Novel therapies for the prevention and treatment of preeclampsia and eclampsia

Technology Opportunity Assessment

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# Acronyms and abbreviations

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<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADMA</td>
<td>asymmetric dimethylarginine</td>
</tr>
<tr>
<td>Ang II</td>
<td>angeotensin II</td>
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<tr>
<td>AT1</td>
<td>angiotensin type 1 receptor</td>
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<tr>
<td>CO</td>
<td>carbon monoxide</td>
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<tr>
<td>CoQ10</td>
<td>coenzyme Q10</td>
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<tr>
<td>CSE</td>
<td>cystathionine g-lyase</td>
</tr>
<tr>
<td>H₂S</td>
<td>hydrogen sulfide</td>
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<tr>
<td>L-NAME</td>
<td>NG-nitro-L-arginine methyl ester</td>
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<tr>
<td>LRS</td>
<td>low-resource setting</td>
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<tr>
<td>NO</td>
<td>nitric oxide</td>
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<tr>
<td>NOS</td>
<td>nitric oxide synthase</td>
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<tr>
<td>PE</td>
<td>preeclampsia</td>
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<tr>
<td>PE/E</td>
<td>preeclampsia and eclampsia</td>
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<tr>
<td>RUPP</td>
<td>uteroplacental perfusion</td>
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<tr>
<td>17 OHP</td>
<td>17α-hydroxyprogesterone caproate</td>
</tr>
<tr>
<td>sFlt-1</td>
<td>soluble Fms-like tyrosine kinase 1</td>
</tr>
<tr>
<td>2-ME</td>
<td>2-methoxyestradiol</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Statement of need

Preeclampsia (PE) is a life-threatening disorder that only occurs during pregnancy, childbirth, and the postpartum period. It is characterized by high blood pressure (hypertension) and protein in the urine (proteinuria) after 20 weeks of gestation. Convulsions (fits) with signs of PE indicate eclampsia, although occasionally convulsions occur in the absence of hypertension with proteinuria.

Preeclampsia and eclampsia (PE/E) are among the leading causes of maternal death and disability worldwide. The World Health Organization (WHO) estimates that PE/E account for at least 16% of maternal deaths in settings with limited resources that lack the skilled providers and facilities required for prevention, identification, and management of the condition. In most countries, PE/E rank second only to hemorrhage as a specific, direct cause of maternal death. The risk of PE/E varies greatly depending on where a woman lives; the risk that a woman in a low-resource country will die of PE/E is approximately 300 times greater than that for a woman in a high-resource country.

Current WHO guidelines recommend two preventive interventions during pregnancy: (1) Administration of low-dose acetylsalicylic acid (aspirin, 75 mg) beginning before 20 weeks of pregnancy, preferably as early 12 weeks, for the prevention of PE in women at high risk of developing the condition and (2) Administration of calcium supplementation during pregnancy (at doses of 1.5–2.0 g elemental calcium/day) to women living in areas where dietary calcium intake is low, especially in those women at high risk of developing PE (WHO, 2011). These interventions are supported by clinical evidence which has shown that their use is associated with a reduction in the incidence of PE in women identified as high risk. The effectiveness of these treatments is limited, low dose aspirin only reduces the risk of PE by 17% and, while calcium supplementation does reduce the incidence of mild PE, it does not affect the risk of severe PE, eclampsia or admission to intensive care for at risk women. An additional complication of current preventative treatment practices is that screening by maternal history risk factors for PE has a low detection rate (around 30%) leading to underutilization of these treatments. In recent years, advances have been made in identifying biomarkers that may be used before the 20th week of gestation to more effectively identify women who are likely to develop PE and can be targeted for interventions to prevent onset of the condition. A number of these biomarkers are reviewed in a previous PATH report, Candidate Blood-based Biomarkers for Preeclampsia Testing. Unfortunately, although currently available preventive interventions can reduce the incidence of PE, they do not halt the development of this condition for all women at risk; furthermore, there are currently no treatments available to prevent the progression of mild to severe PE and eclampsia.

* Women are regarded as being at high risk of developing pre-eclampsia if they have one or more of the following risk factors: previous preeclampsia; diabetes; chronic hypertension; renal disease; autoimmune disease; and multiple pregnancies. This is not an exhaustive list, but can be adapted/complemented based on the local epidemiology of pre-eclampsia. (WHO, 2011)

† Studies are ongoing to evaluate effectiveness of lower doses of calcium and administration of calcium antepartally to women at risk.
Once a diagnosis of severe PE or eclampsia is made, current treatments are only palliative, reducing the incidence and severity of the condition/disorder and progression to eclampsia in cases of severe PE. The only known cure for PE is the delivery of the fetus and placenta, although women may develop PE/E in the postpartum period. Antihypertensives and anticonvulsants may be administered to decrease the pregnant/postpartum woman’s blood pressure or reduce the risk of eclamptic seizures, but these interventions do not correct the underlying disease. The pathogenesis of PE is a heavily debated and controversial topic. No single cause has been identified, although a number of theoretical pathways have been proposed based on observations of the unique physiological and biochemical symptoms expressed in preeclamptic women. Studies are currently under way on promising treatments that may address the underlying issues leading to PE, potentially halting the progression of this disease before it becomes a risk to the health of the woman and her fetus/baby.

Given the limitations of available prevention and treatment modalities, there is a clear need for interventions that address the underlying pathogenic mechanisms. Fortunately, a significant number of novel therapies for prevention and treatment of PE are currently under investigation. If proven to be safe, efficacious, and economical, these therapies may be used in combination with early identification of PE risk factors to prevent the onset or progression of the condition in women living in low-resource settings (LRS), reducing the need for emergency care during the later stages of pregnancy or in the postpartum period and improving maternal and perinatal outcomes for women at risk of developing the condition.

**Technology solutions landscape**

The pathogenesis of PE is still a very controversial and complex area of research. The root cause of the disorder is thought to involve the maternal spiral arteries that provide the blood supply to the placenta and the regulation and exchange of vasoactive compounds transferred at the maternal/placental barrier. Through review of the scientific literature, a large number of animal model and human clinical studies that investigate therapies for prevention or treatment of the underlying causes of PE have been identified. In a search of publications from 2008 to 2013, 42 different therapies characterized into seven categories (statins, anticoagulants, vascular response mediators, anti-inflammatory, angiogenesis/spiral artery remodeling, other) for the prevention of preeclampsia were identified from journal articles, patents and conference proceedings. The majority of these therapies were in the early stages of research and only presented results in animal models. The therapies covered a wide pharmaceutical range. Many studies investigated the use of nutritional supplements as anti-oxidants and immunosuppressants. A number of therapies were designed to address the hypertension observed in PE by enhancing the natural vasodilatory pathways that are observed to be inhibited by PE. Some proposed therapies used antibodies or proteases to decrease the concentration of PE biomarkers in the maternal blood steam and other therapies were designed to supplement maternal biomarkers that show decreased expression in women at risk of PE.

The scope of this landscape was narrowed to showcase the most advanced novel therapies that are suitable for LRS. The therapies selected for further investigation from the initial literature survey could be orally administered, and are likely to be low in cost. (e.g., small molecule drugs, generics in particular,
Table 1 summarizes the potential advantages and disadvantages of the selected therapies.

Table 1. Pros and cons of reviewed therapies.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Pros</th>
<th>Cons</th>
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<tbody>
<tr>
<td>2-methoxyestradiol (2-ME)</td>
<td>Simple, natural hormone molecule. Shows improved placentation in PE models.</td>
<td>Currently under investigation only as an anticancer agent. May need to be delivered within a specific time range to provide a benefit.</td>
</tr>
<tr>
<td>Coenzyme Q10 (CoQ10)</td>
<td>Simple, nontoxic, stable nutritional supplement. Shows promise as an antioxidant/anti-inflammatory agent.</td>
<td>Limited studies.</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Simple, nontoxic, stable nutritional supplement. Complementary with calcium supplementation. Can show significant reduction in PE risk.</td>
<td>Dietary studies are complex and may have hidden cofactors or population specificity. Additional qualified studies are needed.</td>
</tr>
<tr>
<td>Carbon monoxide therapy</td>
<td>Good reduction of PE risk at low levels of exposure. May be beneficial during later stages of gestation or after PE diagnosis.</td>
<td>Toxic gas. Not currently perceived as a drug. Difficult to deliver. Associated with smoking tobacco.</td>
</tr>
<tr>
<td>L-arginine</td>
<td>Simple, nontoxic, stable nutritional supplement. Supports nitric oxide synthesis.</td>
<td>May need to be delivered during a very specific gestational stage.</td>
</tr>
<tr>
<td>Hydrogen sulfide therapy (H₂S-generating compounds)</td>
<td>Simple compound. Could have potential if more drug compounds are discovered. May act on multiple pathways (vasodilation and angiogenesis).</td>
<td>Potentially toxic. Current therapeutic drug compounds are limited and experimental.</td>
</tr>
<tr>
<td>Statins (pravastatin)</td>
<td>Improves angiogenesis and vascular reactivity in PE models. Preclinical study currently under way in humans.</td>
<td>Pregnancy category X. Must undergo testing for teratogenicity and safety in pregnant women. Potentially high cost.</td>
</tr>
</tbody>
</table>

‡ The United States Food and Drug Administration classifies various drugs used in pregnancy into the five categories below.

**Category A:** Controlled studies in pregnant women have not demonstrated any risk to the fetus in the first trimester. These drugs are considered to be relatively safe for use during pregnancy.

**Category B:** No known specific risks are associated with use of the drug in pregnancy, but controlled human studies are lacking. If adverse effects were shown in animal reproduction studies, these were not confirmed in controlled human trials.

**Category C:** Studies in women and animals are not available, or studies in animals have revealed adverse effects on the fetus. Most new drugs fall into this category. These drugs should be given only if the potential benefit justifies the potential risk to the fetus.

**Category D:** These drugs have shown a definite fetal risk in controlled human trials. However, their use may be necessary during pregnancy, and a risk-benefit assessment needs to be considered for the use of these agents.

**Category X:** These drugs have shown a definite risk to the fetus, and their use is contraindicated because the potential risks to the fetus outweigh the potential benefits.
For simplicity, we will discuss these therapies based on the proposed pathogenic mechanisms of PE that they address: aberrant placentation, vasodilator dysfunction, and vasoconstrictor regulation.

**Aberrant placentation**

In a healthy pregnancy, the maternal spiral arteries that provide blood to the placenta are remodeled through processes involving the invasion of fetal cells (trophoblasts) and maternal angiogenesis. This process is inhibited by inflammation, immune response, and incomplete fetal cell invasion in women who develop PE. Extensive infiltration of activated neutrophils is noted in the blood vessels of preeclamptic women as compared to pregnant women without the condition. These neutrophils produce reactive oxygen species that can induce increased arterial contractile reactivity, leading to hypertension.\(^9\)

17α-hydroxyprogesterone caproate

Anti-inflammatory agents delivered early in pregnancy may act to decrease this detrimental immune response. 17α-hydroxyprogesterone caproate (17 OHP) is a form of progesterone used to prevent recurrent preterm birth that may also reduce maternal blood pressure through an anti-inflammatory pathway. When rats with PE-like hypertension, induced by a surgical reduction in uteroplacental perfusion (RUPP), were treated with 17 OHP, they showed a reduction in PE-like symptoms. RUPP rats treated with 17 OHP showed significantly lower increases in blood pressure as compared to the untreated RUPP group. Additionally, RUPP rats treated with 17 OHP expressed normal levels of tumor necrosis factor alpha α and interleukin 6, whereas untreated rats showed twofold to threefold increase in these inflammatory cytokines.\(^10\) This implies that 17 OHP may act as an anti-inflammatory agent to mediate hypertension in a rat model of PE.

2-methoxyestradiol

Appropriate development of the placental/maternal barrier requires the invasion of the uterine epithelia by fetal trophoblasts. Improper invasion or interference by the maternal immune system can lead to abnormal vascular development at the placenta. Studies have been conducted that show the administration of 2-methoxyestradiol (2-ME) can facilitate appropriate cytotrophoblast invasion in a mouse model of PE, resolving the PE-like symptoms.\(^11\) 2-ME is a hormone that is naturally found in maternal serum; reduced plasma levels of 2-ME at 11 to 14 weeks of gestation have been observed to correlate with a higher risk of PE.\(^12\) The observation of this deficiency in the first trimester indicates that 2-ME would need to be administered early, before the diagnosis of PE, to have a therapeutic effect.

Coenzyme Q10

Women living at high altitudes are at significantly greater risk for developing PE.\(^13\) This is thought to be due to oxidative stress and reduced uteroplacental blood flow caused by high-altitude hypoxia. These conditions can result in a maternal inflammatory response at the placental barrier expressed by increased lipid peroxidation which can be mediated with the antioxidant substance coenzyme Q10 (CoQ10), found
at lower levels in PE women. A reduced rate of PE was noted in pregnant women living at altitudes above 2,800 meters who received twice-daily supplements (100 mg) of CoQ10 beginning at 16 to 20 weeks of gestation. The preventive effects were modest but significant (14.4% incidence of PE in the treatment group vs. 25.6% in the untreated control group), but a more robust preventive effect may have been achieved by earlier intervention.

**Vitamin D**

The antioxidant effects of certain vitamins have been investigated as preventive therapies for PE. Although vitamins C and E have proven to be ineffective for prevention of PE, vitamin D supplementation shows promising results. Reduced serum concentrations of vitamin D have been noted in the early gestational stages of pregnancies that progress to PE, and recent studies have shown that maternal vitamin D sufficiency reduces the risk of severe PE by 40%. The immunosuppressive effects of vitamin D may help to guide proper placentaion by reducing oxidative stress, placental perfusion, and endothelial dysfunction in women at risk of developing PE. A study of the reported diet and medical records of 23,000 nulliparous women revealed a 27% reduced risk of PE in women taking daily supplements of 400 to 600 IU/d of vitamin D as compared to women taking no vitamin D supplements.

A recent review article on the role of vitamin D in PE suggests that early maternal vitamin D supplementation can significantly reduce the risk of PE. This review reports a protective efficacy of up to 34% due to vitamin D supplementation (pooled odds ratio of 0.66 and 95% CI 0.52-0.83, p=0.001) based on meta-analysis of four randomized clinical trials. Daily supplementation of 4,000 IU of vitamin D may be required to provide a beneficial concentration of vitamin D in the maternal circulation.

Because the preventive mechanism of vitamin D is thought to be active primarily during placental development, preventive supplementation must begin early in pregnancy, possibly before PE can be diagnosed at week 20 of gestation. There is also evidence that vitamin D supplementation in infancy may reduce the risk of PE in adulthood by up to 50%. Clinical safety trials have shown that vitamin D supplementation is safe during pregnancy, but WHO has not released an official recommendation for vitamin D supplementation of pregnant women, citing the need for more high-quality studies.

**Carbon monoxide**

An interesting paradox in the pathogenesis of PE is that pregnant women who smoke tobacco have a decreased risk of PE. This appears to be a function of the act of smoke inhalation rather than the tobacco itself and that the inhalation of carbon monoxide (CO) from tobacco smoke may play a critical role in this effect. CO is widely known as a toxic gas, and the controversial suggestion of intentional human dosing with CO carries significant health risks. However, it has recently been found that endogenously produced CO, present in all humans at very low concentrations, acts as a vasodilatory gasotransmitter. Reduced CO levels have been observed in pregnant women with PE, and reduced endogenous production of CO may be a risk factor for the development of PE. While the additional complications associated with cigarette smoking make this an unlikely treatment, studies on other methods of CO exposure have shown some PE preventive effects.
A study of data from 121,158 births in Ontario, Canada, compared the observed incidence of PE with the estimated exposure to ambient, environmental CO. Maternal residence was compared to CO measurements from local environmental monitoring stations, and environmental CO exposure showed an inverse trend with PE diagnosis in a linear dose-response relationship (see Table 2).

Table 2. Inverse trend of PE diagnosis with environmental carbon monoxide exposure.

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Average CO concentration (ppm)</th>
<th>Incidence of PE (%)</th>
<th>Crude odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1</td>
<td>0.01-0.16 ppm</td>
<td>2.32</td>
<td>Reference level</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>0.17-0.22 ppm</td>
<td>1.97</td>
<td>0.97 (0.87-1.08)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>0.23-0.28 ppm</td>
<td>1.59</td>
<td>0.78 (0.70-0.88)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>0.29-0.60 ppm</td>
<td>1.26</td>
<td>0.62 (0.55-0.70)</td>
</tr>
</tbody>
</table>

CO reduces pro-inflammatory mediators and may induce the enzyme heme oxygenase-1, which is essential to proper placentation. Testing in a mouse model for PE (with induced interuterine growth restriction) showed that exposure to low levels of CO (50 ppm) in a controlled atmosphere chamber can prevent fetal death through anti-inflammatory, anti-apoptosis, and pro-angiogenesis pathways. This protective effect depended on CO concentration and time/duration of exposure during gestation. All of the current studies on CO as a therapy for PE use inhalation as a delivery method, but new CO-releasing compounds are in the pharmaceutical pipeline that can deliver controlled amounts of CO orally. While this is a complex and controversial therapy, it may warrant further research and monitoring.

Vasodilator dysfunction

One leading theory of PE pathogenesis is that women who develop PE do not express sufficient vasodilatory responsiveness to counteract the vasoconstrictive signals produced by fetal development. Normal maternal vasodilation may be reduced by oxidative damage caused by fetal metabolites or inhibitors to vasodilatory pathways, such as the nitric oxide (NO) pathway. Many researchers are investigating therapies that restore the maternal vasodilatory response to reduce the elevated blood pressure symptomatic of PE.

L-arginine

NO is a gasotransmitter that relaxes vascular smooth muscle tissue and is involved in immune cell signaling and immune response pathways. It is produced endogenously by the metabolism of the amino acid L-arginine by nitric oxide synthase (NOS), but this synthesis pathway may be inhibited by methylarginines such as asymmetric dimethylarginine (ADMA). ADMA is found at high concentrations in amniotic fluid and may be the cause of reduced synthesis of NO in women with PE.

Elevated plasma levels of ADMA (about eight times the normal concentration) in pregnant rats can be induced by auditory stress. This reduces endogenous NO production and produces a PE-like increase in blood pressure. When these stressed rats were provided oral supplements of L-arginine (21 mg/kg/day),
ADMA levels returned to control levels. The blood pressure of the treated rats, while still elevated, decreased significantly from the level in the untreated, stressed rats.

Dietary supplementation with L-arginine has been investigated as a therapeutic to maintain normal NOS activity in women at risk of PE. In a study of pregnant women with previous experience with PE or PE in a first-degree relative, women supplemented with 13.2 g L-arginine/day, in the form of medical food bars, showed a significantly reduced risk of PE versus the control groups. An interesting finding was that L-arginine had no benefit if treatment started after 24 to 28 weeks of gestation or after PE had been diagnosed. This reveals the complexity of PE preventive therapies where the pathogenesis of the condition/disorder is directly linked to gestational stage and early interventions need to be prioritized.

**Type-5 phosphodiesterase inhibitor**

Other therapeutics have been tested to restore proper NO activity in PE women. Sildenafil citrate (Viagra) is a type-5 phosphodiesterase inhibitor that potentiates the vasodilatory action of NO. Sildenafil has been observed to increase uterine blood flow in nonpregnant woman. PE-like symptoms such as hypertension, proteinuria, and intrauterine growth restriction can be achieved in rats through the administration of NG-nitro-L-arginine methyl ester (L-NAME), an inhibitor of NO production. When this rat model of PE received injections of sildenafil citrate (10 mg/kg) from day 7 to 19 of gestation, fetal parameters (number of live pups and pup and placental weight) were significantly improved and matched the values for the control group. Administration of sildenafil citrate decreased the hypertension induced by L-NAME, though not to the levels of the control group.

Escalating-dose-regimen studies (20 to 80 mg) with sildenafil citrate have been conducted in preeclamptic women between 24 and 34 weeks of gestation. Sildenafil did not prolong pregnancy duration but was well tolerated by the subject and fetus. Sildenafil citrate has also shown promise as a treatment for early-onset intrauterine growth restriction in humans.

**Hydrogen sulfide**

NO and CO are not the only gasotransmitters associated with the pathology of PE. Hydrogen sulfide (H2S) is another gas which while toxic at high concentrations can have therapeutic effects at low levels. H2S is produced endogenously by the enzyme cystathionine g-lyase (CSE) and is involved in angiogenic and vasodilatory pathways. Reduced levels of H2S in pregnant women have been identified as a potential PE biomarker where a reduction in the activity of CSE may result in abnormal placentation and placental angiogenesis. The high concentration of H2S-forming organic polysulfides may be the inspiration for previous studies of garlic consumption for the prevention of PE, which is not considered significantly supportive by WHO. Orally delivered H2S-releasing compounds are currently under development as therapeutics for cardiovascular disorders, and the development of these pharmaceuticals would greatly improve the feasibility of H2S therapy.

Pregnant mice with inhibited CSE activity have been used as models for PE. When these mice are dosed with a slow-releasing H2S-generating compound (4-methoxyphenyl)morpholino-phosphinodithioic acid,
elevated levels of the PE biomarkers soluble Fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin are reduced and normal fetal growth is restored in treated mice. Furthermore, in vitro studies of human placental cell models of PE show improved angiogenesis following dosing with the H$_2$S-producing compound sodium hydrosulfide.

**Vasoconstrictor regulation**

As the fetus develops, it produces many metabolically active biological molecules that are removed from the fetal blood supply and transferred to the maternal bloodstream through the placenta. Among these molecules, vasoconstrictive hormones (angiotensin II [Ang II], epinephrine, or norepinephrine) are not observed at elevated levels in the preeclamptic state, and yet increased vasoconstriction-related hypertension is symptomatic of PE. Consequently, it is thought that the hypertension in PE may be the result of increased contractile response of the maternal vasculature, induced at normal levels of vasoconstrictive hormones. Maternal arteries at the placental barrier that are not sufficiently remodeled by trophoblast invasion may be more reactive to vasoconstrictive compounds. Several therapies are currently under investigation to address the vasoconstrictive sensitivity of women with PE.

Studies of the arteries of normal and PE pregnant women have shown that arteries in PE women are significantly more reactive to Ang II. In nonpregnant individuals, angiotensin type 1 receptor (AT1) blockers are prescribed as antihypertensive agents and act to reduce the vasoconstrictive effects of Ang II. The AT1 blocker olmesartan reduced blood pressure in mice with pregnancy-associated hypertension. Additionally, the cardiac injury markers observed in the untreated test group were not observed in the treatment group. AT1 blockers, however, are not a good candidate as a preventive therapy of PE because they are contraindicated in pregnancy and lead to fetal birth defects.

**Statins**

Although statins are classified as pregnancy category X (possible human fetal risk), there has been recent interest in potential use of statins for the prevention of PE. Statins can reduce the extent of endothelial injury, oxidative stress, and angiogenic imbalance, which may be pathogenic mechanisms of PE. The statin drug pravastatin is of particular interest because it is the most polar of the statins, and this characteristic is believed to limit its transfer across the placenta. Human and animal data have not shown pravastatin to be teratogenic, and a clinical trial of this drug for the prevention of PE is currently (2014) being conducted in high-risk pregnant women.

Support for use of pravastatin as a preventive therapy for PE comes from studies using mice with sFlt-1-induced preeclamptic symptoms. A reduction in serum sFlt-1 was observed in mice receiving 5 mg/kg/d of pravastatin in drinking water compared to the untreated group. In response to the reduction in this anti-angiogenic factor, vascular reactivity improved in the treatment group. Another study of pravastatin in this PE-like animal model showed that statins may improve the endothelial NO synthase activity, restoring proper vascular reactivity. Further studies of pravastatin in the sFlt-1 mouse model have shown that 5 µg/day delivered by intraperitoneal injection can induce angiogenic growth and
ameliorate PE-like symptoms.\textsuperscript{46} Still, the classification of all statins as pregnancy category X will need to be removed before more advanced clinical trials can be conducted.

Summary

Because of the complex and controversial pathogenesis of PE, many different animal models are currently in use, each aiming to emulate human PE. All the stated therapies to prevent onset or progression of PE must be evaluated in relation to the animal model used, which makes comparison of experimental therapies very difficult. Ultimately, treatments will be evaluated by their performance in humans because only humans are at risk of suffering from PE/E. Studies in humans, particularly pregnant women, are difficult to interpret because the subjects are undergoing gestational changes throughout the study, and therapies that are effective at early stages of pregnancy may not show the same results when applied at later stages. The selection of subjects for human studies may also influence study comparison as there are numerous definitions of PE risk factors, and the rates of PE incidence vary between populations.

PE presents a uniquely difficult challenge for prevention and treatment. There are accepted behavioral and biological risk factors that can be used to identify women at high risk of developing PE, but many women will develop PE without expressing these factors. Some of these therapies (nutritional supplements) are safe for administration to all pregnant women to reduce risk and improve outcome, but others will only benefit women who are likely to develop PE (pravastatin, 17 OHP, 2-ME) and will need to be coupled with identification of risk. The current preventative therapies (aspirin, calcium) are only prescribed to women who express these risk factors. If PE risk can be specifically and consistently identified using PE-specific biomarkers, preventative therapies can be initiated early for all pregnant women with real risk of developing PE, maximizing efficacy and coverage.

The rise in interest in PE biomarkers should ultimately help in the identification and qualification of PE preventative therapies. Most of the therapies reviewed were identified by research on PE biomarkers, either by observed deficiencies in PE or as remediating factors for the production of PE biomarkers. With improved knowledge of the biochemical diagnostics of PE, future clinical trials of preventative therapies will be more meaningful and quantifiable. If these novel therapies can be developed to specifically address the mechanisms responsible for the expression of PE biomarkers used for the early and specific diagnosis of PE risk, these innovations can be coupled to specifically prevent the development of PE. More studies, particularly in humans, are required to prove the possibility of preventive treatment for PE.

The current WHO recommendation of low-dose aspirin and calcium supplementation have been shown to reduce the incidence of PE in at-risk women by up to 17\%,\textsuperscript{47} but even when available, these interventions are observed to be underutilized in LRS. The novel PE therapies reviewed here may prove to have additive preventative effects when used with the current recommendations or may even prove to have superior preventative potential or rates of use (due to simplified delivery, administration over a shorter period of gestational time). No treatments are available for women who are diagnosed with mild PE, and care for this condition is limited to increased monitoring of blood pressure and proteinuria to diagnose the transition to severe PE. These novel therapies may be able to address the pathology of this condition after
the diagnosis of mild PE, preventing the progression to severe PE/E and reducing the need for emergency care at later stages of pregnancy.

Among the preventive therapies reviewed in this landscape, several therapies stand out as particularly suitable for potential use in LRS. Vitamin D supplementation could be easily applied to the current recommendations of calcium supplementation and low-dose antiplatelet agents for women at risk for PE, particularly due to the complementary effect of vitamin D on calcium uptake. Current evidence suggests that vitamin D supplementation be started during the early stages of gestation to provide the greatest potential for benefit. WHO does not currently recommend vitamin D supplementation for PE, but additional clinical trials are suggested to build supporting evidence.

While many therapeutic drugs are contraindicated in pregnancy, the classification of all statin drugs—especially pravastatin—as pregnancy category X may not be justified, as current clinical safety trials may reveal. Pravastatin shows promise as a preventive drug for PE, potentially acting on several mechanisms of pathogenesis of the condition/disorder.

L-arginine is a safe and simple amino acid that could be incorporated into existing maternal nutritional supplementation programs to address several pathogenic mechanisms of PE related to NOS. CO has a significant influence on PE, most importantly in the later stages of gestation. Because it is perceived as a toxic gas, specific CO gas therapy is infeasible at this point in time, but orally delivered CO-releasing drugs are under development. Another gasotransmitter, H₂S, has a high potential for entering the market as a PE therapeutic. Currently, a number of experimental H₂S-releasing oral drugs are under investigation and have promise for therapeutic clinical trials.

**Investment opportunity**

More research is required to fully understand the pathogenesis and management of PE/E. All the therapies reviewed in this assessment are still in the early experimental stages and will require significant proof—and therefore time—before they can be recommended for preventing the development or progression of PE. It is important to closely follow the research on these therapies, and with strong results in human studies, those showing the most promise will likely advance to large-scale application.

While preventive use of calcium and low-dose antiplatelet agents, as recommended by WHO, can improve outcomes among women at high risk of PE, new interventions—such as the therapies reviewed here—may arise that have complementary preventive effects. These therapies may also prove to be valid alternatives to the aspirin/calcium recommendations if the preventive results are shown to be comparable or improved and are less difficult to administer.

There is a significant opportunity for investment in vitamin D supplementation for the prevention of PE. Maternal vitamin D supplementation is achievable in LRS and, due to the enhancement of calcium uptake when co-administered with vitamin D, it would be complementary with current calcium supplementation regimens. Vitamin D has been investigated in a number of human clinical studies and the results implicate
that supplementation may reduce the risk of PE. While WHO does not specifically recommend vitamin D supplementation for the prevention of PE, they suggest that rigorous randomized trials may provide the evidence needed to justify a recommendation. An investment in such a trial, where vitamin D supplements are provided to pregnant women with consistent PE risk factors over a distinct period of gestational time, is likely to yield meaningful data on the efficacy of this therapy. These data could be used to strengthen the current evidence and persuade WHO to change their stance and officially recommend vitamin D supplementation for the prevention of PE.

A research grant should be established to support a large-scale randomized clinical trial of vitamin D supplementation for the prevention of PE in pregnant women. The study should be designed to investigate PE-specific diagnostics (blood pressure, proteinuria, biomarkers) as primary study outcomes, which has not been the case for previous clinical studies. This is a unique opportunity for Merck and PATH and for maternal health research in general as this study could incorporate PE-specific biomarker tests to monitor the efficacy, providing data on PE biomarkers and the underlying pathology of PE. A large-scale clinical trial could provide direct support for vitamin D supplementation as a preventative therapy for PE and could be used to convince health care regulatory organizations to add this therapy to standard maternal care recommendations. Due to the vast potential scope of this research, funding for a large-scale randomized clinical trial of vitamin D supplementation as a preventative therapy for PE could be expanded by seeking support from multiple funding organizations. With a planning grant, PATH could leverage its experience in initiating and coordinating global health research to establish a consortium of maternal health stakeholders and organizations to:

- Determine what questions must be answered to validate vitamin D supplementation as preventative treatment.
- Engage researchers in PE pathogenesis and treatments and maternal nutrition.
- Publish a consensus paper outlining a large-scale clinical trial of maternal vitamin D supplementation for the prevention of PE, its goals, and a proposed implementation plan.
- Write research funding proposals to interested funders.

Supplementation with L-arginine also holds promise as a PE intervention for LRS. L-arginine is a simple amino acid nutrient that can address the NO pathways that may be specific to the pathogenesis of PE and may help to prevent the progression of this disorder. The studies that have been conducted show that the beneficial effect may depend on the gestational stage at which the supplementation is initiated. This time dependence can influence the interpretation of previous studies, and more consistent and conclusive results may be obtained from larger, more qualified studies. Studies on the biological effects of L-arginine supplementation in pregnant women with known PE risk factors conducted over controlled gestational stages may reveal more useful efficacy data. Due to the simplicity and safety of L-arginine
supplementation and the strength of the supportive evidence, investment in further studies is justified and could reveal L-arginine as an effective preventative therapy appropriate for use in LRS.

Many of therapies identified here are very promising, but require more evidence of efficacy and safety before significant investment can be recommended. Publications of research on these therapies should be closely monitored to reevaluate which preventative therapies have the greatest potential. Therapies for the prevention and treatment of PE have traditionally not garnered much priority in the PE continuum of care but they can greatly improve maternal health outcomes. Preventative therapies should be added as a new category of PE care to better facilitate incorporation into global maternal health. A therapy of particular interest is pravastatin, which shows promise as a PE preventative therapeutic but must overcome its status as a pregnancy category X drug. Current and future clinical trials of pravastatin in humans should be closely monitored for proven maternal and fetal safety and efficacy of PE risk reduction to determine if this preventative therapy is qualified for future investment.

The discovery of all the therapies currently under investigation has been closely related to the study of specific biomarkers for PE. New therapies can be used in conjunction with advanced biomarkers for PE. This would provide PE-specific preventive interventions in response to early diagnosis of PE risk factors.

Finally, there is no current therapy to prevent the progression of mild PE to severe PE. Novel therapies specific to the pathology of PE must be further studied. These specific therapies could ultimately be applied to women who are currently diagnosed with mild PE to improve or halt the progression of their condition, thus reducing the need for constant monitoring and for emergency care during later stages of pregnancy.
References


