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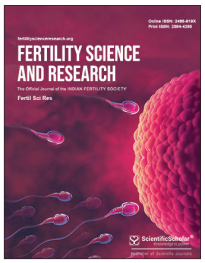

Point of View

Endometriosis is an Oestrogen-Dependent Autoimmune Disorder in Genetically Prone Women

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ABSTRACT

Endometriosis affects 10% of the population. It has a chronic course presenting with pelvic pain, pelvic lesions, subfertility and psychological issues in the affected individual. The existing treatments, like drugs to induce a hypoestrogenic state and the surgical methods of clearing adhesions and removing endometriotic cysts, are not fully effective in preventing the recurrence or restoring fertility. Emerging knowledge on the immunological basis of endometriosis, its association with co-morbidities like autoimmune disorders and the probable genetic association of these disorders with other pain conditions will help in steering research towards finding effective preventive strategies and restoring fertility.

Keywords: Endometriosis, autuimmune, infertility, genetics

Endometriosis is an enigmatic and debilitating condition that causes significant negative impact on the health status of the affected women and creates a significant burden on the healthcare system by escalating the cost of care.

It is a progressive disease leading to intractable pain, severe adhesion of pelvic organs, development of pathological lesions and alteration in pelvic anatomy. Associated infertility is a collateral damage which leads to severe psychological distress.

The true incidence of endometriosis is not known, as it becomes evident only in those who present with severe symptoms or with obvious lesions or infertility. Since its description in 1927, there has been very little progress in identifying the cause. Although there is continued research, what is known is its association with a cycling estrogenic state. Scarce reports on the existence of endometriosis in pre-menarchial and post-menopausal women and the arrest of disease progression in an induced hypoestrogenic state show that cycling oestrogen is the key factor sustaining the disease. Few reports on endometriosis in males exposed to exogenous oestrogen, as in transgender men Women on Gender Affirmation Hormone treatment (GAHT), add evidence to this association. Even in prolonged non-cycling hyper estrogenic states as in chronic anovulation, the incidence is less. So, it is the cycling oestrogen with retrograde menstruation and not sustained hyper estrogenic state which has a strong association.

But what initiates this process?

When most or all women have retrograde menstruation, it is not clear what leads to the vicious cycle of adhesion, proliferation and invasion of endometrial cells in only some of them. When most women remain fertile, lesion and pain-free, why do some women take a downhill course and present with infertility and severe dysmenorrhoea?

Is it simply oestrogen, or are there some other factors involved?

As endometriosis is more common in nulliparous women with unchallenged and prolonged exposure to retrograde menstrual blood and in women with Mullerian anomalies where there is a functional endometrium with outlet obstruction, could there be a threshold of endometrial cell numbers or duration of exposure to retrograde menstruation which initiates the process.

Interestingly, even the severity of symptoms and the stage of endometriosis does not match always.

Research on immunology and genetics in this special group of women could hold answers to these questions.

The immunological changes in endometriosis show an altered Th1/Th2 ratio, raised TNF alpha, C3/iC3b and lowered uterine NK cells[1] which points to a defective cellular apoptosis, favouring the decreased immunological clearance of endometriotic cells and enhancing their survival. Increased presence of lymphocytes, macrophages and mast cells in the peritoneal fluid of women with endometriosis shows the marked inflammatory process associated with the disease. Increased MMPs (Matrix metallo proteinases) show enhanced cellular adhesion. This inflammatory milieu with enhanced cell survival and the presence of factors promoting cell adhesion and proliferation and the presence of angiogenic factors lead to adhesive disease and further lesions in endometriosis.

It is understood that the effectiveness of GnRH therapy and progestins in arresting the progress of endometriosis is not only due to their direct action on the HPO axis but is also due to their profound immunomodulatory effect which indirectly points to the immunological basis for the disease progression.

On the other hand, there are many similarities that exist between the known autoimmune disorders and endometriosis. Both share common features[1] like female preponderance, occurrence during reproductive years and abatement in hypoestrogenic state, familial predisposition, multi-organ involvement, altered immune function and evidence of deranged cellular apoptosis, etc., …, leading us to a logical question as to whether endometriosis is an autoimmune disease.

A recent systematic review on the association of autoimmune disorders in women with endometriosis[2] based on high-quality evidence concluded that there is an increased prevalence of SLE, Sjogren's Syndrome, rheumatoid arthritis, coeliac disease, multiple sclerosis, irritable bowel syndrome and Addison's disease in women with severe endometriosis. This suggests that there could be a shared pathway in the onset of endometriosis and other autoimmune disorders.

A meta-analysis of Genome Wide Association Studies (GWAS) on endometriosis[3] autoimmune disorders and chronic pain conditions in humans identified the presence of multiple association signals which were common to ASRM stage 3/4 endometriosis and autoimmune conditions like asthma and osteoarthritis of probable rheumatoid origin and also in chronic pain conditions like migraine and multisite chronic pain. This probably indicates the convergence of inflammatory, hormonal and neuronal pathways in the pathogenesis of these conditions and the perception of chronic pain. It is also well known that endometriosis has a familial distribution, favouring a genetic association.

To conclude, oestrogen is an essential factor for the occurrence and persistence of endometriosis, but the presence of autoimmune response is probably the cause for pain, inflammation and subsequent development of adhesion and pathology. Intensity of this immune response and the genetic predisposition decides the severity of the lesions found in a subclass of women diagnosed with severe endometriosis.

Currently practiced surgical therapies and inducing hypoestrogenic states address only the later stages of disease, and they are not preventive. Medical community should focus on research in confirming the probable autoimmune nature of this disease and make efforts to establish immune-modulator therapies, as this will save or ameliorate several women from this dreaded condition.

Developing targeted therapies based on immune functions like anti-complements[4] and anti-TNF alpha may help in preventing the onset of the disease and its progression.

For this to become a reality, we need to identify markers which point to women who are susceptible to endometriosis and those with early or no lesions.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent is not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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