

Introduction

Pre-eclampsia and eclampsia are hypertensive disorders of pregnancy that cause significant morbidity and mortality in the fetus and mother. Globally, pre-eclampsia and eclampsia account for 10-15% of maternal deaths (**Duley, 2009**).

Pre-eclampsia is a multi-organ group of related disease processes that occur in up to 5-8% of pregnancies after 20 weeks of gestation. The presentation is variable, but generally includes the combination of maternal hypertension and proteinuria (**Turner, 2010**).

Eclampsia is the new onset of grandmal seizures occurring during and after pregnancy that do not have another identifiable cause (**Turner, 2010**).

The development of eclampsia is associated with increased risk of adverse outcome for both mother and fetus (**Duley, 2009**).

Eclampsia could be prevented in majority of the cases if there was early booking for antenatal care services, permitting early identification of pre-eclampsia and institution of appropriate therapy (**Okeudo et al., 2011**).

Progression of pre-eclampsia to eclampsia may occur during pregnancy, labor or in the postpartum period (**Duley, 2009**).

Neuroaxial block techniques such as spinal anesthesia are considered a safe method of providing anesthesia for the patient with pre-eclampsia and severe pre-eclampsia. This is due to avoidance of the risks associated with general anesthesia such as exacerbated hypertension, failed intubation, and aspiration (**Sudharma et al., 2009**).

The administration of neuraxial anesthesia for labor or cesarean delivery reduces serum catecholamine level and improves uteroplacental blood flow. The sympathetic blockade that results from neuraxial anesthetic techniques has shown to improve intervillous blood flow in preeclamptic parturients by decreasing uteroplacental resistance (**Ankicheetty et al., 2013**).

The intra-operative eclamptic fits would be successfully controlled with intravenously administered diazepam. However, magnesium sulfate is the anti-convulsant of choice for treating eclampsia. It is more effective than diazepam, phenytoin (**Duley, 2009**).

Aim of The Essay

The aim of this essay is to highlighten the perioperative anesthetic management of pre-eclampsia and eclampsia and how to avoid the progression of pre-eclampsia to eclampsia and their complications.

Chapter (1):

PATHOPHYSIOLOGY

Preeclampsia is a pregnancy specific syndrome characterized by new onset hypertension and proteinuria **(Fukui et al., 2012)**.

Despite being one of the leading causes of maternal death and a major contributor of maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of preeclampsia have not been fully elucidated. Hypertension associated with preeclampsia develops during pregnancy and remits after delivery, implicating the placenta as a central culprit in the pathogenic process.

An initiating event in preeclampsia has been postulated to be reduced placental perfusion that leads to widespread dysfunction of the maternal vascular endothelium and hypertension by mechanisms that remain to be defined **(Fukui et al., 2012)**.

The hypertension associated with preeclampsia involves a complex array of factors and multiple organ systems. However, by using integrative approaches, enormous progress has been made towards understanding

the pathophysiology of hypertension during preeclampsia. As mentioned before, placental ischemia/hypoxia is thought to lead to widespread activation of the maternal vascular endothelium, resulting in enhanced formation of endothelin and superoxide, increased vascular sensitivity to angiotensin II, and decreased formation of vasodilators such as nitric oxide. These endothelial abnormalities, in turn, cause generalized vasoconstriction throughout the body including the kidneys, which play a critical role in the long-term regulation of arterial pressure. Although numerous factors including genetic, behavioral, and environmental factors have been implicated in the pathogenesis of preeclampsia (Fukui et al., 2012).

The main focus of this review will be on linking placental ischemia/hypoxia with endothelial cell activation and hypertension.

Abnormal Placentation and Vasculogenesis in Preeclampsia

During normal pregnancy, fetally derived cytotrophoblasts invade the maternal uterine spiral arteries, replacing their endothelium, and differentiating into an endothelial-like phenotype.

The exact mechanisms responsible for the abnormal placental trophoblast invasion and vascular remodeling in preeclampsia are unclear, but a series of studies have now appeared that enhance our understanding of these important adaptations as well as potential mechanisms that may lead to maladaptations. A number of factors have been recently implicated in placentation including the Notch signaling pathway, the transcription factor storkhead box 1 (STOX1), various components of the renin-angiotensin-aldosterone system (**Todkar et al., 2012**) and the intracellular serpin proteinase inhibitor-9 (**Buzza et al., 2006**).

Notch signaling may be a crucial component of the process whereby fetal trophoblast cells invade and remodel maternal blood vessels (**Hunkapiller et al., 2011**). The Notch signaling pathway is thought to play an important role in vasculogenesis by modulating differentiation and function during cell-cell contact. The main pathway consists of four transmembrane receptors (NOTCH1-4) and five ligands (DLL1/3/4 and JAG1/2). Binding of receptors and ligands on adjacent cells triggers serial proteolytic cleavages of the receptor, releasing the Notch intracellular domain that subsequently translocates to the nucleus to bind to transcription factors and induce downstream targets. Support of a role of Notch signaling in vascular remodeling

was provided in a recent report demonstrating that the absence of Notch2 in mice is associated with reduced spiral artery diameter (See Figure 1) and placental perfusion (Hunkapiller et al., 2011).

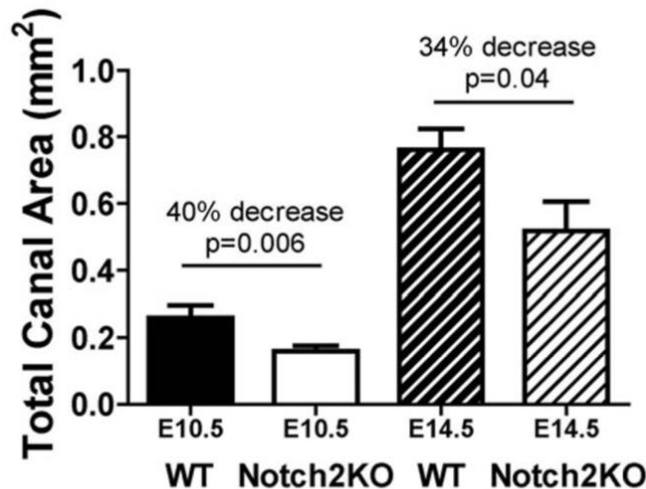


Figure (1): Vascular corrosion casting was used to examine maternal blood spaces of the placenta from mice at embryonic (E) days 10.5 and 14.5. The trophoblast cell-lined vascular canals supplying blood to the placenta were smaller from Notch2 knockout (KO) compared to wild type (WT) rats at both embryonic days. These data indicate that Notch2 is important for proper remodeling of the placental vasculature. Figure adapted from Hunkapiller et al., 2011.

Additional findings that peri- and endovascular cytotrophoblast often fail to express the Notch ligand, JAG1, in preeclampsia provide further evidence that defects in Notch signaling may be important in the pathogenesis of this pregnancy complication (Hunkapiller et al., 2011).

Another recently described molecular pathway implicated in placental vascular development is the STOX1, a member of the winged helix transcription factor family. STOX1 was originally implicated in an epidemiological study that suggested increased rates of STOX1 mutation in women who experienced preeclampsia (**van Dijk et al., 2005**). These initial studies, while promising have been challenged by other research groups who have found little if any association of the observed polymorphisms with preeclampsia (**Rigourd et al., 2008**).

While the disparity between these observations has not been fully explained, several lines of experimental in vivo and ex vivo evidence now indicate that aberrant STOX1 expression or expression of known mutant versions of the gene may have direct effects on preeclampsia associated genes. In the first instance, STOX1 overexpression in choriocarcinoma cells caused a shift in the cells' transcriptional profile mimicking the transcriptional profile observed in preeclamptic placentas (Rigourd et al., 2008). Further, the Y153H mutant identified by van Dijk et al. in their epidemiological study, has been shown to induce α -T-catenin, a cell-cell adhesion molecule known to be overexpressed in the placenta of preeclampsia patients (**van Dijk et al., 2005**).

Likewise, expression of the mutant protein inhibits trophoblasts invasion in vitro, suggesting a possible mechanism by which STOX1 mutation could have a role in the development of preeclampsia. Finally, a recent report from Doridot et al. demonstrated that transgenic overexpression of STOX1 in the mouse leads to a phenotype that mimics preeclampsia in several key ways, most notably a dramatic rise in systolic blood pressure during gestation (See Figure 2) and elevated maternal circulating levels of sFlt-1 and soluble endoglin (**Doridot et al., 2013**). While these data are intriguing, much work remains to be done to elucidate the causative and symptomatic role of STOX1 in the development of preeclampsia.

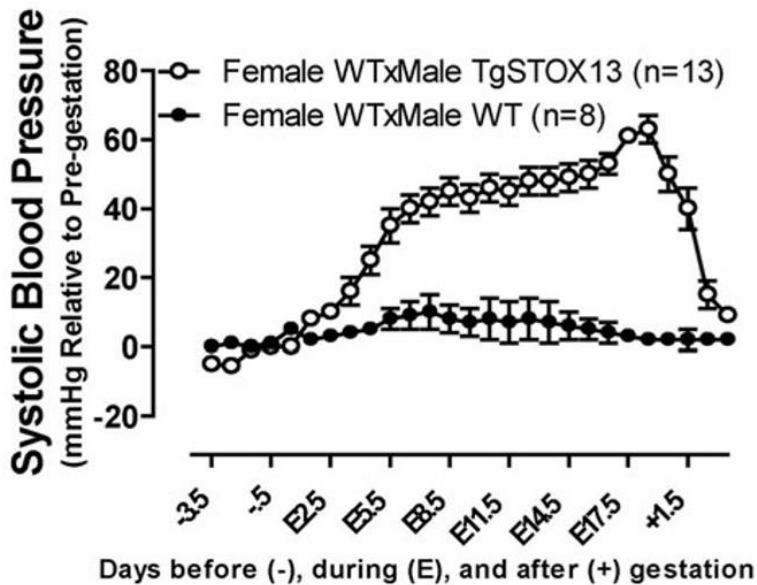


Figure (2): Systolic blood pressure in wild type (WT) female rats mated with transgenic male mice overexpressing the STOX13, one of the transgenic lines generated to overexpress the transcription factor STOX1, or male WT mice. This mating strategy resulted in pregnant female having placentas overexpressing or having normal expression of STOX1, respectively. Female mice with overexpression of placental STOX1 developed a progressive hypertensive phenotype that subsided after parturition. Figure adapted from Doridot et al., 2013.

Recent studies have also suggested that variability of immune system genes that code for major histocompatibility complex molecules and natural killer receptors may also impact human placentation (**Colucci et al., 2011**). These studies reported that specific combinations of fetal major

histocompatibility complex molecules and maternal natural killer receptor genes in humans correlate with the risk of preeclampsia, recurrent miscarriage, and fetal growth restriction. Researchers have begun to explore the similarities and differences between human and mouse natural killer cells and potential trophoblast ligands with the aim of developing mouse models to elucidate how natural killer cell–trophoblast interactions contribute to placentation.

Activation and Dysfunction of the Endothelium in Preeclampsia

The maternal vascular endothelium of women destined to develop preeclampsia appears to be an important target of factors that are presumably generated through placental hypoxia/ischemia (**Gilbert et al., 2008**). The vascular endothelium has many important properties including control of smooth muscle tone through release of vasoconstrictor and vasodilatory substances, and regulation of anti-coagulation, anti-platelet, and fibrinolysis functions via release of different soluble factors. Alterations in the circulating levels of many markers of endothelial dysfunction have been reported in women that develop preeclampsia (**Gilbert et al., 2008**).

The fact that endothelial dysfunction can be demonstrated prior to overt disease, supports a causal role. Maternal status may influence the endothelial response to factors triggered by placental ischemia/hypoxia in preeclampsia. There is compelling evidence, for example, that obesity, a major epidemic in developed countries including the U.S. increases the risk of preeclampsia. A high body mass index, for example, increases this risk three-fold **(Roberts et al., 2011)**. Despite this and many other studies linking obesity to preeclampsia, the pathophysiological mechanisms whereby obesity increases the risk for developing preeclampsia are unclear. Thus, further research into how obesity and metabolic factors such as leptin, insulin, and free fatty acids impact the various stages of preeclampsia is warranted.

Factors Linking Placental Ischemia/Hypoxia with the Microvascular Dysfunction and Hypertension

(A)Angiogenic factors

In response to placental hypoxia, the placenta is proposed to produce pathogenic factors, which enter the maternal blood stream and are responsible for the endothelial dysfunction and other clinical manifestations of the disorder including hypertension and proteinuria. A

variety of molecules are released but amongst them, antiangiogenic and autoimmune/inflammatory factors have received the greatest attention (**Wang et al., 2009**).

One of the most intensely studied pathways in the manifestation of preeclampsia is that related to vascular endothelial growth factor (VEGF) signaling. VEGF and the placental growth factor (PlGF), besides their role in angiogenesis are also important in the maintenance of proper endothelial cell function and health (**Wang et al., 2009**).

This signaling pathway came to prominence with the discovery of elevated circulating and placental levels of the soluble form of the VEGF receptor, fms-related tyrosine kinases (sFlt)-1. sFlt-1 is a circulating soluble receptor for both VEGF and PlGF, which when increased in maternal plasma leads to less circulating free VEGF and free PlGF, thus preventing their availability to stimulate angiogenesis and maintain endothelial integrity. In the kidney this inactivation of free VEGF is believed to cause endotheliosis and proteinuria (**Wang et al., 2009**).

Subsequent studies of the regulation of sFlt-1 in cell culture and placental tissue in vitro have demonstrated that sFlt-1 is released from placental villi and trophoblast cells in

response to reduced oxygen tensions similar to that seen in an ischemic placenta (**Wang et al., 2009**). While sFlt-1 production appears to be regulated by the hypoxia inducible factor-1, other factors such as tumor necrosis factor (TNF)- α and the agonistic autoantibody to the angiotensin II type I receptor (AT1-AA) also appear to be involved.

Several lines of evidence support a role for angiogenic factors in the pathogenesis of preeclampsia. sFlt-1 levels are strongly correlated with the severity of the syndrome (Wang et al., 2009). In addition, chronic administration of sFlt-1 to pregnant rats, to mimic plasma concentrations observed in preeclamptic women, decreases free VEGF and PlGF and produces hypertension and proteinuria (**Gilbert et al., 2008**).

Likewise, VEGF transgenic overexpression or knockout in mouse glomerular podocytes resulted in proteinuria and glomerular endotheliosis, two common preeclamptic features (**Eremina et al., 2003**). Similar findings are observed in cancer patients who have been treated with VEGF monoclonal antibodies, as hypertension and proteinuria are common side effects (**Zhu et al., 2007**). Moreover, a promising pilot study recently demonstrated that sFlt-1 could be removed from the maternal circulation

of preeclamptic women by apheresis safely, and this therapy reduced both blood pressure and proteinuria, with a trend toward increased gestational duration (**Thadhani et al., 2011**).

While compelling data derived from animal and human studies suggest an important role for angiogenic imbalance in the pathophysiology of preeclampsia, there are many unanswered questions and many opportunities for future research. For example, the molecular mechanisms involved in the regulation of sFt-1 production have yet to be fully elucidated. Moreover, while sFt-1 appears to play an important role in the pathogenesis of preeclampsia, specific inhibitors of sFt-1 production are not currently available. Thus research into the discovery of inhibitors of sFt-1, or ways to stimulate greater production of VEGF and PlGF is of critical importance.

(B) Immune factors and Inflammation

One of the earliest and most persistent theories about the origins of preeclampsia is that preeclampsia is a disorder of immunity and inflammation. Of interest is work suggesting that the inflammatory response is triggered by particles, ranging from large deported multinuclear fragments to sub-cellular components, shed from the