biomnis
SPECIALISED MEDICAL PATHOLOGY
Focus
issue 01

What are the markers for pre-eclampsia?

Definitions

Pre-eclampsia (PE), formerly known as toxaemia of pregnancy, is specific to humans. It consists of a maternal syndrome that includes swelling, proteinuria, hypertension, kidney damage and clotting disorders. The foetal syndrome is marked by a decrease in amniotic fluid volume and oxygenation with intrauterine growth retardation (IUGR).

The maternal diagnostic criteria are well-established:

- Blood pressure › 140/90 mm Hg
- Proteinuria › 0.3 g/24 hrs
- Frequent hyperuricaemia
- Other symptoms: swelling, headaches, "floating specks", nausea, vomiting.

Pre-eclampsia may occur in early-onset form (before 34 weeks of gestation), accounting for approximately 30 % of cases (more detrimental for the foetus), or late-onset form (after 34 weeks of gestation). Note that arterial hypertension and proteinuria generally disappear in the days or weeks following delivery.

Eclampsia occurs in cases of uncontrolled PE, resulting in convulsive (epileptoid) attacks, loss of consciousness, swelling (+++), massive proteinuria, placental detachment, acute renal failure (ARF), brain haemorrhaging, and acute pulmonary oedema (APO).

Epidemiology

- The frequency of PE is of the order of 2 to 7 % in healthy nullipara and 20 to 25 % in the event of a major risk factor. Arterial hypertension is severe in 6 to 15 % of cases.
- The frequency of eclampsia is low (‹ 0.1 %), but is the cause of 15 to 20 % of deaths in developed countries.
- Preventive measures and symptomatic treatments: recovery generally occurs without any after-effects and without any recurrence in a subsequent pregnancy. However, in 5 to 11 % of cases, long-term complications may occur.

In cases of severe PE

- Induction of labour and delivery of placenta if › 34 weeks of gestation.
- Preventive corticotherapy if ‹ 34 weeks of gestation but risk of complications (HELPP syndrome, retroplacental haematoma, etc.).

Treatments

- Magnesium sulphate (preferable to phenytoin or diazepam)
- Vascular filling to correct hypovolaemia
- Antihypertensives (nicardipine, nifedipine)
- Aspirin

Risk factors

Major risk factors

- Primiparity, twin pregnancy
- Chronic hypertension
- Diabetes, obesity
- Pre-existing thrombophilia
- APLS, PC/PS deficiency, activated PC resistance, factor V leiden (subject to controversy)

Secondary risk factors

- Paternal or couple-related factors
- Donor insemination
- ICSI using surgically obtained semen
- Genetic factors (predisposition?)
- "Dangerous father" factor

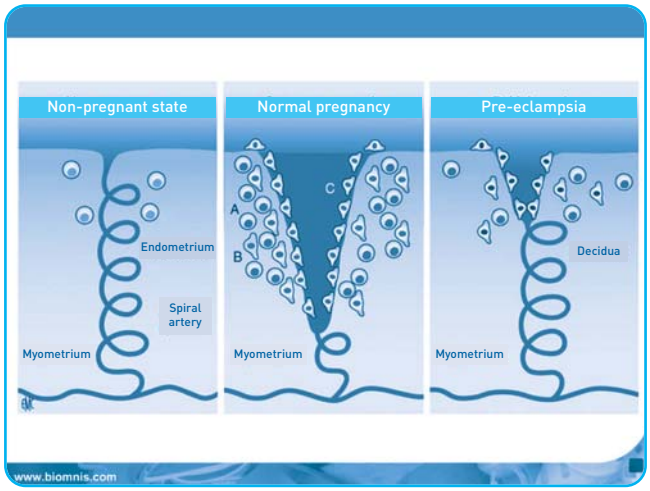
Physiopathology

A number of hypotheses are suggested in the physiopathology of pre-eclampsia, such as unfavourable placentation, release of placental debris, endothelial activation, inflammation, genetic conflict.

Unfavourable placentation

- **In the case of normal placentation,** the trophoblasts invade the myometrium towards the spiral arteries. In this way, the endothelium of the spiral arteries is replaced by trophoblasts: a low-resistance arteriole system with no maternal vasomotor control is created. A protein, PP13 or galectin 13, is involved in placentation and maternal artery remodelling. Several cytokines are involved in angiogenesis and vascular stability, i.e. VEGF, PLGF, Angiopoietin 2, and IFNγ.

In the case of PE: the uterine invasion remains superficial



Cell debris hypothesis

In cases of PE, trophoblast apoptosis would appear to be amplified, with the apoptosis being under the action of TNFα, IL2, IFNγ, FAS-FAS ligand.

Inflammation

The release of debris induces an increase in inflammatory stimuli. Binding with monocytes and neutrophils releases TNFα, IL1 and 2 and superoxide radicals. In this way, oxidative stress is increased in cases of PE. Foetal DNA and cytokeratin are increased.

Other placental reactions

During pregnancy, inhibin A is secreted by the corpus luteum and by the placenta, peaking at 11 weeks of gestation, dropping to a plateau at 14-25 weeks of gestation and subsequently rising again. Its level falls very rapidly in the postpartum period. In cases of PE, inhibin A increases along with activin A.

Endothelial activation

During a normal pregnancy, angiogenic factors such as VEGF and PLGF are released, stimulating placental growth and inducing a systemic vasodilative action. In addition, the prostacyclin/thromboxane A2 ratio is favourable. In PE, a vasoconstrictive effect is predominant (existence of a soluble VGEF receptor inhibiting VGEF binding with its cell receptor). E selectin and P selectin expression is increased.

Oxidant status

The NO* radical (vasodilator) is produced from l-arginine under the effect of NOS III (endothelial). In the case of PE, asymmetric dimethyl-arginine (ADMA) accumulates, inhibiting the vasodilative effect. Similarly, malonic dialdehyde, a lipid peroxidation marker, increases in cases of PE.

Circulatory and renal aspects

Reactivity to vasoconstrictive stimuli is decreased during pregnancy. In the kidney, renal plasma flow (RPF) and the glomerular filtration rate (GFT) are increased. On the other hand, the RPF and GFT are decreased in cases of pre-eclampsia.

PE and haemostasis

The anti-AT1 antibodies present in cases of PE are synchronous with the maternal symptoms. They activate the AT1 (angiotensin 2) receptor and PAI-1 but inhibit trophoblast invasion. They induce free radical production. They also activate the tissue factor (initiating the extrinsic haemostasis pathway). The activity of annexin A5 (protein with anticoagulant action expressed by trophoblasts) decreases in cases of pre-eclampsia.

Assistance expected from a PE marker

The benefit of a biological marker is to be able to:

- Identify the risk of PE from the first trimester of gestation.
- Give a warning on the imminence of the worsening of a condition.
- Be as sensitive and specific as possible.

Markers mentioned

Markers mentioned

Cited in bibliography		To be monitored	
Activin A	+/-	Cell free DNA	+
Inhibin A	+	sFlt1	+
Oxydant statut	+	P-selectin	+
Annexin A5	-	ADMA	+
Anti-AT1 antibodies	+	Uric acid	+
NB Doppler in 2nd trimester		PP13	-
on uterine arteries		Endoglin	+

www.biomnis.com

Some studies have been conducted on the benefits of the **P-Selectin** assay in plasma and have demonstrated that this marker is beneficial between 10 and 14 weeks of gestation with an NPV of 99 % for a 60 ng/ml cut-off. **Endoglin** is an early marker as it increases 2 to 3 months before PE develops. **PP13** has a predictive value in the first trimester of gestation (combined with a Doppler examination and the tests conducted during T21 screening). **ADAM 12** is a metalloprotease involved in placental and foetal growth, bound with adhesion receptors (such as integrins and syndecans) which affect cell differentiation and survival.

It has two molecular forms:

- Membrane-bound ADAM 12-L (long).
- Secreted ADAM 12-S (short).

BNP and **Urotensin II** are relatively new markers to be considered.

It would appear to be of interest to monitor research on PP13, endoglin and ADAM 12 as they could be useful in predicting the occurrence of pre-eclampsia.