CROATIAN MEDICAL JOURNAL
CMJ

44(2):148-156,2003

REVIEW

Trophoblastic Injury: New Etiological and Pathological Concept of Preeclampsia

Naohiro Kanayama

Department of Obstetrics and Gynecology, Hamamatsu University School of Medicine, Hamamatsu, Japan

Aim. To analyze published data related to modern insight in the etiology of preeclampsia.

Methods. We analyzed 38 published articles on the etiology of preeclampsia. The articles were identified by a combined search of PubMed database of the National Library of Medicine, USA, by using the key words "preeclampsia" and "cause/etiology". Full-text articles were retrieved from the library of Hamamatsu University School of Medicine and Japan's library network.

Results. According to the reports, vasospasm and vascular endothelial injury were two major pathological conditions of preeclampsia. They could be classified into 4 types of uteroplacental circulation failure: 1) disturbance in the circulation from the aorta to the uterine artery, 2) disturbance in the circulation of the spiral artery, 3) disturbance in the circulation of the intervillous space, and 4) disturbance in the circulation of the uterine vein reflux disorder. Major vessel bed of the uteroplacental unit consists of trophoblast, not of endothelial cells. Moreover, the trophoblast has many cellular functions, such as endothelial, immune, neural, and hormonal, resulting in production of various vasoactive substances. Thus, trophoblastic injury induced by uteroplacental circulation failure could affect and deteriorate the systemic circulation of the mother, resulting in preeclamptic symptoms.

Conclusion. The development of preeclampsia could be envisioned as a series of events from uteroplacental circulation failure to trophoblastic injury to vascular endothelial injury or vasospasm. The concept of "trophoblastic injury attributable to the uteroplacental circulation failure" can be a signpost for further investigations into the etiology of preeclampsia and type-specific treatment of preeclampsia.

Key words: *endothelial cell injury; etiology, preeclamsia; placenta; trophoblast; uteroplacental circulation; vasospasm*

Preeclampsia is a disorder of unknown etiology, which occurs only during pregnancy and is characterized by gestational hypertension, fluid retention, and proteinuria (1). Vasospasm and vascular endothelial injury are two major pathological features of preeclampsia, which lead to the development of hypertension, proteinuria, and edema (2). Many factors are involved in vasospasm and vascular endothelial injury: endothelin production is increased (3), nitric oxide production is impaired (4), prostacyclin level is decreased (5), and cellular fibronectin concentration is increased (6). As far as the etiology of preeclampsia is concerned, there are many hypotheses. Placental hypocirculation and hypoxia (7,8), poor invasion of extravillous trophoblast (9,10), disorder of angiotensin system (11), stimulation of sympathetic nervous system (12), insulin resistance (13), and thrombophilia (14) are suspected to play a role in the origin of preeclampsia. However, there has been no common hypothesis which could explain these various pathological and pathophysiological changes accompanying the disorder.

The mature placenta consists of 15-20 cotyledons, each beginning with the principal villus, which divides into four villi of the first line. First-line villi divide into the next 10-12 villi of the second line, which end in so-called terminal villi. Some terminal villi protrude freely in the intervillous space, whereas others are attached to the decidua, thus giving the stability to the placenta. Maternal blood flows through the intervillous space, and fetal blood flows through the villous stroma. For placental function to be normal, it is essential that all structures of maternal and fetal circulation develop normally, ie, uteroplacental or hemochorionic membrane, which consists of trophoblast, villous stroma, collagen fibers, and capillary endothelium (15). These structures undergo qualitative and quantitative changes on account of increased nutritional, respiratory, and hormonal needs of the fetus as the end of the pregnancy approaches.

Uteroplacental membrane thickens, allowing a close contact between maternal blood in the intervillous space and fetal blood in the villi. Every pathological process affecting trophoblast, villous stroma,

Table 1. Characteristics of 38 articles on preeclampsia evaluated in this review

Topic of the article	Type of the study	Reference No.
Pathophysiology of preeclampsia:	reviews	2,3,4,5,16
vasospastic mediators (catecholamine, NO, endothelin, serotonin, PGs, angiotensin II)	review and clinical studies	4,5,15
endothelial injury (platelets, white blood cells)	review, cross-sectional studies, and clinical studies	2,3,6
Uteroplacental circulation:		7,8
uterine artery constriction	basic and clinical studies	11,12,13,17,18,19,30
invasion of trophoblast	basic and clinical studies	9, 10,31
villous proliferation	basic and clinical studies	33,34,35,36,37
thrombophilia and pregnancy	case reports and clinical studies	14,42,43
uterine vein reflux disorder	case reports and clinical studies	26,27,38

collagen fiber, or capillary endothelium in the placenta can result in pathological condition if not detected on time.

Mother's adaptation to pregnancy is a complex process resulting in biological changes of the greatest importance for the appropriate perfusion of the feto-placental unit. Because of the lack of autonomous control, feto-placental unit mostly depends on the release of vasoactive substances, which are either produced locally in the endothelial cells or transported by blood circulation. Pregnancy can induce hypertension in normotensive women or make already existent hypertension worse (16). Proteinuria can accompany hypertension (1). In neglected patients, this condition can evolve into the most severe form – eclampsia.

Preeclampsia is accompanied by increased maternal, fetal, and neonatal mortality (16). It mostly appears in the first pregnancy, multiple pregnancies, molar pregnancy, and in pregnant women with pre-existent vascular disorders (16,17). Although the disorder has been known for a long time, the pathophysiological processes leading to its development are still unclear.

The aim of this systematic review was to establish the common concept of etiology of preeclampsia, based on the analysis of published scientific medical articles, with a hypothesis that trophoblastic injury induced by uteroplacental circulation failure could be a major cause of preeclampsia.

Material and Methods

I analyzed 78 articles on the etiology and pathophysiology of preeclampsia, published in the international journals between mid-1960's and 2002. The articles were identified by combined search of PubMed database (National Library of Medicine). For the search, we used "preeclampsia" and "etiology/pathophysiology" as key words. Forty papers published in a language other than English were excluded from the study, and the remaining 38 papers were included in the analysis (Table 1). The selected articles in the full-text format were retrieved from the library of Hamamatsu University School of Medicine and Japan's library network. The articles we analyzed covered pathophysiology of preeclampsia, animal experiments, preclinical studies, and case reports. The selected 38 articles were divided into 2 groups: reports on the pathophysiology of preeclampsia and reports on uteroplacental circulation or other topic. There were 24 papers on uteroplacental circulation, which were further analyzed.

Results

According to the 38 analyzed articles on preeclampsia (Table 1), vasospasm and vascular endothelial injury were the two major pathological pathways for the development of preeclampsia. Other studies also reported similar findings (2,3,16,17). It seems that uteroplacental circulation failure is involved in both conditions and that it can develop at 4 sites or levels: uterine artery, spiral artery, intervillous space, and uterine vein. Furthermore, according to the reports, the major vessel bed of the uteroplacental unit consists of the trophoblast rather than endothelial cells. Thus, trophoblastic injury induced by uteroplacental circulation failure could affect and impair the systemic circulation, resulting in preeclamptic symptoms.

Vasospasm

The vasospasm results from an imbalance between vasoconstrictive and vasodilative substances, with vasoconstriction predominating in the case of preeclampsia. Vasoactive substances involved in the vasospasm in preeclampsia are catecholamine, nitric oxide, endothelin, serotonin, prostaglandins, and angiotensin II.

Catecholamines. Catecholamines are vasoconstrictors and activators of sympathetic nervous system. Increased concentration of $_2$-adrenoreceptors on platelets and higher activity of sympathetic nervous system as measured in the peroneal muscle imply that sympathetic nervous system is more active in preeclampsia (12). Among other vasoconstrictive substances, neuropeptide Y is also increased in preeclampsia (18).

Nitric oxide. Synthetic activity of nitric oxide, a potent vasodilator, and its metabolites is suppressed in preeclampsia (19). Also, animals administered NG-nitro-L-arginine methyl ester (LNAME), an inhibitor of nitric oxide synthesis, develop a preeclampsia-like pathological condition (19). These findings indicate that decrease in nitric oxide could account for vasospasms, suggesting general impairment of vasodilative system in preeclampsia.

Endothelin-1. This is one of the three potent vasoconstrictive substances – endothelin-1, endothelin-2, and endothelin-3 – produced in the vascular endothelium. Binding of endothelin-1 to endothelin-receptors on the vascular smooth muscle cells activates phospholipase C, which leads to the increase in intracellular calcium concentration and contraction of the smooth muscle. The blood concentration of endothelin-1 is increased in severe preeclampsia and HELLP (hemolysis, elevated liver enzyme syndrome, and low platelet) syndrome. Endothelin-1 is likely to be involved in progression of preeclampsia, but it is unknown whether the substance is involved in the early stage of the development of the disorder.

Serotonin. Platelets contain large amounts of this substance and release it into the blood circulation when activated. The concentration of serotonin metabolite 5-hydroxy tryptophan (5-HT) is increased in preeclampsia and administration of ketanserin, a serotonin type-2 receptor blocker, is reported to be an effective treatment of preeclampsia (20).

Prostaglandins. In preeclampsia, production of vasodilative substance prostaglandin I_2 in the vascular endothelial cells is decreased, whereas the production of thromboxane A_2 is increased. This imbalance changes the vessel tone, resulting in vasospasm. It provides a theoretical background for low dose aspirin therapy (21).

Angiotensin II. Angiotensin II directly acts on the vascular smooth muscle and stimulates the sympathetic nervous system. In addition, it increases blood pressure through secretion of aldosterone and enlargement of sodium reserves. In preeclampsia, depressed response to A-II receptor is stronger and causes vasoconstriction. Recently, several studies reported on angiotensin II and angiotensin II receptor gene mutations in women with preeclampsia (22,23).

Vascular Endothelial Injury

Platelet activation, increased blood coagulation, and activation of white blood cells all cause vascular endothelial injury.

Platelet activation and increased blood coagulation. Hematologists suggest that preeclampsia could be viewed as a chronic disseminated intravascular coagulation resulting from excessive production of thrombin due to platelet activation and aggregation. Thus, blood coagulation on the vascular endothelium can be responsible for vascular endothelial injury. Clinical symptoms (hypertension, proteinuria, and edema) of preeclampsia closely correlate with blood coagulation (24).

Activation of white blood cells. White blood cells produce free radicals on stimulation. In preeclampsia, neutrophils are activated and produce free radicals to increase lipid peroxides. In addition, activation of white blood cells causes increased release of elastase or inflammatory cytokines. These factors are also closely associated with occurrence of vascular endothelial injury (25).

Vasospasm induces activation of platelets, white blood cells, and the blood coagulation system, which results in the release of mediators and vascular endothelial injury. On the other hand, vascular endothelial injury induces production of vasoconstrictive substances, thus helping further vasospasm. Thus, vasospasm and vascular endothelial injury enhance each other's effects.

New Etiology of Preeclampsia – Trophoblast Injury Induced by Uteroplacental Circulation Failure

Whereas the systemic vasospasm and vascular endothelial injury are primary pathological conditions of preeclampsia, the uteroplacental circulation attracts attention as a possible cause of preeclampsia. It has been observed that the trophoblast invades decidua and uterine muscle. If the invasion is deep, endothelial cells of the spiral arteries convert to trophoblast, which results in dilatation of spiral arteries. If the invasion is shallow, endothelial cells of the spiral arteries cannot convert to the trophoblast and the circulation in intervillous space is decreased (9,10). Thrombi that are formed in the intervillous space and spiral arteries in the placenta of patients with preeclampsia cause uteroplacental circulation failure. Since preeclampsia disappears soon after the delivery of the placenta, uteroplacental circulation failure must be taken into account as an important etiological factor. The blood in uteroplacental circulation comes from the aorta through the uterine artery and spiral arteries to the intervillous space, and then leaves the intervillous space through the uterine vein to the renal vein and finally the inferior vena cava (Fig. 1).

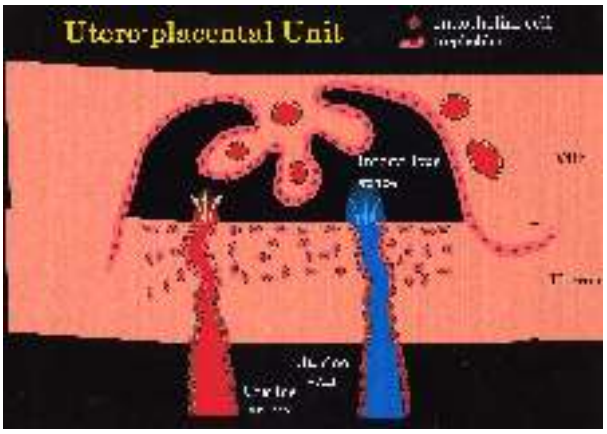

Figure 1. Normal uteroplacental circulation.

There are some well-known risk factors for preeclampsia as well as clinical cases in which preeclampsia frequently occurs. We investigated the clinical cases where preeclampsia was liable to occur and analyzed the uteroplacental circulation (18,27,28). Our hypothesis was that preeclampsia is a pathological result of uteroplacental circulation failure.

Disturbance in Aorta-to-Uterine Artery Circulation

When the circulation from the aorta to the uterine artery is disturbed, a vasoconstricting condition develops, resulting in decreased blood supply to the intervillous space (Fig. 2). This disturbance is caused by insulin resistance, abnormal sensitivity to angiotensin, activation of the sympathetic nervous system, and chronic hypertension (arteriosclerosis).

Insulin resistance. Preeclampsia is quite often accompanied by insulin resistance (13). Insulin resistance is a state of lower insulin intake and, in most cases, a synonym for hyperinsulinemia. The chronic hyperinsulinemia causes thickening of smooth muscle and arteriosclerosis, which leads to the narrowing of the arteries and hypertension. Excessive or irregular ingestion of carbohydrates induces a condition of sustained hyperinsulinemia, resulting in insulin resistance.

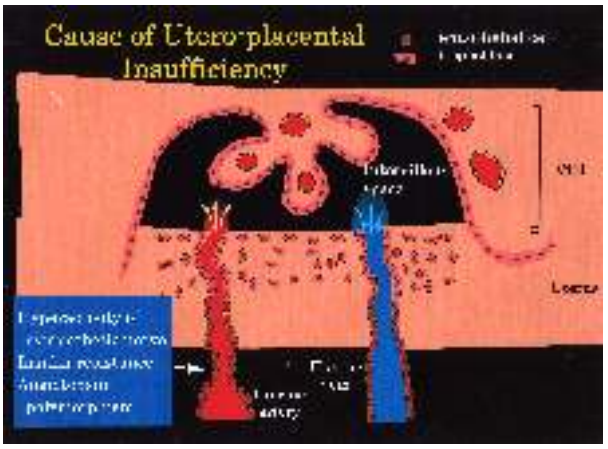

Figure 2. Disturbance in uteroplacental circulation between the aorta and the uterine artery.

Abnormal sensitivity to angiotensin. In preeclampsia, impaired response to angiotensin is more pronounced and elasticity of vessels is decreased. In addition, preeclampsia is more frequent in cases of abnormal genetic coding for the angiotensin receptors (22,23).

Excessive activation of sympathetic nerve system (hyperthyroidism and stress). When pregnant animals are stimulated by various types of stress, symptoms similar to preeclampsia occur (28). Stress can be a trigger for the sympathetic nervous system to cause vasoconstriction. Chronic stress decreases the uteroplacental circulation. In addition, preeclampsia is often a complication of hyperthyroidism. Thyroid hormones may stimulate the activity of the sympathetic nervous system and disturb the uteroplacental circulation. It is known that pregnant women with the positive roll-over test develop preeclampsia more often (29). Some cases of preeclampsia may be caused by the stimulation of the nervous system or large vessels by enlarged pregnant uterus.

Chronic hypertension (arteriosclerosis). Arteriosclerosis, such as in essential hypertension, decreases the blood flow through the uterine artery, resulting in the uteroplacental circulation failure. Many cases of mixed preeclampsia fall under the category of uteroplacental circulation failure. As mentioned above, the arterial circulation failure can be a causative factor for preeclampsia. Actually, a surgical stricture of the uterine artery or aorta in pregnant animals induces symptoms of preeclampsia (30). In addition, chronic stimulation of the abdominal sympathetic ganglia or chronic cold stimulation of the rats also induces chronic hypersympathetic nervous condition, resulting in a pathological preeclampsia-like condition (28). This is probably the result of the stimulation of sympathetic nervous system, which constricts the uterine artery and eventually leads to the uteroplacental circulation failure. Such development of the uteroplacental circulation failure followed by preeclampsia, attributable to the reduction in the arterial blood flow to the uterine artery, has been confirmed in animal models (30).

Abnormal Spiral Artery

In normal pregnancy, the trophoblast invades deep into uterine tissue, migrating into the smooth muscle and vascular endothelia of the spiral artery. The smooth muscle disappears, which leads to the dilatation of the spiral artery. Consequently, the amount of blood that supplies the intervillous space increases. Recent studies have demonstrated that preeclampsia frequently occurs in cases where trophoblast insufficiently infiltrates uterine tissue and walls of spiral arteries (9,10,31). When the trophoblast infiltration is shallow, the spiral arteries do not dilate and the blood flow through the intervillous space remains small, causing uteroplacental circulation failure (Fig. 3). The reason why the invasion of the trophoblast is suppressed is not yet clear, although this shallow trophoblastic invasion is considered one of the etiological factors in many cases of preeclampsia. In addition, preeclampsia is characterized by fetal development deficiency.

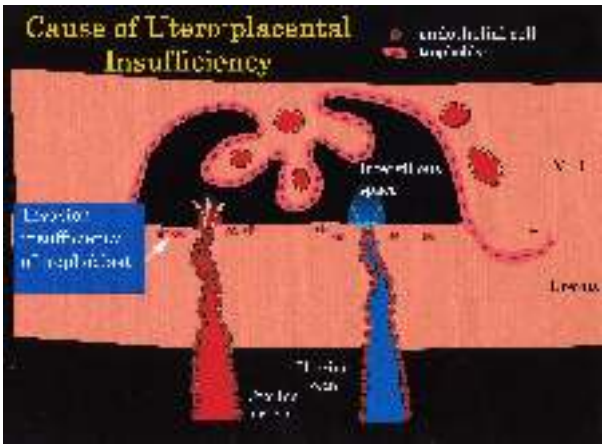

Figure 3. Disturbance in uteroplacental circulation in the spiral artery.

Villous Proliferation and Hyperplasia

Excessive villous proliferation and hyperplasia narrow the intervillous space, reducing the blood flow in the intervillous space and leading to uteroplacental circulation failure (Fig. 4).

Hydatidiform mole. When hydatidiform mole remains until the second trimester, a preeclampsia-like symptoms often occur. A possible pathological condition in which villous proliferation narrows the intervillous space, leading to clot formation, reduction in uteroplacental circulation, and uteroplacental circulation failure, could explain the development of preeclampsia (32).

Pregnancy complicated by diabetes. It is widely known that diabetes is often associated with occurrence of preeclampsia and that pregnant women with diabetes often have a giant placenta (33). The trophoblast actively grows in the giant placenta, probably narrowing the intervillous space and leading to uteroplacental circulation failure. This resembles the mechanism for hydatidiform mole causing preeclampsia. The exact mechanism of giant placenta in diabetic pregnancy is unknown. However, it is suggested

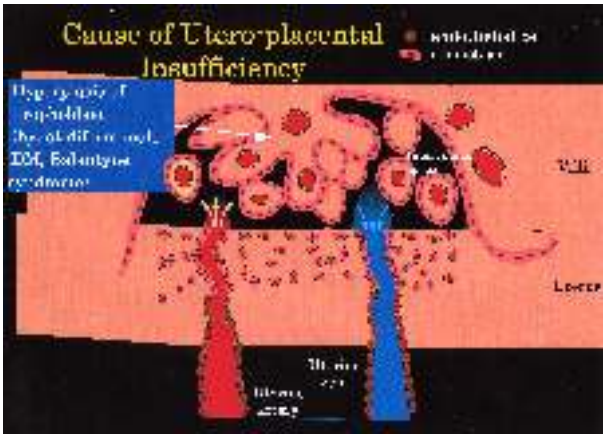

Figure 4. Disturbance in uteroplacental circulation in the intervillous space due to villous proliferation and hyperplasia.

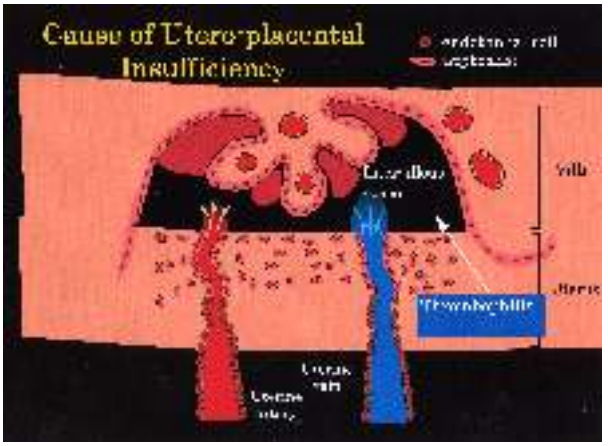

Figure 5. Disturbance in uteroplacental circulation in the intervillous space due to thrombophilia.

that hyperinsulinemia or high levels of insulin-like growth factor in diabetes could be one of the mechanisms involved.

Ballantyne syndrome (mirrors syndrome). This is a syndrome leading to placental hypertrophy, fetal hydrops or preeclampsia, and so-called triple edema syndrome or mirrors syndrome, because of the fetal hydrops, placental hydrops (hyperplasia) or maternal hydrops (34). In the recent case of Ballantyne syndrome, the release of higher concentrations of human chorionic gonadotropin (hCG) from the trophoblast has been found, indicating that Ballantyne syndrome is a state of excessive proliferation of the trophoblast (35). It is suggested that preeclampsia associated with Ballantyne syndrome decreases blood circulation in the intervillous space because of excessive proliferation of trophoblast, leading to the development of uteroplacental circulation failure. We have recently found that the villous cells grow excessively in mice whose cyclin-dependent kinase inhibitor p57kip2 protein has been deactivated (36). These mice have a preeclampsia-like pathological condition and could be viewed as models of Ballantyne syndrome or preeclampsia observed in hydatidiform mole (37).

Thrombogenesis in Intervillous Spaces (Thrombophilia)

Thrombophilia refers to a congenital or acquired condition of hyperproduction of thrombin, which leads to thromb formation. Thrombophilia is frequently associated with preeclampsia (14). Congenital thrombophilia includes abnormality in the blood coagulation factor V, angiotensin-III deficiency, protein S deficiency, and homocystinemia. On the other hand, acquired thrombophilia is represented by antiphospholipid antibody syndrome. The trophoblast contains increased amount of negatively charged phospholipids in the phospholipid components of cellular membranes, which are liable to cause blood coagulation, as compared to the vascular endothelium. Slow blood flow in the intervillous space also assists thrombogenesis. Thus, patients with thrombophilia appear to have blood clots in the trophoblast, which lead to uteroplacental circulation failure (Fig. 5).

Uterine Vein Reflux Disorder

If a pathological condition compromises blood flow from the intervillous space back into the maternal systemic circulation and blocks the outlet of the uteroplacental circulation, blood is retained in the uterine vein and the uteroplacental circulation failure occurs (Fig. 6). Most probably, blood will be retained in the vein from the left ovary to the left kidney, located between the uterine vein and inferior vena cava. The left renal vein crosses over the aorta and can easily be compressed by the pregnant uterus. In the anatomically abnormal cases where the left renal vein passes under the aorta, every pregnancy causes preeclampsia (38). It is also known that congestion can develop in the left renal kidney vein if there is a shunt between the portal vein and the left renal vein, which leads to preeclampsia (26). In our hands, a magnetic resonance angiogram of the repeated type of early-onset preeclampsia and a venogram of the left renal vein revealed dilation of the left renal and ovarian veins (Fig. 7). The left renal venogram indicated that blood was congested in the left renal vein, not reaching the inferior vena cava but flowing into the hemiazygos vein. In this clinical case with abnormal blood reflux in the left ovarian vein, the utero-

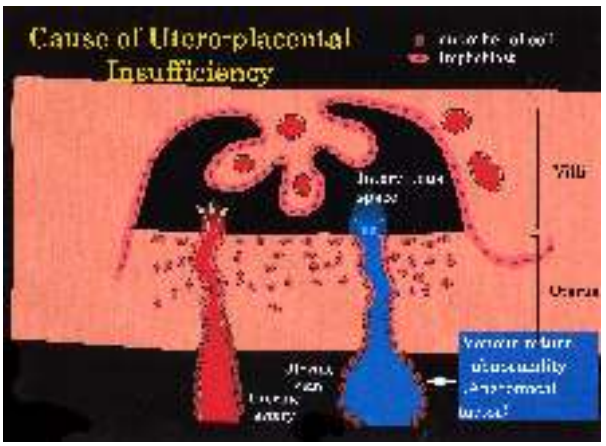

Figure 6. Disturbance in uteroplacental circulation due to the uterine vein reflux disorder.

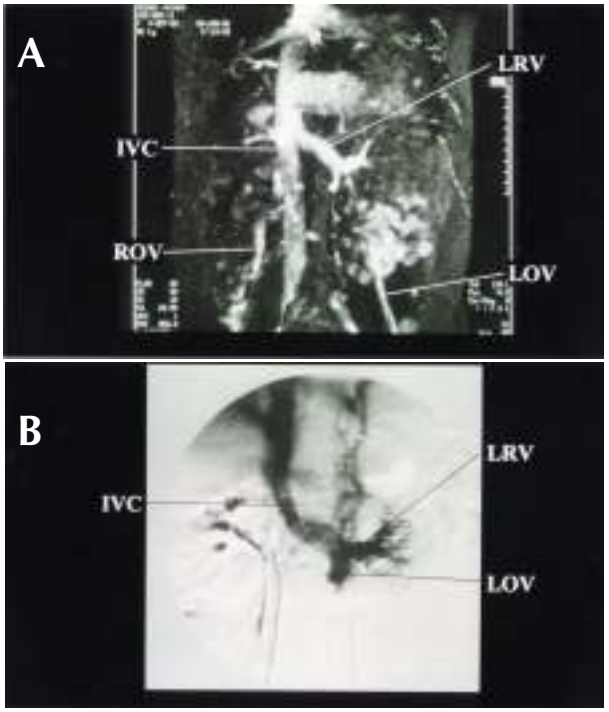

Figure 7. Magnetic resonance angiogram (MRA) of repeated early-onset preeclampsia and a venogram of the left renal vein (LRN). Abnormal blood reflux in the left ovarian vein (LOV) and the uteroplacental circulation are visible. **A**. The MRA image shows dilation of the left renal and ovarian veins. ROV – right ovary vein. **B**. The left renal venogram indicated that blood was congested in the left renal vein, not reaching the inferior vena cava (IVC) but flowing into the left hemiazygos vein.

placental circulation was presumed also to be blocked. In preeclampsia attributable to the uterine vein abnormality, proteinuria-dominated preeclampsia is featured with prominent dilatation of the left renal vein (27). Moreover, it is easy to find the maternal left renal vein by putting the ultrasound probe on the uterine fundus in the second or third trimester. From these viewpoints, the follow-up of the maternal left renal vein at routine examinations for pregnant women is important for early detection of preeclampsia.

Discussion

Although a number of etiologic factors have been proposed, our new hypothesis of etiology of preeclampsia – uteroplacental circulation failure – is close to the previous theory of placental ischemia (7,8). Any disorder or disturbance of blood flow in the uteroplacental circulation from the uterine artery to the uterine vein will result in uteroplacental circulation failure. Preeclampsia can be explained by the uteroplacental circulation failure in most cases, but not in all. It is known that, in some cases, HELLP syndrome and eclampsia occur in puerperal period. These events are difficult to explain by the uteroplacental circulation failure, however, many cases of preeclampsia (hypertension plus proteinuria) could be explained by the trophoblast injury due to the uteroplacental circulation failure.

We could say that the research in the etiology of preeclampsia resembles a blind man touching the elephant. We believe that we have established the common etiological concepts for preeclampsia: "trophoblastic injury". Trophoblastic injury mediates between the uteroplacental circulation failure and leads to preeclampsia accompanied by hypertension or proteinuria (Fig. 8). "Trophoblastic injury" is considered to induce the systemic vascular endothelial impairment and vasospasm. The most important fact is that the trophoblast occupies the major part of the vascular bed for uteroplacental circulation. In uteroplacental circulation, blood is in direct contact not with the vascular endothelial cells but with the trophoblast in the vessels originating from the spiral artery to the part of the uterine vein. In the spiral artery and uterine vein, extravillous trophoblast is in contact with maternal blood (Fig. 1). Thus, extravillous and intravillous trophoblast has a role of the endothelium (Fig. 1). Therefore, uteroplacental circulation failure eventually causes "trophoblastic injury" rather than vascular endothelial injury.

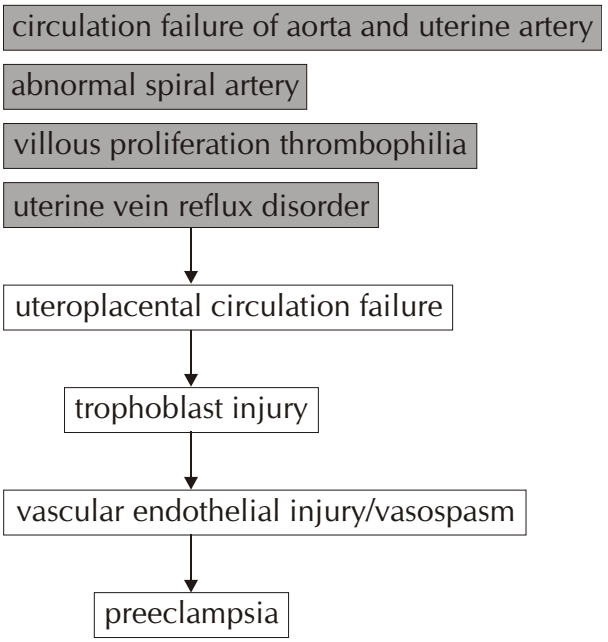

Figure 8. Suggested pathophysiological pathway, etiology, and pathology of preeclampsia.

Which substances are produced during the trophoblastic injury? Gratton et al (39) have recently reported that the supernatant from the trophoblast cultures under a hypoxic condition causes spasms of the arterioles, suggesting that the trophoblast produces vasoconstrictive substances in large quantities.

Trophoblast Characteristics

Neural functions. The trophoblast produces various neuropeptides, including neurokinin and corticotropin releasing hormone (40). The trophoblast also expresses the receptors of nerve-stimulating substances, including neuropeptide Y receptors. In addition, norepinephrine is produced from the villous cells (41). In case of the uteroplacental circulation fail-

ure, the trophoblast produces more of these neurogenic vasoactive substances, which enter the maternal systemic vascular system.

Vascular endothelial functions. The trophoblast clearly has the vascular endothelial functions. Nitric oxide and endothelin production systems are present, while the reduction in nitric oxide production and increase in endothelin production are observed under the uteroplacental circulation failure, as in the case of ordinary vascular endothelial disorder. Nitric oxide binds to soluble guanylate cyclase in the cytoplasm of the vascular smooth muscle to produce cyclic guanosine monophosphate (cGMP) and reduce the intracellular calcium concentration to relax the smooth muscle. Nitric oxide is produced also in the trophoblast. The concentration of the nitric oxide metabolites in patient's blood with preeclampsia is reduced, suggesting that nitric oxide production mechanism in the trophoblasts may be disturbed not only in preeclampsia but also in vascular endothelial disorder. In addition, thrombin receptors and thrombomodulin are present in the vascular endothelium, where blood clots are formed in the trophoblast injury. Production of vasodilatatory factor prostacyclin in the trophoblast decreases.

Cells with many negatively charged phospholipids on the surface. Negatively charged phospholipids, such as phosphatidylserine or ethanolamine, are alternatively expressed on the trophoblast cellular surface (42). Such negatively charged phospholipids are also exposed on the epithelial cells of the small intestine, indicating a characteristic of cells involved in the active transport. Usually, these negatively charged phospholipids exposed on the cellular surface activate blood coagulating factors V and X to produce fibrin. However, the villous cells carry anti-coagulant proteins, such as annexin V, on their surface to prevent blood coagulation (43). When these proteins are reduced for any reason, blood coagulation immediately starts on the cellular membrane. This means that cells constituting the trophoblast are very prone to causing blood coagulation. In addition, plasminogen activator inhibitor I (PAI-1) production is known to be promoted under hypoxic conditions. A reduction in fibrinolytic activity is associated with the promotion of thrombogenesis.

Endocrine cells. The trophoblast produces various hormones: steroid hormones, such as estrogen, progesterone, and cortisol and protein hormones, such as human chorionic gonadotropin (hCG) and human placental lactogen (HPL). Recently, leptin was also found to be produced in the trophoblast (44). Leptin is not only involved in lipid metabolism, but also stimulates production of neuropeptide Y to activate the sympathetic nervous system. In patients with preeclampsia, it is known that leptin production in the trophoblast is increased. Adrenomedullin is also produced by trophoblast. Reduced production of adrenomedullin is reported in patients with circulation failure (45). Reduction in adrenomedullin may be associated with disorders in the vascular dilatation system. In uteroplacental circulation failure, vasoactive hormones from the trophoblast are suggested to be produced in larger amounts.

Immunocytes. Production of inflammatory cytokines, such as interleukin-1 (IL-1) and tissue necrotic factor (TNF), in the trophoblast increases under hypoxic conditions, probably causing vascular endothelial injury. In fact, the concentration of cytokines in amniotic fluid is increased in patients who later develop preeclampsia. This suggests that the trophoblast forming the vascular bed produces and releases the inflammatory cytokines under the uteroplacental circulation failure.

All together, the trophoblast has many functions and may suddenly, upon exposure to an ischemic or hypoxic condition, start to produce and liberate various substances, from endothelial and nerve-derived substances to hormones and blood coagulation activators. A number of vasoactive substances may be released in large amounts as the result of the trophoblast disorder, as opposed to the general vascular endothelium. Consequently, the vascular endothelium-damaging substances and vasoactive substances are suggested to systemically circulate, causing hypertension or proteinuria. Hereby follows a diagram presenting a series of events (from uteroplacental circulation failure to trophoblastic injury to vascular endothelial injury/vasospasm), which could be involved in the development process of preeclampsia.

Suggested Treatment

Preeclampsia should be individually treated. For preeclampsia attributable to the vasoconstriction of the uterine artery, vasodilators should be administered. For preeclampsia attributable to the abnormal spiral arteries, no effective treatment modalities have been available so far. For the treatment of thrombophilia, excessive villous proliferation or abnormal venous reflux, anticoagulants may be desirable. In terms of our theory, the individual therapy for preeclampsia could be possible. Although preeclampsia has long been a disease of unknown cause, etiology of factors involved in the development of the typical preeclampsia clinically accompanied by hypertension, proteinuria, and fetal growth restriction could be narrowed down to the placenta. Many studies on the etiology of preeclampsia were focused on a single feature of the disorder, thus missing the whole picture. We hope that the concept of "trophoblastic injury attributable to the uteroplacental circulation failure" could serve as a signpost for further research in the etiology of preeclampsia.

References

1 Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). Hypertens Pregnancy 2001;20: IX-XIV.

2 Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK. Preeclampsia: an endothelial cell disorder. Am J Obstet Gynecol 1989;161:1200-4.

3 Nova A, Sibai BM, Barton JR, Mercer BM, Mitchell MD. Maternal plasma level of endothelin is increased in preeclampsia. Am J Obstet Gynecol 1991;165:724-7.

4 Seligman SP, Buyon JP, Clancy RM, Young BK, Abramson SB. The role of nitric oxide in the pathoge-

nesis of preeclampsia. Am J Obstet Gynecol 1994;171: 944-8.

5 Bussolino F, Benedetto C, Massobrio M, Camussi G. Maternal vascular prostacyclin activity in pre-eclampsia. Lancet 1980;2:702.

6 Taylor RN, Crombleholme WR, Friedman SA, Jones LA, Casal DC, Roberts JM. High plasma cellular fibronectin levels correlate with biochemical and clinical features of preeclampsia but cannot be attributed to hypertension alone. Am J Obstet Gynecol 1991;165(4 Pt 1): 895-901.

7 Kumar D. Chronic placental ischemia in relation to toxemias of pregnancy. Am J Obstet Gynecol 1962;84: 1323-9.

8 Hodari AA. Chronic uterine ischemia and reversible experimental "toxemia of pregnancy". Am J Obstet Gynecol 1967;97:597-607.

9 Brosens IA, Robertson WB, Dixon HG. The role of the spiral arteries in the pathogenesis of preeclampsia. Obstet Gynecol Annu 1972;1:177-91.

10 Pijnenborg R, Anthony J, Davey DA, Rees A, Tiltman A, Vercruysse L, et al. Placental bed spiral arteries in the hypertensive disorders of pregnancy. Br J Obstet Gynaecol 1991;98:648-55.

11 Woods LL, Brooks VL. Role of the renin-angiotensin system in hypertension during reduced uteroplacental perfusion pressure. Am J Physiol 1989;257(1 Pt 2): R204-9.

12 Schobel HP, Fischer T, Heuszer K, Geiger H, Schmieder RE. Preeclampsia – a state of sympathetic overactivity. N Engl J Med 1996;335:1480-5.

13 Sowers JR, Saleh AA, Sokol RJ. Hyperinsulinemia and insulin resistance are associated with preeclampsia in African-Americans. Am J Hypertens 1995;8:1-4.

14 Dekker GA. Risk factors for preeclampsia. Clin Obstet Gynecol 1999;42:422-35.

15 Castellucci M, Kaufnabb P. Basic structure of the villous trees. In: Benirschke K, Kaufnabb P, editors. Pathology of the human placenta. New York (NY): Springer. p. 50-148.

16 Pridjian G, Puschett JB. Preeclampsia. Part 1: clinical and pathophysiologic considerations. Obstet Gynecol Surv 2002;57:598-618.

17 Pridjian G, Puschett JB. Preeclampsia. Part 2: experimental and genetic considerations. Obstet Gynecol Surv 2002;57:619-40.

18 Khatun S, Kanayama N, Belayet HM, Bhuiyan AB, Jahan S, Begum A, et al. Increased concentrations of plasma neuropeptide Y in patients with eclampsia and preeclampsia. Am J Obstet Gynecol 2000;182:896-900.

19 Bolte AC, van Eyck J, Gaffar SF, van Geijn HP, Dekker GA. Ketanserin for the treatment of preeclampsia. J Perinat Med 2001;29:14-22.

20 Low-dose aspirin in prevention and treatment of intrauterine growth retardation and pregnancy-induced hypertension. Italian study of aspirin in pregnancy. Lancet 1993;341:396-400.

21 Kobashi G, Hata A, Shido K, Kato EH, Yamada H, Fujimoto S, et al. Association of a variant of the angiotensinogen gene with pure type of hypertension in pregnancy in the Japanese: implication of a racial difference and significance of an age factor. Am J Med Genet 1999;86:232-6.

22 Morgan L, Crawshaw S, Baker PN, Edwards R, Broughton Pipkin F, Kalsheker N. Functional and genetic studies of the angiotensin II type 1 receptor in pre-eclamptic and normotensive pregnant women. J Hypertens 1997;15(12 Pt 1):1389-96.

23 Mckay DG. Chronic intravascular coagulation in normal pregnancy and preeclampsia. Contrib Nephrol 1981;25:108-19.

24 Stark JM. Pre-eclampsia and cytokine induced oxidative stress. Br J Obstet Gynaecol 1993;100:105-9.

25 Kobayashi T, Tokunaga N, Sugimura M, Kanayama N, Terao T. Left renal vein and early-onset preeclampsia. Thromb Haemost 2000;84:930-1.

26 Tokunaga N, Kanayama N, Sugimura M, Kobayashi T, Terao T. Dilatation of the left renal vein in preeclampsia. J Matern Fetal Med 2000;9:356-9.

27 Kanayama N, Tsujimura R, She L, Maehara K, Terao T. Cold-induced stress stimulates the sympathetic nervous system, causing hypertension and proteinuria in rats. J Hypertens 1997;15:383-9.

28 Gant NF, Chand S, Worley RJ, Whalley PJ, Crosby UD, MacDonald PC. A clinical test useful for predicting the development of acute hypertension in pregnancy. Am J Obstet Gynecol 1974;120:1-7.

29 Combs CA, Katz MA, Kitzmiller JL, Brescia RJ. Experimental preeclampsia produced by chronic constriction of the lower aorta: validation with longitudinal blood pressure measurements in conscious rhesus monkeys. Am J Obstet Gynecol 1993;169:215-23.

30 Zhou Y, Damsky CH, Chiu K, Roberts JM, Fisher SJ. Preeclampsia is associated with abnormal expression of adhesion molecules by invasive cytotrophoblasts. J Clin Invest 1993;91:950-60.

31 Michael L, DI Saia PJ, Brewster WR. Pelvic malignancies, gestational trophoblastic neoplasia, and nonpelvic malignancies. In: Maternal-fetal medicine. Creasy RK, Resnik R, editors. Philadelphia (PA): WB Saunders Co; 1999. p. 1128-50.

32 Lunell NO. Obstetric complications in diabetic pregnancy. Acta Endocrinol Suppl (Copenh) 1986;279: 117-21.

33 van Selm M, Kanhai HH, Gravenhorst JB. Maternal hydrops syndrome: a review. Obstet Gynecol Surv 1991;46:785-8.

34 Gherman RB, Incerpi MH, Wing DA, Goodwin TM. Ballantyne syndrome: is placental ischemia the etiology? J Matern Fetal Med 1998;7:227-9.

35 Takahashi K, Kobayashi T, Kanayama N. p57(Kip2) regulates the proper development of labyrinthine and spongiotrophoblasts. Mol Hum Reprod 2000;6:1019-25.

36 Kanayama N, Takahashi K, Matsuura T, Sugimura M, Kobayashi T, Moniwa N, et al. Deficiency in p57Kip2 expression induces preeclampsia-like symptoms in mice. Mol Hum Reprod 2002;8:1129-35.

37 Uchide K, Ueno H, Inoue M, Suzuki M. A cause of pre-eclampsia? Lancet 2000;355:114.

38 Gratton RJ, Gandley RE, Genbacev O, McCarthy JF, Fisher SJ, McLaughlin MK. Conditioned medium from hypoxic cytotrophoblasts alters arterial function. Am J Obstet Gynecol 2001;184:984-90.

39 Page NM, Woods RJ, Gardiner SM, Lomthaisong K, Gladwell RT, Butlin DJ, et al. Excessive placental secretion of neurokinin B during the third trimester causes pre-eclampsia. Nature 2000;405:797-800.

40 Manyonda IT, Slater DM, Fenske C, Hole D, Choy MY, Wilson C. A role for noradrenaline in pre-eclampsia: towards a unifying hypothesis for the pathophysiology. Br J Obstet Gynaecol 1998;105:641-8.

41 Katsuragawa H, Rote NS, Inoue T, Narukawa S, Kanzaki H, Mori T. Monoclonal antiphosphatidylserine anti-

body reactivity against human first-trimester placental trophoblasts. Am J Obstet Gynecol 1995;172:1592-7.

42 Sugimura M, Kobayashi T, Shu F, Kanayama N, Terao T. Annexin V inhibits phosphatidylserine-induced intrauterine growth restriction in mice. Placenta 1999;20: 555-60.

43 Masuzaki H, Ogawa Y, Sagawa N, Hosoda K, Matsumoto T, Mise H, et al. Nonadipose tissue production of leptin: leptin as a novel placenta-derived hormone in humans. Nat Med 1997;3:1029-33.

44 Kanenishi K, Kuwabara H, Ueno M, Sakamoto H, Hata T. Immunohistochemical adrenomedullin expression is decreased in the placenta from pregnancies with preeclampsia. Pathol Int 2000;50:536-40.

Received: July 4, 2002
Accepted: November 11, 2002

Correspondence to:
Naohiro Kanayama
3600 Handa-cho
Hamamatsu, Japan 431-31
kanayama@hama-med.ac.jp