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ANTIANGIOGENIC IMBALANCE AND ENDOTHELIAL DYSFUNCTION AS MOLECULAR AND MORPHOLOGICAL DETERMINANTS OF INTRANATAL FETAL DEATH IN PREECLAMPSIA

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Annotation. *This thesis investigates the role of antiangiogenic imbalance and endothelial dysfunction as molecular and morphological determinants of intranatal fetal death in preeclampsia. Dysregulated soluble fms-like tyrosine kinase 1 and placental growth factor are identified as central mechanistic drivers linking placental ischemia to fatal intrapartum outcome.*

Keywords: *preeclampsia, soluble fms-like tyrosine kinase 1, placental growth factor, endothelial dysfunction, oxidative stress, syncytiotrophoblast stress, vascular endothelial growth factor, villous capillary rarefaction, antiangiogenic imbalance, intranatal fetal death*

Nowadays, preeclampsia is recognized as a two-stage pathophysiological syndrome in which defective trophoblast invasion and impaired spiral artery remodeling during the first trimester are followed by a systemic maternal endothelial syndrome driven by an excess of antiangiogenic mediators released from the ischemic placenta into the maternal circulation in the second and third trimesters. This cascade of molecular and structural events accounts for the markedly elevated relative risk of fetal death, documented at 86 at 26 weeks of gestation in preeclamptic compared with normotensive

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pregnancies, with statistically significant elevation persisting throughout the remainder of gestation.

The molecular foundation of intranatal fetal death in preeclampsia resides in a profound and self-perpetuating imbalance between pro-angiogenic and antiangiogenic mediators that originates in the ischemic placental parenchyma and exerts its deleterious effects simultaneously upon the maternal systemic vasculature and the fetoplacental circulation. Syncytiotrophoblast stress, arising from inadequate remodeling of uterine spiral arteries and the consequent ischemia-reperfusion injury to the placenta, triggers pathological overexpression and shedding of soluble fms-like tyrosine kinase 1, which functions as a circulating decoy receptor by sequestering free vascular endothelial growth factor and placental growth factor in the maternal and fetoplacental blood compartments. The resulting deficiency of bioavailable vascular endothelial growth factor impairs endothelial nitric oxide synthase activity, promotes vasoconstriction, and accelerates endothelial apoptosis across multiple maternal organ systems. Within the placental vascular bed, the antiangiogenic milieu manifests morphologically as rarefaction of terminal villous capillaries, reduction in branching angiogenesis, and progressive widening of the diffusion distance between maternal intervillous blood and the fetal capillary endothelium. These structural changes directly and quantifiably impede oxygen and nutrient transfer to the fetus, producing the chronic hypoxemia and intrauterine growth restriction that render affected fetuses profoundly vulnerable to acute decompensation during the additional hemodynamic stress imposed by uterine contractions in labor. Oxidative stress within the syncytiotrophoblast, documented by elevated levels of lipid peroxidation products and reduced activity of superoxide dismutase and glutathione peroxidase, amplifies the antiangiogenic response and perpetuates the cycle of endothelial dysfunction.

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During the intrapartum period, each uterine contraction reduces intervillous oxygen tension in the vasculopathic preeclamptic placenta below the critical threshold required to sustain fetal aerobic cellular respiration. Progressive lactic acidosis, myocardial glycogen depletion, and failure of compensatory cardiovascular redistribution culminate in irreversible cardiac arrest and intranatal death. Serial measurement of serum placental growth factor concentration below the fifth percentile for gestational age represents the most clinically validated and prospectively studied biomarker for stratifying intranatal fetal death risk in this high-risk population.

Antiangiogenic imbalance and endothelial dysfunction are the central molecular and morphological determinants of intranatal fetal death in preeclampsia. Serial placental growth factor measurement offers validated and clinically actionable potential for intrapartum risk stratification and timely intervention.

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