Tumor Necrosis Factor Alpha in Preeclampsia

Fozia A Patigaroo*, Anwar H Siddiqui*,Rajiv Gulati*, ZehraMohsin**

*Department of Physiology and ** Department of Obstetrics & Gynecology, Jawaharlal Nehru Medical College, AMU, Aligarh

Abstract: Pre-eclampsia is one of the most frequent complications of pregnancy, however, little is known about its aetiology. Insufficient adaptation of the decidual and intramyometrial portions of the spiral arterioles in preeclampsia results in reduced utero-placental blood flow, leading to local placental hypoxia. Pre-eclampsia is pregnancy-induced hypertension (PIH) of unknown etiology. Pre-eclampsia can be quite serious as it can lead to various complications both for the mother and the baby. In fact, pre-eclampsia and eclampsia, severe forms of PIH, are the leading cause of infant and maternal death in India. Hypertension complicates an estimated 6-8% of all pregnancies. Significant risk factors identified in univariate analysis included pre pregnancy body mass index (BMI > 25) (OR = 11.27), history of chronic hypertension (OR = 8.65), history of diabetes (OR = 11.0), history of renal disease (OR = 7.98), family history of hypertension (OR = 5.4), history of pre-eclampsia in earlier pregnancy (OR = 9.63), and multiple pregnancy (OR = 4.85). Cytokines are major contributors in pathogenesis of pre eclampsia. Several studies confirm a significant increase ($p<0.01$) in circulating TNF-α levels in the last trimester of pregnancy, compared to the non-pregnant status. Significantly increased serum concentrations ($p<0.001$) were also found in pregnant patients with preeclampsia, compared to normotensive pregnant women. Conclusion: Preeclampsia is an exacerbation of a generalized inflammatory response, physiologically present in the third trimester of pregnancy. TNF-α pro inflammatory cytokine can be a potential marker of the severity of the preeclamptic syndrome, without being an indicator of the fetal status at birth.

Key Words: Preeclampsia, TNF alpha, Cytokines.

Author for correspondence: Dr. Rajiv Gulati, Professor, Department of Physiology, Jawaharlal Nehru Medical College, AMU, Aligarh-202002e- mail:only.anwar@gmail.com , rajivamu17@gmail.com

Introduction: Normal physiological pregnancy undergoes various physiologic and metabolic changes so as to meet the increasing energy needs of the developing fetus. Not only there occurs increase in the weight and blood volume which is required to perfuse the vital organs like kidneys but the pregnant uterus also undergoes vascular remodeling. The uterine spiral arteries are transformed into low-resistance flow vessels that are able to accommodate more blood volume and gain access to the placental intervillous space[1]. Complex cytokine networks also play an important role in a wide range of reproductive and pregnancy related processes. These influence a wide range of uterine functions during the menstrual cycle, implantation, pregnancy and labour. The synergistic interactions between individual cytokines are intricate and dynamic, and modulated by pregnancy hormones. If there is any disturbance in this cytokine signalling adverse pregnancy outcomes such as miscarriage, preeclampsia, preterm labour and foetal brain injury may occur[2].

Immune system in pregnancy: Normal pregnancy requires an appropriate immunological interaction between the mother and the developing fetus because the fetus expresses paternal antigens which are considered semi-allograft to the maternal immune system[3]. The placenta has an important role in normal pregnancy as it acts as an immunological barrier between maternal and fetal antigens. Placenta does not express the usual major histocompatibility molecules like MHC class I, HLA-A, HLA-B or MHC class II molecules and thus it is protected from the cytotoxic effect of T lymphocytes.

To avoid killing by natural killer (NK) cells, which are programmed to recognize HLA-null cells, trophoblast cells express non classical MHC molecules like HLA-G [4], HLA-E, and HLA-F [5]. The decidual NK cells which constitute about 50-70% of all maternal immune cells present in the uterus do not have any lytic activity. These regulate pregnancy through secretion of cytokines and angiogenic factors which have important action on the vascular and decidualtransformations occurring in the

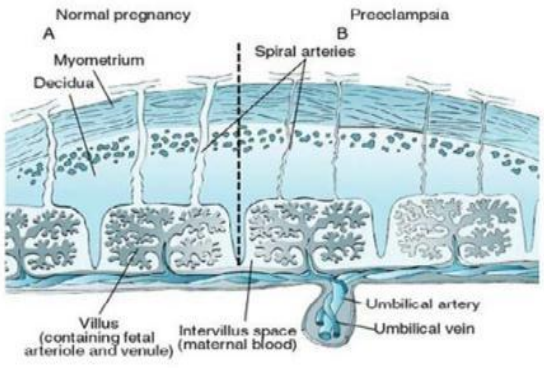
uterine wall during the early weeks of pregnancy [6-8].

In normal pregnancy there is a balance between T helper 1 and T helper 2 cytokines. Th2 immunity is characterized by the dominance of humoral immune responses over cell-mediated, responses which are more destructive and can be detrimental to the fetal allograft. CD4-positive Th2 lymphocytes develop from naïve T helper cells in the presence of interleukin (IL)-4 and IL-10, whereas Th1 cells arise when IL-2 and interferon (IFN)-γ are present. It has been demonstrated that the placental bed encloses a high incidence of the Th2 factors IL-4 and IL-10 [9-13]. Several isoforms of the immunosuppressive transforming growth factor (TGF)β have also been localized in the placenta, adding to the immune privilege of this tissue [14-16].

Cytokines in normal pregnancy: TNF alpha is a 17 kD polypeptide cytokine which is produced in preeclampsia by neutrophils, monocytes and placenta. Cytokines are involved both in normal pregnancy and labour. IL-1, IL-6 and TNF alpha are all detected in placenta and amniotic fluid[17]. TNF alpha is produced in human deciduas in response to bacterial products and it stimulates prostaglandin production by amnion and deciduas[18,19]. Normal pregnancy is a condition of mild maternal systemic inflammation and circulating levels of particular pro-inflammatory cytokines, such as tumor necrosis factor (TNF)alpha, IL-6, and IL-1 are raised compared to nonpregnant women[20,21].TNF alpha regulates trophoblast proliferation and differentiation, cell adhesion tissue remodeling, the apoptosis of villous trophoblast and trophoblast hormone production[22-24]. The low level of uterine TNF alpha is beneficial to pregnancy, whereas elevated concentrations are detrimental.

Preeclampsia: Preeclampsia is a multisystem disorder of pregnancy and is characterized by new onset of hypertension (≥ 140/90 mm Hg) and proteinuria (≥ 300 mg/24 h) after 20 weeks of gestation. It occurs in about 2-8% of pregnancies [25,26]. It is the most common medical complication of pregnancy whose incidence has continued to increase worldwide and is associated with significant maternal mortality and morbidity. Its incidence is more in primigravida and the risk decreases in the subsequent pregnancies. Among the primiparous women there is disparity in the risk among different ethnic groups. The risk is very high in women of Indian origin[27]. Risk factors includeprimiparity, multiple pregnancies, a previous history of preeclampsia, and chronic medical conditions such as obesity, hypertension, vascular disease, or diabetes[28]. However, there is no factor by which we can predict this disease nor there is any preventive treatment available.

The main pathology of the disease lies in the placenta and occurs during the first weeks of pregnancy. The number and distribution of macrophages in placental beds are significantly altered in preeclampsia in comparison to normal pregnancy[29-31]. Activated macrophages induce apoptosis of extravilloustrophoblasts in vitro. The normal vascular remodeling does not take place in preeclampsia. Extravilloustrophoblasts invasion is abnormally shallow, and remodeling and enlargement of the spiral arteries is restricted to their placental–proximal part [32,33].



Inadequate vascular remodeling results in placental ischaemia and release of proinflammatory cytokines such as IL-6 and TNF alpha by the placenta[34-36]. IL-6 increases the endothelial cell permeability and inhibits the prostacyclin permeability. TNF alpha stimulates cell proliferation and hypoxia induced cell activation but inhibits decidual invasion by cytotrophoblasts. Further it leads to alterations in endothelial cells, release of endothelin-1 and inhibition of acetycholine mediated

vasodilatation[37,38]. The levels of endothelin-1 and cytokines (TNF alpha, IL-2 and IF-γ) in the maternal sera have been found higher in preeeclamptics as compared to normal pregnancy suggesting their role in the pathogenesis in the development of preeclampsia[39]. The concentration of TNF alpha is higher in preeclampsia as compared to normal pregnancy during the third trimester [40], [41]. Zhou P et al.[42] found the expression of pentraxin 3(PTX3) and TNF alpha in placental tissues and maternal sera to be higher in preeclampsia and preeclampsia with intrauterine growth restriction suggesting the involvement of these in the pathogenesis of preeclampsia. A doublefold increase was observed in TNF-alpha levels at 36 weeks in patients with pre-eclampsia (P=0.003) which decreased significantly (P=0.001) after delivery. [43]

Conclusion: Preeclampsia is multifactorial and the use of TNF alpha in predicting this disease is still controversial. This cytokine has a role in normal pregnancy from implantation to parturition. Preeclampsia is a major cause of maternal morbidity and mortality. Though many studies have suggested the role of TNF alpha in the pathogenesis of preeclampsia but still the cause is unknown. Further studies are required to find the role of TNF alpha in predicting this disease so as to improve the maternal outcome.

References:

1. Benirschke K, Kaufmann P (2000) Pathology of the human placenta, 4th edn. Springer, Berlin Heidelberg New York.
2. Orsi NM, Tribe RM. Cytokine networks and the regulation of uterine function in pregnancy and parturition. J Neuroendocrinol. 2008 Feb 8
3. Medawar PB (1961) Immunological tolerance. Nature 189:14–17
4. Kovats S, Main EK, Librach C, Stubblebine M, Fisher SJ, DeMars R (1990) A class I antigen, HLA-G, expressed in human trophoblasts. Science 248:220–223
5. Ishitani A, Sageshima N, Lee N, Dorofeev Marquardt H, Geraghty DE (2003) Protein expression and peptide binding suggest unique and interacting functional role for HLA-E, F, and G in maternal–placental immune recognition. J Immunol 171:1376-1384
6. Saito S, Nishikawa K, Morii T, Enomoto (1993) Cytokine production by CD16– CD56 bright natural killer cells in the human earlypregnancy decidua. IntImmunol 5:559–563
7. Hanna J, Goldman-Wohl D, Hamani Y, Avraham I, Greenfield C, Natanson-Yaron S, Prus D, Cohen-Daniel L, Arnon TI, Manaster I, Gazit R, Yutkin V, Benharroch D, Porgador A, Keshet E, Yagel S, Mandelboim O (2006) Decidual NK cells regulate key developmental processes at the human fetal– maternal interface. Nat Med 12:1065–1074
8. Tabiasco J, Rabot M, Aguerre-Girr M, El Costa H, Berrebi A, Parant O, Laskarin G, Juretic K, Bensussan A, Rukavina D, Le Bouteiller P (2006) Human decidual NK cells: unique phenotype and functional properties—a review. Placenta 27 (Suppl A):S34–S39
9. Cadet P, Rady PL, Tyring SK, Yandell RB, Hughes TK (1995) Interleukin-10 messenger ribonucleic acid in human placenta: implications of a role for interleukin-10 in fetal allograft protection. Am J ObstetGynecol 173:25–29
10. Roth I, Corry DB, Locksley RM, Abrams JS, Litton MJ, Fisher SJ (1996) Humanplacental cytotrophoblasts produce the immunosuppressive cytokine interleukin 10. J Exp Med 184:539–548
11. Moraes-Pinto MI, Vince GS, Flanagan BF, Hart CA, Johnson PM (1997) Localization of IL-4 and IL-4 receptors in the human term placenta, decidua and amniochorionic membranes. Immunology 90:87–94
12. Bennett WA, Lagoo-Deenadayalan S, Stopple JA, Barber WH, Hale E, Brackin MN, Cowan BD (1998) Cytokine expression by first-trimester human chorionic villi. Am J ReprodImmunol 40:309–318
13. Sacks GP, Clover LM, Bainbridge DR, Redman CW, Sargent IL (2001) Flow cytometric measurement of intracellular

Th1 and Th2 cytokine production by human villous and extravillouscytotrophoblast. Placenta 22:550–559
14. Dungy LJ, Siddiqi TA, Khan S (1991) Transforming growth factor-beta 1 expression during placental development. Am J ObstetGynecol 165:853–857
15. Graham CH, Lysiak JJ, McCrae KR, Lala PK (1992) Localization of transforminggrowth factor-beta at the human fetal–maternal interface: role in trophoblast growth and differentiation. BiolReprod 46:561–572
16. Ando N, Hirahara F, Fukushima J, Kawamoto S, Okuda K, Funabashi T, Gorai I, Minaguchi H (1998) Differential gene expression of TGF-beta isoforms and TGF-beta receptors during the first trimester of pregnancy at the human maternal–fetal interface. Am J ReprodImmunol 40:48–56
17. Romero R, Mazor M, Sepulveda W, Avila C,Copeland D, Williams J. TNF in preterm and term labour. Am J Obstet Gynecol. 1992;166:1576-1587
18. Romero R, Manogue KR, Mitchell MD, et al. Infection and labor IV cachetin-TNF inamniotic fluid of women with intra amniotic infection and preterm labour. Am J Obstet Gynecol. 1989;336-341
19. Casey MI, Cox SM, Beutter B, Milewich L, Mac Donald PC. Cachetin / TNF formation in human decidua. J Clin Invest.1989;83: 430-436
20. Kupferminc MJ, Peaceman AM, Wigton TR, Tamura RK, Rehnberg KA, Socol ML(1994) Immunoreactivetumor necrosis factor-alpha is elevated in maternal plasma but undetected in amniotic fluid in the second trimester. Am J ObstetGynecol 171:976–979
21. Austgulen R, Lien E, Liabakk NB, Jacobsen G, Arntzen KJ (1994) Increased levels of cytokines and cytokine activity modifiers in normal pregnancy. Eur J ObstetGynecoReprodBiol 57:149–155
22. Yui, J., Garcia-Loret, M., Wegmann, T.G. et al. (1994) Cytotoxicity of tumour necrosis factor-alpha and gamma interferon against primary human placental trophoblasts. Placenta, 15, 819–935.
23. Chard, T. (1995) Cytokines in implantation. Hum. Reprod. Update, 1, 385–396
24. Hunt, J.S., Chen, H.-L. and Miller, L. (1996) Tumor necrosis factors: pivotal components of pregnancy? Biol. Reprod., 54, 554–562.
25. Ghulmiyyah L, Sibai B. Maternal mortality from preeclampsia/eclampsia. Seminars in Perinatology. 2012; 36 (1): 56-59.
26. Moodley J. Maternal deaths associated with hypertensive disorders of pregnancy: a population based study. Hypertension in pregnancy. 2004; 23(3): 247-256.
27. Rao A K, Daniels K, El – sayed YY, Moshesh MK, Caughey A B. Perinatal outcomes among Asian American and Pacific Islander women. Am J ObstetGynecol 2006; 195(3): 834-838
28. Duckitt K, Harrington D (2005) Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies.BMJ 330:565
29. Reister F, Frank HG, Heyl W, KosankeG,Huppertz B, Schroder W, Kaufmann P, Rath W (1999) The distribution of macrophages in spiral arteries of the placental bed in preeclampsia differs from that in healthy patients. Placenta 20:229–233
30. Redline RW (2001) Macrophages in the basalplate of preeclamptic placentae. Placenta 22:890–893
31. Burk MR, Troeger C, Brinkhaus R, Holzgreve W, Hahn S (2001) Severely reduced presence of tissue macrophages in the basal plate of pre-eclamptic placentae. Placenta 22:309–316
32. Robertson WB, Brosens I, Dixon G (1976) Maternal uterine vascular lesions in the hypertensive complications of pregnancy. PerspectNephrolHypertens 5:115–127
33. Graham CH, Burton GJ (2004) Oxygen and trophoblastbehaviour—a workshop report. Placenta 25(Suppl A):S90–S92
34. Conrad KP, Benyo DF. Placental cytokines and the pathogenesis of preeclampsia. Am J ReprodImmunol. 1997;37:240–9.
35. Conrad KP, Miles TM, Benyo DF. Circulating levels of immunoreactive cytokines in women with preeclampsia. Am J ReprodImmunol. 1998;40:102–11.
36. Benyo DF, Smarason A, Redman CWG, Sims C, Conrad KP. Expression of inflammatory

cytokines in placentas from women with preeclampsia. J ClinEndocrinolMetab. 2001;86(6): 2505–12.
37. Founds SA, Powers RW, Patrick TE, Ren D, Harger GF, Markovic N, Roberts JM. comparison of circulating TNF alpha in obese and lean women with and without preeclampsia. Hypertens Pregnancy. 2008;27(1):39–48.
38. Vitoratos N, Economou E, Iavazzo C, Panoulis K, Creatsas G. Maternal serum levels of TNF-alpha and IL-6 long after delivery in preeclamptic and normotensive pregnant women. Mediators Inflamm. 2010;2010:908649
39. Sharma D, Singh A, Trivedi SS, Bhattacharjee J. Role of endothelin and Inflammatory cytokines in preeclampsia. Am J Reprod Immunol.2011; 65(4):428-32
40. Ibrahim SerdarSerin, Bulent Ozcelik, MustafaBasbug, HuseyinKilic, DeryaOkur, RusenErez. European Journal of Obstetrics & Gynecology and Reproductive Biology.100(2002)143-145
41. Muzzamil S, Singhal U, Gulati R, Bano I. Indian J Physiol Pharmacol.2005;49(2):236-240.
42. Zhou P, Luo X, Qi HB, Zoung WZ, Zhang H, liu DD, Li QS. Inflammation Research.2012;61:1005 1012

Source Of Financial Support-Nil
Conflict Of Interest-None