

Analytical Hypotheses on Possible Etiology and Types of Endometriosis

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Abstract

Endometriosis is a debilitating disease, of yet unknown etiology, globally affecting about 70 million women in child-bearing age. Previous hypotheses regarding the pathogenesis of endometriosis include retrograde menstruation grounded on peristaltic discharge of menstrual debris into the pelvic peritoneum to form endometrial tissue; the hematological and lymphatic spread theory which proposes seepage of menstrual wreckage into venous and/or lymphatic outflow leading to metastasis; the immunologic concept which assumes weakened or unresponsive immune system and presence of endometrial antibodies and the genetic hypothesis which is based on endometriosis being coded for in the genes of some females. This study takes into consideration imaginable embryonic origin of one type of endometriosis on one hand and on the other hand, viral assaults on the endometrium causing the other type of endometriosis. Therefore, this paper proposes two types of endometriosis, one arising from within the endometrium, which is labelled “endometrial endometriosis” and the other arising from outside the endometrium, hereby referred to as “endometroid endometriosis.” These two types of endometriosis may have different presentation and probably require different management.

Keywords: Endometriosis, Endometroid, Müllerian duct, Histopathology, Uterine pump, Seepage, Etiology, Hypothesis

Introduction

Many women globally may suffer in silence, oblivious of having endometriosis and simply believing that the pain and debilitation they have, synonymous with endometriosis, is what women have to endure. Endometriosis, the presence of functioning and proliferating endometrial-like tissues found outside the uterus induces chronic inflammatory reaction, scar tissue, and adhesions that may distort a woman’s pelvic anatomy [1,2]. Earlier observation referred to endometrial tissues found in or on ovaries as sources of ovarian cancer [3]. In most cases, this ectopic endometrium is confined to structures in the pelvis but can metastasize to anywhere in the body. Early endometriotic implants are small clear or colored flat patches sprinkled on the pelvic surface [4]. Endometriosis may grow on the surface of the ovary as implants or invade the ovary and develop a blood-filled cyst called an endometrioma, or “chocolate cyst” [4]. In their ectopic location, cells forming endometriosis perform the same functions

as the normal intact intra-uterine endometrial cells – responding to gestational hormones, undergoing similar cyclical fluctuations, as well as effecting cyclical bleeding and shedding. Globally, there is no definitive prevalence of endometriosis because the disease often occurs devoid of any noteworthy warning signs, though the common opinion is that it occurs in 6 to 10% of the general female population, in women with pain, infertility, or both, and with a frequency is 35–50% [5]. The prevalence of endometriosis in general population of women aged 15–44 years is put at 1% to 8% [6] or up to 10% [6,7] and more recent data have shown that the incidence of endometriosis stabilized in the last 30 years at 2.37–2.49/1000/y [7], supporting the general view of its approximate prevalence being 6–8% [8]. However, the absence of reliable non-invasive marker for the diagnosis of endometriosis makes the true prevalence problematic. Endometriosis is primarily found in young menstruating women, rarely observed before puberty, after menopause or in women with amenorrhea but its occurrence is not related to ethnic or social group distinctions

[9]. Endometriosis is often associated with chronic fatigue, acute abdomen and with dyspareunia and dysmenorrhea [10,11]. Most of the organs that are commonly affected by ectopic endometrium are located within the pelvis or are adjacent to it [11,12]. Endometriosis affects over 70 million women and girls worldwide, is often stigmatized as simply “painful periods,” and is a puzzling and widely misunderstood illness [13]. The earliest concept on the etiology of endometriosis is the Sampson’s theory (1925) of retrograde dissemination of menstrual debris through the fallopian tubes into the peritoneal cavity [14]. Studies have however shown that this occurrence is a normal physiological incidence in most women regardless of whether they have endometriosis or not [15-18]. The exact etiology of endometriosis and why it affects some out of many women in menstruating group is still being debated. Proliferation of in-vitro co-cultured endometrial cells is stimulated by autologous peripheral blood monocytes in women with endometriosis whereas, in the same co-culture system, there is suppression of endometrial cells of women without endometriosis [19]. The designs of earlier studies on possible etiology of endometriosis are laudable. The focus of this present study is to further support these earlier studies by putting forward possible hypotheses regarding potential etiology of endometriosis. The objectives of this study are therefore to identify a probable occult agent that might be responsible for triggering endometriosis and to also theorize on two thinkable types of endometriosis

The Argument

While studies show that retrograde menstrual flow is a universal phenomenon among women of reproductive age, this theory falls short of explaining why the tissues survive in some women, but fail in others. Retrograde menstruation describes a possible mechanism by which endometrial cells are transported outside the uterus and does not actually refer to the original cause of the loose endometrial cells. Debris of menstrual flow inadvertently finding their way into the pelvic cavity are expected to trigger immediate inflammatory reaction at an early stage of endometriosis, not after a week, a month, a year or five years or longer. Nevertheless, many victims of endometriosis are initially asymptomatic, which somehow contradicts this theory of seepage into the pelvic cavity.

Endometrial epithelium cells (EECs) that eventually constitute endometriosis are expected to fulfill two conditions: (i) they must emerge before or after menstruation and not during menstruation, especially if all endometrial cells have undergone apoptosis and (ii) if they emerge during menstrual flow, they must be “live” endometrial cells. This study theorizes that all endometrial cells that form endometriosis outside the uterus are live cells. This study does not intend to discuss the mechanism of transportation of these cells from within to outside the uterine cavity. The first argument therefore is that the endometrial cells that cause endometriosis do not necessarily originate from the dead cells shed during menstruation but are live cells that are dislodged by other factors. A recent study suggests diminished spontaneous apoptosis in the endometrial glands of women with endometriosis, especially during late secretory/menstrual and early proliferative phases of the cycle, indicating increased

viability of endometrial cells shed during menstrual period and facilitating ectopic survival and implantation [20].

The second hypothesis proposed in this study is that the endometriosis-like tissues have never been within the uterine cavity. These are probably renegade embryonic cells that did not completely form the uterus but remained outside, spread out in the pelvis or on the surfaces of pelvic organs such as the ovary, or other structures in that area such as the ligaments. These hormone-dependent cells become active when stimulated by hormones that control gestation and this is probably why the disease occurs during the child-bearing age in women. This point will be taken up later in the course of discussion on possible embryogenic etiology of endometriosis.

The Hypotheses

This paper is structured along two lines of argument one of which is embryonic-onset endometriosis for which the term “endometroid endometriosis”, is coined. The other is maturity-onset endometriosis, which the author refers to as “endometrial endometriosis.”

1. Embryonic-onset endometriosis (endometroid endometriosis)

At about the 6th week of intra-uterine life, certain embryonic cells are laid down and become precursors of the reproductive organs. This is the stage of sexual indifference in which there is no morphological distinction between male and female fetus. Some cells form the primitive gonads while others differentiate into Mesonephric or Wölffian duct and others into Paramesonephic or Müllerian duct. By the 9th week of intrauterine life, especially in the genetically female (XX) embryo, the two Müllerian ducts develop into the right and left Fallopian tubes and where both fuse, they form the uterus and the upper part of the vagina. By the 9th to 10th week of life, the reproductive organ is fully formed. It may be that some cells in the lower part of the paramesonephric duct that are destined to form the inner lining of the uterus eventually do not form this inner lining, though they still retain the property of the endometrium, not expressing this property until later in life, at appropriate stimulation. These cells are probably the ancestral origin of hypothesized “endometroid endometriosis,” which “hibernate”, become irresponsive to hormonal commands and impersonate the genuine cells, masquerading as if they are true Müllerian duct cells that had dutifully migrated to become the epithelial cells of the endometrium. They however remain in the pelvic peritoneum, or are located on the surfaces of pelvic organs such as the ovaries, dormant, separated from other similar cells and in solitude, until, probably stimulated by gestational hormones at menarche, are energized and awakened. Nevertheless, although they perform their function dutifully, it is however, at a wrong place (ectopic) and at a wrong time (non-gestational), becoming a nuisance in their ectopic location. Meanwhile, the Wölffian duct degenerates and disappears in the XX embryo but in genetic XY embryo (male), it differentiates to form the male reproductive system consisting of epididymis, vas deferens and seminal vesicles with the disappearance of the Müllerian duct. Endometriosis is a rare condition in males. It may possibly originate from the same embryological origin as endometroid endometriosis or of acquired maturity

onset. It is probable that some paramesonephric duct cells that are supposed to disappear are retained in very few males. In adolescence or adulthood, these cells also respond to hormonal fluctuations and behave as if they are intra-uterine endometrial cells. Another view is that the possibility of male endometriosis might ensue if dislodged endometrial cells are transferred into the male urethra during coitus. Conceivably, these cells might get into the system if there is abrasion in the skin of the male genital and metastasize through hematological or lymphatic system. This phenomenon might be responsible for the rare condition of male endometriosis.

2. Maturity-onset endometriosis (endometrial endometriosis)

Viral infections sub-hypothesis:

Hepatitis B virus (HBV), a partially double-stranded DNA virus, is a member of the Hepadnaviridae family of viruses [21-25] which results in an acute illness with or without a chronic state [26]. Undamaged HBV virions comprise four open frames (S, P, C and X) that encode four major proteins (surface, polymerase, core and X protein respectively) associated with viral replication [21-25, 27,28]. The outermost coating of this virus is an antigen called hepatitis B surface antigen (HBsAg), found in patients with acute or chronic HBV infection and chronic carriers [26]. Two additional proteins called L and M, are also present on the viral outermost coat. The function of L protein appears to be binding to the hepatocyte surface whereas the function of M protein is yet unknown [26], possibly to bind to other cell surfaces such as the epithelial cells of the endometrium. Epidemiologically, approximately 5% of global population is infected with HBV [29-32] and the most prominent risk factors associated with this virus include heterosexual contact (42%), men having sex with men (15%) and injection drug use (21%) [24, 32-34]. Sexual activity is significant mode of its transmission where the prevalence is low [24, 32-35]. Since the majority of patients with chronic HBV infection are unaware of their infection and infectivity status and are "silent carriers," sexual transmission is likely to be a significant mode of worldwide transmission, the risk of which is reduced by condom use [24, 32-34]. Although HBsAg is found in various body fluids such as saliva, tears, sweat, semen vaginal secretions, breast milk, urine and rarely in fecal materials of HbsAg+ve persons, only semen, saliva and serum actually contain infectious HBV [26].

The conceivable pathophysiological pathway of this process is currently beyond the scope of this study, though thinkable explanation is the innocuous invasion of the intact endometrium by HBsAg, concealed in the seminal fluid of a carrier, deposited into the vagina, and introduced into the uterine cavity. Using the M protein in its outer coat, this virus possibly binds to the surface of the EEC, and gains entry into the cell, undergoes viral un-coating in the cytoplasm of the EEC and proceeds to replicate itself in about 7 major steps until many new viral cores are enveloped and excreted as infective virions into the uterine cavity or there is transportation of the viral core back into the nucleus [26,36]. Thus it is more discernible that HBsAg is the likely culprit that infects the endometrium and dislodges EEC which eventually may find their way out of the uterine cavity, sustained by nutrients in the blood or by other means. Having relocated, it may take some

time to settle down in their new "apartment", acclimatize to the surrounding and resume their original function as endometrial tissue.

Repeated un-noticed bacterial infections as possible trigger of initial trauma to endometrium:

The anatomical closeness of the telescopic vaginal and cervical canals and the anal orifice to the outlet of the urethra could be the source of infection of the uterine cavity. Various organisms are present in the perineum which could be primarily responsible for urinary tract infections (UTI), and secondarily for mild but ubiquitous intra-uterine infection. Such organisms include *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Streptococcus*, *Enterococcus faecalis*, *Staphylococcus saprophyticus*, *Enterobacter* and *Pseudomonas aeruginosa*, just to mention a few, presence of which may cause micro-trauma in the endometrium. Concomitant cell-cell communication between the endometrial cells may cause some cells to shed off the stroma and migrate to a safer location – outside the uterus or seep into the blood or lymphatic drainage to be carried away. If these internally displaced endometrial cells (IDECs) are located close to the ostium of either of the fallopian tubes, then this would be the immediate exit route out of the uterine cavity into the pelvis.

Role of endometrial inflammatory cytokines, interleukins, tissue necrosis factor, prostacyclin and Nitrous oxide

Possibly, EECs, just like vascular endothelial cells, release various pro-inflammatory cytokines, vasodilator and vasoconstrictor substances such as interleukin cytokines (IL-1 β , IL-2, IL-6), tissue necrosis factor alpha (TNF- α), prostacyclin, and nitrous oxide (NO) (also known as endothelium-derived relaxing factor) [37-39]). As in patients with heart failure, women with endometriotic endometriosis may likely have elevated levels of these pro-inflammatory cytokines, especially IL-1 β , IL-6 and tissue necrosis factor (TNF- α) [39-41], which may correlate with the staging of endometriosis.

Leucocytes in Endometriosis

Increase in the number of neutrophils is expected if dislodgement of EEC is caused by bacterial or fungal infection, though other manifestations of such infection should be discernible at presentation and by clinical investigation. This is because neutrophils are essential in killing invading organisms [42] though they are also important in the pathogenesis of tissue damage in some non-infectious diseases [43]. The occurrence of endometriosis in any form is expected to raise an alarm in form of cell-mediated immune responses involving the T lymphocytes and/or humoral immune responses by the B lymphocytes. Should the endometrium be incubating viral organisms, lymphocytosis is expected. The number of monocytes is expected to increase, as macrophages, if endometriosis is occasioned by endometrial debris or at any period of endometriosis.

Discussion and Conclusion

Over a decade ago, Leyendecker et al [44] were the first to submit that the cause or causes of endometriosis and adenomyosis may be unpretentious and closely linked with some physiologic processes of reproduction. They argued that trauma followed by tissue-specific inflammatory response and repair involving specific, albeit physiological, cellular, biochemical and molecular mechanisms may be considered the major events in the development of endometriosis. This line of argument is quite similar to the concept of endometrial endometriosis as one of the hypotheses of this paper. In their recent paper, Leyendecker and Wildt [45] discuss the concept of tissue injury and repair (TIAR) occurring in the endometrial epithelial cells. Although it is feasible that cells of the endometrium, under certain conditions such as stress, undergo microtrauma, as these authors suggest, our hypothesis incriminates HbSag as candidate satisfying the role of possible specific agent causing the microtrauma.

The observation of Werth and Grusdew [46] shares a similar view with our hypothesis on “endometroid endometriosis.” Their paper identifies a specific part of the uterus, the archimetra, as of paramesonephric origin, whilst the outer layers, the neometra, are of non-Mullerian origin. This statement further fortifies our second hypothesis that some primordial cells from paramesonephric ducts that were expected to form the archimetra either did not “migrate” to form the archimetra but remained outside and maintained their endometrial property.

Parent-Stevens and Sagraves [2] also shared their knowledge that stimulation (by yet unidentified factor) of the ovarian epithelium and the mesothelium of the pelvic peritoneum may be responsible for their transformation into Müllerian element which then becomes the origin of endometrial tissue. This thinking is quite similar to our endometroid endometriosis hypothesis. The stimulation they refer to is most likely gestational hormone stimulation of the remnants of primordial paramesonephric duct that became the endometria externa. While this paper proposes that endometrial endometriosis might be an acute, irreversible biochemical and histological reaction, once it has started, endometroid endometriosis appears to be a chronic entity and is probably more associated with primary infertility, cancer and more severe illness. Thus, primary infertility may be the outcome of endometroid endometriosis while secondary infertility may be the result of endometrial endometriosis. Endometrial endometriosis may appear more amenable to research as there are now modern techniques to carry out delicate studies. To evaluate endometroid endometriosis, it might be necessary to do ovarian biopsy and conduct complex immunocytogenetic studies and if possible, carbon dating of the ovarian and non-ovarian cells. Probably, the ovarian cells in women with endometroid endometriosis, who present with primary infertility, might be unresponsive to pituitary hormonal stimulation because these cells might have been infiltrated by the renegade cells that missed their way and eventually settled as the ovarian cells. These cells would not respond to follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland because they may still be in dormancy. On the other hand they might require a higher concentration and longer duration of FSH/LH stimulation.

It is thus possible that other genetic aberration is present in these women, necessitating further research.

Endometrial endometriosis may not pose such a severe challenge. Most likely when women present with menstrual disorder, endometrial aspirate may be analyzed for viremia to assess viral load of the uterine cavity. Hepatitis B virus infection has been linked with B-cell non-Hodgkins lymphoma [47] and to ovarian cancer [7]. If viremia or high viral load in uterine aspirate is found more in patients with endometriosis and can be ascertained as causal, then it would be interesting to follow these patients up and observe outcome of antiviral therapy on them, especially those that present with secondary infertility. If they are cleared of their supposed viral load and eventually become pregnant, naturally or otherwise, then this might be a clear demonstration of possible viral etiological in the development of endometriosis. Secondly, should hepatitis virus be incriminated in endometriosis, then, expansion of HBV vaccination is expected to reduce the incidence of endometriosis cases, even though the impact might become evident in about 20 years' time [47].

Hematological profile of women with pain or other symptoms suggestive of endometriosis should be closely scrutinized. Gynecologists and clinicians responsible for women's health should request total white blood cell count in the laboratory investigation of their patients, specifically on the look-out for leucocytic aberrations, mainly the alterations in neutrophils, lymphocytes and eosinophils.

Modern research supports the concept of malignant transformation and the current consensus is that the histogenesis of endometriosis is multifactorial, combining genetic, hormonal, and immunological factors [7].

Empirical data

An on-going study indicates symptomatology such as dysmenorrhea, menorrhagia, dyspareunia and bleeding from other sites as more prevalent in women with primary infertility while the involvement of utero-tubal factors such as unilateral tubal blockage, bilateral tubal blockage, right hydrosalpinx, bilateral hydrosalpinx and adhesion are more frequent among women with secondary infertility. This observation is crucial to the hypotheses proposed in this study in that symptomatology of “endometriosis” in women with primary infertility may be indicative of endometroid endometriosis while tubal blockage, hydrosalpinx and adhesion seen more in secondary infertility may be indicative of endometrial endometriosis.

Consequences of the hypotheses and discussion

Many studies have declared that the etiology and pathogenesis of endometriosis still remain unclear [9,48]. The description of “intermediate stage” in the malignant transformation of “atypical endometriosis” [49], which today is classified by the degree of dysplastic histologic atypia [50] perhaps supports the hypothesis of “endometroid endometriosis” as related to the malignant transformation, and that the hypothesized endometroid endometriosis cells are the “atypical endometriosis.” These cells, on closer examination, may be seen as really atypical and are the source of ovarian cancer, primary infertility and chocolate

cysts that appear on ovaries. Modern cytology should be used to investigate this assertion further.

To conclude, the arguments in this paper are that there are two types of endometriosis with two hypothetical etiologies – (i) endometrioid endometriosis or endometrium-like tissues that have never been within the uterus but have their origin in the primordial cells of the mesonephric duct and (ii) endometrial endometriosis or endometrial tissues that originated from

Table 1 Hypothetical origin of endometrial tissue within and outside the endometrium according to different characteristic of the endometriosis.

	Characteristic of Endometriosis	Hypothetical origin of endometrial tissue	
		Within the endometrium	Outside the endometrium
1	Location		
a	Pelvic	5-10%	90-95%
b	Metastatic	80-90%	10-20%
2	Stage		
a	Minimal	60-75%	25-40%
b	Mild	60-65%	35-40%
c	Moderate	20-30%	70-80%
d	Severe	5-10%	90-95%
3	Infertility		
a	Primary	10-20%	80-90%
b	Secondary	80-90%	10-20%
4	Symptom		
a	Asymptomatic	70-90%	10-30%
b	Symptomatic	10-30%	70-90%

within the uterus as EEC. While the former is hypothesized to be closely associated with primary infertility, the latter may be more related to secondary infertility. Table 1 illustrates hypothetical origin of endometrial tissues from within and from outside the endometrium relative to location and current staging of endometriosis. Table 2 suggests additional investigations that may be carried out in patients presenting with symptoms of endometriosis to distinguish one type from the other.

Table 2 Suggested additional investigations in patients presenting with symptoms suggestive of endometriosis.

	Further investigations
Bacterial infection	Vaginal swab for microscopy, culture and sensitivity
	Screening for tuberculosis (active or latent)
Viral infection	Hepatitis B antibodies
	HIV
Fungal infection	Swab for microscopy culture and sensitivity
Systemic illness	Blood sugar (HB...)
	Creatinine clearance test
	Liver function test
Cancer	Papanicolaou smear
Blood	Complete blood count with differentials
Stool	Ova, cyst, adult worms
Cytology	Ovarian biopsy

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