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Preeclampsia; short and long-term consequences for mother and neonate

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ABSTRACT

Preeclampsia is a common pregnancy specific disease, that presents with hypertension and a variety of organ failures, including malfunction of kidneys, liver and lungs. At present, the only definitive treatment of preeclampsia is end the pregnancy and deliver the neonate and placenta. For women with mild preeclampsia in the preterm phase of pregnancy, expectant management is generally indicated to improve fetal maturity, often requiring maternal medical treatment. Last decades, more evidence is available that the underlying mechanism of preeclampsia, endothelial disease, is not limited to pregnancy but increases cardiovascular risk in later life.
In this review, we present the most recent insight in preeclampsia with focus on impact on the fetus, short and long-term outcome of offspring's, and long-term outcome of women with a history of preeclampsia.

Contents

Preeclampsia is a common pregnancy specific disease with potential adverse maternal and neonatal outcome, that affects 3–5% of all pregnancies [1]. Recently, preeclampsia is re-defined by de-novo hypertension manifested after 20 weeks of gestation combined with one of the following new-onset conditions: proteinuria (>300 mg/day); or maternal organ dysfunction (including renal insufficiency, liver involvement, neurological or haematological complications); or uteroplacental dysfunction (potential causing fetal growth restriction) [2]. Two subtypes are clinically recognized by the time of onset of the disease: early onset preeclampsia (<34 weeks gestation) and late onset preeclampsia (≥34 weeks gestation). Early onset preeclampsia is less prevalent but has higher rates of maternal morbidity, perinatal death and severe neonatal morbidity compared to the late onset disease [3].

The main pathologic feature of *early* onset preeclampsia is an abnormal development of the placenta. The placentation in preeclampsia is typically characterized by abnormal vascular remodelling of the spiral arteries starting in the first trimester of pregnancy, weeks before clinical manifestation is evident. Due to failure of the cytotrophoblast cells penetrate into the myometrial segment of the spiral arteries, the musculoelastic wall cannot be replaced with fibrinoid material. Due to this failure, spiral arteries fail to change into large vessels with low resistance and remain narrow with high pressure, resulting in placental hypoperfusion. Local hypoperfusion results in release of various factors, including inflammatory cytokines and antiangiogenic proteins increasing the ratio between the antiangiogenic factor soluble fms-like tyrosine kinase-1 (sFlt-1) and the proangiogenic placental growth factor (PlGF),

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that might contribute to systemic endothelial response, manifested clinically as preeclampsia and intrauterine fetal growth restriction [4,5].

Women who have had a pregnancy complicated by *late* onset preeclampsia have most often minimal or no abnormal vascular remodelling of the spiral arteries and no intrauterine fetal growth restriction. Interaction of placentation and endothelium results in impairment of the latter with microvascular damage, generalized vasoconstriction and reduced blood flow to multiple organs. Despite intensive research over the last decades the pathophysiology is still not completely understood and the division described above is not always clear [6]. Subtypes may help in understanding the pathophysiology, but most patients have entities of both pathologies [6].

Factors reported to be associated with increased risk of preeclampsia include a history of preeclampsia, family history of hypertensive disorders in pregnancy, the presence of antiphospholipid antibodies, nulliparity, multiple pregnancy, donor oocyte pregnancy, advanced maternal age and pre-existing diabetes, renal disease, high blood pressure and/or high body mass index [7].

1. Management of preeclampsia

The only definitive treatment of preeclampsia is to deliver the placenta and thus the neonate. Because of the two conflicting interests of mother and child, timing of delivery is one of the main challenges of preeclampsia, especially in women with early onset preeclampsia. Women with preeclampsia are at risk of developing acute kidney or hepatic failure, hepatic rupture, pulmonary edema, cerebral haemorrhage, disseminated intravascular coagulation and progression to eclampsia, while their risk of placental abruption, IUGR and intrauterine fetal death is increased as compared to non-preeclamptic women. On the other hand, the neonate is likely to benefit from a prolongation of pregnancy because of the sequelae of prematurity, although a compromised intrauterine environment might jeopardize this advantage [8]. If preeclampsia is diagnosed beyond 37 weeks of gestation, induction of labour is the best choice for mother and neonate [9]. If mild preeclampsia or pregnancy induced hypertension occurs at 34–37 weeks' gestation, expectant monitoring until clinical deterioration is justified; immediate delivery significantly increased the risk of neonatal respiratory distress syndrome and adverse maternal outcomes were not clinically relevant reduced [8]. Delivery is indicated regardless of gestational age if there is evidence of advanced disease or impeding eclampsia.

2. What are consequences of preeclampsia for the neonate?

Placental hypoperfusion can cause fetal growth restriction and oligohydramnios. Children born after a pregnancy complicated by preeclampsia have an average of 5% lower birth weight as compared to children born after an uncomplicated pregnancy. This reduction is even more prominent in women with pregnancies complicated by early onset preeclampsia, who have on average a 23% lower birth weight than expected based on gestational age [10]. In line with this is an increased fetal death rate; 5.2 per 1000 fetal death in women with preeclampsia versus 3.6 per 1000 in women with uncomplicated pregnancies. In women with early onset preeclampsia, the risk of stillbirth is even sevenfold higher compared to normotensive pregnancies [11]. The deprived intrauterine environment in women with preeclampsia is a significant contributor to preterm birth, most often iatrogenic [12]. Preterm birth is the world's leading cause of neonatal morbidity and mortality [13]. It is associated with higher rates of infant respiratory distress syndrome, intraventricular haemorrhage, sepsis, bronchopulmonary dysplasia and neurodevelopmental disability in childhood [14]. In preterm birth antenatal corticosteroid therapy reduces neonatal morbidity and mortality; in spontaneous preterm birth as well as in pregnancies complicated preterm by hypertensive disorders [15].

The leading cause of maternal death from preeclampsia is cerebral haemorrhage, which is presumably the consequence of severe hypertension [16]. The ideal drug for urgent treatment of severe hypertension during pregnancy should act quickly, be reliable, avoiding hypotension that may reduce placental blood flow and is without adverse neonatal effects. No such agent is currently neither available nor exact maternal blood pressure targets. As a consequence a variety of drugs has been used with the aim to reduce maternal morbidity. We will focus on the neonatal effects of women treated for severe hypertensive disorders.

A meta-regression analysis of RCTs (42 trials, 3892 women) raised concerns that antihypertensive therapy in general may increase the risk of intrauterine fetal growth restriction [17]. Meta-regression of RCTs described a significant relationship between the antihypertensive-induced fall in mean arterial pressure and the risk of small for gestational age infants or lower birth weight (odds ratio 1·31 [95% CI 0·98–1·75], $n =$ 15 trials, 1782 women) [18,19]. Labetalol is one of the most common used antihypertensive drugs in severe and non-severe hypertension. It is an adrenergic inhibitor with combined β and α 1-blocking properties. Labetalol has been compared with other hypertensive drugs. A Cochrane systematic review of these trials showed calcium-antagonists and labetalol to provide the best control of blood pressure, although there was insufficient information to make reliable conclusions about the effectiveness and fetal safety of these drugs [20]. Effects on the neonate are persistent fetal bradycardia, hypotension (49% of children exposed to labetalol in utero vs 7% in controls) and neonatal hypoglycaemia (47% of children exposed to labetalol in utero vs 42% in controls [21]. The latter findings suggest a potential side effect of hypotension due to labetalol and hypoglycaemia that might also be contributed by preterm delivery. The neonatal side effects of maternal labetalol treatment in preeclampsia underline the importance of frequent blood glucose and blood pressure measurements in the first days of life. Labetalol may be present in low concentrations in breast milk but is not anticipated to have a pharmacologic effect. There is no compelling evidence that labetalol is associated with adverse neurodevelopmental effects later in life. In a Dutch prospective cohort study, hyperactivity disorder (ADHD) was twice more often observed in 4–10 year old children in utero exposed to labetalol as compared with those exposed to methyldopa (OR 2.3; 95% CI 0.7–7.3). Other reviews describe no differences in neurodevelopmental outcome between children age 3–10 years exposed to labetalol or exposed to other or no antihypertensive drugs [22]. However, there is a baseline risk for neurodevelopmental problems, since gestational hypertension and preeclampsia may themselves be associated with an increase in adverse paediatric neurodevelopmental effects mainly due to preterm delivery [17].

Labetalol intravenously has been adopted internationally as antihypertensive agent of choice in severe hypertension in pregnancy, because it does not lead to reflex tachycardia or increased intracranial pressure. Reported side effects of labetalol are evident for both women (lack of blood pressure control in 37–53% of patients) and fetus [23]. Intravenous nicardipine, a calcium-channel blocker, may be an attractive alternative for the treatment of severe hypertension in pregnancy since it has high potential to lower maternal blood pressure, a fast onset of action and a short elimination half-life (2 to 5 min). Reflex tachycardia seems to be the most troublesome side effect The expected faster and tight control of maternal blood pressure using intravenous nicardipine as compared to oral nifedipine, also a calcium-channel blocker, might better control its downsides; compromise of cerebral perfusion or jeopardize uteroplacental blood flow for women with severe preeclampsia [20,23]. Data from one trial (50 women) suggested that nifedipine was associated with a better safety profile than labetalol (RR 2.17, 95% CI 0.98 to 4.79). However, there are insufficient data for reliable conclusions about the comparative effects of these two agents [24].

Hydralazine is a direct arteriolar vasodilator that directly affects the smooth muscle in precapillary resistance vessels with minimal effect on postcapillary venous capacitance vessels resulting in decreased

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