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Review article

Preeclampsia: from Pathophysiology to Treatment

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Abstract

Preeclampsia is a multisystem disorder unique to human pregnancy and is its most common glomerular complication. It occurs in 2% to 8% of pregnancies and is a major contributor to maternal mortality worldwide.
Although the pathophysiology of this syndrome is not fully understood, many pathogenetic mechanisms are involved in this disorder.
The role of the placenta is crucial in the development of this disorder. Some pathogenetic mechanisms involved in this disease comprise defective deep placentation, autoantibodies to type-1 angiotensin II receptor, endothelial dysfunction, oxidative stress, platelet and thrombin activation, intravascular inflammation, and the imbalance between angiogenic and antiangiogenic factors which is thought to be one of the most crucial mechanisms.
Further understanding of the full picture could enhance our current knowledge of the pathogenesis of preeclampsia and improve its treatment.
Thus, based on specific biomarkers the diagnosis and subclassification of preeclampsia might be more accurate in identifying patients at risk, monitoring disease progression and providing effective interventions.

Keywords: preeclampsia, angiogenesis, sFlt-1, spiral arteries, metformin

Introduction

Preeclampsia is a multisystem disease of the widespread vascular endothelial malfunction that is unique to human pregnancy, depicted by decreased GFR, proteinuria, and hypertension after 20 weeks of gestation, which can progress to include coagulopathies and affect liver function (HELLP syndrome) as well as cause seizures (eclampsia). It is the most common encountered glomerular complication in pregnancy [1,2].

Epidemiology and risk factors

Preeclampsia occurs in 2% to 8% of pregnancies, the risk is highest in those with a past history of preeclampsia, with rates ranging from 15% to 65% depending on the gestation at onset and the severity of preeclampsia [3].
Preeclampsia is more common in first pregnancies and lowers in subsequent pregnancies. The risk of preeclampsia returns to that of the first pregnancy in women who have a new partner for successive pregnancies, implying that prior exposure to paternal antigens could be protective [4]. However, this may be also explained by a longer interpregnancy interval rather than a change of partners, with the incidence increasing after about 7 years between pregnancies [5].
Smoking reduces the risk of preeclampsia by one third, increases the risk of preterm labor, intrauterine growth restriction (IUGR) and placental abruption [6].
Although in the majority of cases there is no family history, the presence of preeclampsia in the first degree relative increases the risk of severe preeclampsia two- to four-fold, suggesting genetic factors likely contribute to the pathogenesis of this condition. The risk is increased in subsequent pregnancies in women with preeclampsia in a previous pregnancy. Trisomy 13 in the fetus is associated with a high risk of preeclampsia in the mother.

Pathogenesis

The pathogenesis of preeclampsia is complex. The placenta likely causes preeclampsia, with other maternal organs (e.g., kidney) amplifying the disease process.
Observations have shown that gestational hypertensive disorders are more likely to develop in women who:

- are exposed to chorionic villi for the first time;
- are exposed to a great number of chorionic villi, as with multiple gestations or hydatidiform mole;
- have preexisting conditions of endothelial cell activation or inflammation such as diabetes or renal or cardiovascular disease;

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- have a genetic predisposition to develop hypertension during pregnancy [8].

Regardless of etiology, preeclampsia is characterized by the following pathophysiologic triad:

- vasoconstriction
- platelet activation with intravascular coagulation (usually local but occasionally disseminated)
- maternal plasma volume contraction.

This triad leads to further impairment of blood flow through the placenta as well as through the maternal kidneys, liver, and brain. It is unknown why these organs are most often affected in preeclampsia or why other vascular beds (e.g., gut) are unaffected, even in severe cases [4].

An imposing number of mechanisms have been proposed to explain the cause of preeclampsia:

1. Superficial placentation with insufficient remodeling of spiral arteries and the impaired shear stress response

After the implantation of the blastocyst into the endometrium the trophoblasts continue to invade the uterine endometrium until they reach the spiral arteries, and during this period they also differentiate into an endothelial-like cell type.

Then the trophoblasts start spiral artery remodelation by replacing the smooth muscle and endothelial cells. The transformation of the thick muscular arteries into high-capacity vessels as a consequence of the increase in vessel diameter and the creation of a high blood flow, low resistance regions, permits more blood flow to the uteroplacental unit and also reduce the ability of these vessels for vasoconstriction [9]. During normal pregnancy trophoblast cells invade not only the deciduas, but also one-third of the myometrial thickness [10]. Thus researchers suggest that an abnormal trophoblast may result in shallow placentation and insufficcient transformation of the spiral arteries leading to preeclampsia [11]. The deeper myometrial arterioles keep their endothelial lining and musculature, and their mean external diameter is only half that of corresponding vessels in normal placentas [12] (Figure 1).

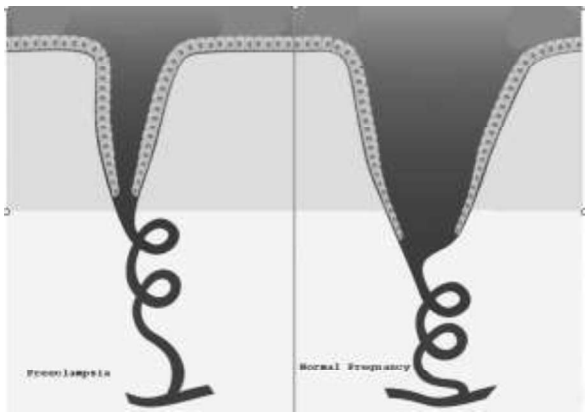

Fig. 1. The left side shows a preeclamptic situation in which there is insufficient extent and depth of remodeling compared to a normal pregnancy. The right side shows the endometrium in the second half of normal pregnancy with spiral arteries remodeled to a depth that penetrates the myometrium

Moreover, these nontransformed arteries are susceptible to atherosis, characterized by the presence of lipid-laden macrophages within the lumen, mononuclear perivascular infiltrate and fibrinoid necrosis [13,14].

The increased blood flow is essential for the developing embryo and the insufficient transformation of the spiral artery is linked with complications in pregnancy such as preeclampsia and intra-uterine growth retardation. In preeclampsia, this insufficient transformation of the spiral arteries into high capacity vessels is not complete and these arteries remain high resistance vessels which results in inadequate oxygen delivery, causing placental ischemia and infarction. The latter are responsible for the release of many factors that induce maternal vascular endothelial dysfunction. Probably, placental ischemia alone is not sufficient to cause preeclampsia because IUGR, also characterized by failure of physiological transformation of spiral arteries and placental insufficiency, does not often occur with preeclampsia [9,15].

Early preeclamptic changes include endothelial damage, accumulation of plasma components into vessel walls, proliferation of myointimal cells, and medial necrosis. Lipids are first accumulated in the myointimal cells and then inside the macrophages. These lipid-laden cell changes were referred to as atherosis by Hertig in 1945. In addition, it is thought that this acute atherosis identifies a group of women at increased risk of later atherosclerosis and cardiovascular disease [8,16].

Diminished perfusion and a hypoxic environment eventually lead to release of placental debris or microparticles that trigger a systemic inflammatory response [17, 18].

The effect of shear stress, besides trophoblast abnormalities, can also affect the spiral arteries' remodeling. The lumen of uterine arteries increases prior to completion of placentation.

There is also blood flow change in uterine arteries throughout the first few weeks of pregnancy, and after the remodeling of the spiral arteries into low-velocity and high flow comparments, the reduction of the downstream resistance (spiral arteries) increases blood flow velocity in afferent (radial and arcuate) arteries, causing high shear stress on the arterial wall [19]. This shear stress induced by the flow is a modulator of vascular tone in isolated arteries from normal pregnant women, mediated by nitric oxide (NO) production [20] resulting in vasodilatation, further lowering the uterine vascular resistance and normalizing the shear stress on the arterial wall [19]. In preeclampsia there is impaired shear stress-mediated NO release, which could play a role in vasoconstriction and increased vascular resistance, which

might also further impair the uteroplacental blood flow in this condition [21,22].

2. Hypoxia and trophoblast invasion: the role of HIF-1α and TGF-β3 in preeclampsia

During the early phases of implantation, the gestational sac is in a low oxygen tension medium, which favors trophoblast proliferation. Trophoblasts anchor the blastocyst to the endometrium, and also fill in the tips of the spiral arteries within the deciduas [23]. After the lacunae formation within the syncytiotrophoblast, these lacunae fuse with each other to create the intervillous space. The oxidative stress generated from the initial burst of blood inside this intervillous space due to high oxygen tension, promotes trophoblast differentiation from a proliferative to an invasive phenotype. These differentiated trophoblasts go deeper into the decidua, reaching into the superficial myometrium and making easier the physiological remodeling of spiral arteries. This means that the initial phase of placentation occurs under conditions of relative hypoxia [24].
Hypoxia-inducible factor-1 (HIF-1) is a key regulator of the cellular response to low oxygen tension and has an important role maintaining the oxygen homeostasis. It is a heterodimeric transcription factor made up by two subunits, α and β. While HIF-1β is always active, HIF-1α is oxygen-sensitive, which is quickly inactivated and degraded in normoxia [25].
In early gestation, there are high levels of HIF-1α in a low-oxygen placental milieu. These levels fall at around 9 weeks of gestation, when placental oxygen levels increase, suggesting an important role of HIF-1α in the placental development and function [26]. This early placental development is characterized by hypoxic environment and increased HIF-1α expression, leading to TGF-β3 upregulation and inhibition of trophoblast invasion. The increase in placental oxygen levels, around 10-12 weeks of gestation in a normal placenta, downregulates HIF-1α expresion and restores the trophoblast-invasive capabilities. In preeclampsia there is failure to downregulate HIF-1α and its persistent expression induce high placental TGF-β3 expression resulting in inhibition of placental explant trophoblast differentiation and invasion. These abnormalities are characteristic for this disease [27].
In addition, endoglin, the membrane-bound protein that gives rise to its proteolytic product sENG (a truncated form of a TGF-β receptor), is upregulated by HIF-1α [28] and sENG can be induced by hypoxia in trophoblasts [29].
Persistent placental hypoxia, present in the preeclamptic placenta, induces also the expression of angiotensin II type I receptor agonistic autoantibodies (AT1-AA), which stimulate the production of soluble fms-like tyrosine kinase-1 (sFLT-1), soluble endoglin (sENG), and endothelin-1. These factors lead to endothelial dysfunction and clinical manifestations of preeclampsia [30].

3. The role of renin-angiotensin-aldosterone system and angiotensin II type I receptor agonistic autoantibodies

For a long time, the renin-angiotensin-aldosterone (RAA) system has been suspected to play a role in the pathogenesis of preeclampsia. Normal pregnancy is characterized by reduced vascular responsiveness to angiotensin II. Conversely, in pregnant women with preeclampsia there is an increase in AT-II sensitivity [31]. Genetic predisposition, maladaptive immune responses and environmental stimuli are held responsible for the decrease or increase sensitivity to AT-II in normal and preeclamptic pregnancies [32].
Also, plasma renin activity (PRA) in patients with preeclampsia is lower compared to that in women with normal pregnancy [33]. Renin, the key enzyme that cleaves angiotensinogen precursor to angiotensin I is released in response to a decrease in blood pressure and/or perfusion to the kidney. Low PRA has been associated with increased circulatory volume [34] and it is thought that this is a compensatory response to hypertension in preeclampsia. There is also increased vascular responsiveness to AT-II in patients with preeclampsia [35].
In 1999, Wallucat *et al*. identified a subgroup of women with preeclampsia having [36] an agonistic autoimmune antibody to angiotensin II receptor type I (AT1-AA) in the circulation, but not present in healthy pregnant women. Since then, many studies have indicated that AT1-AA plays a role in the pathogenesis of preeclampsia. Stimulation of AT1 receptor by AT1-AA *in vitro* resulted in the inhibition of trophoblast invasiveness [37], a well-known characteristic of preeclampsia, and in the AT1 receptor activation in endothelial cells, vascular smooth muscle cells and mesangial cells [36]. Administration of these antibodies in pregnant rats leads to hypertension, proteinuria, glomerular capillary endotheliosis, increased production of sFLT-1 and sENG (leading to an anti-angiogenic state), placental abnormalities, and IUGR [38]. Data suggest that AT1 receptor activation by AT1-AA can induce calcium release in vascular smooth muscle cells and mediate the vascular changes in preeclampsia [39,40]. Some studies have shown that this autoantibody is present in the serum of more than 95% of women with preeclampsia and that its serum concentrations correlate with disease severity, which gives further support to the role of AT1-AA in the pathogenesis of preeclampsia [41].
Another interesting finding is that reduced uterine perfusion pressure in rats induces production of anti-AT1 autoantibodies, sFLT-1, TNF and endothelin-1, as well as hypertension and proteinuria. Also, the administration of TNF, IL-6 or IL-17 to pregnant rats is associated with hypertension, placental oxidative stress and increased AT1 activity, the effects of which can be counteracted by the administration of losartan (a selective angiotensin II type 1 receptor) or by B-cell depletion using rituxi-

mab [42]. Furthermore, anti-AT1 autoantibodies mediate hypertension during pregnancy through activation of complement C3 and production of antiangiogenic factors [43]. However, the underlying mechanism that leads to the production of AT1-AA in preeclampsia is still unknown and several controversies remain before one can accredit a pathogenetic role for AT1-AA in preeclampsia. First, the fact that the incidence of preeclampsia is greatest in the first and does not worsen in subsequent pregnancies is in contrast with an autoimmune basis for this disease. Second, AT1-AA is not specific to preeclampsia or to pregnancy; it also occurs in patients with graft rejection and accelerated hypertension [44]. And third, levels of aldosterone, which is downstream to angiotensin II signaling, are decreased in preeclampsia rather than being up-regulated [45].

4. Angiogenic imbalance in the pathophysiology of preeclampsia

Angiogenesis, the formation of new blood vessels from pre-existing ones, is essential for a successful pregnancy [46]. Defective angiogenesis in the pathogenesis of preeclampsia points toward an imbalance between proangiogenic factors, such as vascular endothelial growth factor (VEGF), placental growth factor (PLGF) and transforming growth factor-β (TGF-β), and antiangiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFLT-1) and soluble endoglin (sENG) [4].
Experiments suggest that sFLT-1 and sEng neutralize their ligands acting like antiangiogenic agents lowering the serum concentration of VEGF, PLGF, and TGF-β, which shifts the angiogenic balance towards antiangiogenesis, and leads to endothelial damage triggering hypertension and proteinuria in up to 67% and 63% of patients, respectively [47,48].
The measured mRNA levels of the soluble VEGF receptor-1 (sFlt-1) are higher in the placentas of patients with preeclampsia than in those of healthy pregnant women. Many manifestations in preeclampsia have been reported to be induced by iatrogenic VEGF inhibition in humans supporting the role of sFlt-1 in the pathogenesis of preeclampsia [49-51]. Sera from women with preeclampsia showed antiangiogenic effects on endothelial tube formation assays (used as a test of angiogenesis), which could be reversed by addition of VEGF and PlGF. In pregnant animals high levels of sFlt-1 induced hypertension, proteinuria and glomerular capillary endotheliosis [49].
In preeclampsia, serum samples taken from the uterine vein show significantly higher levels of sFlt-1 than those taken from the antecubital vein, but not in normal pregnant women. Placenta is the main source of the elevated serum levels of sFlt-1 in preeclampsia [49]. Maternal plasma levels of sFlt-1 increase proportionally with the severity of the disease, and they are higher in early than in late preeclampsia [50]. Also, maternal plasma concentrations of sFlt-1 are increased before the clinical diagnosis of preeclampsia and decrease markedly after delivery [49].
A second antiangiogenic factor implicated in the pathogenesis of preeclampsia is soluble endoglin, a cell-surface co-receptor of TGF-β1 and TGF-β3 that induces migration and proliferation of endothelial cells. Suggestions of soluble endoglin involvement in the pathogenesis of preeclampsia include its higher maternal plasma concentrations in women with preeclampsia compared to healthy pregnant women, both before and at the time of clinical diagnosis; also these levels correlate with the severity of the disease [52,53].
Reduced uteroplacental blood flow [54,55], damage to the villous trees, syncytial shedding of antiangiogenic factors [56], oxidative stress [57], anti-AT1 autoantibodies [40], proinflammatory cytokines [38], excess thrombin [58] and hypoxia [59] have all been proposed to be responsible for the increased weight of the antiangiogenic state in preeclampsia (Figure 2).

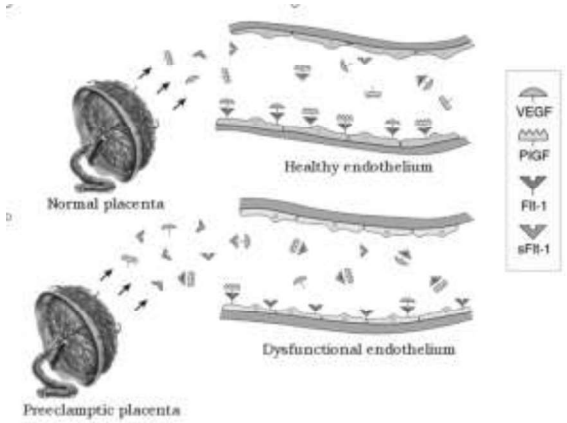

Fig. 2. sFlt-1 and sEng cause endothelial dysfunction by blocking VEGF and TGF-β1 signaling

5. The role of oxidative stress

Oxidative stress, the presence of reactive oxygen species in excess of antioxidant buffering capacity, is a prominent feature of preeclampsia. Oxidative stress is known to damage proteins, cell membranes, and DNA and is a potential mediator of endothelial dysfunction. Maternal blood enters into the intervillous space at higher pressure and faster rate because of the impaired arterial remodeling of the spiral arteries. This exposes the placental villi to fluctuating oxygen concentrations, leading to oxidative stress and activation of nuclear factor- κB, a transcription factor central to the inflammatory response [60].

Kidney manifestations of preeclampsia

The pathologic swelling of glomerular endothelial cells in preeclampsia is known by the term glomerular endotheliosis. The primary injury is specific to endothelial cells. The glomeruli are enlarged and swollen primari-

ly as a result of hypertrophy of the endothelial cells, which occlude the capillary lumina, giving the appearance of bloodless glomeruli [61]. Fibrinogen and fibrin deposits are found within and under the endothelial cells, and electron microscopy shows vacuolization and loss of glomerular endothelial fenestrae [62]. The podocyte foot processes are intact at early stages of disease, a finding not commonly seen in other nephrotic diseases. There are also changes described in the afferent arteriole, including atrophy of the macula densa and hyperplasia of the juxtaglomerular apparatus [63].

Until recently, glomerular endotheliosis was considered a pathognomonic finding in preeclampsia, but new studies have shown that mild glomerular endotheliosis also occurs in pregnancy without preeclampsia, particularly in gestational hypertension.

This suggests that the endothelial dysfunction of preeclampsia may in fact be an exaggeration of a process present in normal healthy pregnancies [64]. Both GFR and renal blood flow are low in preeclampsia as compared to normal pregnancy, the former more than the latter, leading to a 25% reduction in filtration fraction. Due to glomerular capillary endotheliosis there is GFR reduction as a result of both a decrease in renal blood flow and a decrease in the ultrafiltration coefficient (Kf). Renal blood flow decreases as a result of high renal vascular resistance, mainly because of increased afferent arteriolar resistance.

Even though acute renal failure can occur in preeclampsia, the only renal manifestations of disease are typically proteinuria (with bland urinary sediment) with renal sodium and water retention. Because GFR increases in pregnancy, serum creatinine levels in preeclampsia may still appear relatively normal. Proteinuria is generally nonselective and can appear late in pregnancy. In preeclampsia, the podocytes are normally intact, so the etiology of proteinuria is uncertain. There is impaired excretion of sodium and uric acid. The latter is an important marker of preeclampsia and is the cause of hyperuricemia. In contrast to normal pregnancy, preeclampsia is often associated with hypocalciuria [3, 9].

Treatment and Novel Therapies for Preeclampsia

Extracorporeal Removal of Soluble Fms-Like Tyrosine Kinase 1

Recent advances in understanding the pathophysiology of preeclampsia have shown new potential therapeutic targets. Interfering with the production or signaling of sFlt1 may ameliorate the endothelial dysfunction of preeclampsia, allowing to postpone more safely the delivery [7].

Currently there are no target therapies to prevent the clinical manifestations and prolong pregnancy in preeclampsia. New therapies aimed at circulating sFlt-1 can improve the signs and symptoms of preeclampsia and probably lengthen the time of pregnancy in women presenting with very preterm (gestational age <32 weeks) preeclampsia. The challenge for the researcher is to find effective therapies that would be safe for both mother and baby. Instead of administering an agent to the mother, a safe form of therapeutic apheresis would be the extracorporeal removal of sFlt-1 using a selective adsorption column, which would create a concentration gradient and augment its removal from maternal circulation. The depletion of circulating sFlt-1 was found in some trials to prolong pregnancy in women with very preterm preeclampsia. These therapies were well tolerated by both mother and baby, but further clinical studies may be required to determine if this intervention can safely prolong pregnancy in women with very preterm preeclampsia [65].

Metformin as a prevention and treatment of preeclampsia

Some researchers have found that a cheap drug already used to treat diabetes can block the release of toxins from the placenta when preeclampsia is present. This drug, called metformin, has the potential to prevent or treat preeclampsia, and is safe in pregnancy. Metformin is also reported to inhibit hypoxic inducible factor 1α by reducing mitochondrial electron transport chain activity which is upregulated in preterm preeclamptic placenta. Given the mitochondria appears to positively regulate sFlt-1 and sENG secretion, it is hypothesized that preeclamptic placentas might have increased mitochondrial electron transport chain activity. Metformin reduced fms-like tyrosine kinase 1 and soluble endoglin secretion from primary human tissues, possibly by inhibiting this mitochondrial electron transport chain [66].

Metformin reduces VCAM-1 expression on endothelial cells. Endothelial dysfunction is associated with increased VCAM-1 expression in the endothelium. VCAM-1 is an adhesion molecule that is expressed on the luminal surface of blood vessels and plays a major role in the recruitment of circulating blood cells enhancing the inflammation. Preeclampsia is also associated with increased circulating TNFα, which is a proinflammatory cytokine that upregulates VCAM-1 [67-69]. The administration of metformin significantly reduced TNFα-induced VCAM-1 expression, which suggests that it may have effects on decreasing endothelial dysfunction [66].

A trial involving 40 women showed that metformin at a dose of 1.7 g per day was associated with a significantly lower rate of preeclampsia than the rate among women who received placebo [70].

Conclusions

In conclusion, metformin reduces endothelial dysfunction, enhances vasodilation in omental arteries, induces angiogenesis and also seems to heal injured blood vessels. Thus, metformin may be a novel preventative or

therapeutical agent for preeclampsia and has the potential to reduce the disease, which affects many pregnant women around the world each year, causing many to deliver premature babies. However, further clinical studies are warranted.

Conflict of interest statement. None declared.

References

1. Gilbert SJ, Weiner DE. *National Kidney Foundation's primer on kidney diseases*. Sixth edition 2014; 430.
2. Thomas M Coffman *et. al. Schrier's Diseases of the Kidney*, 9th ed. 2015; 1697-1700.
3. Pettit F, Brown MA. The management of preeclampsia: What we think we know. *Eur J Obstet Gynecol Reprod Biol* 2012; 160: 6-12.
4. Johnson RJ, Feehally J, Floege J. *Comprehensive Clinical Nephrology 5th ed.* 2014; p: 506-521.
5. Shachar BZ, Lyell DJ. Interpregnancy interval and obstetrical complications. *Obstet Gynecol Surv* 2012; 67: 584-596.
6. Conde-Agudelo A, Althabe F, Belizan JM, *et. al.* Cigarette smoking during pregnancy and risk of preeclampsia: A systemic review. *Am J Obstet Gynecol* 1999; 181: 1026-1035.
7. Maarten WT, *et al.* Brenner and Rector's. *The Kidney*, 9th Edition 1795-1808.
8. Cunningham FG, Leveno KJ, Bloom SL, *et. al. Williams Obstetrics* 24/E 24th Edition 2014; 731-732.
9. http://www.rcdrg.sgul.ac.uk/research/trophoblasts
10. Brosens I, Robertson WB, Dixon HG. The physiological response of the vessels of the placental bed to normal pregnancy. *J Pathol Bacteriol* 1967; 93, 569-579.
11. Zhou Y, Damsky CH, Fisher SJ. Preeclampsia is associated with failure of human cytotrophoblasts to mimic a vascular adhesion phenotype. One cause of defective endovascular invasion in this syndrome? *J Clin Invest* 1997; 99: 2152-2164.
12. Fisher S, Roberts JM. The placenta in normal pregnancy and preeclampsia. In: Taylor RN, Roberts JM, Cunningham FG (eds): *Chesley's Hypertensive Disorders in Pregnancy*, 4th ed. Amsterdam, Academic Press, 2014.
13. Hertig AT. Vascular pathology in hypertensive albuminuric toxemias of pregnancy. *Clinics* 1945; 4: 1011-1015.
14. De Wolf F, Robertson WB, Brosens I. The ultrastructure of acute atherosis in hypertensive pregnancy. *Am J Obstet Gynecol* 1975; 123: 164-174.
15. Young J. The aetiology of eclampsia and albuminuria and their relation to accidental haemorrhage: (an anatomical and experimental investigation.). *Proc R Soc Med* 1914; 7: 307-348.
16. Staff AC, Sibai BM, Cunningham FG. Prevention of preeclampsia and eclampsia. In: Taylor RN, Roberts JM, Cunningham FG (eds): *Chesley's Hypertensive Disorders in Pregnancy*. Amsterdam, Academic Press, 2014.
17. McMahon K, Karumanchi SA, Stillman IE, *et. al.* Does soluble fms-like tyrosine kinase-1 regulate placental invasion? Insight from the invasive placenta. *Am J Obstet Gynecol* 2014; 10: 66.
18. Lee SM, Romero R, Lee YJ, *et. al.* Systemic inflammatory stimulation by microparticles derived from hypoxic trophoblast as a model for inflammatory response in preeclampsia. *Am J Obstet Gynecol* 2012; 207(4): 337.
19. Chaiworapongsa T, Chaemsaithong P, Yeo L, *et al.* Preeclampsia part 1: current understanding of its Pathophysiology. *Nature Reviews Nephrology* 2014; 10: 466-480.
20. Kublickiene KR, Cockell AP, Nisell H, *et al.* Role of nitric oxide in the regulation of vascular tone in pressurized and perfused resistance myometrial arteries from term pregnant women. *Am J Obstet Gynecol* 1997; 177: 1263-1269.
21. Cockell AP, Poston L. Flow-mediated vasodilatation is enhanced in normal pregnancy but reduced in preeclampsia. *Hypertension* 1997; 30: 247-251.
22. Kublickiene KR, Lindblom B, Kruger K, *et al.* Preeclampsia: evidence for impaired shear stress-mediated NO release in uterine circulation. *Am J Obstet Gynecol* 2000; 183(1): 160-166.
23. Burton GJ, Hempstock J, Jauniaux E. Nutrition of the human fetus during the first trimester-a review. *Placenta* 2001; 22 (Suppl. A): S70-S77.
24. Genbacev O, Joslin R, Damsky CH, *et al.* Hypoxia alters early gestation human cytotrophoblast differentiation/invasion in vitro and models the placental defects that occur in preeclampsia. *J Clin Invest* 1996; 97: 540-550.
25. Reshef T. The Role of Hypoxia and Hypoxia-Inducible Factor-1Alpha in Preeclampsia Pathogenesis. *Biology of Reproduction* 2012; 87 (6): 134.
26. Caniggia I, Mostachfi H, Winter J, *et al.* Hypoxia-inducible factor-1 mediates the biological effects of oxygen on human trophoblast differentiation through TGFbeta(3). *J Clin Invest* 2000; 105(5): 577-587.
27. Caniggia I, Grisaru-Gravnosky S, Kuliszewsky M, *et al.* Inhibition of TGF-beta 3 restores the invasive capability of extravillous trophoblasts in preeclamptic pregnancies. *J Clin Invest* 1999; 103(12): 1641-1650.
28. Sanchez-Elsner T, Botella LM, Velasco B, *et al.* Endoglin expression is regulated by transcriptional cooperation between the hypoxia and transforming growth factor-beta pathways. *J Biol Chem* 2002; 277(46): 43799-43808.
29. Yinon Y, Nevo O, Xu J, *et al.* Severe intrauterine growth restriction pregnancies have increased placental endoglin levels: hypoxic regulation via transforming growth factor-beta 3. *Am J Pathol* 2008; 172(1): 77-85.
30. Redman CW, Sargent IL. Placental stress and preeclampsia: a revised view. *Placenta* 2009; 30 (Suppl. A): S38-S42.
31. Gant NF, Chand S, Whalley PJ, *et al*. The nature of pressor responsiveness to angiotensin II in human pregnancy. *Obstet Gynecol* 1974; 43: 854.
32. Dechend R, Luft FC, Lindheimer M. Chesley's Hypertensive Disorders in Pregnancy (eds Lindheimer MD, Roberts JM & Cunningham GC) *Elsevier* 2009; 287-296.
33. Brown MA, Zammit VC, Mitar DA, *et al.* Renin-aldosterone relationships in pregnancy-induced hypertension. *Am J Hypertens* 1992; 5(6): 366-371.
34. Blumenfeld JD, Laragh JH. Management of hypertensive crises: the scientific basis for treatment decisions. *Am J Hypertens* 2001; 14(11): 1154-1167.
35. Gant NF, Daley GL, Chand S, *et al.* A study of angiotensin II pressor response throughout primigravid pregnancy. *J Clin Invest* 1973; 52(11): 2682-2689.
36. Wallukat G, Homuth V, Fischer T, *et al.* Patients with preeclampsia develop agonistic autoantibodies against the angiotensin AT1 receptor. *J Clin Invest* 1999; 103(7): 945-952.
37. Xia Y, Wen H, Bobst S, *et al*. Maternal autoantibodies from preeclamptic patients activate angiotensin receptors on human trophoblast cells. *J Soc Gynecol Investig* 2003; 10(2): 82-93.
38. Parrish MR, *et al*. The effect of immune factors, tumor necrosis factor-alpha, and agonistic autoantibodies to the angiotensin II type I receptor on soluble fms-like tyrosine-1 and soluble endoglin production in response to hypertension during pregnancy. *Am J Hypertens* 2010; 23: 911-916.
39. Thway TM, Shlykov SG, Day MC, *et al.* Antibodies from preeclamptic patients stimulate increased intracellular Ca2+ mobilization through angiotensin receptor activation. *Circulation* 2004; 110(12): 1612-1619.

40. Zhou CC, Zhang Y, Irani RA, *et al.* Angiotensin receptor agonistic autoantibodies induce preeclampsia in pregnant mice. *Nat Med* 2008; 14(8): 855-862.
41. Siddiqui AH, Irani RA, Blackwell SC, *et al.* Angiotensin receptor agonistic autoantibody is highly prevalent in preeclampsia: correlation with disease severity. *Hypertension* 2010; 55(2): 386-393.
42. Novotny SR, Wallace K, Heath J, *et al.* Activating autoantibodies to the angiotensin II type I receptor play an important role in mediating hypertension in response to adoptive transfer of CD4+ T lymphocytes from placental ischemic rats. *Am J Physiol Regul Integr Comp Physiol* 2012; 302: R1197-R1201.
43. Girardi G, Yarilin D, Thurman JM, *et al.* Complement activation induces dysregulation of angiogenic factors and causes fetal rejection and growth restriction. *J Exp Med* 2006; 203: 2165-2175.
44. Fu ML, Herlitz H, Schulze W, *et al.* Autoantibodies against the angiotensin receptor (AT1) in patients with hypertension. *J Hypertens* 2000; 18(7): 945-953.
45. Langer B, Grima M, Coquard C, *et al.* Plasma active renin, angiotensin I, and angiotensin II during pregnancy and in preeclampsia. *Obstet Gynecol* 1998; 91(2): 196-202.
46. Ferrara N, Carver-Moore K, Chen H, *et al.* Heterozygous embryonic lethality induced by targeted inactivation of the VEGF gene. *Nature* 1996; 380: 439-442.
47. Yang JC, Haworth L, Sherry RM, *et al.* A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003; 349: 427-434.
48. Gressett SM, Shah SR. Intricacies of bevacizumab-induced toxicities and their management. *Ann Pharmacother* 2009; 43(3): 490-501.
49. Maynard SE, Min JY, Merchan J, *et al.* Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest* 2003; 111: 649-658.
50. Levine RJ, Maynard SE, Qian C, *et al.* Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med* 2004; 350: 672-683.
51. Chaiworapongsa T, Romero R, Espinoza J, *et al.* Evidence supporting a role for blockade of the vascular endothelial growth factor system in the pathophysiology of preeclampsia. Young Investigator Award. *Am J Obstet Gynecol* 2004; 190: 1541-1550.
52. Gilbert JS, Babcock SA & Granger JP. Hypertension produced by reduced uterine perfusion in pregnant rats is associated with increased soluble fms-like tyrosine kinase-1 expression. *Hypertension* 2007; 50: 1142-1147.
53. Levine RJ, Lam C, Qian C, *et al.* Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. *N Engl J Med* 2006; 355: 992-1005.
54. Venkatesha S, Toporsian M, Lam C, *et al.* Soluble endoglin contributes to the pathogenesis of preeclampsia. *Nat Med* 2006; 12: 642-649.
55. Makris A, Thornton C, Thompson J, *et al.* Uteroplacental ischemia results in proteinuric hypertension and elevated sFLT-1. *Kidney Int* 2007; 71: 977-984.
56. Rajakumar A, Cerdeira AS, Rana S, *et al.* Transcriptionally active syncytial aggregates in the maternal circulation may contribute to circulating soluble fms-like tyrosine kinase 1 in preeclampsia. *Hypertension* 2012; 59: 256-264.
57. Zhao H, Wong RJ, Kalish FS, *et al.* Effect of heme oxygenase-1 deficiency on placental development. *Placenta* 2009; 30: 861-868.
58. Lockwood CJ, Toti P, Arcuri F, *et al.* Thrombin regulates soluble fms-like tyrosine kinase-1 (sFlt-1) expression in first trimester decidua: implications for preeclampsia. *Am J Pathol* 2007; 170: 1398-1405.
59. Nagamatsu T, Fujii T, Kusumi M, *et al.* Cytotrophoblasts up-regulate soluble fms-like tyrosine kinase-1 expression under reduced oxygen: an implication for the placental vascular development and the pathophysiology of preeclampsia. *Endocrinology* 2004; 145: 4838-4845.
60. Ahn KS, Aggarwal BB. Transcription factor NF-κB: A sensor for smoke and stress signals. *Ann NY Acad Sci* 2005; 1056: 218-233.
61. Spargo BH, McCartney C, Winemiller R. Glomerular capillary endotheliosis in toxemia of pregnancy. *Arch Pathol* 1959; 13: 593-599.
62. Lafayette RA, Malik T, Druzin M, *et al.* The dynamics of glomerular filtration after caesarean section. *J Am Soc Nephrol* 1999; 10: 1561-1565.
63. Govan AD. Renal changes in eclampsia. *J Pathol Bacteriol* 1954; 67: 311-322.
64. Strevens H, Wide-Swensson D, Hansen A, *et al.* Glomerular endotheliosis in normal pregnancy and pre-eclampsia. *BJOG* 2003; 110: 831-836.
65. Thadhani R, Kisner T, Hagmann H, *et al.* Pilot study of extracorporeal removal of soluble fms-like tyrosine kinase 1 in preeclampsia. *Circulation* 2011; 124: 940-950.
66. Brownfoot FC, Hastie R, Hannan NJ, *et al*. Metformin as a prevention and treatment for preeclampsia: effects on soluble fms-like tyrosine kinase 1 and soluble endoglin secretion and endothelial dysfunction. *Am J Obstet Gynecol* 2016; 214: 356.e1-15.
67. Austgulen R, Lien E, Vince G, *et al.* Increased maternal plasma levels of soluble adhesion molecules (ICAM-1, VCAM-1, E-selectin) in preeclampsia. *Eur J Obstet Gynecol Reprod Biol* 1997; 71: 53-58.
68. Chaiworapongsa T, Romero R, Yoshimatsu J, *et al.* Soluble adhesion molecule profile in normal pregnancy and pre-eclampsia. *J Matern Fetal Neonatal Med* 2002; 12: 19-27.
69. Borzychowski AM, Sargent IL, Redman CW. Inflammation and preeclampsia. *Semin Fetal Neonat Med* 2006; 11: 309-316.
70. Fougner KJ, Vanky E, Carlsen SM. Metformin has no major effects on glucose homeostasis in pregnant women with PCOS: results of a randomized double-blind study. *Scand J Clin Lab Invest* 2008; 68: 771-776.