UNIVERSITY OF NIŠ
The scientific journal **FACTA UNIVERSITATIS**
Series: **Medicine and Biology** Vol.6, No 1, 1999 pp. 97 – 102
Editor of Series: Vladisav Stefanović, e-mail: factacivil@medfak.medfak.ni.ac.yu
Adress: Univerzitetski trg 2, 18000 Niš, YU, Tel: +381 18 547-095 Fax: +381 18 547-950
http://ni.ac.yu/Facta

UC 618.2;612.65

CHRONIC DISEASES IN CHILDHOOD AS A CONSEQUENCE OF IMMUNE SYSTEM DISFUNCTION OF MOTHER DURING PREGNANCY

Borislav Kamenov, Hristina Dimitrijević, Gordana Tasić, Svetlana Pljaskić

Clinic of Pediatrics and Department of Microbiology University School of Medicine Niš, Yugoslavia
Health Center Niš, Yugoslavia

Summary: *Growth and development of the embryo and fetus in the antigen "privileged" environment and Th2 response predominance of mother's immune system are necessary for appropriate development of the immune system (prevention of clonal abortion anergy, apoptosis) as well as for the development of other organs and tissues. Cytokines of Th1 response, oxygen free radicals and nitrites with their potential to influence gene expression may seriously interfere with cell proliferation, differentiation, apoptosis and migration. Many acute viral infections are known to cause death of the embryo or serious anomalies. Prenatal development of Th1 microenvironment is analyzed as a possible factor for the immune system dysfunction and its possible influence on chronic diseases in childhood. 250 children, having in common chronic disease, were analyzed in relation to Th1 response predominance of mother's immune system during pregnancy in a paralell with 100 Chlidren and they mothers treated because of acute infactions and without sighns of chronic diseases. Beside the specific examinations for appropriate organ or system the following parameters were analyzed: red and white blood cell counts, hemoglobin level serum immunoglobulin level ELISA : HSV, CMV, EBV, HIV; NBT, phenotyping of peripheral blood mononuclear cells: CD2 CD3, CD4, CD8, DR, CD25, CD56; electrophoresis of the serum proteins immune complexes, autoantibodies, enzymes: CPK, LDH, AST and ALT. Chronic disease with Th1 type response was present in 231 mothers: iron resistant anemia 163, viral infections 114 (HSV and CMV the most often), bacterial infections 6, autoimmune diseases 15, acute viral infections in 21 mothers. 75 mothers were treated during pregnancy with hormones or tocolitics. Problems with previous pregnancies had 28 because of sterility 163-spontaneous abortions, 5-dead born newboms. The most of the children had problems after birth manifested as hypo or hypertrophy, inappropriate respiratory, cardiovascular and termoregulatory adaptation. Clinical manifestations in examined children were: anemia-197, lymphadenopathy-155, higher incidence of infections-87, vasculitis-72, nervous system dysfunction-54, asthma-36, angioedema- 32, stomatitis-21, hepatitis-19, polyarthritis-15, leucopenia-14, anomalies-13 rachitis-8 non epidemic parotitis-7, malapsorption-6, malignant diseases in the later follow up-4, and chromosomal aberrations-3. 82 % of the patients had higher activity in most of the examined enzymes (CPK, LDH, AST and ALT).*

Key words: *Immune system dysfunction, Th1 cytokines in pregnancy, chronic diseases in childhood*

Introduction

A growing body of evidence indicates that, in addition to the hormones of hypothalamic, pituitary and gonadal origin, autocrine/paracrine regulators play important roles in the reproductive functions as well as in the intrauteral growth and development of the embryo. Cytokines, originally known as immunoregulatory proteins, may affect the neuroendocrine events of reproduction, ovarian function, endometrium, the developing embryo, placenta and parturition and postnatal growth and development (1). Cytokines can modulate and mediate the actions of hormones at their target cells and, in the opposite way, hormones may regulate the production and action of cytokines at three different levels: cytokine secretion, cytokine receptor expression and cellular responses (2). Cytokines may also function in an endocrine manner affecting distant targets. As many of the cyclic changes that occur in the ovary and endometrium during the normal menstrual cycle are similar to those associated with the inflammatory and regenerative processes, it is likely that cytokines are involved in these reactions. Furthermore, cytokines secreted by endometrial white blood cells may influence embryo development and trophoblast growth and may play a fundamental role in the mechanisms of immunological reproductive failure (3). Cytokines have also been implicated in the mechanisms

responsible for the onset of parturition.

Embryonic implantation and maintenance of pregnancy is influenced by the maternal immunological response (4). Type 2 T-helper (Th2) cells secrete interleukins 4, 5, 6 and 10 and are associated with suppression of cell-mediated immunity. Temporal changes in the expression of these cytokines were detectable by immunohistochemistry throughout the menstrual cycle. In pregnancy, 10-fold or greater increases in interleukin 6 and 10 secretion were detectable by enzyme-linked immunoassay compared with the non-pregnant state (5). The pattern of expression of Th2 cytokines suggests that progesterone may influence endometrial cytokine secretion (6).

Pregnant females are susceptible to intracellular pathogens and are biased towards humoral rather than cell-mediated immunity (7). Since Th1 cytokines compromise pregnancy and Th2 cytokines are produced at the maternal-fetal interface, it is hypothesized that these Th2 cytokines inhibit Th1 responses, improving fetal survival but impairing responses against some pathogens (8). Statistically significant increased production of both IL-2 and IFN-γ and reduced production of IL-10 characterized pathologic pregnancies and distinguished them from normal pregnancies (9).

Maternal immune responses can influence fetal survival and several cytokines have harmful or protective effects on pregnancy (10). The Th1 cytokines IFN-gamma and IL-2 can cause fetal loss, whereas the Th2 cytokine IL-10 is protective. However, infections such as leishmaniasis show the opposite pattern: resistance is associated with the preferential mounting of a Th1 response, whereas a Th2 response exacerbates the disease. The curative Th1 response against Leishmania major in genetically resistant C57BL/6 mice was associated with a decreased production by placental cells of the Th2 cytokines IL-4 and IL-10 and increased production of IFN-γ and TNF. These results suggest that a beneficial anti-parasite Th1 response can adversely affect pregnancy outcome. Furthermore, Th1 cytokines may be deleterious for not only placental maintenance but also preimplantation events (11).

To evaluate the hypothesis that the proinflammatory cytokines IL-1, IL-6, and tumor necrosis factor-alpha might be the link between prenatal intrauterine infection (IUI) and neonatal brain damage, it is shown that maternal IUI appears to increase the risk of preterm delivery, which in turn is associated with an increased risk of intraventricular hemorrhage, neonatal white matter damage, and subsequent cerebral palsy. IL-1, IL-6, and TNF-α have been found associated with IUI, preterm birth, neonatal infections. and neonatal brain damage (12). Unifying models not only postulate the presence of cytokines in the three relevant maternal/fetal compartments (uterus, fetal circulation, and fetal brain) and the ability of the cytokines to cross boundaries (placenta and blood-brain barrier) between these compartments, but also postulate how proinflammatory cytokines might lead to IVH and neonatal white matter damage during prenatal maternal infection. Interrupting the proinflammatory cytokine cascade might prevent later disability in those born near the end of the second trimester.

Material and Methods

The study includes 250 children and their mothers having in common chronic disease. Mothers had chronic illness before pregnancy compared with 100 children treated because of acute infections and absence of chronic disease in mother. The mothers were examined for the presence of chronic disease, spontaneous abortions, treated sterility and seropositivity on CMV, HSV, EBV and HIV, as well as the examined children. Laboratory investigation including standard hematological parameters: RBC, WBC, Hb level, presence of monocytes, virocytes, LGL, the level of LDH, CPK, AST and ALT. Selected patients and mothers were analyzed by the expression of CD2,CD3, CD4, CD8, CD25, CD56, and DR on the peripheral blood mononuclear cells by the indirect immunoflorescence method.

Results

Chronic disease with Th1 type response was present in 231 mothers defined on the clinical basis and the presence of LGL and CD56 positive peripheral blood mononuclear cells: iron resistant anemia 163, CNS dysfunction 59, viral infections 114 (HSV and CMV the most often), bacterial infections 6, organ specific autoimmune diseases 15, acute viral infections in 21 mothers. 75 mothers were treated during pregnancy with hormones or tocolitics. Problems with previous pregnancies had 28 because of sterility 63-spontaneous abortions, 5-dead born newboms (Fig 1.). 92,4% of the mothers were seropositive on CMV, 51,2% on HSV, 23,6% on EBV and 1,2% on HIV. The mothers from the control group were seropositive to CMV in 75%, HSV 15% and EBV 12%, but without clinical manifestations of chronic disease, spontaneous abortion, or dead born children. The children from the control group had no chronic disease, except 5% anemic, which was iron sensitive. The most of the examined children had problems after birth manifested as small for date, hypo or hypertrophy, inappropriate respiratory, cardiovascular and termoregulatory adaptation. Clinical manifestations in examined children were: iron resistant anemia-197, lymphadenopathy-155, higher incidence of infections-87, vasculitis-72, nervous system dysfunction-54, asthma-36, angioedema- 32, stomatitis-21, hepatitis-19, polyarthritis-15, leucopenia-14, anomalies-13 rachitis-8 non epidemic parotitis-7, malapsorption-6, malignant diseases in the later follow up-4, and chromosomal aberrations-3 (Fig 2). Almost all of the children with exception of those suffering asthma, and angioedema had Th1 response (presence of LGL and CD56 and

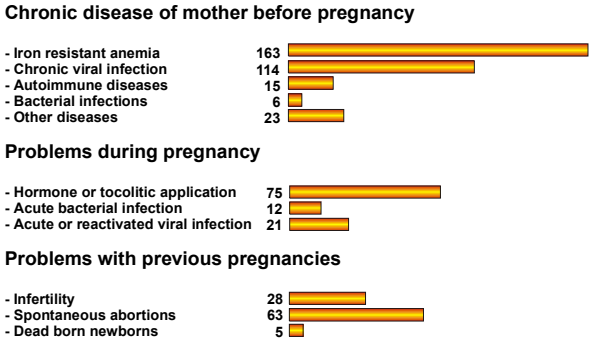

Fig. 1. Elements suggesting immune system dysfunction of mother

CD25 positive cells in the peripheral blood). 82 % of the patients had higher activity in most of the examined enzymes (CPK, LDH, AST and ALT).

Discussion

Even though it is known that women are more susceptible to infection during menstrual cycle, and the fact that viral infections during pregnancy are often followed by miscarriage or occurrence of anomalies in the developing embryo, the idea of the immune system involvement in conception, maintenance of pregnancy and development and growth of embryo is becoming actual those days.

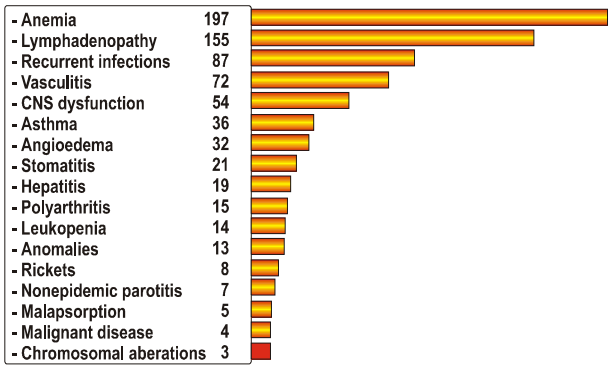

Fig. 2. Clinical manifestations in examined children

Human pregnancy is not nearly as successful as one might imagine, considering the fact that the rate of early pregnancy loss after implantation may be as high as 31%. Despite years of research, information is lacking on all the etiologies of RSA, which is the most common complication of reproductive failure (13). Chromosomal defects, which are among the few unequivocally established causes of RSA, are found in only 3-7% of couples with a history of recurrent pregnancy loss. Other causes include anatomical anomalies, endocrine disorders and infections. In 60-70% of abortions are of unknown origin and it has long been suspected that immunological factors may contribute to the pathogenesis of many of the unexplained RSAs (14).

The first studies to show human RSA-associated abnormal immune reactivity, in the context of the Thl-Th2 paradigm, demonstrated in vitro that trophoblast antigens activate the lymphocytes of RSA-susceptible women to produce the embryotoxic cytokines IFN-γ and TNF-α (15, 16). Peripheral blood mononuclear cells (PBMCs) from a significant proportion of women with a history of RSA showed greater cell proliferation and produced soluble factors and were toxic to mouse embryos and human trophoblast cell lines when stimulated in vitro with trophoblast antigen extracts. Of 244 women with unexplained RSA, 160 were shown to have PBMCs that responded in vitro to trophoblast antigens by producing embryotoxic activity and high levels of IFN-γ and TNF-α, but very low levels of IL-4 and IL-10. Conversely, women who are not prone to RSA responded without the production of Thl-type cytokines, but had IL-10 activity. This suggests that Th2-type immunity may be a natural response to trophoblast antigens, while Thl-type responses are aberrant and associated with unexplained RSA, and may therefore play a role in reproductive failure (17). Furthermore, it can be argued that the primary defect in these women could be an inability to mount a Th2 response to fetoplacental antigens, a reaction that would normally serve to downregulate harmful Thl-type responses (18).

Among the earliest hypotheses put forward to explain the success of the fetal allograft was the idea that the pregnant female is in a state of immunosuppression during gestation (19). Current trends support the possibility of modulation or deviation of maternal responses rather than a blanket suppression. This immune deviation, besides comprising a shift from cellular to humoral immunity, also comprises a deflection from a cytotoxic IgG2 (Thl-induced) to a noncytotoxic IgG1 (Th2-induced) antibody response. Several cells and soluble factors have been proposed as prospective candidates for mediators of such immunomodulation (20). Trophoblast cells, decidual cells and cells of the lymph nodes draining the uterus have been shown to suppress immune responses in vitro. Similarly, a progesterone-induced blocking factor (PlBF) produced by lymphocytes and factors secreted by cultured placental cells and trophoblast cell lines have been proposed to serve immunoregulatory roles (21). Besides these, cytokines themselves may play extremely important roles in immune regulation during pregnancy. In fact it has been proposed that the major role of Th2 cells is to control Thl-dependent reactivity via cytokines such as IL-10. Cytokines that merit special attention are IL-10 and transforming growth factor β (TGF-β). Some or all of these factors and cytokines could play useful immunoregulatory roles in maintaining the balance of the immune reactivity in favor of a Th2-pathern (22).

Pregnant women, especially primigravidas, are highly susceptible to malaria infection, resulting in maternal anemia and low birth weight infants. Because

circulating parasitemia is rare in the newborn, the cause of poor fetal outcomes has been unclear. We measured cytokine concentrations in placentas collected from women delivering in urban hospitals in malaria-holoendemic or nonendemic areas of Kenya (23). Normal placentas displayed a bias toward type 2 cytokines; type 1 cytokines IFN-gamma and IL-2 were absent in placentas not exposed to malaria but present in a large proportion of placentas from a holoendemic area. TNF-alpha and TGF-beta concentrations were significantly higher, and IL-10 concentrations significantly lower, in placentas from the holoendemic area (24). Among primigravidas, placental TNF-alpha concentrations were significantly higher in the presence of severe maternal anemia, and both IFN-gamma and TNF-alpha were significantly elevated when a low birth weight, rather than normal weight, infant was delivered. We conclude that maternal malaria decreases IL-10 concentrations and elicits IFN-gamma, IL-2, and TNF-alpha in the placenta, shifting the balance toward type 1 cytokines (25). This is the first demonstration that these placental cytokine changes are associated with poor pregnancy outcomes in humans.

Since certain cytokines are necessary for the success of pregnancy it was proposed that a deficiency in these cytokines may lead to poor placentation, subnormal growth and possibly even fetal deaths. Certain deleterious cytokines may lead to adverse effects on the conceptus either by direct embryotoxic activity or by damaging the placental trophoblast: IFN-γ inhibits trophoblast outgrowth in vitro, and IFN-γ and TNF-α inhibit embryonic and fetal development as well as the proliferation of human trophoblast lines in vitro. IFN-γ, in combination with TNF-α, is cytotoxic to rodent embryonic fibroblast-like cells, and TNIF-α mediates apoptotic death of trophoblast cells. Most significantly, the inflammatory cytokines IL-2, TNF-α and IFN-γ terminate normal pregnancy when injected into pregnant mice (26).

These Thl-type cytokines may damage the placenta directly or indirectly via the activation of cytotoxic cell types. TNF-α may cause fetal expulsion due to uterine contraction or may cause necrosis of implanted embryos; alternatively, TNF could act by thrombosing the blood supply to the conceptus. IFN-γ has been shown to inhibit the secretion of granulocyte-macrophage colony-stimulating factor (GM-CSF) from the uterine epithelium (27, 28). Since GM-CSF promotes the growth and/or differentiation of trophoblast, the loss of this cytokine may be deleterious to the trophoblast. Thl type cytokines may also act by inducing NK and LAK cell activity. Since Thl-type cytokines mediate pregnancy loss, a shift towards Thl-type immunity may help resolve natural killer NK and lymphokine-activated killer - LAK cells. NK activity has now been unquestionably linked with spontaneous fetal resorption in mice, as demonstrated by studies showing that activation of NK cells in pregnant mice, following injection with double-stranded RNA poly-IC, induces fetal resorption. This effect can be adoptively transferred with poly-IC-unexplained pregnancy failure (29, 30).

Furthermore, NK cells and cytotoxic T lymphocytes (CTLs) may cause fetal loss by developing in the presence of TNF and IL-2 into LAK cells, which have been shown to be capable of killing trophoblast cells. In humans, the levels of NK cells in peripheral blood of nonpregnant women with a history of recurrent spontaneous abortions (RSA) have been shown to be elevated as compared with normal nonpregnant women; a significant increase in peripheral NK levels has also been demonstrated in pregnant women with RSA as compared with normal pregnant women (31, 32).

Interestingly, the three cytokines that are potentially the most harmful to pregnancy are those that most clearly fit into the Thl-type profile. It is a possible that maternal T cells, in some situations, respond to stimulation by fetoplacental antigens in an aberrant manner by producing these cytokines. This might be true in CBA/J females mated with DBA/2J males (CBA/J X DBA/2J) which experience very high fetal resorption rates, whereas CBA/J females mated with males of other strains, including those of the same major histocompatibility complex (MHC haplotype as DBA/2J, have low resorption rates. The reasons for the susceptibility of the CBA/J X DBA/2J mating combination to fetal resorption are not known, but pregnancy loss in this mating combination is immunologically mediated, as demonstrated by various lines of evidence: (1) an increased infiltration of NK cells and at the fetomaternal interface in these matings; (2) the downregulation of NK activity by the injection of anti-NK antibodies followed by a reduction in fetal resorption's ; (3) the prevention of fetal resorptions by immunization of prospective CBA/J mothers with BALB/c cells prior to mating and the transferability of this anti-abortive effect by adoptive transfer of T cells from immunized mice (33).

Theoretically, the Th1 to Th2 shift in a proportion of pregnancies may be due to one or more factors. Deficiencies in one or more of the putative immunomodulatory molecules, such as PIBF, placental factors, IL-10 or TGF-β, may effect such a shift. In addition, while B cells, macrophages and dendritic cells can generally present antigens in such a way as to initiate both Th1 and Th2 responses, a preponderance of certain cytokines in the local milieu during T-cell activation may cause a shift in either direction. It is likely that a balance between IL-12 (favoring a Th1 response) and IL-4 (favoring a Th2 response) determines the eventual outcome of the Thl-Th2 dichotomy during an immune response.

Infection during pregnancy particularly by intracellular parasites, may well be an important factor that drives the response in a certain direction. Krishnan et al. examined whether the curative Thl response against Leishmania major in resistant C57BL mice is detrimental to pregnancy. They found that the number

of fetal resorptions in infected resistant mice was significantly higher than in uninfected mice, and that IL-4 and IL-10 production in the placenta decreased while IFN-γ and TNF production increased in the former (34).

What happens when resident viral infection (CMV, HSV) gets reactivated because of Th1 to Th2 cytokine pattern switch? There are two possibilities: to keep to Th2 cytokine pattern which may protect the embryo and increase the risk of viral progression, or to switch to Th1 response which is protective for the mother but may lead to miscarriage. The maternal immune system is faced with a rather difficult choice: if the mother has to eliminate an intracellular infection via a Thl response, she may end up endangering her conceptus. But, in attempting to nurture and protect the fetus by maintaining a Th2 bias, she may herself succumb to the parasitic infection. Fortunately for the conceptus, it appears that, while a Th2 response is either not convertible or is very difficult to convert to a Thl response, Thl reactivity can be converted into a Th2 response. The most of the time in practice we seems to get both consequences: viral activation and damage of the immune system of mother and the baby leading to chronic disease in both particularly in the embryo and lather in childhood. These compromises appear to be main reason for chronic suffering because of development and growth of embryo in immunological inappropriate microenvironment with altered cytokine profile and development of the immune system in immunological unprotected environment (tolerance induction to viral antigens)

The ongoing systemic Thl response against an infectious agent may prove detrimental to gestation. Thl-type cells induced by the infection may traverse the fetal interface or may produce cytokines that affect the trophoblast. Alternatively, cytokines produced elsewhere may circulate to the placenta and affect local cytokine networks. Hill speculates that a previous abortion due to some other (non-immunological) cause may prime the mother for subsequent Thl-biased response (35, 36)

Conclusion

Development of a child in the immunologicaly inappropriate microenvironment of a mother with Th1 response might be responsible for an inappropriate development of the immune and other systems and organs. We may speculate that prenatal immune system activation with production of Th1 response cytokines, oxidative and nitric metabolites may modulate the proliferation, differentiation, migration, and apoptosis of cells with the final consequences: immune system and other organ disjunction, anomalies or death.

References

1. Piccinni MP, Romagnani S. Regulation of fetal allograft survival by a hormone-controlled Th1- and Th2-type cytokines. Immunol Res 1996; 15: 141-50
2. Athanassakis I, Iconomidou B: Cytokine production in the serum and spleen of mice from day 6 to14 of gestation: cytokines/placenta/spleen/serum. Dev Immunol 1996; 4: 247-55
3. Schust DJ, Hill JA. Correlation of serum cytokine and adhesion molecule determinations with pregnancy outcome. J Soc Gynecol Investig 1996; 3: 259-61
4. Martal J, Chene N, Camous S, Huynh L, Lantier F, Hermier P, L'Haridon R, Charpigny G, Charlier M, Chaouat G. Recent developments and potentialities for reducing embryo mortality in ruminants: the role of IFN-tau and other cytokines in early pregnancy. Reprod Fertil Dev 1997; 9: 355-80
5. Stallmach T, Hebisch G, Joller H, Kolditz P, Engelmann M. Expression pattern of cytokines in the different compartments of the feto-maternal unit under various conditions. Reprod Fertil Dev 1995; 7: 1573-80
6. Stallmach T, Hebisch G, Joller-Jemelka HI, Orban P, Schwaller J, Engelmann M. Cytokine production and visualized effects in the feto-maternal unit. Quantitative and topographic data on cytokines during intrauterine disease. Lab Invest 1995; 73: 384-92
7. Rutanen EM: Cytokines in reproduction. Ann Med 1993; 25: 343-7
8. Vinatier D, Monnier JC. Immunological recognition in pregnancy: physiology. J Gynecol Obstet Biol Reprod (Paris) 1993; 22: 709-21
9. Szereday L, Varga P, Szekeres-Bartho J. Cytokine production by lymphocytes in pregnancy. Am J Reprod Immunol 1997; 38: 418-22
10. Raghupathy R. Th1-type immunity is incompatible with successful pregnancy. Immunol Today 1997; 18: 478-82
11. Krishnan L, Guilbert LJ, Wegmann TG, Belosevic M, Mosmann TR. T helper 1 response against Leishmania major in pregnant C57BL/6 mice increases implantation failure and fetal resorptions. Correlation with increased IFN-gamma and TNF and reduced IL-10 production by placental cells. J Immunol 1996; 156: 653-62
12. Dammann O, Leviton A. Maternal intrauterine infection, cytokines, and brain damage in the preterm newborn. Pediatr Res 1997; 42: 1-8
13. Feinberg BB, Anderson DJ, Steller MA, Fulop V, Berkowitz RS, Hill JA. Cytokine regulation of trophoblast steroidogenesis. J Clin Endocrinol Metab 1994 Mar 78:3 586-91
14. Krasnow JS, Tollerud DJ, Naus G, DeLoia JA. Endometrial Th2 cytokine expression throughout the menstrual cycle and early pregnancy. Hum Reprod 1996; 11: 1747-54
15. Chaouat G, Menu E, Delage G, Moreau JF, Khrishnan L, Hui L, Meliani AA, Martal J, Raghupathy R, Lelaidier C, et al. Immuno-endocrine interactions in early pregnancy. Hum Reprod 1995; 10 Suppl 2: 55-9
16. Yagami Y. Pathogenesis on infertility; its immunological aspects Nippon Sanka Fujinka Gakkai Zasshi 1993; 45: 735-47
17. Lin H, Mosmann TR, Guilbert L, Tuntipopipat S, Wegmann TG. Synthesis of T helper 2-type cytokines at the maternal-fetal interface. J Immunol 1993; 151: 4562-73
18. Wilder RL. Hormones, pregnancy, and autoimmune diseases. Ann N Y Acad Sci 1998; 840: 45-50
19. Arck PC, Ferrick DA, Steele-Norwood D, Croitoru K, Clark DA. Regulation of abortion by gamma delta T cells. Am J Reprod Immunol 1997. 37: 87-93
20. Hill JA, Polgar K, Anderson DJ. T-helper 1-type immunity to trophoblast in women with recurrent spontaneous abortion. JAMA 1995; 273: 1933-6
21. Formby B. Immunologic response in pregnancy. Its role in endocrine disorders of pregnancy and influence on the course of maternal autoimmune diseases. Endocrinol Metab Clin North Am 1995; 24: 187-205

22. Matsuzaki N. Immunological analysis of the mechanism of maternal tolerance of a fetus and the cytokine-mediated regulation of feto-placental functions. Nippon Sanka Fujinka Gakkai Zasshi 1994; 46: 697-706
23. Fried M, Muga RO, Misore AO, Duffy PE. Malaria elicits type 1 cytokines in the human placenta: IFN-gamma and TNF-alpha associated with pregnancy outcomes. J Immunol 1998; 160: 2523-30
24. Reinhard G, Noll A, Schlebusch H, Mallmann P, Ruecker AV. Shifts in the TH1/TH2 balance during human pregnancy correlate with apoptotic changes. Biochem Biophys Res Commun 1998; 245: 933-8
25. Tranchot-Diallo J, Gras G, Parnet-Mathieu F, Benveniste O, Marcé D, Roques P, Milliez J, Chaouat G, Dormont D. Modulations of cytokine expression in pregnant women. Am J Reprod Immunol 1997; 37: 215-26
26. Shaarawy M, Nagui AR. Enhanced expression of cytokines may play a fundamental role in the mechanisms of immunologically mediated recurrent spontaneous abortion. Acta Obstet Gynecol Scand 1997; 76: 205-11
27. Austgulen R, Lien E, Liabakk NB, Jacobsen G, Arntzen KJ. Increased levels of cytokines and cytokine activity modifiers in normal pregnancy. Eur J Obstet Gynecol Reprod Biol 1994; 57:3 149-55
28. Jones CA, Finlay-Jones JJ, Hart PH. Type-1 and type-2 cytokines in human late-gestation decidual tissue. Biol Reprod 1997; 57: 303-11
29. Robertson SA, Seamark RF, Guilbert LJ, Wegmann TG. The role of cytokines in gestation. Crit Rev Immunol 1994; 14: 239-92
30. Steinborn A, Günes H, Röddiger S, Halberstadt E. Elevated placental cytokine release, a process associated with preterm labor in the absence of intrauterine infection. Obstet Gynecol 1996; 88: 534-9
31. Hillier SL, Witkin SS, Krohn MA, Watts DH, Kiviat NB, Eschenbach DA. The relationship of amniotic fluid cytokines and preterm delivery, amniotic fluid infection, histologic chorioamnionitis, and chorioamnion infection. Obstet Gynecol 1993 81: 941-8
32. Saito S, Nishikawa K, Morii T, Enomoto M, Narita N, Motoyoshi K, Ichijo M. Cytokine production by CD16-CD56bright natural killer cells in the human early pregnancy decidua. Int Immunol 1993; 5: 559-63
33. Gendron R.L. Farookhi R. and Baines M.G. Resorption of CBA/JXDBA/2J mouse conceptuses in CBA/J uteri corelates with failure of the fetoplacental unit to suppress natural killer cell activity. J Reprod Fertil.1990; 98: 277-84
34. Yanushpolsky EH, Ozturk M, Polgar K, Berkowitz RS, Hill JA. The effects of cytokines on human chorionic gonadotropin (hCG) production by a trophoblast cell line. J Reprod Immunol 1993; 25: 235-47
35. Wegmann TG, Lin H, Guilbert L, Mosmann TR. Bidirectional cytokine interactions in the aternal-fetal relationship: is successful pregnancy a TH2 phenomenon? Immunol Today 1993; 14: 353-6
36. Marzi M, Vigano A, Trabattoni D, Villa ML, Salvaggio A, Clerici E, Clerici M. Characterization of type 1 and type 2 cytokine production profile in physiologic and pathologic human pregnancy. Clin Exp Immunol 1996; 106: 127-33

HRONIČNE BOLESTI U DETINJSTVU KAO POSLEDICA DISFUNKCIJE IMUNSKOG SISTEMA MAJKE ZA VREME TRUDNOĆE

Borislav Kamenov, Hristina Dimitrijević, Gordana Tasić, Svetlana Pljaskić

Dečja klinika i Institut za mikrobiologiju, Medicinski fakultet Niš, Jugoslavija, Dom zdravlja Niš, Jugoslavija

Kratak sadržaj: *Rast i razvoj embriona i fetusa u antigeno ptivilegovanoj sredini i dominacija Th2 odgovora majke su neophodni za adekvatni razvoj imunskog sistema (prevencija abortusa klona, anergije i apoptoze) kao i za razvoj drugih organa i tkiva. Citokini Th1 odgovora, slobodni radikali kiseonika i nitriti sa svojim potencijalom da utiču na ekspresiju gena mogu ozbiljno da interferiraju sa ćelijskom proliferacijom, diferencijacijom apoptozom i migracijom. Mnoge akutne virusne infekcije su poznate po svom potencijalu da izazovu smrt ploda ili dovedu do ozbiljnih anomalija. Prenatalno uspostavljanje Th1 odgovora se analizira kao mogući faktor disfunkcije imunskog sistema i njegovog uticaja na pojavu hroničnih bolesti u detinjstvu. Analizirano je 250 dece koja su bolovala od hroničnih bolesti u odnosu na postojanje Th1 odgovora majke u toku trudnoće u poređenju sa 100 dece i njihovih majki lečenih zbog akutne infekcije, a bez znakova hronične bolesti. Pored ispitivanja specifičnih za organ ili sistem, analizirani su sledeći parametri: broj eritrocita i leukocita, LGL, nivo hemoglobina, ELISA test na HSV, CMV, EBV, HIV; NBT, fenotipizacija mononuklearnih leukocita periferne krvi: CD2, CD3, CD4, CD8, DR, CD25, CD56; elektroforeza serumskih proteina, imunske komplekse, autoantitela, anzime: CPK, LDH, AST i ALT. Hronična bolest majke sa Th1 odgovorom je postojala kod 231 majke: gvožđe rezistentna anemija kod 163, virusna infekcija kod 114 (najčešće HSV i CMV), bakterijska infekcija 6, autoimunskih bolesti 15, akutnih virusnih infekcija 21. Kod 75 majki primenjeno je lečenje hormonima i tokoliticima u toku trudnoće, 28 majki je lečeno zbog steriliteta, 63 je imalo spontani abortus, a 5 je rađalo mrtvu decu. Većina dece je pokazivalo hipo ili hipertrofiju i neadekvatnu respiratornu, kardiovaskularnu i termoragulacionu adaptaciju posle rođenja. Kliničke manifestacoije kod ispitivane dece su bile: anemija 197, limfadenopatija 155, česte infekcije 87, vaskulitis 72, disfunkcije CNS-a 54, astma 36, angioedema 32, stomatitis 21, hepatitis 19, poliartritis 15, leukopenija 14, anomalije 13, rahitis 8, neepidemijski parotitis 7, malapsorpcioni sindrom 6, maligne bolesti u kasnijem periodu 4, hromozomske aberacije 3. 82% ispitanika pokazivala je povišene vrednosti bar jednog od ispitivanih enzima (CPK, LDH, ALT, AST).*

Ključne reči: *Disfunkcija imunskog sistema, Th1 citokini u trudnoći, hronične bolesti u detinjstvu*

Received: October 5, 1998