The Dilemma of Endometriosis; Is the Solution Immunomodulation?

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Since 1965, there has been a great increase in publications on endometriosis, however, as we learn more about endometriosis, we also realise how little we know about this. First publications were mostly about its clinical aspects, but especially since 1990, more and more researches were directed to pathophysiological aspects (1).

Immediately after tedious work by Jansen and Russel (2), not only the pathogenesis but also the diagnosis of endometriosis has become confusing. Another interesting study revealed that biopsies of visually normal peritoneum from women with and without endometriosis were histologically positive for endometriosis in 13 % and 6 %, respectively (3).

There is striking evidence of that menstruation constitutes a substantial stimulus for the development of endometriosis (4). However, retrograde menstruation is probably universal in women during reproductive ages (5). Then, what is the reason for the growth of endometriotic fragments in only some women? In an interesting study from Merrill (6), the development of endometriosis has been seen 20 of 22 rabbits when they have received implants of healthy endometrium enclosed in a small diffusion chambers that were impermeable for endometrial cells but permeable to soluble factors released from healthy endometrium. Are there some local factors to facilitate endometrial growth ectopically, or -perhaps- metaplasia? Recent reports concentrated on immunologic basis, and it has been shown that abdominal cavity is prepared to discard the regurgitated menstrual debris by its defence mechanism via leukocytes (7). On the way we are talking about the solution, we should better first briefly review immunology in endometriosis.

The immune system is quite complicated but simply, it works for the protection of the organism through interacting different cells and secreted products. Main characteristic of the immune system is to eliminate foreign, but not self-antigic pieces. This can easily explain how destructive autoimmune diseases would be, since they go along with immune response to self-antigens. However, we still do not know why this type of response happens.

Altered Immune System in Endometriosis

There is increasing evidence of altered immune system in endometriosis. Furthermore, it has also been suggested that endometriosis, rather than being a local disease, is likely to be a systemic immune disease (8). The characteristics of autoimmune processes, such as preponderance of females, familial occurrence, multiorgan involvement, tissue damage, predisposition to concomitant autoimmune diseases, nonspecific and organ-specific antibodies, polyclonal B-cell activation, clinical improvement and decreased antibody titers with the immunomodulatory effects of danazol are well-adjusted with endometriosis (9). One can argue, then, whether immunologic abnormalities precede or follow endometriosis. Presence of abnormal immunity in "precursor-stages" of endometriosis, and inverse correlation between these abnormalities and the stage of endometriosis favour the presumption...
that altered immune system precedes endometriosis (8).

Alterations in Cellular Immunity: Since reduced T-cell immunity and increased B-cell response has been demonstrated in 1980 by Starzseva (10), many investigators have confirmed the alteration in cellular immunity in endometriosis. Cellular immunity is widely investigated both in sera and peritoneal fluid (PF) of women with endometriosis by using different techniques (11-14).

Natural killer cells. Most studies revealed decreased NK activity (15-18). The intensity of this NK cell activity suppression inversely correlated with the stage of endometriosis (15). In that study, Garzetti et al. evaluated sera from 33 women with laparoscopically-proven endometriosis and also found inverse relationship between serum estrogen levels and cytotoxicity. They suggested this immunomodulatory interaction might be important in endometriotic progression. A study by Oosterlynck et al. (16) showed no difference between the cytotoxic effects of lymphocytes of sera from women with or without endometriosis against target cells, indicating suppressive factor for lymphocyte action is in PF rather than being in serum. In another study, however, Kanzaki et al. (17) determined the suppressive effect of sera from women with endometriosis on NK cells obtained from healthy women and found significant inhibition of NK cell activity with those sera.

Macrophages. Studies revealed increased activity and/or the number of peritoneal macrophages in women with endometriosis (9,19,20). It has been stated that monocyte/macrophage system in peritoneal cavity is basically a "disposal system", and this system removes all debris as well as endometrial cells regurgitated from abdominal tubal ostii. (21). When this system is defective or saturated completely, endometrial cells would be permitted to implant. Increased activity and/or activity of macrophages may cause tissue damage and adhesions. They have the ability to release some local factors like cytokins, prostaglandins, components of complement and hydrolytic enzymes. These factors will activate T-lymphocytes and also will cause tissue damage and probably adhesion formation (21,22).

Cytokins. They are secreted by macrophages, lymphocytes, and other nucleated cells. They include interleukins (IL-I to IL-VI), colony-stimulating factors (CSF), interferons (IFN alpha, beta, gamma), tumor necrosis factors (TNF alpha, beta), transforming growth factors (TGF alpha, beta), platelet-derived growth factor (PDGF) and many more. In endometriosis, especially IL-I has been found to be elevated in PF of stage I and II endometriotic patients (23). IL-I stimulates synthesis of prostaglandins, proliferation of fibroblasts, and deposition of collagen, thus, contributes adhesion formation. In a study of 24 women, PF from cases with mild endometriosis, and adhesions due to the factors other than endometriosis showed two to fourfold higher levels of IL-VI, interestingly in cases with moderate to severe endometriosis, levels of IL-VI were lower (24). TGF is another cytokine found to be increased in activity in PF of women with endometriosis (25). Another study indicated that RANTES, a cytokine with potent chemotactic activity for human monocytes, were also elevated in PF of women with endometriosis, and this elevation is correlated with the severity of the disease (26). Increased cytokine activity, in turn, causes activation of T-cells and B-cells, and contribute suggested pathophysiology in endometriosis.

Alterations in humoral immunity: Multiple antibodies both nonspecific and organ-specific were found in patients with endometriosis, thus, suggest polyclonal B-cell activation in endometriosis (9,10). Antibodies may play an important role in the cause of infertility via their embryo-toxicity, implantation.

Nonspecific antibodies (autoantibodies to cell components). Glicicher et al (27) studied 59 laparoscopically staged patients with endometriosis for nonspecific antibodies in their sera. Of those, 28.8% were positive for antinuclear antibody, and of 44, 45.5% were positive for lupus anticoagulant. Furthermore in 31 endometriotic patients, 64.5% exhibited immunoglobulin G (IgG), 45.2% demonstrated immunoglobulin M (IgM) to at least 16 antigens tested. El Rociy et al. (28) have also found that increased autoantibodies, predominantly in the phospholipid group and of the IgG type, were decreased with danazol therapy, a synthetic steroid, known to have immunomodulatory effects.
Organ-specific antibodies. Antiendometrial antibodies, anticytdothelial antibodies, antiovarian antibodies were the specific antibodies studied in cases of endometriosis. Antiendometrial antibodies were found significantly higher in patients with endometriosis comparing with the controls (29). Another study from United Kingdom (30), also revealed that antiendometrial autoantibodies in sera obtained from patients with endometriosis were higher in frequency than in sera from controls, besides a proportion of antiendometrial antibody-containing sera also reacted with vascular endothelium. However, the role of antiendometrial antibodies remains controversial because of contradictory studies (31). Conflicting results may be due to different techniques, and most importantly differing responses, that can be obtained under the same conditions, with the same serum samples. This may imply that antiendometrial antibodies may play a role in endometriosis, but may also show low affinity and be functionally less important. This is also why the presence of antiendometrial antibodies is not a reliable method to diagnose endometriosis. In sera from women with endometriosis, antiovarian antibodies were in higher frequency comparing with sera from "normal" controls, but this was correlated with neither the severity of the lesion nor the ovarian involvement (32).

**New Treatment Modalities in Endometriosis**

Since there is convincing evidence of altered immunity in endometriosis, the logical and suggested therapeutic approach is treatment with drugs that normalize the peritoneal inflammatory environment. It sounds reasonable to have the same approach for the infertile patients with low-grade endometriosis. These "immunomodulatory" drugs must be effective, safe for the patient and non-teratogenic for the fetus. Danazol, being used commonly in the management of endometriosis, may have the ability to modulate the immunological functions but the increases in fertility rates are not as satisfactory as expected (33-35). Moreover, its side effects are not always tolerable. High-dose corticosteroids as classical immunosuppressive drugs have some well-known risks and do not seem to be a proper choice in this condition. Recently, recombinant IL-2 has been suggested for therapy, since it has corrected immune defects in vitro (36). We need to see whether the results are also similar for human studies. Steinlander et al. (37) have shown in an animal model that verapamil, a calcium channel blocking agent, improved the fertility rates by nonspecifically modulating the immune system. They proposed this study assuming that the endometriotic patients have gametotoxic peritoneal fluid due to the prostanooids and cytokines from hyperactivated immune competent cells. Up to date, there is no controlled trial with calcium channel blockers in women with endometriosis-associated subfertility. There is another hope for treatment modality as immunomodulation with periovulatory pentoxifylline. It is a methylxanthine derivative related to theophylline. Pentoxifylline reduces the severity of inflammatory conditions mediated by activated macrophages and neutrophils (38,39). It has also been shown that pentoxifylline enhanced sperm motility and improved the fertilization rates in vitro in couples with severe male factor infertility (40). In an animal model by Steinleitner et al. (41), inhibition of fertilization caused by transfer of hyperactivated macrophages was reversed by periovulatory pentoxifylline treatment. The main advantage of immunomodulatory drugs such as pentoxifylline, in contrast to danazol for example, is the ability to affect the inflammatory status without interfering with folliculogenesis. Available data shows that pentoxifylline may be suitable for this indication. Now, a prospective controlled research is underway to evaluate the effect of pentoxifylline on patients with endometriosis-associated subfertility.

**Conclusion**

It has been well known that, at least for low-grade endometriosis, surgical or endocrine therapies are only symptomatic and temporally effective. Also for the infertile patients with endometriosis, improvement of fecundity with the treatment by these means are not promising (42,43). Since there is confirmed alteration in immune status in endometriosis and it is accepted as a systemic disease, it requires a systemic treatment by immunomodulation. However, more and more researches are needed to find the best therapeutic approach in this enigmatic immunological disease.


