Hypothesis: selective phosphodiesterase-5 inhibition improves outcome in preeclampsia

J.W. Downing\textsuperscript{a,*}, R. Ramasubramanian\textsuperscript{a}, R.F. Johnson\textsuperscript{a}, B.H. Minzter\textsuperscript{a}, R.L. Paschall\textsuperscript{a}, H.W. Sundell\textsuperscript{b}, B. Engelhardt\textsuperscript{b}, R. Lewis\textsuperscript{c}

\textsuperscript{a} Department of Anesthesiology, Vanderbilt University School of Medicine, 1313 21st Ave. So. 504 Oxford House, Nashville, Tennessee, USA
\textsuperscript{b} Department of Pediatrics, Vanderbilt University, Nashville, Tennessee, USA
\textsuperscript{c} Department of Obstetrics and Gynecology, Vanderbilt University, Nashville, Tennessee, USA

Received 22 April 2003; accepted 13 March 2004

Summary The pathogenesis of preeclampsia stems from aberrant changes at the placental interface. The trophoblastic endovascular invasion of tonic spiral arteries that converts them to passive conduits falters. Uteroplacental insufficiency and fetoplacental hypoxemia result. Secondary maternal oxidative stress and an excessive inflammatory response to pregnancy generate the clinical syndrome of preeclampsia. Current treatment focuses on preventing seizures, controlling hypertension, preserving renal function and delivering the baby.

We propose that the pathophysiological changes induced by preeclampsia in the placenta parallel those caused by persistent hypoxemia in the lungs at high altitude or with chronic obstructive pulmonary disease. Unrelenting pulmonary hypoxic vasoconstriction induces pulmonary hypertension and cor pulmonale. Inhalation of nitric oxide and phosphodiesterase-5 inhibitors opposes pulmonary hypoxic vasoconstriction, alleviates pulmonary hypertension and improves systemic oxygenation. Notably nitric oxide donor therapy also counters hypoxic fetoplacental vasoconstriction, a biological response analogous to pulmonary hypoxic vasoconstriction. Fetal oxygenation and nutrition improve. Placental upstream resistance to umbilical arterial blood flow decreases. Fetal right ventricular impedance falls. Heart failure (cor placentale) is avoided. Emergency preterm delivery can be postponed.

Other than low dose aspirin and antioxidants vitamins C and E no available therapy specifically targets the underlying disease profile. We hypothesize that, like nitric oxide donation, pharmacological inhibition of placental phosphodiesterase-5 will also protect the fetus but for a longer time. Biological availability of guanosine 3'5'-cyclic monophosphate is boosted due to slowed hydrolysis. Adenosine 3'5'-cyclic monophosphate levels increase in parallel. Cyclic nucleotide accumulation dilates intact tonic spiral arteries and counters hypoxic fetoplacental vasoconstriction. Intervillous and intravillous perfusion pick up. Maternal to fetal placental circulatory matching improves. Enhanced placental oxygen uptake alleviates hypoxic fetal stress. Appropriate fetal nutrition resumes. Cor placentale and severe intrauterine growth restriction are averted.

Increased maternal cyclic nucleotide concentrations promote systemic vasodilatation so that blood pressures fall. Preemption of oxidative stress initiated by "consumptive" oxidation of nitric oxide stabilizes the vascular endothelium and corrects coagulopathy. Anti-inflammatory and immunosuppressant adenosine 3'5'-cyclic monophosphate offsets the extreme gestational inflammatory response. Cellular injury and multi-organ damage are prevented.

\* Corresponding author. Tel.: +1-615-322-8476; fax: +1-615-343-1732.
E-mail address: john.downing@vanderbilt.edu (J.W. Downing).

0306-9877/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.mehy.2004.03.042
One tablet a day of the new long acting phosphodiesterase-5 inhibitor, tadalafil (half life of 17.5 h) theoretically should allow a preterm pregnancy affected by preeclampsia to continue safely. Selective monitoring of vital organ functions guards against life-threatening maternal complications. Regular biophysical profiling warns the obstetrician of impending fetal compromise. Fetal growth and vital organ maturation can continue.

As a result workloads imposed upon neonatal intensivists will lighten. Parental anxiety and concern will be allayed. The cost of treating preeclamptic mothers and their extremely low birth weight infants will decrease. Money saved by midwifery services in poorer states can be used to pay for better prenatal care. Severe preeclampsia/eclampsia will be less common. Maternal and perinatal morbidity and mortality will be reduced. Because the human immunodeficiency virus often infects individuals at a workforce eligible age, the global acquired immunodeficiency syndrome pandemic has already brought many nations to the brink of economic ruin. Potentially productive lives saved for the future will help restore them fiscally.

Background

Preeclampsia is a leading cause of maternal morbidity and death worldwide [1]. Intrauterine growth restriction (IUGR) and hypoxemic fetal distress associated with preeclampsia are indications for expedient delivery in almost 15% of preterm births [2]. Extremely low birth weight (ELBW) babies delivered for both maternal and fetal indications are likely to die. Survivors are often both mentally and physically handicapped [3].

Contemporary treatment of preeclampsia seeks primarily to avoid life-threatening maternal complications. Control of hypertension and seizure prevention is paramount. Careful observation of the output of urine and invasive hemodynamic monitoring as indicated guide the restoration of the characteristic restricted plasma volume and guard against circulatory overload. Treatment failure compels premature delivery, the only known cure for preeclampsia.

Evidence

In 1832 John Burns of Glasgow, Scotland wrote that: "...there is nothing either more difficult, or more mysterious, [than] the etiology of puerperal convulsions" [4]. More than 170 years later the pathogenesis and pathophysiology of preeclampsia/eclampsia remain conundrums that still provide fertile areas for on-going research [5]. Abnormal maternal vascular reactivity, coagulopathy, uteroplacental insufficiency and poor fetoplacental perfusion are pathognomonic of this disorder. Especially remarkable is the random failure of endovascular trophoblastic invasion to replace the endothelium and destroy the musculoelastic architecture of the spiral arteries. The widespread conversion of these normally tonic vessels into passive, low resistance uteroplacental conduits during placentation is thwarted. Reported adverse changes in placental Doppler flow velocity wave form patterns associated with preeclampsia support the notion that its pathophysiology stems largely from this well-described vascular anomaly [6]. Unmodified spiral arteries remain intact and retain their responsiveness to key endogenous vasoconstrictor and vasodilator compounds. These vasoactive agents include endothelin, thromboxane, catecholamines, 5-hydroxytryptamine (5-HT), angiotensin, prostacyclin and nitric oxide (NO) donors. Other factors that inhibit normal placentation are intervillous thrombosis and placental atherosclerosis, infarction, and abruption [7].

In the lungs efficient gaseous exchange is contingent upon optimum matching of ventilation to perfusion (V/Q matching) brought about by activation of the pulmonary hypoxic vasoconstrictor (PHV) response. In 1987, Howard [8] suggested that a similar biological response, hypoxic fetoplacental vasoconstrictor (HFPV), might control fetoplacental intravillous blood flow. Studies using the dual perfused, single isolated, human placental cotyledon support this assertion [9–12]. Healthy transplacental exchange probably hinges around HFPV dependent regional adjustments of previllous umbilical arteriolar tone that optimize maternal/fetal (\(Q_m/Q_f\)) blood flow distribution and matching.

A favorable \(Q_m/Q_f\) ratio promotes umbilical venous uptake of oxygen and nutrients from the intervillous space and facilitates their carriage and delivery to the fetus. Regional uteroplacental insufficiency and consequent reduced fetal oxygen availability trigger compensatory HFPV. This physiologically protective response steers umbilical arteriolar blood flow away from hypoxemic villi towards better-oxygenated areas of the placenta. HFPV thus guards against fetal biochemical imbalance and starvation.
Myatt et al. [13] studied the influence of NO on thromboxane and endothelin induced fetomaternal vasoconstriction in the dual perfused, single isolated human placental cotyledon. They concluded that: "Nitric oxide appears to contribute to maintenance of basal vascular tone and to attenuate the actions of vasoconstrictors on this circulation." Using the same laboratory model NO donation and PDE5 inhibition have been shown to counteract HFPV provoked by both 5-HT and hypoxia [14–17].

The signal transduction pathway believed to be responsible for the characteristic maternal vasodilatation and low placental vascular resistance of a healthy pregnancy begins with NO synthesis under the control of NO synthetase (Fig. 1). NO release activates guanylate cyclase (sGC) to convert guanine triphosphate (GTP) to guanosine 3′,5′-cyclic monophosphate (cGMP) [18]. Cyclic GMP receptor stimulation causes smooth muscle cell cGMP-dependent protein kinases to initiate myosin light chain dephosphorylation, relaxing smooth muscle. Adenosine 3′,5′-cyclic monophosphate (cAMP) concentrations in vascular smooth muscle and platelets increase in parallel with the accumulating levels of cGMP.

Substrate specific phosphodiesterases (PDE5 and PDE4, respectively), hydrolyze cGMP and cAMP. Cyclic GMP-binding phosphodiesterases (PDE3 and PDE5), cGMP (PKA1) dependent protein kinase and cAMP (type 1PKA) dependent protein kinase have been identified in the human placenta [19,20]. Cyclic GMP and cAMP inhibit platelet aggregation and preserve microvascular integrity by preventing capillary hyperpermeability and vascular leakage.

In addition, cAMP exhibits immunosuppressant and antiinflammatory properties.

The NO–sGC–cGMP first and second messenger pathways in the lungs probably regulate PHV to optimally adjust pulmonary V/Q distribution and matching. At lower altitudes PHV maintains V/Q equilibrium to secure normal arterial oxygen and carbon dioxide tensions. But at high altitude a low ambient O2 pressure and therefore reduced alveolar O2 tension provokes a vigorous PHV response that increases pulmonary artery pressure without improving gas exchange [21]. Persistent PHV increases pulmonary arteriolar resistance and causes pulmonary arterial hypertension, ultimately leading to cor pulmonale. Hypoxemic chronic obstructive pulmonary disease (COPD) predicates a similarly protracted pathological course and outcome.

Analogous biochemical strategies probably influence HFPV in order to adjust placental perfusion and Qm/Qf distribution and matching [8–12]. The low resistance, high flow fetoplacental circulation lacks innervation but does possess tonic previllous umbilical arterioles responsive to humoral and reagent

**Figure 1** Failure of the normal nitric oxide (NO)–cyclic guanosine monophosphate (cGMP) first and second messenger transduction pathway together with aberrant NO production and almost simultaneous "consumptive" superoxide and lipid oxidation underlie the pathogenesis of severe preeclampsia. NO, nitric oxide; NOS + nitric oxide synthetase; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate; cAMP, cyclic adenosine monophosphate; SGMP, 5-guanosine monophosphate; [O2], superoxide; OONO, peroxynitrite; PDE5, phosphodiesterase-5; SOD, superoxide dismutase.

**Figure 2** The hypothetical pathophysiological cascade induced by vasoconstriction of the uteroplacental and fetoplacental circulations in preeclampsia. Cor placental is potentially lethal to the fetus. IUGR and in particular hypoxemic fetal stress demand emergent preterm delivery often before 26 weeks gestational age. Neonatal death or a poor long-term outcome, for example, cerebral palsy may result. cGMP, cyclic guanosine monophosphate; HFPV, hypoxemic fetoplacental vasoconstriction; Ua, umbilical artery; UV, umbilical vein; RV, right ventricular; Qm/Qf, uteroplacental/fetoplacental-blood flow match; IUGR, intrauterine growth restriction; VO2, oxygen availability/uptake.
stimuli. In preeclampsia chronic fetoplacental hypoxemia induces persistent HFPV and $Q_m/Q_i$ inequalities (Fig. 2). Unrelenting previllous arteriolar spasm increases upstream umbilical arterial resistance manifesting as absent or reversed umbilical arterial end diastolic Doppler flow waveforms that correlate well with adverse perinatal outcome [22]. Fetal right ventricular impedance, workload and myocardial oxygen demand increase leading to hypoxic fetal right heart failure and circulatory decompensation.

The above scenario mirrors the inexorable but more drawn out course of events seen in adults at high altitude or with COPD that induce and perpetuate pulmonary hypertension leading to cor pulmonale and death. Consequently Sebire and Talbert [23] have aptly labeled this potentially lethal fetal condition "cor placentale". Clinically these changes manifest initially as a non-reassuring fetal heart rate patterns. Unchecked they lead to agonal fetal bradycardia, a clinical sign that mandates immediate delivery to save the baby’s life.

Placental NO synthetase (NOS) activity reportedly may decrease, increase or not change in pre-eclampsia [24,25]. Oxygen dependent NOS activity decreases with hemoglobin desaturation [21]. Reduced production or increased "consumption" (see below) of NO in preeclampsia limit its bioavailability and hence decreases cGMP and cAMP expression. A dearth of vasodilatory cyclic nucleotides favors maternal vasoconstriction leading to uncontrolled maternal hypertension (Fig. 3). Further consequences of severe maternal vasospasm are plasma volume restriction, hemococoncentration and hyperviscosity. Other anomalies that threaten the mother include platelet aggregation, coagulopathy and an unbridled inflammatory response to pregnancy.

Concurrently, spiral artery vasospasm, placental atherosclerosis, placental infarction and placental abruption induced by the mother’s excessively high blood pressures cause uteroplacental hypoxemia. Widespread reflex HFPV is invoked in a compensatory effort to reestablish an overall placental $Q_m/Q_i$ match compatible with fetal survival (Fig. 2). Fetal nutrient supplies are jeopardized and oxygen availability to the fetus is seriously curtailed.

Referring once again to Fig. 1, hypoxemia promotes an interaction between NO and superoxide ($O_2^\cdot -$) that produces peroxynitrite (ONOO$^-$), a potent pro-oxidant that nitrosylates cellular proteins and lipoproteins [26]. Increased ONOO$^-$ production from the placenta induced by fetoplacental hypoxemia in concert with the generation of other NO based reactive oxygen species or ROS [nitrogen dioxide (NO2) and nitrogen trioxide (NO3)] trigger maternal oxidative stress (Fig. 4). NO “consumption” by superoxide further erodes its bioavailability and limits its vasodilatory potential. In addition, the antioxidant reaction normally facilitated by NO that converts pro-oxidant hydrogen peroxide ($H_2O_2$) to water and oxygen is slowed...
leading to a build up of H$_2$O$_2$, further fueling maternal oxidative stress. Collectively, these events in the mother lead to an explosive pro-oxidant cascade as depicted in Fig. 4. Maternal oxidative stress coupled with an exaggerated inflammatory response to pregnancy causes endothelial swelling and dysfunction, capillary hyperpermeability, vascular leakage, platelet aggregation, thrombosis and atherosis. The end results, irreversible cellular damage and multi-organ failure are lethal [27].

The NO–sGC–cGMP signaling system and lipid peroxidation reactions not only preserve vascular homeostasis in health but also paradoxically may instigate arterial disorders [28]. Additionally, NO possesses both proinflammatory and anti-inflammatory properties [29]. Perturbations in NO production and biological inactivation are therefore often blamed for organ dysfunction and disease. We surmise that in preeclampsia reduced NO bioavailability translates into a decrease in cGMP expression and cAMP co-production. Maternal endothelium dependent vasodilatation is impaired. Biological constraints that normally offset vasoconstriction and the inflammatory response to pregnancy are blunted.

Uncontrolled maternal hypertension can precipitate hemorrhagic stroke and in concert with the pro-oxidant related increase in capillary permeability provoke cerebral edema. Furthermore, a major increase in left ventricular impedance and afterload may precipitate left heart failure. Left ventricular overload coupled with increased vascular leakage leads to pulmonary edema. Increased NO “consumption” by superoxide triggered by fetoplacental hypoxemia further depletes NO bioactivity and leads to a dangerous build up of ROS (ONOO$^-$, NO$_2$, NO$_3$ and H$_2$O$_2$). The delicate balance between organic pro-oxidant and antioxidant activity is upset initiating and then fueling maternal oxidative stress [2,27,30,31]. Cyclic AMP’s immunosuppressive and anti-inflammatory influences diminish [32]. These potentially lethal pathophysiological events are summarized in Figs. 3 and 4.

Hypothesis

Based on the assumptions outlined previously, we postulate that selective placental PDE5 inhibition will forestall the cataclysmic pathophysiological changes that provoke the clinical onset and progression of preeclampsia. With two exceptions, low dose aspirin ingestion and antioxidant vitamin C and E administration [33,34], no other previously suggested remedies for preeclampsia cite prevention as their chief objective. Targeting PDE5 enzyme activity with a specific phosphodiesterase inhibitor to impede cGMP hydrolysis (Fig. 1) increases intracellular cGMP and cAMP concentrations to vasodilate uteroplacental and fetoplacental vasculature. Intervillous and intravillous perfusion improve and $Q_m/Q_l$ matching stabilizes. Fetoplacental hypoxemia is alleviated. Appropriate fetal nutrition resumes.

Maternal hypertension subsides as cGMP and cAMP induced vasodilation counteracts the profound vasoconstriction pathognomonic of severe preeclampsia. The risks of a catastrophic cerebral bleed and swelling of the brain recede. The onset of the pro-oxidant cascade that generates maternal oxidative stress is forestalled. The likelihood of left heart failure and pulmonary edema diminishes. Proinflammatory cellular and mediator activities subside. Maternal endothelial and platelet functions recover. Irreversible cellular damage, multiple organ failure and maternal death are averted. Delivery can thus be delayed with relative safety for the mother. Fetal organ maturation and physical development proceed unabated.

Rationale

Uteroplacental insufficiency targets the fetoplacental unit, the alleged pathogenic epicenter of preeclampsia [7]. Impaired intervillous perfusion predicates IUGR and fetoplacental hypoxemia. Fetoplacental hypoxemia triggers maternal vasoconstriction that is the foundation for the development of severe hypertension, a plasma volume deficit, hemoconcentration, hyperviscosity, and renal failure. Loss of capillary endothelial integrity leads to a further depletion in maternal plasma volume and the development of flagrant tissue and organ edema. For example, gross laryngeal edema may hamper attempts to intubate the trachea during rapid sequence induction (RSI) of general anesthesia for cesarean section [35]. Worsening of preexisting cerebral edema and the sudden onset of left ventricular failure and pulmonary edema are other dangerous consequences of a poorly conducted RSI that fails to control the reflex hypertension induced by laryngeal stimulation.

Uncontrolled hypertension coupled with oxidative stress and an excessive gestational inflammatory response in the mother increase the chances of serious clinical complications appearing. For the mother these include hemorrhagic stroke, cerebral thromboses, thrombocytopenia, the HELLP syndrome (hemolysis (H) with elevated liver enzymes,
(EL) and a low platelet count (LP), liver hematoma, cardiomyopathy and the adult respiratory distress syndrome (ARDS) (Fig. 4).

From the fetal point of view IUGR is a hallmark of severe preeclampsia. Other hazardous conditions that threaten the fetus include hypoxemic stress, metabolic and respiratory acidemia, cor placental and, in association with uncontrolled maternal hypertension, placental abruption. Since delivery is currently the only known cure for preeclampsia, the presence of any of these life-threatening pathological entities in the mother or her baby necessitates urgent premature delivery by cesarean section in order to avoid permanent injury or death.

Inhaled NO and PDE5 inhibitors are used to treat adult and neonatal pulmonary arterial hypertension [21,36]. PHV is abolished and pulmonary arterioles dilate. Intrapulmonary V/Q matching and oxygenation improve. Metabolic and respiratory acidemia is relieved. Pulmonary artery pressures fall, right ventricular impedance and afterload decrease and cor pulmonale is avoided. Notably sildenafil, a well-established PDE5 inhibitor, has been shown to modulate the harmful rebound pulmonary hypertension that follows inhaled NO withdrawal in newborns and infants [37].

In severe preeclampsia nitrovasodilators modulate maternal hypertension and improve Doppler uterine artery pulsatility indices [38]. In theory NO donors increase cGMP expression and the parallel increase in cAMP production. Tonic spiral arteries serving the uteroplacental circulation dilate. Umbilical previllous arteriolar spasm (HFPV) within the fetoplacental circuit relaxes. Uteroplacental insufficiency and fetoplacental hypoxemia are alleviated. Placental Qm/Qf matching improves. Better fetal oxygenation assuages fetal metabolic and respiratory acidemia. Fetal nutrition is enhanced. Upstream resistance to umbilical artery blood flow returning to the placenta falls. Fetal right ventricular impedance and afterload are reduced. Myocardial workload and oxygen demand diminish. Right heart function improves and cor placental is averted. The signs and symptoms of fetal stress abate.

We submit that selective placental PDE5 inhibition, by slowing placental cGMP breakdown and increasing cyclic nucleotide availability will provide the same benefits as NO donation but without the risk of precipitating relative maternal systemic hypotension and for a longer time. Excess NO expression brought on by the vicious cycle of oxidative "consumption" as depicted in Fig. 1 will be suppressed by the accumulation of cGMP and cAMP, a well-established negative feed-back biomechanism. Hazardous complications related to uncontrolled maternal hypertension, rampant maternal oxidative stress and an extreme inflammatory reaction to pregnancy are less likely to arise.

Verification of hypothesis

Our central tenet is that placental PDE5 inhibition in preeclampsia dilates spiral arteries and umbilical previllous arterioles. Uteroplacental insufficiency and fetoplacental hypoxemia are alleviated to protect both mother and child. We propose that the therapeutic merits of PDE5 inhibition might conveniently be tested in rats [39–41]. If increasing placental cGMP and cAMP availability alleviates rodent hypertension, proteinuria and IUGR caused by NO synthetase inhibition, an argument could be made for conducting preliminary clinical studies in humans with severe refractory preeclampsia. However, in the light of sildenafil’s reported effects on the pulmonary circulation in neonates and infants [37], the influence of PDE5 inhibition on the fetal circulation should be taken into account before clinical trials are started.

If animal studies support the efficacy and safety of PDE5 inhibitors and subsequent clinical trials prove successful, how could mankind benefit in the future? The recent introduction of tadalafil, a new longer acting PDE5 inhibitor with a half life of 17.5 h, may make it possible for a mother with preeclampsia to continue her pregnancy safely beyond 25 weeks based on a one tablet a day regime [42]. Selective monitoring of vital organ functions backed by conventional management will help prevent the occurrence of life-threatening maternal complications. Time bought by PDE5 inhibitor therapy will allow further fetal brain, lung and kidney development. The fetus will continue to mature physically. Regular biophysical profiles will be used to monitor fetal progress. A better neonatal outcome will result. Consequently, maternal and fetal mortality and morbidity will decrease. Many women and their babies worldwide will benefit [1]. Parental anxiety and concern will diminish.

The costs incurred in treating these very sick mothers and their ELBW babies will be substantially reduced. The burden borne by doctors and nurses staffing neonatal intensive care units will be lightened. Potentially productive lives will be saved, an important consideration in the light of the current worldwide AIDS pandemic and its continuing devastating effect on the work force and peoples’ living conditions in Africa and other parts of the developing world. Much needed fiscal relief will be
provided for the financially strapped governments that fund midwifery services in the poorer nations of the globe.

References


