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Review article

Imitators of preeclampsia: A review

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ABSTRACT

This review article describes disorders that may imitate preeclampsia (PET), preeclampsia with haemolysis, elevated liver enzymes and low platelets (HELLP syndrome) and eclampsia.

1. Introduction

Preeclampsia (PET) is a common disorder complicating approximately 4.6% of pregnancies. The incidence is 1.5 to 2-fold higher in first compared with subsequent pregnancies. PET may affect multiple organ systems (Table 1) and as a result many less common disorders may imitate its presentation (Table 2). Correct diagnosis is critical regarding management of the index pregnancy, the risk of recurrence in future pregnancies, and prognostic implications for the mother in the long term. The objective of this review is to describe disorders that may imitate preeclampsia, HELLP syndrome and eclampsia, focusing on clinical features, laboratory tests and imaging that differentiate between PET and alternative diagnoses, and why this is important with regard to management.

Abbreviations: ACTH, adrenocorticotroph; AFLP, acute fatty liver of pregnancy; aOR, adjusted odds ratio; ARR, aldosterone:renin ratio; ATIII, Antithrombin III; CAPS, catastrophic antiphospholipid syndrome; CPAP, continuous positive airway pressure; CS, Cushing's syndrome; CT, computerised axial tomography; CVST, cerebral vein sinus thrombosis; FMD, fibromuscular dysplasia; HELLP, haemolysis, elevated liver enzymes and low platelets; HSVH, herpes simplex viral hepatitis; IUFD, intrauterine fetal death; IUGR, intrauterine growth restriction; LCHAD, long chain hydroxyacyl coA dehydrogenase; LDH, lactate dehydrogenase; MEN, Multiple Endocrine Neoplasia; MRI, magnetic resonance imaging; MS, mirror syndrome; NF, neurofibromatosis; NND, neonatal death; NSAID, non-steroidal anti-inflammatory drug; PA, primary aldosteronism; PET, preeclampsia; PRA, plasma renin activity; PRES, posterior reversible encephalopathy syndrome; RADU, renal artery duplex ultrasound; RAS, renal artery stenosis; RCVS, reversible cerebral vasoconstriction syndrome; SDHB, Succinate Dehydrogenase B gene mutations; TTP-HUS, thrombotic thrombocytopenic purpura and haemolytic-uremic syndrome; 24 h UFC, 24 hour urine free cortisol; VHL, Von Hippel-Lindau syndrome.

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2. Imitators of PET without features of HELLP syndrome

PET is usually a disorder of the second half of pregnancy, though cases have been reported as early as 15 weeks gestation in the setting of antiphospholipid syndrome [1]. A meta-analysis of subjects with an index pregnancy complicated by PET reported rates of PET, HELLP, gestational hypertension (GH) and small for gestational age infants to be 16%, 0.2%, 6% and 3.3% in the subsequent pregnancy [2]. The diagnosis of PET is associated with significant long term implications for both maternal and fetal health [3]. A meta-analysis demonstrated that compared with women with uncomplicated pregnancy, subjects with PET had relative risks for hypertension of 3.7, ischaemic heart disease 2.16, stroke 1.81, venous thromboembolism 1.79 and overall mortality 1.49 [4]. Another study demonstrated a 2-fold increase in death due to cardiovascular events in women with PET over a 30 year follow-up period [5]. The risk of subsequent cardiovascular disease death was notably higher among women with onset of PET by 34 weeks of gestation. Women with PET or GH also have a 2-fold increased risk of developing diabetes when followed up for 16.5 years, even in the absence of gestational diabetes mellitus [6]. The offspring of women with PET have higher risk of elevated blood pressure, lipids and body mass index in both adolescence and adulthood.

2.1. Secondary hypertension – renal

2.1.1. Pre-existing renal disease/hypertension

Any disorder associated with hypertension or proteinuria, whether undiagnosed pre-conception, or occurring de novo during pregnancy, may imitate PET. In normal pregnancy, blood pressure

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Table 1
Clinical manifestations of Preeclampsia.

Renal
Proteinuria with inactive urine sediment, hypertension, renal dysfunction, hyperuricaemia, hyponatraemia, peripheral oedema
Cardiorespiratory
Pulmonary oedema, left ventricular dysfunction, pleural and pericardial effusions? Elevated troponin, myocardial ischaemia
Hepatic
Nausea/vomiting, epigastric pain and tenderness, elevated hepatic transaminases, hyperbilirubinaemia/jaundice, hepatic haemorrhage/rupture/infarction, hepatic synthetic dysfunction (hypoalbuminaemia, prolonged prothrombin time), ascites
Haematological
Thrombocytopenia, microangiopathic haemolytic anaemia, disseminated intravascular coagulation
Neurological
Headache, visual abnormalities, altered mental state, cerebrovascular accident, seizures, posterior reversible encephalopathy syndrome, cortical blindness
Fetal
Oligohydramnios, growth restriction, absent or reversed end-diastolic flow on Doppler velocimetry
Placenta
Placental abruption, placental infarction

Table 2
Imitators of PET.

Without features HELLP
Secondary hypertension – Renal
Pre-existing renal disease/hypertension
Renal artery stenosis due to fibromuscular dysplasia
Secondary hypertension – Endocrine
Phaeochromocytoma
Cushing's syndrome
Primary aldosteronism
Obstructive Sleep Apnoea
Mirror Syndrome
Other – Non-steroidal anti-inflammatory drugs, Severe hypothyroidism
HELLP syndrome
TTP-HUS
Acute Fatty Liver of Pregnancy
SLE and Antiphospholipid syndrome
Herpes simplex hepatitis
Other Infections – arthropod-borne, leptospirosis, bacterial sepsis
Other – cocaine, medications, pulmonary hypertension, B12/folate deficiency, Wilson's disease
Eclampsia
Cerebral vein sinus thrombosis
Reversible cerebral vasoconstriction syndrome
Dural puncture
Metabolic – hyponatraemia, hypoglycaemia, hypocalcaemia

Table 3
Features suggestive of "imitators" rather than preeclampsia.

Condition	Features suggestive
Pre-existing renal disease	Hypertension and/or proteinuria pre-conception or before 20 weeks gestation Active urine sediment
Renal artery stenosis	Early onset severe hypertension without proteinuria Neurofibromatosis
Phaeochromocytoma	Paroxysms pallor, diaphoresis, palpitations, headache, chest pain Postural hypotension, weight loss Marked lability blood pressure
Cushing's syndrome	Easy bruising, proximal myopathy, thin skin, pathological fracture, hypokalaemia, early onset hypertension
Primary aldosteronism	Hypokalaemia, hypertension preconception or prior to 20 weeks gestation; postpartum exacerbation/ onset hypertension
Obstructive Sleep Apnoea	Snoring, apnoeas, daytime somnolence
Mirror syndrome	Hydropic fetus, high amniotic fluid volume, haemodilution

Table 4
Features suggestive of "imitators" rather than HELLP.

Condition	Features suggestive
TTP/HUS	Severe haemolysis, marked thrombocytopenia, only mild elevation LFTs, fever LDH:AST ratio > 22.12, reduced ADAMS-TS 13 activity
Acute Fatty Liver of Pregnancy	Severe coagulopathy with minimal/no haemolysis, mild thrombocytopenia, hypoglycaemia, elevated ammonia, markedly depressed Antithrombin III
SLE	Extra renal manifestations disease, active urine sediment, decreased C3 and C4, elevated ds DNA
Catastrophic Antiphospholipid S	Rapidly progressive multiorgan failure with widespread thrombosis
Herpes Simplex Viral Hepatitis	Fever, vesicles, markedly elevated AST and LDH, minimally elevated bilirubin, coagulopathy, absence proteinuria or hypertension

Table 5
Features suggestive of "imitators" rather than Eclampsia.

Condition	Features suggestive
CVST	Absence hypertension or proteinuria, cranial nerve palsies
RCVS	Thunderclap headache, focal neurological deficits
Dural puncture	Post-dural puncture headache, absence hypertension or proteinuria

falls in 2nd trimester, rising to pre-conception levels in last trimester. The degree of proteinuria increases substantially during pregnancy in nearly all types of underlying renal disease [7]. The significant increase in blood pressure and proteinuria in third trimester in subjects with underlying hypertension and/or protein-