The Dilemma of Endometriosis; Is the Solution Immunomodulation?

ENDOMETRIOZIS ÇIKMAZI; ÇOZUM IMMUNOMODULASYON MU?

Solman LAÇİN,* Ümit SUNGURTEKİN*, Refik ÇAPANOĞLU**

* Assist.Prof.,Celal Bayar University, School of Medicine, Department of Obstetrics and Gynecology,
** Prof,Celal Bayar University, School of Medicine, Department of Obstetrics and Gynecology, MANİSA, TURKEY

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 Russcl (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. Arc there some local factors to facilitate endometrial growth cctopically, 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 arc 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 sclf-antigcnic 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

Geliş Tarihi: 02.05.1997

Yazışma Adresi: Dr. Sclman LACİN
162. Sok. No: 40 D: 7
35040 Bornova IZMIR

that altered immune system precedes endometriosis (8).

Alterations in Cellular Immunity: Since reduced T-ccll immunity and increased B-cell response has been demonstrated in 1980 by Starseva (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-provcn endometriosis and also found inverse relationship between serum estrogen levels and cytotoxicity. They suggested this immunoendocrinc interaction might be important in endomctriotic progression. A study by Oostcrlynck 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 scrum. In another study, however, Kanzaki ct 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 arc secreted by macrophages, lymphocytes, and other nucleated cells. They include intcrlcukins (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 foutid to be increased in activity in PF of women with endometriosis (25) Another study indicated that RANTES, a cytokin 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-ccll 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). Glcicher 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, anticndothclial 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 (3 1). Conflicting results may be due to different techniques, and most importantly differing responses, that can be obtained under the same conditions, with the same scrum 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 not 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 arc not always tolerable. High-dose corticosteroids as classical immunosupressive drugs have some well-known risks and do not seem to be a proper choice in this condition. Recently, recombinant 1L-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. Steinlandcr et al. (37) have shown in an animal model that verapamile, a calcium channel blocking agent, improved the fertility rates by nonspccifically modulating the immune system. They proposed this study assuming that the endometriotic patients have gametotoxic peritoneal fluid due to the prostanoids and cytokines from hyperactivated immune competent cells. Up to date, there is no controlled trial with calcium channel blockers in women with endomctriosis-associated subfertility. There is another hope for treatment modality as immunomodulation with periovulatory pentoxifylline. It is a methylxanthinc 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 ct al. (41), inhibition of fertilization caused by transfer of hyperactivatcd 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 arc needed to find the best therapeutic approach in this enigmatic immunological disease.

1. Barlow DH: What is endometriosis in the 1990s?, BJCP 1972(suppl): 1-7.

2. Jansen RPS, Russell P: Nonpigmented endometriosis: Clinical, laparoscopic, and pathologic definition, Am J Obstet Gynecol 1986; 155: 1154-9.

3. Nisollc M, Paindaveine B, Bourdon A, Berliere M, Casanas-Roux F, Donnez J: Histologic study of peritoneal endometriosis in infertile women. Fertil Steril 1990; 53: 984-8.

4. Janscn RPS: Pathogenesis ofendometriosis. Winthrop-O&G page, ADIS press, 1990.

5. Halme J, Hammond MG, Hulka JF et al. Retrograde menstruation in healthy women and in patients with and without endometriosis. Obstet Gynecol 1984; 57; 667-70.

6. Merrill JA: Endometrial induction of endometriosis across Millipore filters. Am J Obstet Gynecol 1966; 94: 780-90.

7. Evers JL: The defence against endometriosis. Fertil Steril 1996; 66: 3

8. Gleicher N. Pratt D: Abnormal (auto)immunify and endometriosis. Int J Gynecol Obstet 1993; 40 (suppl): 21-7.

9. Dmowski WP. Gcbel HM. Rawlins RG: Immunologic aspects of endometriosis. Obstet Gynecol Clin North Am 1989; 16: 93-103.

lO.Starseva NV. Clinico-immunological aspects of genital endometriosis. Akush. Ginecol. (Mosk.) 1980; 3: 23-6.

I 1.Dmowski WP. Steele RW. Baker GF. Deficient cellular immunity in endometriosis. Am J Obstet Gynecol 1981; 141: 377-83.

12.0osterlynck DJ. Meuleman C. Waer M. Koninckx PR. Vandeputte M. Immunosuppressive activity of peritoneal fluid in women with endometriosis. Obstet Gynecol 1993; 82: 206-12.

13. Kikuchi Y. Ishikawa N. Hirata J. Imaizumi E. Sasa H. Nagata I. Changes of peripheral blood lymphocyte subsets before and after operation of patients with endometriosis. Acta Obstet Gynecol Scand 1993; 72: 157-61.

14. Gilmore SM. Aksel S. Hoff C. Peterson RD. In vitro lymphocyte activity in women with endometriosis- an altered immune response. Fertil Steril 1992, 58: 1148-52.

15. Garzetti GG. Ciavattini A. Provinciali M. Fabris N. Cignitti M. Romanini C. The natural killer cell activity in endometriosisxorrelation between serum estradiol levels and cytotoxicity. Obstet Gynecol 1993; 81: 665-8.

16.0osterlynck DJ. Cornillie F.I. Waer M. Vandeputte M. Koninckx PR. Women with endometriosis show a defect in natural killer activity resulting in a decreased cytotoxicity to autologous endometrium. Fertil Steril 1991; 56: 45-51.

17. Kanzaki H. Wang HS. Kariya M. Mori T. Suppression of natural killer cell activity by sera from patients with endometriosis. Am J Obstet Gynecol 1992; 167: 257-61.

18. Tanaka E. Sendo P. Kawagoe S. Hiroi M. Decreased natural killer cell activity in women with endometriosis. Gynecol Obstet Invest 1992; 34: 27-30.

19. Zeller JM. Henig I. Radwanska E. Dmowski WP. Enhancement of human monocyte and peritoneal macrophage chemiluminescence activities in women with or without endometriosis. AM J Reprod Immunol Microbiol 1987; 13: 78-82.

20. Halme J. White C. Kanma S. Estcs J. Haskill S. Peritoneal macrophages from patients with endometriosis release growth factor activity in vitro. J Clin Endocrinol Metab 1988; 66: 1044-9.

21. Dmowski WP. Etiology and histogenesis of endometriosis. Ann N Y Acad Sci 1991; 622: 236-41.

22. Haney AF: Endometriosis, macrophages, and adhesions. Prog Clin Biol Res 1993; 381: 19-44.

23. Fakih H. Baggeth B. Holtz G. et al. lnterleukin-1: a possible role in the infertility associated with endometriosis. Fertil Steril 1987; 46: 213-17.

24. Rier SE. Parsons AK. Becker JL. Altered intcrleukin-6 production by peritoneal leukocytes from patients with endometriosis. Fertil Steril 1994; 61: 294-924.

25,Oostcrlynck DJ. Meuleman C. Waer M. Koninckx PR. Transforming growth factor-beta activity is increased in peritoneal fluid from women with endometriosis. Obstet Gynecol 1994; 83: 287-92.

26. Khorram O. Taylor RN. Ryan IP. Schall TJ. Landers DV. Peritoneal fluid concentrations of the cytokine RANTES correlate with the severity of endometriosis. Am J Obstet Gynecol 1993; 169: 1545-9.

27. Gleicher N. El-Roeiy A. Confino E. Friberg J. Is endometriosis an autoimmune disease? Obstet Gynecol 1987; 70: 115-22.

28. El-Rociy A, Dmowski WP, Gleicher N, Radwanska E, Harlow L, Binor Z, Tummon I, Rawlins RG: Danazol but not gonadotropin-relcasing hormone agonist suppress autoantibodies in endometriosis. Fertil Steril 1988; 50: 864-71.

29. Gorai I. Ishikawa M. Onosc R. Hirahara F. Minaguchi H. Antiendometrial autoantibodies generated in patients with endometriosis. Am J Reprod Immunol 1993; 29: 1 16-23.

30. Fcrnandez-Shaw S. Hicks BR. Yudkin P. Kennedy S. Barlow DH. Starkey PM. Anti-endomctrial and anti-endothelial autoantibodies in women with endometriosis. Hum Reprod 1993; 8: 310-5.

31.Swichenko AC. Kauffman RS. Becker M. Are there antiendometrial antibodies in sera of women with endometriosis ? Fertil Steril 1991; 56: 235-41.

32.Mathur S. Peress MR. Williamson HR. et al. Autoimmunity to endometrium and ovary in endometriosis. Clin Exp Immunol 1982; 88: 410-3.

33.Seibel M. Berger M. Weinstein F. Taymor ML. The effectiveness of danazol on subsequent fertility in minimal endometriosis. Fertil Steril 1982; 38: 534-7.

34. Bayer S. Seibel M. Saffan D. Berger M. Taymor ML. Efficacy of danazol treatment for minimal endometriosis in infertile women, a prospective randomized study. J Reprod Med. 1988; 33: 179-85.

35. Evers J. The pregnancy rate of the no-treatment group in randomised clinical trials of endometriosis therapy. Fertil Steril 1989; 52: 906-7.

36. Melioli G, Semino A, Vcnturini PL, Ragni N: Recombinant interleukin-2 corrects in vitro the immunological defect of endometriosis. Am .1 Obstet Gynecol 1993;30:218-27.

37. Steinlcitner A. Lambert H. Suarez M. Serpat N. Robin B. Cantor B. Periovulatory calcium channel blockade enhances reproductive performance in an animal model for endometriosis-associated subfertility. Am J Obstet Gynecol 1991; 164: 949-52.

38. Sullivan GW. Carper HT. Novvick WJ. Mandell GL. Inhibition of the inflammatory action of interleukin-1 and tumor necrosis factor (alpha) on neutrophile functions by pentoxifylline. Infect İmimin 1988; 56: 1722-5.

39. Chalkidakis et al. Pentoxifylline in the treatment of experimental peritonitis in rats. Arch Surg 1985; 120: 1141-7.

40. YovichJM. Edirisinghe WR. Cummins JM. Yovich JL. Influence of pentoxifylline in severe male factor infertility. Fertil Steril 1990; 53: 715-21.

41. Steinleitncr A. Lambert H. Roy S. Immunomodulation with pentoxifylline abrogates macrophagc-medialcd infertility in an in vivo model: a paradigm for a novel approach to the treatment of endometriosis-associated subfertility Fertil Steril 1991; 55: 26-31.

42. The pregnancy rate of the no-treatment group in randomized clinical trials of endometriosis therapy. Fertil Steril 1989; 52: 906-11.

43. Fedele L. et al. Buserelin acetate versus expectant management in the treatment of infertility associated with minimal or mild endometriosis: A randomized clinical trial. Am J Obstet Gynecol 1992; 166: 1345-50.