

Tumor Necrosis Factor Alpha In Preeclampsia

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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.

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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 space¹. 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 occur².

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 system³. 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-G⁴, HLA-E, and HLA-F⁵. 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 decidual transformations occurring in the

uterine wall during the early weeks of pregnancy⁶⁻⁸.

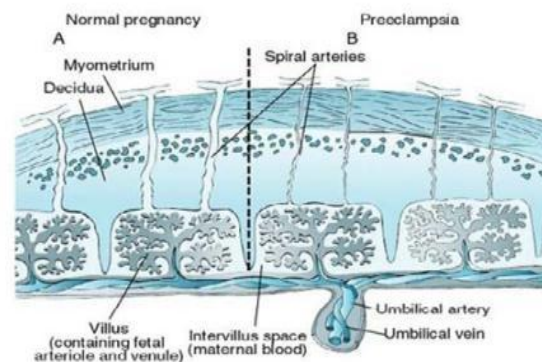
In normal pregnancy there is a balance between T helper 1 and T helper 2 cytokines. Th2 immunity is characterized by the dominance of humoral immune responses over cell-mediated, responses which are more destructive and can be detrimental to the fetal allograft. CD4-positive Th2 lymphocytes develop from 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-10⁹⁻¹³. Several isoforms of the immunosuppressive transforming growth factor (TGF) β have also been localized in the placenta, adding to the immune privilege of this tissue¹⁴⁻¹⁶.

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 fluid¹⁷. 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 production²²⁻²⁴. 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 ($\geq 140/90$ 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 origin²⁷. Risk factors include primiparity, multiple pregnancies, a previous history of preeclampsia, and chronic medical conditions such as obesity, hypertension, vascular disease, or diabetes²⁸. 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 pregnancy²⁹⁻³¹. Activated macrophages induce apoptosis of extravillous trophoblasts in vitro. The normal vascular remodeling does not take place in preeclampsia. Extravillous trophoblasts 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 placenta³⁴⁻³⁶. 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 acetylcholine 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 preeclampsia as compared to normal pregnancy suggesting their role in the pathogenesis in the development of preeclampsia³⁹. 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.

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