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Original research Articles

# Review of Villi Chorialis Necrosis in Preeclampsia Based on Lactate Dehydrogenase and Vitamin D Levels

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**Abstract:-** Preeclampsia is a cause of maternal-perinatal morbidity and mortality and ranks first as a cause of maternal death in Indonesia. Although the leading cause remains unclear, abnormal placentation is believed to be the underlying cause of endothelial dysregulation, leading to vasoconstriction and increased vascular permeability, which in turn contribute to the development of preeclampsia. Vitamin D, as an antioxidant, can help maintain the trophoblast invasion process and increase anti-inflammatory cytokines, thereby reducing the formation of necrotic debris and maternal clinical deterioration.

**Keywords:** preeclampsia; syncytial nuclear aggregates (SNA); villous necrosis.



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## BACKGROUND:

Preeclampsia is known to be one of the causes of maternal-perinatal mortality and morbidity, with an estimated 2-8% of women worldwide suffering from it.[1] Based on 2016 data from the Health Research and Development Agency (Litbangkes), preeclampsia ranks first in maternal mortality in Indonesia, accounting for 33%, followed by bleeding and infection.[2] The high incidence of preterm labor in preeclampsia also results in complications in newborns, such as intraventricular hemorrhage, necrotizing enterocolitis, and bronchopulmonary dysplasia, which can affect growth, often resulting in a birth weight below the 10th percentile in childhood.[3]

The diagnosis of preeclampsia, according to the International Society for the Study of Hypertension in Pregnancy (ISSHP), is clinically determined by hypertension (blood pressure ≥140/90 mmHg on two measurements 4 hours apart) occurring at 20 weeks of gestation and proteinuria (≥300 mg/24 hours, protein/creatinine ratio ≥0.3/day, or 1+ in urine protein dipstick), or hypertension without proteinuria but with systemic abnormalities in the form of thrombocytopenia (<100,000µL), renal insufficiency (creatinine >1.1mg/dL or an increase in creatinine 2 times the normal value in the absence of previous kidney disorders), increased liver enzymes, pulmonary edema and central nervous or visual disturbances.[4]

Several conditions have been identified as risk factors for preeclampsia, such as primigravida, pregnant women over 40 years of age, and obesity. Lack of exposure to sperm and semen, and pregnancies with oocyte or embryo donors are also considered contributing factors. A family history of preeclampsia, especially on the mother's side, and a history of preeclampsia in a previous pregnancy increase the risk of recurrent preeclampsia. Similarly, multiple pregnancies, diabetes mellitus, systemic lupus erythematosus (SLE), chronic hypertension, and kidney disorders are also pathologies that increase the incidence of preeclampsia.[4,5]

## Pathogenesis of Preeclampsia

Preeclampsia is a maternal syndrome in which the placenta is confirmed to be the organ most closely related to the event.[6] Although the leading cause is still not fully understood, the occurrence of abnormal placentation is the cause of endothelial dysregulation resulting in vasoconstriction and increased vascular permeability, resulting in a varied clinical picture of preeclampsia.[6,7] Decreased uteroplacental blood flow due to abnormal placentation causes placental stress, triggering the release of necrotic trophoblast debris originating from the syncytiotrophoblast and causing a maternal systemic inflammatory response.[6,8] This is because the remodeling process of the spiral artery does not run perfectly. Cytotrophoblast invasion only reaches the decidua area, so that the myometrium remains narrowed and produces high-pressure blood flow that causes damage to the placental villi.[8-10] Meanwhile, in normal placentation, cytotrophoblast invasion reaches the endothelial layer of the spiral artery's smooth muscle, forming blood vessels with a larger capacity, which allows maternal blood flow to the intervillous space, resulting in adequate placental perfusion for fetal growth.[9,10]

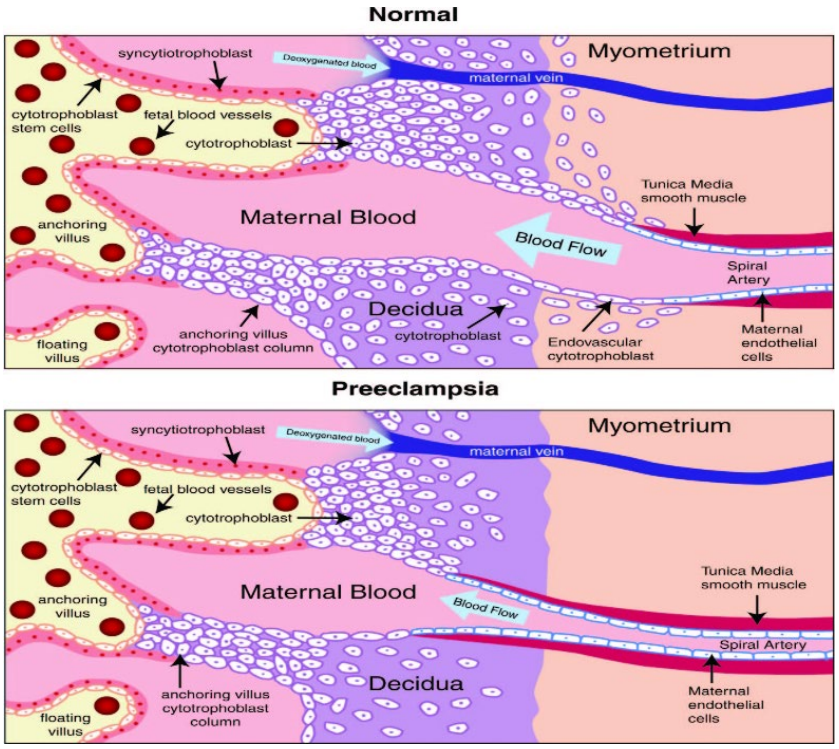


Figure 1. Abnormal placenta in preeclampsia.[9]

## *Syncytial nuclear aggregates* (SNA)/*syncytial knots*

Many mechanisms contribute to the pathogenesis of preeclampsia, where these mechanisms are interrelated and provide a synergistic effect causing the clinical symptoms of this disease. Placental factors, in the form of trophoblast debris, triggering the dysfunction or activation of maternal endothelial cells, have become a widely studied pathogenesis.[11,12] Trophoblast debris originates from the syncytiotrophoblast layer, which is in direct contact with maternal blood and exhibits various shapes and sizes, ranging from the largest structure, multinuclear syncytial nuclear aggregates (SNA), to mononuclear structures, microparticles, and nanoparticles, which can enter the maternal bloodstream.[13,14] In normal pregnancy, SNA is formed as a result of the apoptosis process. Phagocytosis of apoptotic SNA by maternal immune cells produces a tolerant immune response to the placenta/fetus and prevents endothelial cell activation.

The absence of a rejection response from the maternal immune system proves that in normal pregnancy, there is no excessive inflammatory response.[11] While phagocytosis of necrotic trophoblast debris causes an inflammatory response, such as that which occurs in preeclampsia,[14,15] where syncytiotrophoblast dysfunction due to malperfusion of uteroplacental flow in early pregnancy gives a vascular inflammatory reaction that is stronger than in a normal placenta.[16]

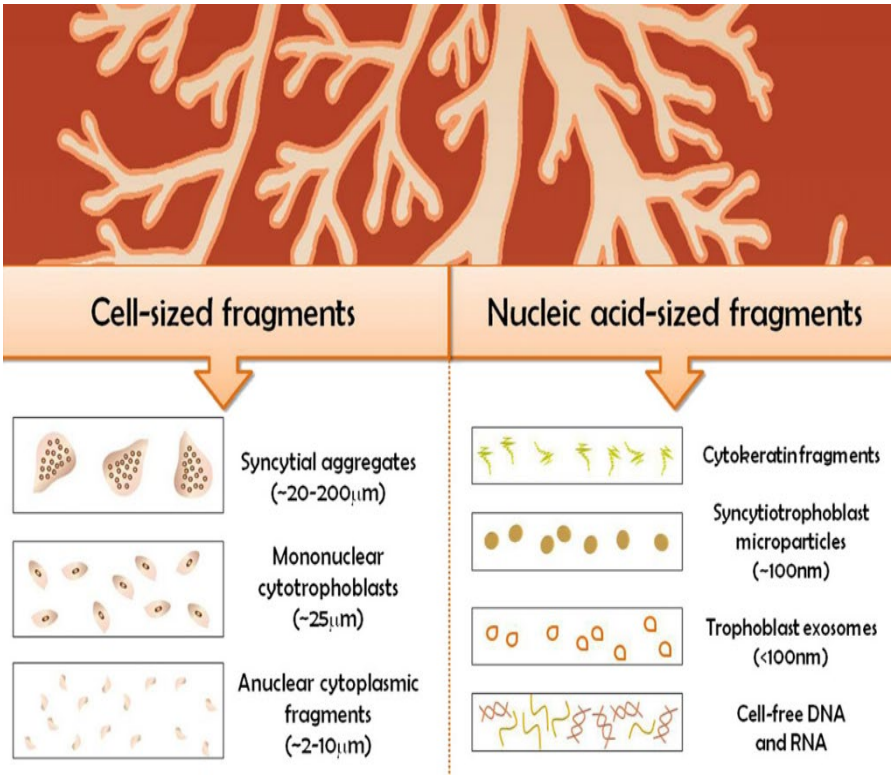


Figure 2. Trophoblast material enters the maternal circulation.[13]

Inflammation and hypoxia in the placenta lead to microscopic structural changes, accompanied by an increase in the number of SNA formations. Complicated pregnancies also show SNA formation earlier than normal pregnancies. 17 In preeclampsia, although SNA formations attached to the villi appear more numerous, syncytial bridges, the clusters of SNAs connecting two villi, appear to be reduced. 1817,18 Nearly 4 decades ago, Jones and Fox discovered the appearance of syncytial bridges, which at that time were stated to possibly have a mechanical function to maintain placental stability 19 and maintain adequate oxygen exposure to prevent the formation of reactive oxygen species that exacerbate cell necrosis.[18]

## Effect of Lactate Dehydrogenase (LDH)

LDH is an intracellular enzyme found in living cells. Its activity increases in pathological conditions, making it frequently used as an indicator of cell damage.[20,21] Preeclampsia is associated with necrotic cell death due to systemic maternal endothelial damage. Morphologically, necrotic cells appear swollen and eventually rupture, releasing plasma and intracellular components. The enzyme's location in the cytoplasm results in high serum LDH levels as the number of ruptured cells increases.[20] In preeclampsia, increased LDH concentrations are associated with increased blood pressure and more severe complications for both mother and baby.[22] Increased LDH is also directly proportional to increased TNF-α, a pro-inflammatory cytokine, and increased evidence of villous necrosis.[23,24] Furthermore, hypoxia in placental tissue indicates extensive necrosis, despite the presence of increased trophoblasts in some parts of the villi, which maintains the balance of cell formation.[24]

## The role and influence of vitamin D

Vitamin D deficiency is a public health problem. Prevalence in Asian countries ranges from 14 to 59%, with a figure of 25% in Jakarta, where the rate is particularly high, reaching 99.6%.[25,26] It is known that many factors contribute to the occurrence of preeclampsia, including maternal disease factors, angiogenesis factors, endothelial dysfunction, and the formation of necrotic trophoblast debris, as well as the activation of pro-inflammatory factors that lead to placental damage.[27]

Background malnutrition has also been stated as a trigger for this occurrence. The active form of vitamin D, 1,25-dihydroxyvitamin D3, functions as a steroid hormone that regulates gene transcription and cellular function, and is associated with placental implantation and trophoblast invasion. It plays a role in cell proliferation and the angiogenesis process. This can occur because the placenta, being one of the organs outside the kidney, can synthesize the active form of vitamin D through the activity of 1α-hydroxylase in the trophoblast and decidua.[28,29] Research on the role of 1,25-dihydroxyvitamin D3 in cell proliferation and repair outside bone cell metabolism has been widely conducted.[29] One of them is the placenta that can respond to vitamin D because it has a vitamin D receptor (VDR), so that it can function to help the production of anti-inflammatory cytokines in the trophoblast and decidua, and support the process of placental implantation.[28] The occurrence of preeclampsia, which is closely related to abnormal implantation, requires adequate nutrition, one of which is vitamin D, to maintain the process of trophoblast invasion and increase anti-inflammatory cytokines, so that it can reduce the formation of necrotic debris and maternal clinical deterioration.[30,31]

Vitamin D during pregnancy plays a role in maintaining and enhancing the appropriate maternal immune response by preventing the release of antiangiogenic substances into the bloodstream. On the other hand, vitamin D is also thought to increase the production of angiogenic substances in endothelial progenitor cells by increasing the expression of vascular endothelial growth factor VEGF and the activity of pro-matrix metalloproteinase (pro-MMP2).[30] Research has also found that vitamin D has a potential immunosuppressive effect, which plays a role in placental development. Vitamin D deficiency will increase the inflammatory process in the placenta. This is proven by research that found that preeclampsia sufferers have an average vitamin D level 14% lower than that of normal pregnant women.[31]

The numerous functions of vitamin D, particularly its immunomodulatory properties and beneficial effects on angiogenesis, have led to its potential role in preventing preeclampsia. However, several randomized studies have shown that vitamin D supplementation is ineffective in preventing preeclampsia. One such study by Mirzakhani et al. showed that vitamin D supplementation initiated at 10-18 weeks of gestation was ineffective in reducing the incidence of preeclampsia. However, vitamin D levels of 30 ng/mL or higher at 32-38 weeks of gestation were associated with a reduced risk of preeclampsia. [32-34]

## CONCLUSION AND RECOMMENDATION :

Preeclampsia, a cause of maternal morbidity and mortality whose cause remains unknown, provides ample scope for discussion to clarify the pathological processes involved. Trophoblastic debris, a result of the inflammatory process caused by syncytiotrophoblast dysfunction, leads to uteroplacental blood flow malperfusion and exacerbates the maternal vascular inflammatory response. In preeclampsia, although SNA formation in the villi appears more numerous, syncytial bridges, as clusters of SNA connecting two villi, appear to be reduced. Further research is needed to determine whether the presence of syncytial bridges indeed functions as a mechanism for maintaining placental stability. Furthermore, vitamin D, a nutrient that plays a role in placentation and increases anti-inflammatory cytokines, needs further investigation to understand the mechanisms by which this vitamin supplementation can reduce necrotic debris formation and prevent maternal clinical deterioration.

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