outside the uterine cavity, is a perplexing disease with a protean clinical presentation and pathology, and is associated with chronic pelvic pain and infertility, with a significant influence on the quality of life and health cost financial implication (Ozkan et al., 2008). The estimated prevalence of endometriosis among in the women of reproductive age is between 2% and 10% in Rivers State (Eskenazi & Warner, 1997). Chronic pelvic pain and dyspareunia are two clinical presentation of endometriosis with a major impact on physical and mental constituents of quality of life (Warner et al., 2013). The onset of symptoms of the endometriosis and its surgical diagnosis has a diagnostic delay of 6.7 years. Endometriosis is a true chronic disease with a significant impairment of quality of life due to endometriosis-associated symptoms (chronic pelvic pain, dysmenorrhoe, dyspareunia and infertility) even when the management of the disease is in a tertiary centre. Endometriosis is connected to discomfort/pain, anxiety/depression and social dysfunction, which affect health related quality of life. Endometriosis treatments cost has an economic burden that is comparative to that of managing chronic disease such as rheumatoid arthritis, crohns disease and diabetes mellitus (Simoens et al., 2012).

In women afflicted with endometriosis, the physical HRQoL is remarkably reduced when compared with women with no endometriosis with similar symptoms; due to reduced effectiveness in work there is a loss of 10.8 hrs per week in each of the women afflicted with endometriosis (Nnoaham et al., 2011). Poor yield in work was expressed into remarkable costs per woman/week from US $4 in Nigeria to US $456 in Italy.

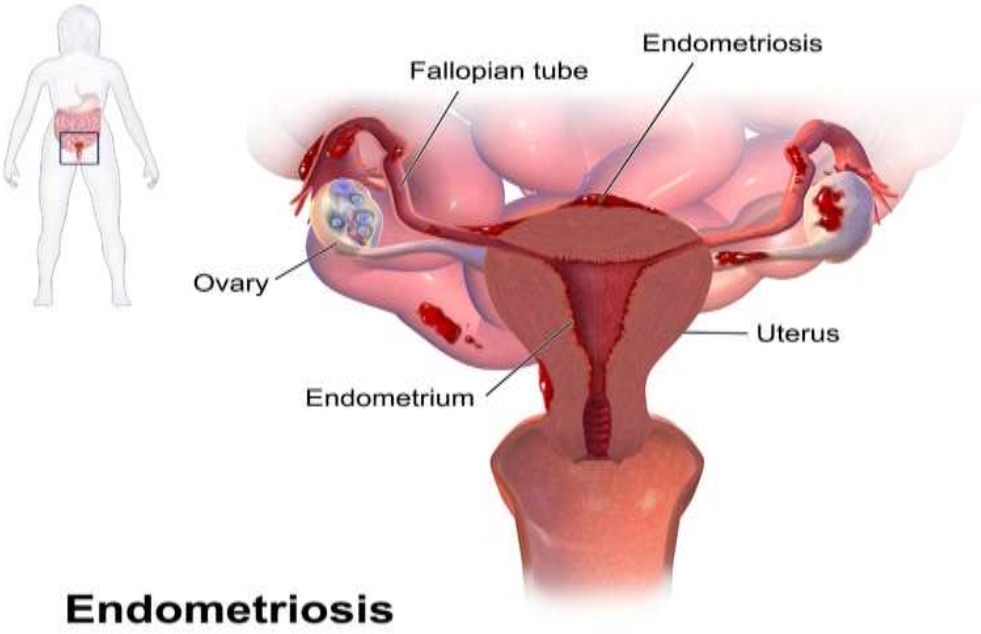
Meaning of Endometriosis

Endometriosis is a full body condition in which cells similar to those in the endometrium, the layer of tissue that normally covers the inside of the uterus, grow outside the uterus. Most often this is on the ovaries, fallopian tubes, and tissue around the uterus and ovaries; however, in rare cases it may also occur in other parts of the body. Some symptoms include pelvic pain, heavy periods, pain with bowel movements, and infertility (*Bulletti et al., 2010*). Nearly half of those affected have chronic pelvic pain, while in 70% pain occurs during menstruation. Pain during sexual intercourse is also common. Infertility occurs in up to half of affected individuals. About 25% of individuals have no symptoms and 85% of those seen with infertility in a tertiary center have no pain. Endometriosis can have both social and psychological effects (*Culley et al., 2013*).

The cause is not entirely clear. Risk factors include having a family history of the condition. The areas of endometriosis bleed each month (menstrual period), resulting in inflammation and scarring. The growths due to endometriosis are not cancer. Diagnosis is usually based on symptoms in combination with medical imaging; however, biopsy is the surest method of diagnosis. Other causes of similar symptoms include pelvic inflammatory disease, irritable bowel syndrome, interstitial cystitis, and fibromyalgia. Endometriosis is commonly misdiagnosed and women often report being incorrectly told their symptoms are trivial or normal (*Culley et al., 2013*). Women suffering from endometriosis see an average of seven physicians before receiving a correct diagnosis, with an average delay of 6.7 years between the onset of symptoms and surgically-obtained biopsies, the gold standard for diagnosing the condition. This average delay places endometriosis at the extreme end of diagnostic inefficiency (*Zondervan et al., 2020*).

Tentative evidence suggests that the use of combined oral contraceptives reduces the risk of endometriosis. Exercise and avoiding large amounts of alcohol may also be preventive. There is no cure for endometriosis, but a number of treatments may improve symptoms. This may include pain medication, hormonal treatments or surgery. The recommended pain medication is usually a non-steroidal anti-inflammatory drug (NSAID), such as naproxen. Taking the active component of the birth control pill continuously or using an intrauterine device with progestogen may also be useful. Gonadotropin-releasing hormone agonist (GnRH agonist) may improve the ability of those who are infertile to get pregnant. Surgical removal of endometriosis may be used to treat those whose symptoms are not manageable with other treatments (*Vercellini et al., 2011*).

One estimate is that 10.8 million people are affected globally as of 2015. Other sources estimate 6 to 10% of the general female population and 2 to 11% of asymptomatic women are affected. In addition, 11% of women in a general population have undiagnosed endometriosis that can be seen on magnetic resonance imaging (MRI) (*Shafrir et al., 2018*). Endometriosis is most common in those in their thirties and forties; however, it can begin in girls as early as eight years old. It results in few deaths with unadjusted and age-standardized death rates of 0.1 and 0.0 per 100,000. Endometriosis was first determined to be a separate condition in the 1920s. Before that time, endometriosis and adenomyosis were considered together. It is unclear who first described the disease (*Brosens, 2012*).



Types Of Endometriosis

Endometriosis is also grouped by what area of the pelvis or abdomen it affects. There are four main types:

1. Superficial peritoneal endometriosis
2. Endometriomas
3. Deeply infiltrating endometriosis (DIE)
4. Abdominal wall endometriosis

- **Superficial peritoneal endometriosis.** The peritoneum is a thin membrane that lines your abdomen and pelvis. It also covers most of the organs in these cavities. In this type, the endometrial tissue attaches to the peritoneum. This is the least severe form.
- **Endometriomas.** These are dark, fluid-filled cysts. They're also called chocolate cysts. They vary in size and can appear in different parts of your pelvis or abdomen, but they're most common in the ovaries.
- **Deeply infiltrating endometriosis (DIE).** In this type, the endometrial tissue has invaded the organs either within or outside your pelvic cavity. This can include your ovaries, rectum, bladder, and bowels. It's rare, but sometimes a lot of scar tissue can bond organs so they become stuck in place. This condition is called frozen pelvis. But this only happens to 1%-5% of people with endometriosis.
- **Abdominal wall endometriosis.** In some cases, endometrial tissue can grow on the abdominal wall. The cells may attach to a surgical incision, like one from a C-section.

Symptoms of Endometriosis

Pain and infertility are common symptoms, although 20–25% of women are

A major symptom of endometriosis is recurring pelvic pain. The pain can range from mild to severe cramping or stabbing pain that occurs on both sides of the pelvis, in the lower back and rectal area, and even down the legs. The amount of pain a person feels correlates weakly with the extent or stage (1 through 4) of endometriosis, with some individuals having little or no pain despite having extensive endometriosis or endometriosis with scarring, while others may have severe pain even though they have only a few small areas of endometriosis. The most severe pain is typically associated with menstruation. Pain can also start a week before a menstrual period, during and even a week after a menstrual period, or it can be constant. The pain can be debilitating and result in emotional stress. Symptoms of endometriosis-related pain may include:

- dysmenorrhea (64%) – painful, sometimes disabling cramps during the menstrual period; pain may get worse over time (progressive pain), also lower back pains linked to the pelvis
- chronic pelvic pain – typically accompanied by lower back pain or abdominal pain
- dyspareunia – painful sexual intercourse
- dysuria – urinary urgency, frequency, and sometimes painful voiding
- mittelschmerz – pain associated with ovulation
- bodily movement pain – present during exercise, standing, or walking

Compared with patients with superficial endometriosis, those with deep disease appear to be more likely to report shooting rectal pain and a sense of their insides being pulled down (*Ballard et al., 2010*). Individual pain areas and pain intensity appear to be unrelated to the surgical diagnosis, and the area of pain unrelated to the area of endometriosis (*Ballard et al., 2010*).

There are multiple causes of pain. Endometriosis lesions react to hormonal stimulation and may "bleed" at the time of menstruation. The blood accumulates locally if it is not cleared shortly by the immune, circulatory, and lymphatic system. This may further lead to swelling, which triggers inflammation with the activation of cytokines, which results in pain. Another source of pain is the organ dislocation that arises from adhesion binding internal organs to each other. The ovaries, the uterus, the oviducts, the peritoneum, and the bladder can be bound together. Pain triggered in this way can last throughout the menstrual cycle, not just during menstrual periods (*Ballard et al., 2010*).

Also, endometriotic lesions can develop their own nerve supply, thereby creating a direct and two-way interaction between lesions and the central nervous system, potentially producing a variety of individual differences in pain that can, in some cases, become independent of the disease itself. Nerve fibres and blood vessels are thought to grow into endometriosis lesions by a process known as neuroangiogenesis.

Infertility

About a third of women with infertility have endometriosis. Among those with endometriosis, about 40% are infertile (*Bulletti et al., 2010*). The pathogenesis of infertility is dependent on the stage of disease: in early stage disease, it is hypothesised that this is secondary to an inflammatory response that impairs various aspects of conception, whereas in later stage disease distorted pelvic anatomy and adhesions contribute to impaired fertilization.

Causes Of Endometriosis In Rivers State

During a regular menstrual cycle, your body sheds the lining of your uterus. This allows menstrual blood to flow from your uterus through the small opening in the cervix and out through your vagina (Valinda, 2019).

The exact cause of endometriosis in Rivers State is not known, and there are several theories regarding the cause, although no one theory has been scientifically proven.

One of the oldest theories is that endometriosis in Rivers State occurs due to a process called retrograde menstruation. This happens when menstrual blood flows back through your fallopian tubes into your pelvic cavity instead of leaving your body through the vagina (Valinda, 2019).

Another theory is that hormones transform the cells outside the uterus into cells similar to those lining the inside of the uterus, known as endometrial cells.

Others believe the condition may occur if small areas of your abdomen convert into endometrial tissue. This may happen because cells in your abdomen grow from embryonic cells, which can change shape and act like endometrial cells. It’s not known why this occurs (Valinda, 2019).

These displaced endometrial cells may be on your pelvic walls and the surfaces of your pelvic organs, such as your bladder, ovaries, and rectum. They continue to grow, thicken, and bleed over the course of your menstrual cycle in response to the hormones of your cycle.

It’s also possible for the menstrual blood to leak into the pelvic cavity through a surgical scar, such as after a cesarean delivery (also commonly called a C-section).

Another theory is that the endometrial cells are transported out of the uterus through the lymphatic system. Still another theory purports it may be due to a faulty immune system that isn't destroying errant endometrial cells.

Some believe endometriosis might start in the fetal period with misplaced cell tissue that begins to respond to the hormones of puberty. This is often called Mullerian theory. The development of endometriosis might also be linked to genetics or even environmental toxins (Valinda, 2019).

Treatment of Endometriosis

There are many different treatment options to help manage endometriosis. These treatments may change if a person is pregnant or trying to get pregnant:

- **Pain medication**: Prescription or over-the-counter pain-relievers can help reduce endometriosis pain. However, if a person gets pregnant, a doctor may advise them to stop using some types of pain-relievers, as they can affect the developing fetus.
- **Hormonal medications**: Pills and other devices containing synthetic estrogen, progestin, or both are a common way to manage endometriosis symptoms. However, they are not suitable for women trying to get pregnant or who are already pregnant.
- **Surgery**: During laparoscopy, a specialist will insert a fiber optic instrument through small incisions in the abdomen to view the organs inside. Laparotomy is major open-abdominal surgery. Both of these procedures aim to remove the endometrial lesions while leaving the surrounding healthy tissue intact. Surgery to remove lesions may improve a person's chance of getting pregnant.
- **Infertility treatment**: A woman with endometriosis may require infertility treatment in order to conceive. In vitro fertilization may be the best option for many women with endometriosis, especially those who did not conceive after laparoscopy.
- **Hysterectomy**: Some doctors recommend a hysterectomy, or the removal of the uterus, especially for women who do not wish to become pregnant. However, a hysterectomy is not a complete cure for endometriosis, as there is a small chance that symptoms may return after surgery.

When speaking to a doctor about endometriosis treatment, it is vital to be clear about the goals of the treatment, such as wanting to improve fertility and get pregnant.

Some treatments for endometriosis are not suitable for a person who is trying to conceive.

Someone who is already taking hormonal medications to manage their symptoms, for example, will need to stop taking them if they are actively trying to get pregnant (Valinda, 2019).

METHODS

This paper adopted qualitative analysis approach; relevant literatures were sourced from journals and textbooks in the internet for data. All the materials used in this paper are open access articles under Creative Commons Attribution License which means that a researcher is free to use them provided that credit is given to the authors.

CONCLUSION

Endometriosis is a disease of the female genital system principally characterized by the presence of endometrial tissue, consisting of glands and/or stroma outside the uterus. The ovary is the most common site for endometriosis. Other commonly affected sites include pelvic peritoneum and rectovaginal septum. Rarely lesions have been identified on the umbilicus, diaphragm, pleura and 1 pericardium. The definitive diagnosis of endometriosis is based on histologic examination of tissue biopsies. The histologic diagnosis of endometriosis is typically based on the presence of endometriotic glands and stroma in extra-uterine biopsy tissue.

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