

# The role of tissue factor in normal pregnancy and in the development of preeclampsia: A review

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**Background.** Tissue factor (TF) is a key element for normal gestation, especially in the first trimester. TF levels are hence raised in pregnancy, producing an adaptive hypercoagulable state. Potentiated hypercoagulability however, is associated with disorders of pregnancy such as pre-eclampsia but the results of TF and its inhibitor, tissue factor pathway inhibitor (TFPI), measurement, in pre eclamptic women are ambiguous and the data conflicting. This review covers the current knowledge status of the role of TF assessment in pregnancy with a focus on its diagnostic utility.

**Methods.** A review of the literature using the following key words: tissue factor, thrombosis, inflammation, pregnancy, preeclampsia.

**Results.** The published literature shows raised and unchanged TF levels in various studies of pre-eclampsia along with equally conflicting data for TFPI. The various study designs and methods used in these studies makes valid comparison difficult. Meta analysis of 34 randomized trials showed that low-dose aspirin in early phases of gravidity (starting from the 16th week or earlier) significantly reduces the incidence of preeclampsia.

**Conclusions.** Overall, the results of the literature search together with knowledge of the structure and biological effects of TF, suggest that measuring the level of plasma TF/TFPI is not ideal for determining the actual levels of TF in the uteroplacental circulation. The current view that endothelial dysfunction is the trigger for preeclampsia, suggests that aspirin may be an effective prophylaxis. Further research will be necessary: measuring the expression of tissue factor on monocytes using flowcytometry and comparing the development of this expression during normal pregnancy and pregnancy complicated by preeclampsia, for example. Another possibility is immunohistochemical determination of the level of TF expression directly in placental tissue.

**Key words:** tissue factor, thrombosis, inflammation, pregnancy, preeclampsia

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## TISSUE FACTOR - STRUCTURE AND ORGANS EXPRESS

Tissue factor (TF), also called factor III, is a transmembrane glycoprotein weighing 46 kDa. It is an integral part of the cell wall in various tissues and released when cell wall integrity is disrupted. TF may be detected on the surface of activated endothelial cells, leukocytes and thrombocytes<sup>1</sup>. It is composed of an extracellular domain containing 219 aminoacids, a transmembrane domain comprising 23 aminoacids and an intracellular domain containing 21 aminoacids<sup>2,3</sup>. The extracellular domain has a receptor site for binding to F VII/VIIa complex (factor VII and activated factor VII complex). The intracellular domain is the signal site regulating TF expression<sup>4</sup>.

Individual organs express varying quantities of TF. Its greatest expression is found in brain (astrocytes), placenta (trophoblast cells) and lungs (alveoli), a moderate amount in heart, kidneys, intestines, testes and uterus and the lowest expression seen in spleen, thymus, skeletal

muscle and liver<sup>5-7</sup>. Most TF circulating in the blood is expressed on blood elements- thrombocytes and their microparticles, granulocytes, monocytes, and macrophages; a smaller amount of TF in plasma is the product of endothelial cells and circulates in the form of endothelial microparticles or as soluble TF (ref.<sup>1,8,9</sup>). Under physiological conditions, this amount is very low compared with the amount contained in the vascular wall, especially in smooth muscle cells and adventitial fibroblasts<sup>10</sup>. The level of expression on blood cells and endothelial cells significantly increases on damage or activation. TF may be detected on the cell surface as the markers CD 142 or CD 16. The amount of circulating tissue factor measured by the ELISA method in healthy individuals ranges from 149-172 pg/mL (ref.<sup>11</sup>). Membrane-bound TF is released upon disruption of the integrity of the vascular wall or upon cell activation due to mechanical damage, inflammation or atherosclerosis.

## TISSUE FACTOR - BIOLOGICAL FUNCTIONS

Tissue factor, specifically its extracellular domain, in contrast to other elements in the coagulation cascade, does not require enzymatic cleavage for its activation. TF activation on cell surfaces and particles containing TF in blood and damaged tissues occurs due to a change in their cell membrane. During this change, phospholipids are transferred to the external membrane surface (flip-flop mechanism) following stimulation or cell damage, which leads to the uncovering of the receptor site for F VII in the TF extracellular domain<sup>12</sup>. Tissue factor initiates blood clotting by gradual activation of inactive zymogens of F VII, X and II to active serine proteases VIIa, Xa and IIa (the “external pathway” of the coagulation cascade in the traditional sense). This leads to the cleavage of fibrinogen and the formation of fibrin deposits with subsequent activation of other components of the coagulation cascade (primarily F IX, and hence the “internal pathway” of the coagulation cascade), thrombocytes and also protease-activated receptors (PAR) (ref.<sup>13</sup>). The TF intracellular domain with signaling function leads to a number of biological “noncoagulatory” processes in cells on whose surface binding of TF to F VII occurs, such as the synthesis of cytokines, adhesion molecules and growth factors. These products play a key role during inflammation, wound healing, angiogenesis, apoptosis, cell migration, embryo development, but also in the growth and metastasis of tumors<sup>14,15</sup>.

The gene for TF synthesis is located on chromosome 1. Tissue factor is the only coagulation factor in which a congenital deficiency has not been described which supports the assumption that this condition is incompatible with life<sup>13</sup>. Tissue factor is a key product of blood clotting in all tissues; in addition, its high levels of expression in vitally important organs (brain, lungs, heart and placenta) most likely ensure additional hemostatic protection for these organs<sup>13</sup>.

Tissue factor is inhibited by a specific inhibitor, tissue factor pathway inhibitor (TFPI), synthesized and expressed by endothelial cells in the microcirculation. 50-80% of TFPI forms the endothelial pool, 10-50% circulates in plasma and less than 2.5% is found in thrombocytes<sup>16</sup>. TFPI prevents excessive thrombin formation by binding to activated factor X in the TF/FVIIa/FXa complex<sup>17,18</sup>. Another tissue factor inhibitor in this complex is anti-thrombin<sup>19</sup>.

## TISSUE FACTOR - REGULATION OF ITS EXPRESSION

The integral role of TF during coagulation activation due to the disruption of the integrity of the vascular network caused by trauma has long been accepted. Today, a wide range of other biological effects of TF is under study. Hyperexpression of TF with subsequent shift of the hemostatic equilibrium towards hypercoagulation has been observed in cardiovascular diseases, diabetes, metabolic syndrome, inflammatory conditions, generalization

of malignant diseases, and also in cases of pregnancy complications such as repeated miscarriages and pre-eclampsia<sup>20,21</sup>. In all of these clinical situations, two basic pathogenic mechanisms associated with the activation of TF apply and they potentiate each other: thrombotization and inflammation<sup>1</sup>. Thrombin as a direct consequence of coagulation activation in these pathological conditions, leads to the formation of fibrin and activates thrombocytes and TAFI (thrombin activated fibrinolysis inhibitor) by signal induction with subsequent suppression of PA (plasminogen activator) and overexpression of PAI (plasminogen activator inhibitor) (ref.<sup>22-24</sup>). In addition, thrombin activates an entire group of protease-activated receptors (PAR), which leads to thrombocyte activation (PAR-1) and induces inflammation by producing interleukins, adhesion molecules, growth factors, serotonin, histamine and other inflammation mediators in cells, which amass at the thrombotization site (monocytes, macrophages, granulocytes, thrombocytes) (ref.<sup>3,25-27</sup>). The inflammation mediators induced by thrombotization lead to further coagulation activation by suppressing natural coagulation inhibitors - antithrombin, activated protein C and TFPI (ref.<sup>28,29</sup>). Products of activation of TF - F IIa, F VIIa, Xa - cause further overexpression of tissue factor, which closes the vicious circle: thrombosis-inflammation-thrombosis, linked by tissue factor<sup>30,31</sup>.

Research on the biological functions of TF has revealed both situations associated with overexpression of TF, as well as mediators and pharmaceuticals capable of influencing TF. Expression of TF is decreased by anticoagulants (for ex. LMWH, heparin, hirudin, antithrombin), metformin, ACE inhibitors, COX inhibitors, inhibitors of HMG-CoA reductase and others. ; In contrast, increase in TF is found after oral contraceptives, dexamethazone,

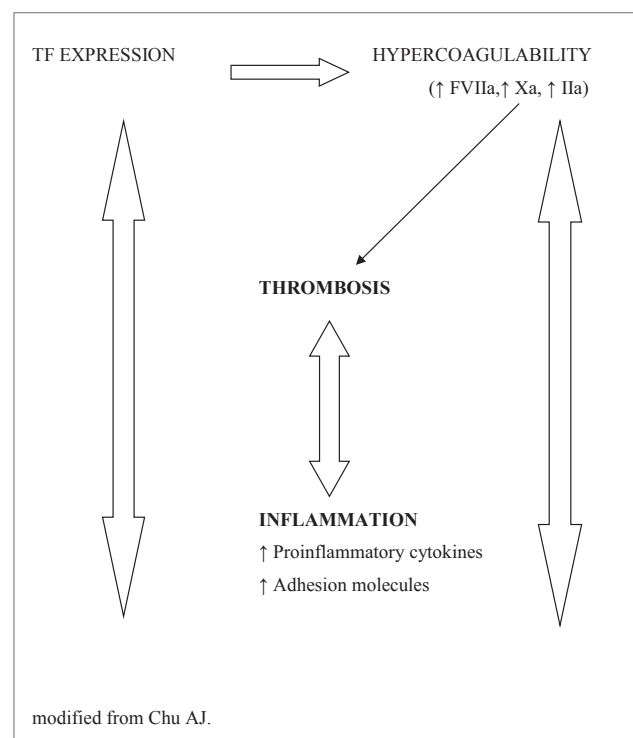


Fig. 1. “Vicious circle” thrombosis - inflammation - thrombosis.

estrogen, in cigarette smokers and in hyperhomocysteinemia<sup>32-48</sup>.

## TISSUE FACTOR - ITS ROLE DURING NORMAL PREGNANCY AND THE DEVELOPMENT OF PREECLAMPSIA

Tissue factor is a key element for normal gestation, especially in the first trimester. Endometrial stromal cells are known to prevent hemorrhage during invasion of the trophoblast during implantation, also in part due to increased expression of tissue factor<sup>49</sup>. It seems that the large amount of TF and resulting physiological hypercoagulation state in uteroplacental circulation is essential for maintaining local hemostatic equilibrium on the maternal and fetal side<sup>50</sup>. Tissue factor also plays a significant role in embryogenesis, shown by the results of research on mouse embryos with TF deficit, which showed lethal hemorrhaging during embryonic development and dysfunctional development of embryonic vascular structures independent of the coagulation function of TF (ref.<sup>51-53</sup>).

Preeclampsia is one of the most serious causes of maternal and neonatal morbidity and mortality with a prevalence of 6-8% of pregnancies<sup>54</sup>. It is a disease that develops from placental ischemia caused by an abnormal immune response of the maternal organism to fetal tissue that expresses antigens of paternal origin. The foundation of this clinical entity is endothelial damage due to defective invasion of the fetal trophoblast into spiral arterioles of the maternal circulation<sup>54</sup>. In pregnancy complicated by preeclampsia, there is insufficient invasion of trophoblast vessels into the uterine mucosa, which leads to placental ischemia. Patients develop multiple microthrombi in placental tissue causing the release of fragments of syncytiotrophoblasts and vasoactive mediators into the maternal circulation. Placental ischemia-induced release of circulating factors is part of a systemic inflammatory response which leads to the alteration of vascular reactivity and causes damage to endothelial cells which become the target tissue of these changes<sup>55</sup>. Generalized endothelial dysfunction causes the clinical symptoms of preeclampsia which are hypertension, increased vascular permeability causing proteinuria, coagulopathy and damage to various organs as a result of thrombotic microangiopathy. A higher risk for future cardiovascular morbidity was found in women who had preeclampsia during pregnancy, which supports the idea of lasting endothelial dysfunction even after pregnancy and the cessation of preeclampsia symptoms<sup>54,56,57</sup>.

In women with preeclampsia, increased signs of a hypercoagulation condition were found<sup>58,59</sup>. These changes had often already occurred prior to the onset of clinical symptoms. In pregnancies complicated by preeclampsia, increased levels of coagulation factor VIII, von Willebrand factor, thrombin-anti-thrombin, d-dimer complex, soluble fibrin and thrombomodulin have been found<sup>60-65</sup>. Other confirmed changes include the activation of granulocytes and monocytes and the associated release of inflamma-

tory cytokines<sup>66,67</sup>. The results of a large number of studies on the role of tissue factor and its primary inhibitor, TFPI, are ambiguous and often conflicting. Both increased<sup>68-71</sup>, as well as unchanged<sup>72-74</sup> levels of plasma TF in preeclampsia compared to normal pregnancy have been reported. According to various studies, the level of plasma TFPI was also unchanged<sup>70,72</sup>, increased<sup>69,74,75</sup> or decreased<sup>71</sup>. The conflicting data appear to reflect study design and methods issues, rendering comparison problematic. Overall, the results of the studies found in the literature search together with knowledge of the structure and biological effects of TF indicate that measuring the level of plasma TF/TFPI is not ideal for determining the actual levels of TF in the uteroplacental circulation.

Current information suggests that endothelial dysfunction is the trigger for preeclampsia. In this regard, aspirin may be an effective prophylaxis. Meta analysis of 34 randomized trials (Bujold et al.) confirmed that low-dose aspirin administration in early phases of gravidity (starting from the 16<sup>th</sup> week of pregnancy or earlier) significantly reduces the incidence of preeclampsia<sup>76</sup>. At present, the use of aspirin in this indication is recommended for pregnant women with risk factors of preeclampsia.

Further research will be necessary in this field, for example measuring the expression of tissue factor on monocytes using flowcytometry and comparing the development of this expression during normal pregnancy and pregnancy complicated by preeclampsia looks promising. Another interesting possibility is immunohistochemical determination of the level of expression of tissue factor directly in placental tissue.

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