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Chapter

Placental Adaptation to Hypoxia as a Predictive Marker for Preeclampsia

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Abstract

The ability of the placenta to interact with surrounding microenvironment of hypoxia can serve as a predictive marker for the development of preeclampsia. Lessons can be studied from highlands inhabitants and their ability to survive extreme conditions of hypobaric hypoxia. Many candidate genes loci that are associated with adaptation to high altitude hypoxia and healthy exercise are also associated with adaptation to hypoxia in normal pregnancy. This can pave the way to a new approach based on the concept of evolution and adaptation stating that "genes can undergo a process of natural selection for the fittest adaptive variants, so as to reach a state of adaptation to the scarce microenvironments." Accordingly, the degree of adaptation in candidate genes and their polymorphisms can serve as predictive markers for the development of preeclampsia. This can be seen in the high degree of concordance between gene expression and the lesions seen in the placenta and other remote organs in the different subtypes of preeclampsia. To conclude, "adaptive or less adaptive" can be the genetic result that answers the question of disease prediction, recurrence, and possible complications.

Keywords: placenta, adaptation, hypoxia, predictive marker

1. Introduction

Throughout the lives of individuals, their genes interact with their environments to cause variations in phenotype traits. Because individuals with certain traits tend to survive and reproduce more than others with less successful traits, the population evolves. In 1859, Charles Darwin set out his theory of evolution by natural selection as an explanation for adaptation and speciation. He defined natural selection as the "principle by which each slight variation [of a trait], if useful, is preserved" [1]. Although the Darwinian theory was ages before the genome era, it can also explain the process of natural selection at molecular levels; cells with successful traits are best adapted to their microenvironments, and more likely to survive and proliferate. The selection between cells favors those with the most advantageous genetic polymorphisms. The genetic variability is usually enhanced by the scarce microenvironments like low oxygen, low temperature, and high radiation that act as competitive milieus for cells. The useful genetic variants are preserved and can be heritable.

Some 2.4 billion years ago, photosynthesis leads to the accumulation of oxygen to levels that were likely toxic to many microorganisms. Organisms that could

defend themselves against oxidative stress and at the same time utilize oxygen for energy, survived and evolved. As time went on, cellular requirement for oxygen became critical, and animals developed a physiological response to the low levels of oxygen. The cellular ability to compete in such scarce microenvironments became the "microevolutionary" exam for survival in many physiological processes as in hematopoiesis, spermatogenesis, normal pregnancy, and embryogenesis. Genetic studies suggest that hypoxia-inducible factors (HIFs) are a family of master transcriptional regulators for the hypoxic response inside the body. HIF-α transcription factors (HIF-1α and HIF-2α/EPAS1) dimerize with HIF-1β/ARNT subunits, and translocate to the nucleus, where it binds to the hypoxia responsive element (HRE) in the genetic material to regulate the transcription of some 200 genes, leading to the adaptive response to hypoxic stress. In turn, hypoxia responsive genes promote the tolerance of hypoxia by decreasing the cellular requirement for oxygen and increasing the supply of oxygen. They mainly involved in angiogenesis, erythropoiesis, energy metabolism, and autophagy [2].

On ascent to high attitudes, lowlanders become at risk of conditions like acute mountain sickness (AMS), pulmonary edema, cerebral edema, and polycythemia in the chronic type of the disease. These conditions, which resemble many symptoms associated with preeclampsia, are considered to be a maladaptive response to the low oxygen levels at high altitudes. However, ancient indigenous populations like Tibetans through generations acquired unique integrated physiological processes for defending their body against oxygen deprivation. This gives them the advantage of being protected from hypoxia-related disorders, like hypertension, diabetes mellitus, cardiovascular disorders, and preeclampsia. Yet, physiological acclimatization can occur in lowlanders over days to weeks following ascent and can serve as the first steps of adaptation. This led to the idea that adaptation to hypoxia can also protect from pathological disorders that result in dysregulation of hypoxia pathways like in preeclampsia [3].

2. Preeclampsia as a maladaptive disorder

In spite of the extensive research in the pathophysiology of the disease, the etiology is still poorly understood. It was suggested to be due to the insufficient adaptation of spiral arterioles or due to the shallow trophoblastic invasion, resulting in reduced uteroplacental blood flow leading to placental hypoxia. The placenta initially develops in a low oxygen environment of 1–2% oxygen until after the 10th week of pregnancy. This maternal hypoxia is an effective stimulus eliciting adaptations at the maternal-fetal interface, which include activation of the invasive endovascular trophoblast cell lineage and modifications of uterine blood vessels supplying the developing chorioallantoic placenta. Reduced or absent cytotrophoblast invasion of the maternal uterine spiral arterioles is a common clinical finding in studies of pregnancies complicated by preeclampsia, suggesting that the mechanism mediating invasion of these cells is perturbed. While, it is proposed that hypoxia-inducible factors are the key regulators of the first trimester [4–7].

The exposure of pregnant women to hypobaric hypoxia at high altitudes leads to arterial maternal hypoxia and intervillous blood hypoxia at the maternal-fetal interface. This renders pregnant women from low-altitude to be at risk of many complications including reproductive loss, intrauterine growth restriction, and preeclampsia. However, high-altitude residents have low rates of preeclampsia compared to other populations at the same altitudes. Such population differences are due, at least in part, to differences in maternal vascular responses to pregnancy. It was hypothesized that natural selection acting on hypoxia-inducible factor

(HIF)-targeted or -regulatory genes has enabled maternal vascular adaptation to pregnancy in long-resident high-altitude groups. Earlier studies support this hypothesis and demonstrate that the potent genes can be differentially regulated between adaptive and less adaptive populations. Moore et al. show that HIF-targeted vasoconstrictor, endothelin-1 (ET-1), is differentially regulated by pregnancy in Andean vs. European residents at high altitudes. Andeans, who live longer at high altitude, show normal, pregnancy-associated fall in ET-1 levels; whereas, Europeans have higher ET-1 levels and little pregnancy-associated change, like in preeclamptic women. Another hopeful study revealed that high-altitude Tibetans, who have lived the longest at high altitude, can share similar genotypic and allelic frequencies of adaptive variants with sea level Sojourners who undergo acclimatization on ascent [8–10].

This led to the question that, if lowlanders on ascent have the ability to acquire allele and genotype frequency as in adaptive native individuals, can preeclamptic women undergo acclimatization, and can it be used as a predictive marker for the disease.

3. From preeclampsia to normal pregnancy: the hidden adaptation!

There are a very large number of both prospective and retrospective studies investigating the preeclampsia recurrence rate, with different sample sizes, target populations, study designs, and main outcome measures, resulting in contrasting conclusions. Yet, maternal and perinatal outcomes in the subsequent pregnancy are generally better than in the first; most women will not have recurrent preeclampsia, and those who do usually will give birth at a greater gestational age compared with their index birth. Even though, women who have experienced a pregnancy complicated by preeclampsia, including their caregivers, undoubtedly have a fear of recurrence and should be counseled about their reproductive future. Many of these mothers and babies are at increased risk of severe adverse outcomes that include acute renal or hepatic failure, antepartum and postpartum hemorrhage, stroke, maternal death, intrauterine growth restriction, and perinatal death. Long-term, the burden of preterm birth is immense, particularly in terms of neurodevelopmental impairment, impaired learning, cerebral palsy, and need for special care resources [11].

Another evidence for the hidden adaptation is the ability of the placenta to survive the oxidative stress. Uterine artery Doppler studies are proposed to be abnormal in the second trimester of pregnancy because of increased vascular resistance indicating failed remodeling of the vessels of the intervillous space. About half of women with abnormal uterine artery Doppler findings go on to have preeclampsia, preterm birth, or pregnancies complicated by IUGR, while, the other half go on to normal outcomes. Besides to the Doppler scans, biochemical markers, like reduced circulating ascorbate, increased concentrations of nitric oxide synthase, and AT1 angiotensin receptor inhibitors, show evidence of oxidative stress both in women with or without abnormal uterine artery velocimetry. These markers are present regardless of whether the pregnancy proceeds to IUGR, preeclampsia, or a normal outcome.

These findings support the concept that poor placentation (Stage 1 of the model) alone is not sufficient to cause preeclampsia, and that there are other factors that adjust the physiological wheel of oxidative stress toward adaptation and normal pregnancy or toward preeclampsia (stage 2 of the model) [12]. In other words, it appears that the placenta starts as preeclamptic, and then somehow overcomes the oxidative stress and continues the placentation normally. This raises many questions

on what are the hidden mechanisms that enable the placenta to survive the oxidative stress and overcome the disease? What could happen in a subsequent pregnancy that renders them to be protected? Why the placenta from normal pregnancies survives the oxidative stress?

4. Hypoxia and natural selection

It is known that hypoxic microenvironment acts as a stress-induced mutagenesis by increasing genetic instability in human cell through highly regulated genetic mechanisms. The stabilization of HIF, the master transcriptional factor in hypoxia, down-regulates the major DNA repair mechanisms; mismatch repair and homologous recombination. This leads to a switch from the high-fidelity repair mechanisms to the error-prone mutagenic non-homologous end joining mechanisms, which result in a high degree of genetic variability. In earlier study, our findings revealed that genetic variability in periods of high hypoxic pressure in preeclamptic samples was more confined to certain genomic loci, in particular the HIF master regulators of hypoxia, compared to normal pregnancy [3, 13].

Different scenarios of genetic variability under stressful condition of hypoxia are proposed, and represent the basis for natural selection and adaptation. **Figure 1** shows

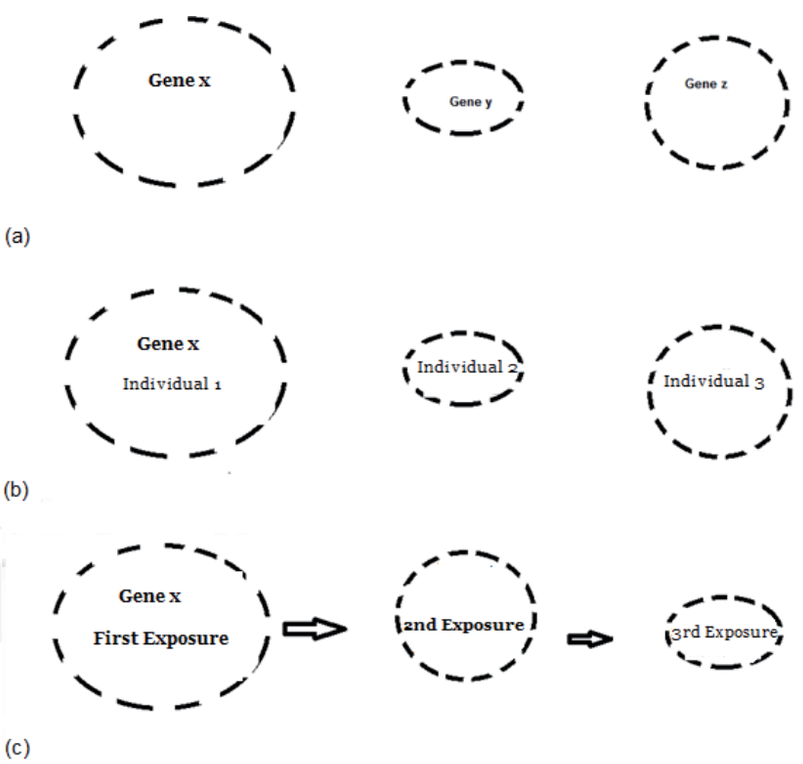

Figure 1.
The degree to which the genes can be reprogrammed by mutations can be termed genetic flexibility [14]. Genetic variability permits flexibility and survival of a population in the changing environments. Here, the genetic variability is represented by circles. The dots in the circles are the number of genetic variants in a particular gene. The more the variants are, the highest is the genetic flexibility. (a) Different genes in the same individual with the same degree of stressful condition. Gene x shows a larger circle with more variants, and this may indicates that gene x is more influential at a particular stressful condition, and probably is more affected by the signals of that particular condition. (b) The same gene in different individuals under the same extreme condition. Individual 1 with a larger circle of genetic variability is more flexible and have higher chance to adapt under the certain condition than 2 and 3. Individuals 2 and 3 are either less flexible due to different reasons, or (c) may undergo a previous acclimatization experience that renders them to show a less degree of variability. In (c), gene x is in the same individual, but the larger circle is showing genetic variants in the first exposure to stressful microenvironment (hypoxia), followed by the second, and the third exposure. The decrease in the number of genetic variants in subsequent exposures reflects the stress relief, and probably acclimatization.

dotted circles that represent the flexibility of hypoxia pathway genes under stressful conditions. The dots represent the genetic variants or mutations. The more flexible the gene is, the larger the circle of genetic variability, and thus the higher chances for natural selection to the fittest variants. This can predict the possible path of evolutionary events, and the possible roles of the genes with larger circles under stressful conditions.

In a previous report, we showed that preeclamptic samples had higher genetic variability in the key regulators of hypoxia pathway genes like EPAS1 and EGLN1 compared to normal pregnancy, which indicates that they were under a high level of stress. We also hypothesized that the high genetic variability that are reflected by the high number of mutations in preeclamptic samples can be considered as a "positive response" toward adaptation by increasing the chance of having adaptive mutations, yet they are still evolutionary late compared to controls. In other words, normal pregnancy has higher rate of fixation to the adaptive variants compared to preeclampsia, and this can be the reason for the delay in the process of adaptation in some types of preeclampsia [3].

5. Genetic association studies and preeclampsia

Genome-wide linkage studies of preeclampsia and pregnancy-induced hypertension have identified different loci associated with preeclampsia that segregate with different populations: on 4q (between D4S450-D4S610 markers, found in Australia), 2q23 (between D2S112-D2S151 markers, Australia, NZ), 2p13 (D2S286, Iceland), 2p25 (D2S168, Finland), 9p13 (D9S169, Finland), and 10q22 (Netherlands). Additional loci are expected to exist in preeclamptic patients with certain complications, such as the locus 12q in patients with hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome [15–18].

Candidate genes studies have provided evidence for an association with preeclampsia, frequently with inconsistent results. One of the common candidate genes is endothelial nitric oxide synthase gene (eNOS) on 7q36, which is responsible for nitric oxide production in endothelial cells. The endothelial dysfunction in preeclampsia reveals a strong association with eNOS polymorphisms. However, several other genome scans could not confirm this association. Another study found an evidence of moderate association with an increased risk for preeclampsia in women having mutations in coagulation factor genes; F5 Leiden (rs6025, G1691A), and the prothrombin (F2) gene (rs1799963, G20210A). This evidence may explain the association of the disease with coagulation disorders. Several studies found associations between renin-angiotensin-aldosterone system with gestational hypertension and preeclampsia. Earlier linkage studies found an association with angiotensinogen (AGT) locus, on 1q42-43 and the risk for hypertensive disease in different sets of population. They also found an association between specific allele AGT (T235, rs699) with essential hypertension and preeclampsia. Angiotensin converting enzyme (ACE) along with AGT receptor 1 (AGTR1) were also found to have a role in the pathogenesis of the preeclampsia. Another candidate gene that link preeclampsia to the risk of hypertension is the T allele (C677T) of the methylenetetrahydrofolate reductase (MTHFR) gene [19–23].

To conclude, no single gene or chromosomal locus currently known can explain the pathogenesis of preeclampsia. This indicates that preeclampsia is a polygenic disorder, and it reflects an integrated pathophysiological process of insufficient adaptation, not only in the placenta, but also in other tissues and organs. On the other hand, the geographical distribution of candidate genes and loci in association with the pathogenesis of preeclampsia may reflect the interaction between the different environments and the gene pool of populations.

6. Adaptive polymorphisms of hypoxia genes

Here, we discuss some of the known genetic polymorphisms that influence maternal vascular adaptation in normal pregnancy and preeclampsia, high-altitude adaptation, and adaptive variants in healthy exercise. These genetic changes affect the protein activity and production, and can be set as early predictive markers for adaptation.

6.1 Endothelial nitric oxide synthase (eNOS): (rs1799983, G894T, Glu298Asp)

Healthy pregnancy is associated with enhanced endothelium-dependent vasodilation in the brachial artery, a response mediated by NO. These changes are thought to be an important physiological adaptation that accommodates the increased circulating blood volume and cardiac output during pregnancy. A common polymorphism of the eNOS gene is G894T in the mature protein that has been associated with the differences in endothelium-dependent dilation at 12-week gestation. There are several reports on the association between eNOS 894T allele polymorphism and PE susceptibility. They also provide a potential mechanism linking eNOS polymorphism with the prediction of cardiovascular disorders and pulmonary edema in which NO bioactivity is impaired [24–26].

In high-altitude adaptation, previous studies showed that the eNOS G894T polymorphism contributed to physiology and pathophysiology of humans at high altitude by regulating the production of NO. The 894G allele carriers and GG genotype might be a beneficial factor for HA adaptation through enhancing the level of NO, and 894T allele and heterozygous G/T of the 894G/T variant are associated with the susceptibility to high-altitude pulmonary edema (HAPE) at Qinghai-Tibet. In acclimatization to high altitude, NO levels increase dramatically above the baseline levels, while visitors ill with high-altitude pulmonary edema at the time of the study or in the past, have NO levels were lower than those of their healthy counterparts. Highland indigenous populations like Tibetans have high NO levels in the lung, plasma, and red blood cells that were at least double the levels that can be found in other populations regardless of altitude. With respect to NOS3 G894T and its relation to athletic performance or status, the over-representation of the GG genotype and G allele in all athletes suggests that the G894 allele may favor many types of sports [27, 28]. This supports the adaptive function of 894G allele and genotype.

Probably adaptive: 894G allele; less adaptive: 894 T allele

6.2 Angiotensin converting enzyme (ACE): (rs4646994, ACEI/D)

Circulating angiotensin I-converting enzyme (ACE) exerts a tonic regulatory function in circulatory homeostasis, through the synthesis of vasoconstrictor angiotensin II. ACE I/D (insertion/deletion) polymorphism is associated with ACE level. The presence (insertion, I allele) rather than the absence (deletion, D allele) of a287 bp Alu sequence insertion fragment is associated with lower serum and tissue ACE activity and thus lower angiotensin II production. The D allele of the ACE I/D polymorphism along with higher ACE levels were over-represented in Han Chinese who was afflicted with AMS. On ascent to extreme altitudes, the I allele of the ACEI/D polymorphism may tend to have more sufficient/efficient acclimatization and consequently have less risk of developing AMS. It was hypothesized that the pioneer lowlanders who migrated to high altitude might have the I-related

genotypes (the II or ID genotype) as an "inner predisposition" to overcome altitude illnesses during migration and adaptation and finally was able to settle at high altitude permanently. However, some evidence shows that they may gain their adaptation through the long period of settlement. Along with elite mountaineers, the I allele has been associated with some aspects of endurance performance in Marathon runners, rowers, cyclists, handball players, and others in different population. In the prediction of the disease, it was shown that the ACE D allele leads to increased expression of plasminogen activator inhibitor-1 (PAI-1), which can increase the risk of preeclampsia and thrombotic events and enhances the production of angiotensin II from angiotensin I [29, 30].

Probably adaptive: ACE I allele; less adaptive: ACE D allele

6.3 Vascular endothelial growth factor (VEGFA): (rs3025039, C 936T)

Vascular endothelial growth factor (VEGF) is a major angiogenic factor that acts as a regulator of endothelial cell proliferation and vascular permeability. VEGF has been shown to be markedly up-regulated in hypoxic conditions. A common polymorphism of VEGFA is 936 C>T (rs3025039). The carriers of the 936T allele have lower VEGF plasma level by one-third of non-carriers. In a comparison between two groups of lowlanders on ascent to high altitude; those with 936T allele have a decreased risk of acute mountain sickness. In acute exercise, VEGF levels increases in sedentary individuals "less adaptive," whereas exercise adaptation attenuates VEGF gene expression in human skeletal muscle in trained "well adaptive" individuals. Both findings appear to be related in preeclamptic women, where the increased VEGF level is accompanied by the C allele of VEGFA. Thus, it is possible that the T allele associates with the maintenance of normal pregnancy and may confer a protective effect against the development of preeclampsia and is consistent with the concept of having the T allele and low VEGF levels among women with normal, uncomplicated pregnancies [31].

Probably adaptive: 936T allele; less adaptive: 936 C allele

6.4 HIF-2α/EPAS-1: high-altitude adaptive gene

It was recently shown that the gene encoding HIF-2α/EPAS-1 represents a key mutated gene in the adaptation of Tibetan populations at high altitudes. Although it is highly similar to HIF-1 and has the potential to bind and mediate many of the same genes as HIF-1, its biological actions in response to hypoxia are distinct from those of HIF-1. By now, several of these HIF-2 mediated processes have been implicated in the human response to high-altitude exposure including erythropoiesis, iron homeostasis, metabolism, and vascular permeability, which are perturbed in preeclampsia. HGB-decreasing allele of EPAS1 is under very strong positive selection in Tibetans and is strongly associated with Hb, red cell count, and hematocrit. Although there is no association between HIF-2α/EPAS-1 polymorphisms and preeclampsia in the literature, few studies found up-regulated expression of HIF-2α in preeclampsia. In earlier work, we discussed the association between EPAS1 polymorphisms and preeclampsia. Based on the strong positive association signal of adaptation in Tibetans, I emphasized on the role of EPAS1 in preeclampsia, and suggest and for the first time that the mutated EPAS1, has to be considered as a major player for placental adaptation in normal pregnancy and preeclampsia.

Further experimental studies are needed to confirm the biological function of EPAS-1 in normal pregnancy [3, 32–34].

6.5 Methylenetetrahydrofolate reductase (MTHFR) (rs1801133, A222 V, C677T)

The effects of MTHFR on preeclampsia are of great interest to researchers in the field. MTHFR plays a key role in homocysteine metabolism. Tibetans have an increased frequency of the homocysteine-decreasing allele of rs1801133 at the MTHFR locus more than other individuals from Eastern Asian ancestry. The homocysteine level in Tibetans is even lower than in Han, who lives at the same highlands of Tibet's but for shorter period. This renders them to be less adaptive compared to Tibetans. On the other hand, several studies found significant association at this locus with PE. The gene promoter of MTHFR is found to be hypermethylated in preeclamptic women, and this results in a high level of homocysteine. The same can be found in high-altitude sickness as a result of mal adaptation [35, 36].

7. Adaptive or less adaptive

Looking for adaptive variants is the "half-full" interpretation for the prediction of a multiple disorder like preeclampsia. The genetic scan can include adaptive genes and polymorphisms, their functional importance, i.e., effect on enzyme activity and production, their protective effect, i.e., protective from/at risk of cardiovascular disorders, pulmonary edema, thrombosis, thrombophilia, retinopathy, etc.

Earlier predictive markers for preeclampsia are believed to be in the first trimester, but it could be earlier even before the pregnancy period. Exercise stress test can be done to measure the levels of oxidative stress during and after the exercise to predict the possible response of the body. Allele and genotype frequencies of adaptive variants before the pregnancy, gene expression during and after the exercise can also be studied. In short, women who are less adaptive in their exercise have the potentials to develop preeclampsia. The same in high-altitude adaptation, women who suffer on ascent to high altitude are more likely to be preeclamptic.

"Adaptive or less adaptive" can be simply the final result of genetic tests that predict the disease, recurrence, and possible complications. DNA analysis for potential genetic markers may serve to screen for the risks of preeclampsia/eclampsia and other adverse pregnancy outcomes. Those with positive adaptive status are considered to be at decreased risk of developing preeclampsia. Certain genetic polymorphisms are attributed with certain adverse pregnancy outcomes.

8. Ischemic reperfusion stress: adaptation or insult

In 1964, Martin et al. show that maternal blood flow of spiral arteries in the intervillous space is intermittent in all normal pregnancies, and they wondered if this intermittency is a mechanism for regulating maternal placental blood flow. In preeclampsia, it is believed that the process of intermittent placental perfusion (ischemic/reperfusion) secondary to deficient trophoblast invasion is a key intermediary step in the pathogenesis of preeclampsia.[37, 38].

However, the process of ischemia and reperfusion is well known to be used in clinical settings in the area of coronary heart diseases to protect the heart from the harmful effects of subsequent, prolonged ischemia by the exposure of tissues to certain degrees of intermittent periods of hypoxia and reoxygenation. The process

termed ischemic preconditioning has been demonstrated in patients with cardiovascular disease as well as in many other organs. The process, termed ischemic preconditioning, has been demonstrated in patients with cardiovascular disease as well as in many other organs. Recent evidence suggests that there are actually two distinct types of protection afforded by preconditioning, acute and delayed preconditioning. The protective effects of acute preconditioning are protein synthesis independent in short intervals, while the effects of delayed preconditioning require protein synthesis in tissues subjected to prolonged ischemia. Delayed preconditioning appears to be an adaptation response that is dependent on altered gene expression as well as the synthesis of new proteins, including NO pathway.

It has been postulated that hypoxic preconditioning might occur normally in placentae that develop at high altitude. Laboring placentae at 3100 m have little or no oxidative stress at the time of delivery, suggesting greater resistance to ischemia-reperfusion. Unlike pregnancies at sea level subjected to labor display evidence of oxidative stress. In fact, exercise can be considered as a form of remote ischemic conditioning, in which the stimulus is distant from the organ being protected. Remote ischemic conditioning has been termed "exercise in a device," especially suited for patients who are unable or unwilling to work out [39–41].

The question is can we consider the intermittency of maternal blood flow as a regulatory mechanism for natural hypoxic preconditioning that can occur in placentae from high altitude, and can it be the answer for the earlier question from the 1960s.

8.1 Genetics and ischemic preconditioning

Ischemic preconditioning reprograms the response to ischemic injury via transcriptional changes that resemble evolutionarily conserved responses to decreased blood flow and oxygen availability. The response to ischemia alters gene expression and induces cellular adaptations and hypoxia tolerance. One of the regulatory mechanisms is the genetic reprogramming through microRNAs. MiRNA-144 and -21 have been associated with ischemic preconditioning and normal pregnancy, and can be considered as adaptive miRNAs.

MicroRNA-144 is a circulating effector of remote ischemic preconditioning. Systemic release of microRNA-144 plays a pivotal role in inducing early and delayed cardioprotection with improved functional recovery and reduction in infarct size. Comparably, miRNA-144 was down-regulated in severe preeclampsia during the early stages of pregnancy, which supports the maladaptive nature of the disease.

***MicroRNA*-21** stimulates angiogenesis by inducing VEGF production. MiRNA-21 expression is required for local and remote ischemic preconditioning in multiple organ protection, including kidneys, heart, liver, and lungs. In sport genomics, several studies support the protective role of miRNA-21 as an important regulator of exercise adaptation and in the protection of many disorders including cardiovascular disorders. In normal pregnancy, miR-21 has been shown to enhance trophoblast proliferation and invasion via modulating the nodal signaling pathway, and involve in angiogenesis process positive regulator of VEGF-A and HIF-1α. Yet, the persistent of miRNA-21 angiogenic signal can be deleterious [42–46].

9. Structural adaptations of the placenta

The prominent histological changes represent the structural adaptations for placental ischemia, which creates a hostile environment for the preeclamptic placentae. A number of these histopathological changes have been described; namely placental

infarcts, increased syncytial knots, hypovascularity of the villi, increased cytotrophoblastic proliferation, thickening of the sub-trophoblastic basement membrane, obliterated enlarged endothelial cells in the fetal capillaries, and atherosis of the spiral arteries in the placental bed. The volume of the intervillous space and the terminal villi are also decreased in proportion to the degree of preeclampsia. Some of the histological features like syncytial knots, cytotrophoblastic proliferation, thickening of sub-trophoblastic basement membrane, and hypovascular villi were observed in the placentae of normotensive women in varying degrees yet within normal limits [47].

Placental infarcts are small yellowish-white deposits of fibrin (a fibrous protein) of the placenta caused by the inadequate blood supply. They occur normally in the placenta as pregnancy progresses, and account about 25–30% of term normal pregnancies. The fetus usually is not affected by infarction of the placenta, unless the process is extensive. However, infarcts are found in nearly all cases of moderate or severe PIH. They are strongly associated with pregnancy-induced hypertension (PIH) and with growth-restricted babies. Moreover, several studies have found a direct correlation between the degree of PIH and the amount of infarction of the placenta. At molecular levels, plasminogen activator inhibitors (PAI-1/PAI-2), which regulate fibrinolysis, could be responsible for the very high levels of fibrin deposition in the intervillous space and the placental infarction observed in these pregnancies. The hypofibrinolytic genotypes 4G/4G and A/A of the PAI-1 gene are associated with the occurrence of mild preeclampsia. The insertion/deletion PAI-1 4G/5G polymorphism (rs1799889) was also found to have a significant association with preeclampsia [48, 49].

Acute atherosis is characterized by subendothelial lipid-filled foam cells, fibrinoid necrosis, and perivascular lymphocytic infiltration. This lesion is generally confined to non-transformed spiral arteries and is frequently observed in patients with preeclampsia. In early-onset preeclamptic patients, the polymorphisms in the regulator of G protein signaling 2 gene (RGS2) 3′UTR (C1114G, rs4606) of CG or GG genotype is more frequent in decidual spiral arteries in women with acute atherosis (resembling early stage of atherosclerosis). PIA-1, as an important regulator within the fibrinolytic system, has also been shown to be a risk indicator for venous and arterial thrombosis [50, 51].

Retroplacental hematoma (placental abruption) is having bleeding behind the placenta. This happens when the placenta starts separating prematurely due to bleeding and instability of uteroplacental vessels. The maternal MTHFR C677T polymorphism was found to be a risk factor for placental abruption. This agrees with the association of hyperhomocysteinemia with placental abruption [52, 53].

Syncytial knots: For oxygen requirement, the syncytium depends on the maternal blood flow to the intervillous space through the uteroplacental circulation. Reduced uteroplacental blood flow in hypertension may result in hypoxic damage to the syncytium. The damaged syncytium stimulates syncytial nuclear proliferation leading to syncytial knots formation. In an attempt to replace the degenerated syncytium, the cytotrophoblast cells undergo proliferation. Increased numbers of syncytial knots have been reported in placentae of pregnancies complicated by preeclampsia, probably to be induced by hypoxia. Syncytins 1 and 2 genes play a crucial role in trophoblast fusion stage of syncytial knot formation [47, 54].

10. The cross talk between syncytiotrophoblast and other remote organs

Throughout pregnancy, the cross talk between the placenta and other parts of the body is mainly relying on messages released from the syncytium into the

maternal circulation. There are extracellular vesicles often referred to as syncytiotrophoblast extracellular vesicles (STBEVs) due to their syncytiotrophoblast cell of origin. They are believed to play an important role both in normal and dysfunctional pregnancies. They are released in form of exosomes, microvesicles, and apoptotic bodies that carry many syncytiotrophoblast derived factors such as mRNA, miRNA, proteins, and lipids. This gives a potentially rich source of biomarkers in complications involving placental dysfunction [55, 56].

Vascular endothelial cells: In preeclampsia, there is an increased release of placental STBEVs into the maternal circulation. It has been suggested that release of factors from the placenta in response to ischemia results in endothelial dysfunction of the maternal circulation. As a result, an imbalance of anticoagulation and procoagulation forces is found in preeclampsia as increases in proteins of the coagulation cascade, proangiogenic and antiangiogenic imbalance resulting in high sflt-1 levels that inactivate VEGF function, increased adhesion cell molecules are also significantly elevated including VCAM-1, ICAM-1, and E-selectin. An example of angiogenic imbalance is the syncytial knots that are enriched with sFlt1 protein. At least 25% of the measurable sFlt1 in the third-trimester maternal plasma is bound to circulating placental microparticles. The free detached syncytial knots are loaded with sFlt1 protein and mRNA. These findings suggest that STBEVs may cause endothelial damage and contribute to the endothelial dysfunction [57].

Paranchymal organs: In general, the histological changes, mainly in eclamptic phase of preeclampsia, are hemorrhagic and thrombotic in nature. They are found in the main parenchymatous organs: liver, kidneys, placenta, brain, and adrenals. The liver lesions, when present, take the form of irregular, focal subcapsular, and intraparenchymal hemorrhages. On histologic examination, there are fibrin thrombi in the portal capillaries and foci of hemorrhagic necrosis. The kidney lesions are variable. The glomeruli show marked swelling of endothelial cells, amorphous dense deposits on the endothelial side of the basement membrane, and mesangial cell hyperplasia. Immunofluorescent studies show an abundance of fibrin in glomeruli. In advanced cases, fibrin thrombi are present in the glomeruli and capillaries of the cortex. If widespread and severe, these thrombi may produce complete destruction of the cortex in the pattern referred to as bilateral renal cortical necrosis. The brain may have gross or microscopic foci of hemorrhage along with small vessel thrombosis. Similar changes are often found in the heart and the anterior pituitary [58].

At molecular level, circulating STBEVs can directly affect these remote organs (**Figure 2**). An example of this is the STBEVs uptake by the primary human coronary artery endothelial cells and the transfer of placenta specific miRNAs from STBEVs inside these recipient cells. The transferred miRNAs were functional, causing a downregulation of specific target genes, including the PE associated gene fms related tyrosine kinase 1 (FLT1). This suggests the ability of the placenta for endothelial reprogramming that may underlay the increased risk of cardiovascular disease reported for women with preeclampsia later in life. In kidneys, renal ischemic preconditioning up-regulates the expression of microRNA-21 in serum extracellular vesicles of exosomes in kidney and remote organs. This results in decreased apoptosis and reduced proinflammatory cytokines production in multiple organs including kidneys, heart, liver, and lungs. Another example is the role of STBEVs in thrombi formation. STBEVs released from preeclamptic placenta exhibit increased procoagulant tissue factor activity. Tissue factor is the primary initiator of coagulation in vivo. The increased numbers of circulating STBEVs in the blood of women with preeclampsia, along with the greater expression of tissue factor on preeclampstic STBEVs would be expected to comprise a substantial intravascular pro-thrombotic stimulus. A majority of deep venous thrombosis

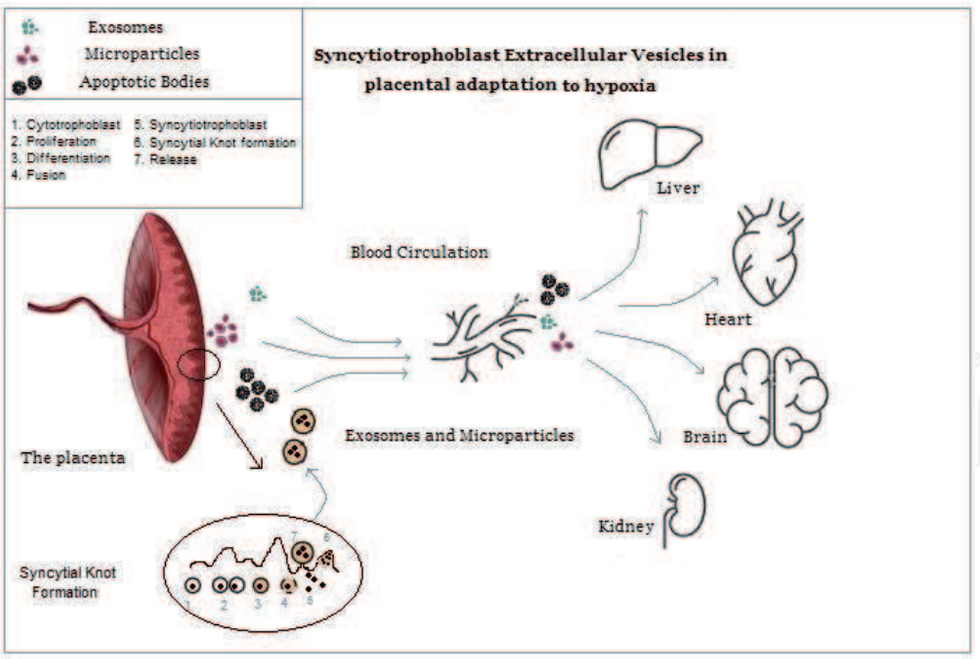

Figure 2.
The role of syncytiotrophoblast extracellular vesicles (STBEVs) in the cross talk between the placenta and other tissues and organs include exosomes, microvesicles, apoptotic bodies, and syncytial knots. Adequate blood flow from a limited number of EVs are shed from the placenta into the maternal circulation, while increased number of STBEVs are shed from preeclamptic placenta. The cargo of STBEVs including microRNAs, mRNAs, proteins, lipids, and glycans may be "planned" by the placenta. This cargo controls gene expression in vascular endothelial cells and other tissues and organs. STBEVs contents and deportations are controlled by the placental hypoxia. In preeclampsia, high levels of hypoxia lead to reduce syncytin-1 expression, and thus increased syncytial knots deportation [64].

occur within the valve pockets of deep venous valves that are exposed to "periods of stasis" and low oxygen levels, resembling the I/R oxidative stress. Venous valves have adapted to this phenomenon by expressing higher levels of anticoagulants thrombomodulin and endothelial cell protein C receptor, which are both decreased in preeclampsia [59–61].

To conclude, the high degree of concordance between placental lesions and gene expression across different subtypes of preeclampsia, reflects the importance of appropriate communication in successful pregnancy [62, 63].

11. Evolutionary steps: from preeclamptic cells, cancer to adaptive cells

Preeclamptic cells are genetically late compared to cancer cells, and this is probably the reason behind their protection from cancer. For example, angiogenesis are balanced in normal cells, and shift to the lift in preeclampsia and to the right in cancer cells and adaptive cells. The shift of preeclamptic cells from the left to the right can take longer time (**Figure 3**). Longer prospective studies show that preeclamptic women can lose their protective advantage by time, while adaptive individuals, according to the evolutionary steps, can show better protection than preeclamptic cells [65]. Normal cells can avoid cancer and jump to adaptive status by gradual adaptation or preconditioning. This is why normal multiple pregnancies are naturally protected from cancer and other oxidative stress disorders, due to their intermittent exposure to hypoxia that act as natural ischemic preconditioning. Accordingly, both preeclamptic cells and adaptive cells are protective against cancer, but for different reasons. In a different context, cancer cells, due to their high cellular turnout and high evolutionary rate, have a higher ability to gain mutations,

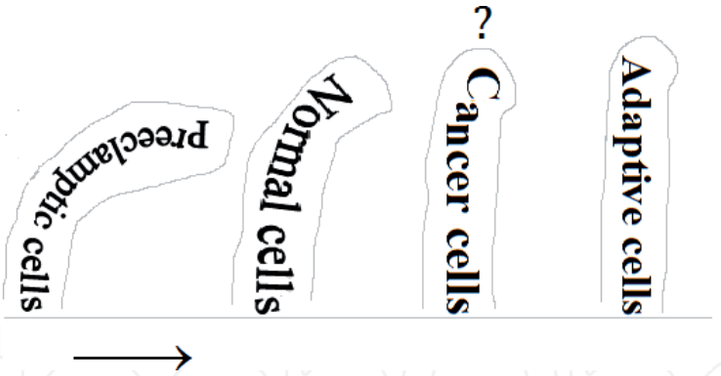

Figure 3.
Evolutionary steps from preeclamptic cells, normal cells, cancer cells, and adaptive cells.

and thus have a high probability for adaptive mutations. This can be used to study the protective function of adaptive variants in pregnancy and preeclampsia under different stressful conditions.

12. Conclusion

Future genetic studies are required for assaying additional adaptive variants near the candidate, HIF-targeted and -regulatory genes for testing functionality, and verify the existence of natural selection [9]. Such studies present a novel and relatively unexplored approach that enable the normal cells to adapt to their scarce microenvironment to the highest possible extent. No matter of the reasons that lead to preeclampsia, which are probably different, the advanced integrated biological system of genetic and epigenetic adaptive polymorphisms can "vaccinate" the body against the detrimental consequences and complications of the disease, and can reflect the ability of the body for survival and recovery. Methods of inducing natural adaptive mechanisms, like in ischemic preconditioning, has been attempted in clinical practice in the area of coronary heart disease in an attempt to limit the injury caused to the heart via ischemia and reperfusion injury. Such injury would occur when a patient has an acute myocardial infarction followed by reperfusion by either percutaneous coronary intervention or thrombolysis. Although, placental preconditioning was suggested to occur as an adaptive response to the hypobaric hypoxia at high altitudes, the area of placental preconditioning in clinical practice is yet to be explored. At molecular levels, adaptation to hypoxia can enhance the ability of the placenta to acquire genetic adaptive experience resulting in a stress relief, protection, and probably recovery in subsequent pregnancies. The messages released from the placenta into the maternal circulation transfer the genetic experience throughout the body. It can dramatically modify the histological picture in the placenta and other remote organs, and modulate the function of these organs.

Conflict of interest

The author declares no conflict of interest.

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