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Endometriosis and Infertility

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Introduction

Endometriosis is present in about 10-20% of adult women leading to various symptoms affecting women's health and functions. The disease can lead to various symptoms depending on the affected organs in the body since it is not only confined to the pelvic cavity. Endometriosis can affect the intestines especially the pelvic colon, ileum, cecum and appendix [1]. Endometriosis have been seen in the liver and diaphragm [2]. Patients may also present with chest symptoms as hymoptysis, and or hydrothorax or hemothorax due to pulmonary endometriosis [3]. So endometriosis is a disease that affects the whole body spreading to locations outside the pelvic cavity via blood vessels and lymphatics. The disease was described over three hundred years ago. The annual health care cost was estimated to be 69.4 billion dollars in 2009.

The incidence of infertility is about 30-50 percent in patients with endometriosis. This may be related to inflammatory changes in the pelvic cavity leading to adhesions and, interference with ovum pick up and fertilization. There are specific factors related to endometriosis that cause infertility including: e Endometrial antibodies

a) Changes in the eutopic endometrium that renders it as a poor environment for implantation, including aromatase and growth hormones.

b) Progesterone resistance in the endometrium.

Endometrial Antibodies

Using a passive hemagglutination assay, we found endometrial antibodies in the serum and peritoneal fluid of patients with pelvic endometriosis. This is of value to help in follow up of patients with endometriosis to study the effect of treatment, and also recurrence of the disease after treatment [4]. Endometrial antibodies were also demonstrated by other methodologies [5]. The antigen antibody reaction within the endometrium leads to infertility [6].

Because of the presence of endometrial antibodies in the patients with endometriosis, the question arises whether endometriosis is to be considered an autoimmune disease. Women with endometriosis are at increased risk for chronic fatigue syndrome, multiple sclerosis, Lupus, hypothyroidism, rheumatoid arthritis, inflammatory bowel disease as Chron's disease and ulcerative colitis 30 to 50 percent of women with endometriosis are infertile. This may be due to several factors including, ovarian dysfunction, tubal disease including adhesions, and in addition auto antibodies. These endometrial antibodies interact with the stroma and glands of the endometrium thus leading to defective decidual reaction. This leads to failure of implantation and infertility [7-9].

There are several factors leading to infertility in these patients, including the presence of aromatase in the eutopic endometrial cells, leading to estrogenic effect on the endometrium [10]. In addition, there is progesterone resistance with failure of implantation due to lack of decidual preparation [11]. Furthermore, uterine contractions are increased due to high levels of prostaglandins in peritoneal fluid [12]. All of these factors add a negative effect on implantation of the embryo.

Eutopic Endometrium in Endometrioisis Patients

Studies have shown that there is decreased apoptosis in eutopic endometrium of patients with endometriosis. This may explain the ability of the eutopic endometrial cells to continue their growth and lead to development of endometriosis. Furthermore, there is excess BCL.2 that protects the endometrium thus preventing apopstosis [13,14]. Increased integrin activity has been demonstrated in mesothlial cells and menstrual effluent in patients with endometriosis. This will lead to adhesions of endometrial cells to peritoneum, and increased proliferation thus developing endometriosis. Another factor is ECadherin/Catenin protein expression in the eutopic endometrium, might be involved in the attachment of the eutopic endometrium to the peritomal surface leading to the endometriosis [15,16].

Increased levels of tissue matrix metalloproteinases in the endometrium leads to invasion of endometriosis to surrounding tissue [17]. Another factor that leads to the survival of eutopic endometrium is the suppression of natural killer (NK) cell activity. This is due to soluble inter cellular adhesion molecule that binds with leucocyte function antigen which is a surface molecule on natural killer cells, thus leads to their inhibition. This will lead to survival of eutopic endometrium to develop endometriosis [18].

Some investigators reported the presence of aromatase in endometrial biopsies of endometriosis patients, and suggested that this is a marker for the diagnosis of endometriosis. Another marker is the presence of nerve fibers in the endometrium of patients with endometriosis, and this can be used also for the diagnosis of endometriosis [19,20]. The embryo implantation rate is decreased in the eutopic endometrium. This is due to increased aromatase activity, and decreased progesterone uptake by the eutopic endometrium. This will result in inadequate decidua formation. The end result is continued cell proliferation and failure of implantation. This process of progesterone resistance is also shown in endometriosis cells [21].

One of the significant findings in endometriosis is the progesterone resistance. This has been found also in the eutopic endometrium. Some investigators suggest that the progesterone resistance in the endometriosis tissue is an acquired phenomenon. More studies are needed. Chronic inflammation can produce progesterone resistance. This is the case in the presence of chronic inflammation in the peritoneum due to the presence of endometriosis. Progesterone resistance may result from genetic factors including progesterone receptor gene polymorphism. This phenomenon will lead to failure of the development of decidual effect and this results in infertility in these patients [22,23].

Progesterone resistance in the eutopic endometrium of patients with endometriosis may be due to the inadequate rise in systemic progesterone levels, however some studies do not confirm this finding. Other investigators suggest that it is the intrinsic progesterone resistance in the endometrial tissue that is responsible for the lack of response of the endometrial tissue to progesterone. Progesterone resistance is important to know because these patients will not respond to progesterone treatment. However, the response to other synthetic progestational agents as Levonorgeserel, depot medroxyprogesterone acetate

has been found to have an effect on the endometrium showing low proliferation [24].

Endometriomas are a type of endometriosis that leads to cystic lesions in the pelvic area, mostly in the ovaries. These cysts are distended with dark brown bloody discharge and that leads to the expression of chocolate cysts. In our laboratory, we developed endometrioma cell lines and treated them with purified chocolate cyst fluid. We found that this increased the endometrioma cell lines growth. This is due to the presence of transforming growth factor Bl in chocolate cyst fluid [25]. In addition to the growth promoting effect of transforming growth factor Bl, it has been found to increase vascularity, and increase inflammatory reaction that leads to adhesions. Evaluation of chocolate cyst fluid found high concentrations of nitric oxide. This may be a factor in increasing vascularity in endometriomas [26].

e Growth Factor and Auto Immunity in Endometriosis

Effect on endometriosis growth

Epidermal growth factors immunoreactivity was demonstrated in normal and eutopic edometrium of patients with endometriosis. That study concluded that endometrial growth factor may play a role in the proliferation of normal and endometriotic endometrium. It is also found in other studies that epidermal growth factor receptor is necessary for the development of decidua and successful implantation and pregnancy [27] Other studies demonstrated epidermal growth factor, transforming growth factor in the endometrium, and their role in the growth and proliferation of the endometrium, and suggested the possible role in embryonic development [28].

The role of stem cells in endometriosis

Stem cells has been shown in the endometrium. They originated from endomentium as well as from the bone marrow. These stem cells can migrate to distant locations and lead to development of endometriosis [29]. Multi potent stem cells have been isolated from bone marrow, umbilical cord, periosteum, skeletal muscle, pancreas, dental pulp, adipose tissue and endometrium. The contribution of stem cells to the regeneration of endometrium was proposed in 1978 by Pryrianishnikov [30]. It appears that these stem cells originate from the basalis layer of the endometrium that leads to regeneration following menstruation and the loss of the functional layer of the endometrium.

Conclusion

there are many factors that affect the development of the endometrium in patients with endometriosis. This will affect the fertility potential in these patients.

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