Preeclampsia: Update on epidemiologic parameters, etiology and management

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Abstract

Preeclampsia (PE) remains the major cause of maternal and neonatal mortality and morbidity. This pregnancy-specific syndrome is characterized by the onset of hypertension and proteinuria later than 20 weeks of gestation. Several factors have been associated with increased risk of preeclampsia such as nulliparity, ethnicity, overweight before pregnancy, history of vascular complications of pregnancy, chronic hypertension before pregnancy and high blood pressure in the first trimester of pregnancy. The underlying pathogenetic mechanisms of this maternal syndrome are much debated. Current hypotheses include inflammatory disease, vascular-mediated factors, placental ischemia, genetic predisposition, and immune maladaptation. Placental hypoxia is responsible for the maternal vascular dysfunction via the increased placental release of anti-angiogenic factors such as soluble Flt1 and endoglin. The recent advances in the

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comprehension of the pathophysiology of preeclampsia have leaded to the development of new therapeutic approaches, and screening tools based on clinical parameters and biomarkers early in pregnancy. Interventional studies are now needed to demonstrate the real interest of these tests in the general population and their potential place in the primary prevention of the disease.

Keywords: preeclampsia, placenta, PlGF, sFlt-1, prediction, prevention

Public declaration of interest

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I. EPIDEMIOLOGY AND RISK FACTORS

Preeclampsia (PE) remains the major cause of maternal and neonatal mortality and morbidity worldwide with 500.000 maternal deaths each year. In Latin America and in the Caribbean, hypertensive disorders are responsible of one quarter of maternal deaths. In the United-States the prevalence of the disease is around 2-8% of pregnancies, and its incidence is increasing probably because of increased prevalence of risk factors. In Europe, the prevalence of preeclampsia is lower [1]. It affects 1% to 2% of general population and is responsible of 30% of induced preterm deliveries.

This pregnancy-specific syndrome is characterized by the onset of hypertension and proteinuria at or after 20 weeks of gestation. Hypertension is defined by a systolic blood pressure ≥ 140mmHg and a diastolic blood pressure ≥ 90mmHg. Proteinuria is usually considered as significant when ≥ 300mg/24 hours. Several recent classifications use other definitions for proteinuria such a dipstick ≥ 1+ and a random protein-to-creatinine ratio over 30mg/mmol (the Society of Obstetricians and Gynaecologists of Canada (SOGC) and the American Society of Hypertension (ASH)) [1]. Several risk factors have now been

clearly identified. Among those, nulliparity, preeclampsia in a previous pregnancy, family risk of preeclampsia, multiple pregnancy, pre-existing diabetes and antiphospholipid syndrome are the one with higher relative risk [2]. Oocyte donation also appears to be a factor associated with high risk of preeclampsia. Other factors such maternal age over 40 years, pre-existing hypertension pre-existing renal disease, and ethnicity, are associated with a higher incidence of preeclampsia [3]. These risk factors have been combined to several biomarkers (PAPP-A, PlGF) and uterine Doppler for early prediction of pre-eclampsia. Very promising results have been reported by Poon *et al.*, with a high detection rate of early onset severe preeclampsia. It was estimated that 93.1% of early preeclampsia could be detected with a 5% false-positive rate and that 1 in 5 pregnancies classified as being screen positive would develop pregnancy hypertension [4]. However, this high sensitivity has not been confirmed by more recent studies and whether or not these tests will be useful across the range of placenta-related complications remains unknown [5].

II. PATHOPHYSIOLOGY

The underlying pathogenetic mechanisms of this maternal syndrome are much debated. Current hypotheses include inflammatory disease, vascular-mediated factors, placental ischemia, genetic predisposition, and immune maladaptation [6]. The leading hypotheses strongly rely on placental dysfunction mainly due to defective uteroplacental vascularisation, early in pregnancy. Angiogenesis and vascular transformation of the uteroplacental unit, which are crucial to normal fetal development, are impaired leading to chronic hypoperfusion of the placenta. Myometrial vascular network is poorer compared to normal pregnancies and myometrial spiral arteries have a more pronounced muscular coat and elastica leading to reduced uteroplacental blood flow and episodes of irregular placental perfusion. Reduced and intermittent perfusion of the intervillous space leads to hypoxia and/or reoxygenation episodes generating reactive oxygen species and leading to placental oxidative stress and placental dysfunction. The initial mechanisms responsible for abnormal trophoblast invasion are not clearly understood but are supposed to be linked to excessive or atypical maternal immune response to trophoblastic cells, and also to impaired decidualisation.

Placental hypoxia is responsible for the maternal vascular dysfunction via the increased placental release of pro-inflammatory agents (cytokines, oxidized placental debris) and anti-angiogenic factors such as soluble Flt-1 and endoglin [7, 8]. These soluble receptors bind VEGF, PLGF and TGFbeta in the maternal circulation, causing endothelial dysfunction in many maternal tissues. The anti-angiogenic factors are released weeks before the onset of clinical symptoms and could therefore be used for preclinical diagnosis of preeclampsia. Recently another important pathophysiological pathway has been described. It involves activating autoantibodies to the Angiotensin 1 receptor in maternal circulation.

III. MANAGEMENT OF PREECLAMPTIC PATIENTS [1, 9, 10]

Until today, the only treatment of preeclampsia is delivery. Therefore before 37 weeks of gestation, managing preeclamptic patients consists in balancing the risks for the mother of prolonging pregnancy and the risks for the neonate of a preterm delivery. Complications of preeclampsia are frequent in early and late onset preeclampsia. Maternal and perinatal complications are listed in table 1.

Table 1 - Complications of preeclampsia

	Complications
Central nervous system	Eclampsia (seizures) Cerebral hemorrhage (stroke) Cerebral edema Cortical blindness Retinal oedema Retinal blindness
Renal system	Renal cortical necrosis Renal tubular necrosis
Respiratory system	Pulmonary oedema
Liver	HELLP syndrome Hepatic rupture
Coagulation system	Disseminated intravascular coagulation Microangiopathic heamolysis
Fetus - Neonate	Death Intra-uterine growth retardation Preterm delivery

There is no universally accepted standard of care for preeclampsia. For the mother, the aim of clinical management is to avoid severe systolic and diastolic hypertension, to prevent and treat seizures of eclampsia, and to avoid the use of aggressive rehydration. Severe hypertension defined by systolic blood pressure ≥ 160mmHg or diastolic blood pressure ≥110mmHg must systematically be treated. It is also recommended to treat non-severe hypertensions even if improvement on pregnancy outcomes has not been clearly demonstrated. The control of blood pressure should be progressive to avoid sudden maternal hypotension leading to acute placental hypoperfusion. Antihypertensive drugs usually used during pregnancy are nifedipine, labetalol, urapidil, hydralazine. Angiotensin converting enzyme inhibitors, angiotensin II receptor inhibitors, atenolol, and prazosin should be avoided. The blood pressure target is a mater of debate. Diastolic blood pressure should be maintained between 85mmHg and 95mmHg. Prevention and treatment of eclampsia is based on magnesium sulfate given intravenously. Primary prevention of eclampsia is recommended for patients with severe preeclampsia. Magnesium sulfate can be associated to nifedipine effectively and safely. Plasma expansion should not be considered anymore because of increased risk of pulmonary edema. In case of women with early onset HELLP syndrome, expectant management may be offered with extreme vigilance in very specific centers. In such cases corticosteroids have not been shown to be associated with significant maternal or perinatal benefits.

For the fetus clinical management depends on gestational age. Before 34 or 36 weeks of gestation, according to the severity of the disease, conservative management is usually proposed and a course of steroids is administered to the mother. Based on studies with patients in preterm labor, magnesium sulfate for fetal neuroprotection is now recommended for fetuses at risk of preterm birth. Whether this beneficial effect exist in fetuses from preeclamptic patients, often growth restricted, needs to demonstrated. In utero transfer to appropriated perinatal center according to gestational age should also be considered before 36 weeks of gestation. For women developing preeclampsia before 24 weeks of gestation, perinatal survival is extremely poor. In such cases, termination of pregnancy should be recommended to patients to avoid maternal complications. After 36 weeks of gestation, the delivery should be considered.

IV. PREVENTION

There is still no demonstrated primary prevention for preeclampsia. Nutritional preventive measures such diet low in salt, antioxidant (vitamine C and or E), calcium, fish oil or magnesium sulfate are not effective. Low-dose aspirin is associated with a significant reduction of preeclampsia when administered before 20 weeks of gestation to high-risk patients, especially those with a history of severe early onset of preeclampsia. In this group of patients the risk of recurrence may be up to 40%.

Several models predicting the risk of preeclampsia have shown that it is possible to identify, early in pregnancy, a population of pregnant women who later develop preeclampsia. To date, these models haven't been used in interventional trials and therefore their utility in clinical practice is not clearly established.

V. PERSPECTIVES

The recent advances in the comprehension of the pathophysiology of preeclampsia have leaded to the development of new tools for preclinical diagnosis of preeclampsia and potential new therapeutic approaches. Recent prospective studies suggest that the measurement of PlGF or sFLT-1/PlGF ratio predict quite accurately severe maternal and perinatal outcomes in patients with a suspicion of preeclampsia [11]. These tools could be of great interest in helping to detect patients that require specific managements (*in utero* transfer, injection of corticosteroids) before the diagnosis of established preeclampsia. Further studies are needed to assess the real benefit of these tools compared to already available parameter (uric acid, fetal dopplers).

New therapeutic approaches are also emerging. It has recently been shown that extracorporeal apheresis can lower circulating levels of sFLT-1 [12]. Further studies are warranted to determine whether this intervention safely and effectively prolongs pregnancy and improves maternal and fetal outcomes. There is also increasing experimental evidence supporting the idea that statins could be useful in the management of preeclampsia. A randomized, placebo-controlled, double-blind trial (Statins to Ameliorate Pre-eclampsia; ISRCTN 23410175 and EudraCT 2009-012968-13; web site *www.stamp.bham.ac.uk*)

has been initiated in the UK in order to study the effects of pravastatin in severe early-onset preeclampsia.

CONCLUSION

Preeclampsia is a multifactorial disease responsible for an important part of maternal and perinatal morbidity in developing and non-developing countries. Recent advances in the comprehension of the pathophysiology of the disease have led to the development of new tools for early prediction or preclinical diagnosis of preeclampsia, and also of potential new therapeutic approaches. Further studies are needed to determine the place of these recent developments in clinical practice.

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