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REVUES GÉNÉRALES ET ANALYSES PROSPECTIVES

Serum markers for pre-eclampsia: An update on the analytes to be determined in the first, second, and third trimester☆,◊

Les marqueurs sériques de la pré-éclampsie : le point sur les molécules à déterminer au premier, deuxième et troisième trimestre

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Summary Pre-eclampsia is a pregnancy-specific disorder which affects up to 10% of pregnancies and which contributes substantially to perinatal morbidity and mortality of both mother and newborn. Many molecules have been evaluated as potential serum markers for the presence and confirmation of the disease in the third trimester, and subsequently for its prediction in the second trimester. With the increasing sensitivities of the laboratory assays, these efforts are now focused to the first trimester. Impaired early trophoblast invasion is supposed to be at the origin of the events leading to pre-eclampsia, suggesting that it should be possible to detect abnormal levels of certain molecules or markers, in particular those related to trophoblastic activity, at the very early stages of pregnancy. The scope of this paper is to review, with data from the literature as well as from an in-house study, the usefulness of various maternal serum markers, with a special focus on those of placental origin, for the early prediction of pre-eclampsia occurring later during gestation. It remains difficult to predict late-onset pre-eclampsia in early pregnancy, and no ''miracle'' first trimester serum marker has so far been found to be specifically associated to this pathology. The use of formulae combining concentrations of a set of markers, which must be regulated independently from each other, may increase the detection rate. Elevated concentrations of Inhibin A, Activin A and soluble endoglin (sEng), or reduced levels of Placenta Growth Factor (PLGF), Pregnancy-associated Plasma Protein A (PAPP-A), or Placental Protein-13 (PP13) indicate, with high sensitivity but low specificity, an increased risk of a later occurring gestational pathology and should alert the clinician.

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Dépistage ;
Premier trimestre

Résumé La pré-éclampsie est une pathologie gestationnelle qui touche jusqu'à 10 % de grossesses et qui contribue substantiellement à la morbidité et la mortalité périnatale de la mère et du nouveau-né. Plusieurs molécules ont été évaluées comme marqueurs sériques potentielles pour la présence et la confirmation de la maladie dans le dernier trimestre et par la suite pour sa prédiction au cours du deuxième trimestre. Avec les sensibilités augmentées des méthodes immuno-analytiques courants, ces efforts sont de plus en plus focalisés sur le premier trimestre. Une invasion trophoblastique compromise est supposée être à l'origine des événements menant à la pré-éclampsie, ce qui suggère qu'il devrait être possible de détecter, aux premiers stades de la grossesse par le biais de niveaux sériques anormaux de certaines molécules, un risque augmenté de pré-éclampsie ultérieure. Entrent particulièrement en ligne les marqueurs apparentés à l'activité trophoblastique. Cet article essaie de résumer, avec les données de la littérature de même que d'une étude interne, l'utilité de divers marqueurs sériques maternels pour la prédiction précoce d'une pré-éclampsie arrivant tard dans la gestation. Ce dépistage de pré-éclampsie tardive (*late onset*) au premier trimestre reste difficile, et aucun marqueur « miracle », associé spécifiquement à cette pathologie, a pu être identifié à ce jour. L'application de formules combinant plusieurs marqueurs, qui doivent être indépendants les uns des autres, pourrait augmenter le taux de détection. Des concentrations élevées d'inhibine A, d'activine A, de l'endogline soluble, ou des niveaux réduits de Placenta Growth Factor (PLGF), de la PAPP-A ou de la protéine placentaire 13 (PP13) indiquent, avec une bonne sensibilité mais une spécificité assez basse, un risque augmenté d'une pathologie gestationnelle ultérieure et devrait alerter le praticien.

Introduction

Pre-eclampsia, a pregnancy-specific disorder affecting 8—10% of gestations [1,2] and defined by gestational hypertension and proteinuria, contributes substantially to the perinatal morbidity and mortality of both mother and newborn. It is thought to be an early placental dysfuntion [3], characterised by insufficient invasion of the spinal arteries by the trophoblast, placental ischaemia [4], and impaired perfusion of the uteroplacental unit which can lead to fetal growth restriction (FGR). In spite of a large number of investigations, the underlying aetiology of the disease remains unclear. The release of substances of trophoblastic origin such as placental debris, growth factors, placental hormones, and pro-inflammatory cyctokines lead to an excessive maternal inflammatory response [5,6]. The maternal symptoms (hypertension, proteinuria) appear later in pregnancy, and are the consequences of endothelial activation and dysfunction [7,8]. Currently, the delivery of the placenta is the only effective therapy of pre-eclampsia, but this carries for the baby the sequelae of an induced preterm delivery.

The assessment and the prediction of pre-eclampsia has traditionally been on the basis of risk factors in the maternal history and the examination for the presence of hypertension, proteinuria and oedema. More recently, measurable manifestations of abnormal placentation and reduced placental perfusion associated with the disorder have been added to the panel of investigations. Research initially focused on non biochemical markers such as midtrimester blood pressure measurements [9,10] or an increased sensitivity to vasoactive substances [11], but none of these has so far been shown to be of clinical value. The exception to this fact is Doppler sonography of the uterine artery, which is currently under intense investigation but which is not within the scope of this paper on biochemical pre-eclampsia markers.

In the mid-nineties, the focus shifted towards biochemical markers. The purpose of this article is to review, in terms of laboratory predictive performance rather than biological function and pathogenetic role, those of these substances with a potential clinical usefulness for the assessment and the prediction of pre-eclampsia. Given the large and ever increasing number of them, this can only be done in a non exhaustive way.

Third-trimester assessment using serum markers

Before reviewing the serum markers playing a potential clinical role in the second and first trimester screening, we are taking a brief look on the information available on the molecules showing an abnormal circulating concentration pattern in the third trimester or after the onset of the maternal symptoms of pre-eclampsia. We have previously confirmed the presence of elevated serum levels of the three placental products pregnancy-associated plasma protein A (PAPP-A), inhibin A, activin A, and the non placental soluble endothelial (sE-) selectin [12]. Other adhesion molecules circulating in soluble form (ICAM-1, VCAM-1) show similarly elevated serum levels [13], and the same was suggested to be the case for some inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor α (TNF-α) [14]. There are, however, a few serum marker proteins on which the literature is inconsistent in terms of the deviation of their serum levels in women with pre-eclampsia in comparison to healthy pregnant controls of identical gestational age. While significantly reduced serum concentrations of placenta growth factor (PLGF) have been confirmed