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Is pravastatin a milestone in the prevention and treatment of preeclampsia?

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Introduction

Preeclampsia (PE) is one of the major disorders of pregnancy and it is considered to be one of the main causes of morbidity and mortality in pregnant women. It is a systemic vascular disorder which complicates 3%–5% of pregnancies and increases the risk for severe disorders and death in mothers, fetuses and neonates.

Abnormal implantation and placentation are of key importance for the development of PE. Angiogenic imbalance, i.e. an imbalance in anti- and pro-angiogenic factors together with local inflammation result in generalized vascular endothelial dysfunction leading to impaired vascular response to placentation.

An angiogenic imbalance seems to be of crucial importance for PE pathophysiology and it strongly correlates with disease severity and clinical manifestations of PE. It is characterized by the decreased production of vasodilating and angiogenic factors, the vascular endothelial growth factor (VEGF), placental growth factor (PlGF) and transforming growth factor- β (TGF- β) as well as overexpression and release of anti-angiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1), a VEGF antagonist and soluble endoglin (sEng) [1–3]. Another theory explaining the pathophysiology of PE claims that PE is linked to the decreased expression or loss of placental heme oxygenase-1 (Hmox-1)/carbon monoxide

(CO) activity. The Hmox-1 system is responsible for the anti-inflammatory and anti-oxidative mechanisms but it also negatively regulates the anti-angiogenic factors. The impairment of this endogenous protective system results in endothelial damage and can contribute to the maternal endothelial dysfunction [4]. Abnormal placentation resulting from endothelial dysfunction, in turn, leads to the emergence of clinical manifestations, including organ failure (Figure 1).

PE may lead to complications, both short- and long-term, afflicting the mother and the fetus. Early complications observed in pregnant women include seizures, stroke, intracranial bleeding, renal failure, hepatic failure and hemolysis. A history of PE predisposes to future hypertension, renal disease, ischemic heart disease, stroke and premature death. The impact of PE on the course of pregnancy may include placental abruption or disseminated intravascular coagulation. PE may also affect the fetus leading to intrauterine growth restriction, chronic and acute hypoxia, short- and long-term consequences of prematurity or even fetal death *in utero*. Children from mothers with PE are at a higher risk for arterial hypertension, cardiovascular disease and metabolic disease in later life [5, 6].

Numerous studies have been conducted for several years on the development of effective methods to prevent PE. The results of a meta-analysis published in 2014 indicate that low-dose aspirin treatment in pregnant women resulted in a small but significant reduction in the risk of PE and other complications due to impaired placentation. However, to reduce the risk, the treatment should be initiated not later than 16 weeks of gestation [7]. There is also interest in low-molecular-weight heparin (LMWH) to prevent placenta-mediated pregnancy complications, including PE. However, the data concerning its efficacy are conflicting.

Despite recent advances in the prevention and treatment of PE, in severe PE, induced labor and delivery of the placenta remain the only effective method used to prevent serious maternal complications. Such an approach, however, is usually associated with premature delivery and complications of prematurity in the newborn.

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Figure 1: Schematic diagram of preeclampsia pathomechanism model and pleiotropic effects of statins which contribute to their therapeutic effect on preeclampsia.

HO-1/CO=Heme oxygenase-1/carbon monoxide, eNOS=nitric oxide synthase, ROS=reactive oxygen species, sFlt=soluble fms-like tyrosine kinase-1, sEng=soluble endoglin, VEGF=vascular endothelial growth factor, PIGF=placental growth factor, TGF- β =transforming growth factor- β .

Over the past several years, there have been more studies focused on the pathophysiology of PE and their results promise the development of treatments targeting the causes of PE.

The pathophysiology of preeclampsia and its association with cardiovascular disease

Earlier hypotheses for the pathogenesis of PE did not allow its full elucidation but now as PE has become the subject of extensive research carried out in many centers worldwide, more is known about its pathophysiology.

Over the last years there has been a growing interest in the association between PE and cardiovascular disease. The underlying mechanism of both conditions involves vascular endothelial dysfunction with endothelial inflammation. There are a number of risk factors shared by PE and cardiovascular disease, such as obesity, a history of hypertension, impaired vascular epithelial function, insulin resistance, diabetes and dyslipidemia [8]. A common pathophysiology has been proposed for gestational hypertension (GH), PE and cardiovascular disease.

The association between a history of GH and the risk of future cardiovascular disease is most likely related to the risk factors preceding pregnancy and pregnancy has been described as a “stress test” for future cardiovascular disease. According to another hypothesis, PE-triggered metabolic stress may cause vascular injury, thus contributing to the development of cardiovascular disease [9–11].

The risk of future cardiovascular disease, stroke and chronic kidney disease is higher in women with a history of PE [9, 11, 12]. The American Heart Association in their latest guidelines [13] included a history of GH as a risk factor for cardiovascular disease. The risk for ischemic heart disease is increased 2-fold, for stroke nearly 2-fold and for venous thromboembolism 1.5-fold. Also the overall mortality after PE was increased [14].

Statins

Statins are a class of active substances that lower the level of low-density lipoprotein (LDL) cholesterol in the blood by competitively inhibiting 3-hydroxy-3-methylglutaryl-coenzyme reductase (HMG-CoA), which is the enzyme of key importance in the process of endogenous cholesterol synthesis. Mevastatin was the first statin drug

isolated from the mold *Penicillium citrinum* by Akira Endo in 1971. Other statins followed, both natural (lovastatin, pravastatin and simvastatin) and synthetic (atorvastatin, fluvastatin and rosuvastatin). Used in the treatment of cardiovascular disease, statins are nowadays among the most commonly prescribed drugs worldwide. Apart from their effect on LDL cholesterol, statins also reduce the level of total cholesterol and increase the level of high-density lipoprotein (HDL) cholesterol. Also, numerous clinical studies have confirmed the multiple therapeutic benefits resulting from lipid-independent or pleiotropic effects of statins [15].

Pleiotropic effects of statins

The multiple cholesterol-independent effects of statins and a broad spectrum of their pharmacological activities are associated with their huge therapeutic potential.

Clinical trials have demonstrated that statins improve endothelial dysfunction by protecting vascular endothelium and stimulating its regeneration. The antioxidant action of statins involves increasing the density of receptors for endothelial nitric-oxide synthase (eNOS), activation of eNOS and modulating eNOS mRNA stability. The synthesis of NO which has antithrombotic and vasodilating activities is of key importance for the protection of vascular endothelium. The anti-oxidative effect is also associated with a decreased production of reactive oxygen species (ROS). This effect prevents the formation of free radicals and the oxidation of lipids, including the formation of cytotoxic lipid fractions within LDL, very-low-density lipoprotein (VLDL) and HDL.

Statins improve the regeneration of vascular endothelium by increasing the viability of endothelial progenitor cells and their release from the bone marrow and stimulating the migration toward the site of injury. By this mechanism, angiogenesis is promoted at the sites of ischemia [16].

Also, statins have been shown to quench the inflammatory response and reduce endothelial inflammation as well as stabilizing plaque [17].

The anti-inflammatory action of statins results from their impact on different mechanisms of the immune response. Numerous trials in patients with cardiovascular disease and increased expression and blood levels of inflammatory markers and mediators such as C-reactive protein (CRP), L-, E- and P-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) have demonstrated that statins decrease the expression of adhesion molecules and reduce blood

levels of CRP thus preventing atherosclerosis progression, endothelial dysfunction and prothrombotic processes.

Additionally, statins may increase the expression of Hmox-1, the enzyme with anti-inflammatory and antioxidative properties. Upon stimulation, Hmox-1 statins inhibit sFlt-1 and sEng and directly improve endothelial dysfunction by reducing the secretion of sFlt-1 and sEng [18]. The regulation of sFlt-1 by statins seems to be mediated via the inhibition of HMG-CoA reductase. By this mechanism, statins reverse endothelial dysfunction and angiogenic imbalance underlying the pathophysiology of PE (Figure 1).

Statins also exert anticoagulant activity. They have antiplatelet properties which decrease platelet aggregation and activity and modulate the coagulation system through their impact on the different coagulation factors involved in the coagulation cascade, including thrombin, factor VII, factor Va and von Willebrand factor, factor XIII and prothrombin, as well as act on the fibrinolysis system and increase the fibrinolytic activity of the plasma [17].

Statins also have immunomodulatory properties as they have been shown to inhibit the expression of class II major histocompatibility complex (MCHII) molecules on the surface of endothelial cells and macrophages [19].

Pravastatin in obstetrics

The pathophysiology similarities and risk factors shared by PE and cardiovascular disease have prompted the search for PE treatments among agents used to treat vascular disease. Considering the pleiotropic effects of statins, especially their anti-inflammatory, antioxidative and antithrombotic properties and improvement of endothelial dysfunction, a hypothesis has been put forward for similar effectiveness of statins in the prevention or treatment of PE.

The selection of pravastatin for further studies is justified by its high hydrophilicity. Due to its low lipophilic properties, the transplacental transfer of pravastatin from mother to fetus is fairly limited.

Over the past few years, studies on animals have shown that statins are effective in the prevention of major complications of pregnancy such as habitual abortion or PE [20–23].

Pravastatin used in animal models of PE reduced arterial blood pressure, improved vascular function, reduced levels of circulating sVEGFR-1 (sFlt-1) and sEng and increased the levels of PlGF and VEGF [24–27].

The benefits of pravastatin were observed in both mothers and their offspring. Studies in mouse models

showed that treatment with pravastatin in pregnant female mice with induced PE had beneficial effects in the offspring such as improved blood pressure, birth weight, blood glucose and cholesterol levels, cerebral volume as well as the function of the vestibular system, balance and coordination [28–34].

The first ever multicenter randomized controlled trial (RCT) evaluating the use of statins in pregnant women was conducted in the UK in the years 2011–2014 (StAmP study – Statins to Ameliorate early Onset PE, EudraCT number 2009-012968-13, clinicaltrialsregister.eu) [35]. The aim of the study was to examine the hypothesis based on the results of experimental studies claiming that statins can suppress elevated levels of anti-angiogenic factors in the placenta observed in preeclamptic patients. The study examined if the use of pravastatin versus placebo helped to decrease the levels of specific biomarkers associated with the onset and progression of PE.

The molecular mechanism of the statin-mediated stimulation of the *HMOX-1* gene expression seemed especially promising as it increases the activity of oxygenase and inhibits the release of soluble VEGF receptor 1 (sFlt1) [3, 4]. The final results of the study have not been published to date.

Since 2012, a phase I clinical trial of the use of pravastatin for the prevention of PE (clinicaltrial.gov identifier: NCT01717586) has been conducted in the USA. The aim of this pilot study was to evaluate the pharmacokinetics and safety of pravastatin used as a prophylactic daily treatment in high-risk pregnant women [36].

In the trial high risk of PE women cohorts were assigned to daily pravastatin at a dose of 10 mg or placebo orally starting before 16 weeks' gestation until delivery.

The results showed that no identifiable safety risks were associated with pravastatin use in this cohort. The majority of umbilical cord and maternal pravastatin plasma concentrations at the time of the delivery were below the lower limit of quantification of the assay. Pravastatin reduced maternal cholesterol concentrations but not in the fetuses.

Additionally, although not statistically significant, in the pravastatin intake group there was a lower rate of PE, indicated preterm delivery and also improved proangiogenic profile (lower sFlt-a, sEng and higher PlGF).

In 2016, Chaiworapongsa et al. [37] reported the first case of pravastatin use to reverse an imbalance in angiogenic/anti-angiogenic factors. The authors succeeded in preventing fetal death in a patient with massive perivillous fibrin deposition of the placenta and maternal floor infarction, and a history of recurrent pregnancy losses. Treatment with pravastatin effectively corrected the

abnormalities in plasma anti-angiogenic and angiogenic factors, decreasing the sVEGFR-1 levels and increasing the PlGF levels, thus demonstrating the potential use of pravastatin in the setting of an angiogenic imbalance.

Studies on the uses of pravastatin for the prevention of PE obviously need to be continued, but even with the present findings pravastatin seems to be a strong candidate for the effective prevention and/or treatment of PE and possibly other hypertensive disorders of pregnancy.

Safety of pravastatin use in pregnancy

Safety of pravastatin in pregnant women is a concern and its careful investigation is mandatory. Whether statins are associated with congenital anomalies or other complications of pregnancy remains an important clinical question.

Statins have been assigned to the pregnancy X category by the Food and Drug Administration (FDA) and according to the current FDA pregnancy and lactation labeling rule, statins are contraindicated in pregnant women because of embryo/fetal toxicity.

The known mechanism of biological effects of statins and the suspicion of their potential teratogenic effect are of great concern.

For pravastatin the X category of safety in pregnancy results mainly from the lack of clinical data on the effects on pregnant women and human fetuses and not from observed risk.

The available data on the adverse effects of statins in pregnant women include reports of skeletal malformations following exposure to lovastatin, cerivastatin and fluvastatin, and central nervous system defects [38]. One *in vitro* study [39] suggests that statins (simvastatin) might adversely affect placental formation. However, a systematic review and meta-analysis of statin use in pregnancy [40] concluded that in humans the observed congenital anomalies were isolated and no consistent pattern emerged to suggest that a common mechanism could underlie these observations.

To date, epidemiological studies have not revealed any adverse effects of maternal statin use on the fetus. In a report of the Merck pharmacovigilance database for exposure to simvastatin or lovastatin during pregnancy there was no evidence of an increase in congenital anomalies in children [41]. An epidemiological study conducted in Quebec [42] failed to support the potential teratogenicity of statins. A prospective cohort study at the Motherisk Program conducted by Taguchi et al. [43] did not observe any malformation patterns in infants from mothers

exposed to a statin during the first trimester of pregnancy. Also, the postmarketing surveillance of simvastatin and lovastatin has not found any adverse pregnancy outcomes in patients with early exposure to these drugs [41, 44].

Summarizing, to date, no controlled studies have investigated the teratogenicity of statins in humans. Most of the available studies, including small population-based epidemiological studies, in fact suggest that statins are unlikely to be teratogenic [40, 45–47].

Importantly, pravastatin has a specific pharmacokinetic profile. Unlike lipophilic statins such as atorvastatin, simvastatin and lovastatin, pravastatin and rosuvastatin are hydrophilic, i.e. water-soluble. That is why the cross-placental transfer of pravastatin molecules to the fetus is slow and of moderate degree – according to experimental results only 18% of pravastatin is transferred from the maternal to the fetal circuit [48, 49].

The pharmacokinetic features of pravastatin have a significant impact on its adverse effect and safety profile in pregnant women. According to the current data, no abnormal pregnancy outcomes have been reported following exposure to pravastatin or fluvastatin [39]. Furthermore, the interim results of a randomized trial currently conducted in the USA to evaluate the pharmacokinetics and collect the preliminary safety data in pregnant women at high risk of PE [36] have not demonstrated any increased risk with pravastatin.

Summing up, there is a large body of clinical data on the use of statins in pregnancy. The available epidemiologic data suggest that statins are not teratogenic, but there are no data from controlled studies investigating the possible human teratogenic effect. Many studies are currently ongoing and there are no consistent data on the safety of statin use, especially pravastatin, in pregnant women. Any clinical guidelines and recommendations need to be based on further research.

Summary

The pathophysiology of PE has not been fully elucidated while the course of PE is complex, often dynamic and unpredictable, and PE remains difficult to prevent and/or treat. A search for optimal treatment(s) continues and over the past few years considerable advances have been made in the area of the pathomechanism of GH and PE. Identification of an angiogenic/anti-angiogenic imbalance as a factor underlying abnormal placentation is a step toward finding effective treatments targeting the causes of PE.

Pravastatin seems to be the most promising of the various novel agents proposed for the prevention and/or treatment

of PE. The preliminary results of clinical studies confirm that the use of pravastatin could be a potential prevention or even treatment of PE and related pregnancy complications. However, more data from large clinical trials are needed. The clinical benefits of pravastatin treatment are related to the pleiotropic effects of statins, especially their ability to reverse an angiogenic imbalance and correct endothelial dysfunction. However, the safety of pravastatin in pregnancy remains a significant concern. Hence, a considerable interest of researchers and clinicians in the ongoing pilot RCT of “Pravastatin for prevention of preeclampsia” conducted by Constantine et al. and assessing the pharmacokinetics and safety of pravastatin [36] as the results will be of significant importance for the future management of PE.

Author's statement

Conflict of interest: Authors state no conflict of interest.

Material and methods: Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The research related to human subject use has complied with all the relevant national regulations, and institutional policies, and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

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