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Pre-eclampsia screening
during the first three months of pregnancy

The cause and pathogenesis of the pre-eclampsia (PE) disorder is almost certainly the result of multiple factors. It affects 1 to 4% of pregnancies and develops during the first three months. Yet, the symptoms do not appear until the third trimester of pregnancy. Almost half of all cases of PE occur early on, before 34 weeks of gestation. These cases are the most dreaded cases as they are often associated with iatrogenic prematurity or foetal adverse effects (intrauterine growth retardation IUGR or retroplacental haematoma).

Physiopathology and the interest of performing PE screening

The definition of PE is mainly clinical: systolic arterial blood pressure › 140 mmHg and/or diastolic BP › 90 mmHg combined with proteinuria › 0.3 g/24 hrs occurring after 20 weeks of amenorrhoea. Oedema is a classic symptom of the disease but is not a discriminatory factor. Approximately 20% of cases cannot be dissociated (without proteinuria).

This maternal endothelial disease dissipates after delivery (sometimes persisting for up to 6 weeks). Nevertheless, it causes vascular damage: Some 20% of women develop chronic hypertension and/or a metabolic syndrome following PE.

The zone of PE: the placenta

During a normal pregnancy, the implantation of a blastocyst with its trophoblast crown occurs in a vascularised, oxygen depleted (hypoxia) environment. This relative hypoxia means that the trophoblast proliferates instead of differentiates and colonises the vascular wall of the spiralled arteries, at the decidua and in the internal section of the myometrium. The depth and spread of the invasion of the spiralled uterine arteries are key factors in obtaining normal implantation.

In cases of PE, trophoblastic placental invasion is poor, incomplete and not deep enough. The arterial walls remain muscular and elastic, undilated and with insufficient output, which evolves into a generalised maternal endothelial disorder.

With regards to the trophoblast, there are angiogenesis regulation factors (positive and negative), notably VEGF (Vascular Endothelial Growth Factor), whose expression is modulated in function to local conditions and genetic interactions. These angiogenic growth factors act on membrane receptors including Flt1. This receptor, when bound, stimulates angiogenesis by favouring VEGF recognition. In cases of poor implantation and unfavourable environmental factors, a different form of this receptor proliferates (sFlt1: the soluble part of the receptor). These incomplete forms (sFlt1, but also soluble endoglins) act as a lure to capture and neutralise growth factors that favour implantation (VEGF, PIGF: Placental Growth Factor).

At the placenta, the key elements are therefore good trophoblastic implantation and an unbalanced angiogenic/anti-angiogenic ratio.

The role of the aldosterone-angiotensin-renin system (AARS)

During a normal pregnancy, there is a decrease in peripheral vascular resistance, an increase in cardiac output by approximately 40%, an increase in vascular compliance and a decrease in vasopressor sensitivity (angiotensin II, norepinesphrine). AARS is normally stimulated. During cases of PE, AARS is inhibited thus causing hypovolemia and hypersensitivity to angiotensin II causing a significant vasoconstricting effect.

The role of immunity

Incompatibility between the mother and foetus has been investigated in depth through the model of transplant rejection. In certain cases, a reaction against the paternal antigens transferred to the foetus occurs, which leads to a decrease in the cytokines that favour implantation, notably prostacyclins. The role of immunity is fixed by certain elements: PE is more frequent in primiparous women, in cases of a change in paternity or in cases of IVF by surgical ICSI (intracytoplasmic sperm injection) (whereby the sperm is unlikely to come into contact with the endometrium), PE risk factor for the next pregnancy.

The genetic line of inquiry

PE in first-degree relations increases the risk of PE in the following pregnancies by 2-4 fold. A man whose previous partner experienced PE increases the risk of PE in his new partner by 2-fold when compared to the general population.

Three hypotheses of genetic transmission have been discussed: homozygous mother-foetus transmission for a recessive gene, polygenic transmission or paternal suppressive fingerprinting on a recessive gene.

The PE mechanism is therefore multi factorial, relying on a combination of factors that are directly implicated in the placental lesion and cofactors (treatments or diseases), which have an effect that favours a state of hypercoaguability (APS, thrombophilia etc), deregulated inflammation and/or oxidative stress during the pregnancy. The other factors that favour PE are chronic hypertension, gestational diabetes, connectivity, type 1 diabetes, an increased maternal age, limited exposure to semen, family history of PE and previous PE during a prior pregnancy.

Pre-eclampsia and intrauterine growth restriction (IUGR) prevention by aspirin

Over the last 30 years, 60 randomised trials have been performed to determine the role of aspirin in PE.

In 1985, an observational study, carried out on women at high risk of PE and who received aspirin at a dose of 150 mg/day from the 12th week of pregnancy, showed a decrease in PE, IUGR and perinatal deaths. Some 97% of the cases in the studies (61 trials with 59004 patients) involved low-dose aspirin (50-80 mg/day) treatment from the 16th week, whereas only 3% of patients started their treated before the 16th week at a dose of 100 - 150 mg/day.

As such, if all of the randomised trials with aspirin were grouped together into a meta-analysis, aspirin would have a modest or minimal affect on women at risk of PE. Several experts have put forward the idea that the heterogenity of the results observed could be explained by the effect of the gestational age. Indeed, the lack of transformation of the spiral arteries (SA) plays a major role in the origin of PE. The earlier the onset of PE, the lower the percentage of SA transformation: 75% of SA are untransformed in early-onset PE (delivery before reaching full term) whereas less than 35% of SA transformation occurs in late-onset PE (deliver at full-term). Meaning spiral artery transformation occurs between 10 and 16 weeks of pregnancy. As such, if we want to stop this process, we need to intervene early on in pregnancy. It has been shown that aspirin treatment given in the first trimester improves deep placentation, which reiterates the importance of early treatment intervention.

As such, if we only consider the studies involving aspirin given before 16 WA, the results are homogenous. They show a reduction of at least 50% in the risk of PE (RR= 0.47 [0.34 – 0.65]; p < 0.00001). This aspirin effect is much more significant in early onset of PE (prevented in up to 80% of cases), most likely due to the stronger association with a placenta implantation defect. With regards to late-onset PE, the effect of aspirin is not as significant. Finally, the beneficial effect of low-dose aspirin initiated before 16 weeks of amenorrhoea has also be seen in intrauterine growth restriction (IUGR) and peri-natal death.

Which women would benefit from aspirin treatment?

Women with a previous medical history of pre-eclampsia (RR = 0.39 (0.24 -0.64), p< 0.001) or with an abnormal Doppler scan result during the first 3 months of pregnancy (RR = 0.46 (0.26 -0.82), p< 0.01).

Wouldn't all women benefit from aspirin treatment during the first three months of pregnancy?

No, because only 3-4% will have a placentation defect and the compliance rate for the treatment is <50%. In addition, if we don't identify women 'at risk', they will not be given adequate and adapted care (Doppler etc.). ; finally, although side-effects with aspirin are rare, they would become frequent should all pregnant women be given it.

Currently, the NICE Guidelines recommend treating women 'at risk' (with selection based on risk factors, which represents 19-45% of pregnant women!). with 75 mg/day of aspirin from the 12th week of amenorrhoea until delivery. In France, recommendations from the Collège National des Gynécologues et Obstétriciens (French National College of Gynaecologists and Obstetricians)(2009) are to start aspirin treatment with 75-160 mg/day in patients considered high-risk for PE, before the 20th WA.

When should aspirin treatment be initiated?

Between the 8th and the 14th WA (if not clinically beneficial to start earlier). Administration in the evening before going to bed seems to be the most efficient regime in the prevention of placental disorders (circadian rhythm)

At what dose?

The majority of the studies used a dose of 75 mg/day; today, the trend leans towards administering 100 to 150 mg/day due to a 'resistance' at doses of 75-80 mg/day seen in approximately 1/3 of women. Indeed, a dose of 100 to 150 mg/day has been associated with less severe forms of PE in women considered 'resistant' to aspirin.

When should treatment be stopped?

Between 34 and 37 WA? Up until delivery? There is no real answer to this question.

Conclusion

Aspirin initiated between 10-16 weeks of pregnancy prevents pre-eclampsia (especially early-onset forms), intrauterine growth restriction (IUGR) and perinatal death. Treatment must be prescribed early on, at a dose of ≥ 100 mg/day in high risk women, with assessment based on their previous medical history of PE and biomarkers.

Risk calculation for pre-eclampsia in the laboratory

The clinical interest of screening for early-onset pre-eclampsia lies in the possibility of establishing prophylaxis through aspirin. The implementation of such a screening programme could benefit the dosage regimes already given during pregnancy for the evaluation of Down's syndrome (T21) risk. The idea is to select women at risk in function to their clinical details and to combine this information with the biophysical markers and biological quantification results.

Clinical details

- BMI: obesity is a PE risk factor,
- Geographical origin of the patient: increased risk of PE in women from sub-Saharan Africa and the West Indies, parity: nulliparity, PE risk factor,
- previous personal or familial history of PE,
- chronic hypertension (treated or otherwise),
- Smoker status: an active smoker decreases the risk of pre-eclampsia (correction of the biological marker distribution expressed in MoM).

Biophysical measurements

- Arterial pressure: measured at between 11+0 weeks of amenorrhoea (WA) and 13+6 WA, ideally on both arms (if this is not possible, then on one arm), enables us to calculate the mean arterial pressure (MAP) from the systolic and diastolic pressures:

$$MAP = \frac{\text{Diastolic} + (\text{systolic} - \text{diastolic})}{3}$$

- Doppler scan of the uterine arteries: pulsatility index (PI).

PAPP-A and PlGF serum assays

They are performed on samples collected between 11+0 WA and 13+6 WA (1st three months of pregnancy), in combination with foetal Down's syndrome screening.

- **PlGF** (*Placental Growth Factor*), which is produced by the placenta, is an angiogenic factor that belongs to the vascular endothelial growth factor family (VEGF), which is a marker of endothelial function. The circulating concentration of PlGF decreases before the onset of clinical symptoms of PE.
- **PAPP-A** (*Pregnancy-Associated Plasma Protein-A*) is a vascular marker and is quantified routinely as a serum marker for Down's syndrome screening during the first trimester of pregnancy. The more its concentration decreases, the greater the risk of PE, especially severe PE.

The risk calculation is undertaken in the laboratory; it can be performed despite a lack of arterial pressure measurements and/or Doppler scan results (but is less precise); the dates of biophysical measurements and biological sampling must be as close as possible. The greater the details supplied (clinical details, biophysical measurement etc.) the better the risk calculation is. The combination of the serum markers results along with the clinical details and biophysical markers enables the detection of up to 93% of cases of early pre-eclampsia (with approximately 5% of false positives).

Treatment using an appropriate software programme of all of the data enables an early PE risk calculation (<34 WA) or late onset (≥ 34 WA) to be estimated. This calculation can only be used for single foetus pregnancies.

The decision threshold is 1/20. A risk below 1/20 does not put the patient into a high-risk group for PE.

Carole Emile, following a communication by Prs Yves Ville, Howard Cuckle, Emmanuel Bujold, Cyril Huissoud and Dr Corinne Sault during a symposium on 'Le dépistage de la pré-éclampsie au 1er trimestre de la grossesse' (Pre-eclampsia screening in the first three months of pregnancy), Lyon and Paris, 23 and 24 June 2014.

To find out more, visit: 'Pre-eclampsia screening during the first three months of pregnancy'.