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FUNCTION TESTING AND THERAPEUTIC FOLLOW-UP

Second-trimester serum levels of placenta growth factor (PLGF) and inhibin A are increased in smokers. Implications for pre-eclampsia risk assessment

Retentissement du tabagisme sur le taux sérique du facteur de croissance placentaire (PLGF) au 2e trimestre. Considérations par rapport au dépistage de la prééclampsie

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Abstract Biochemical risk assessment in pregnancy based on circulating marker protein levels has been introduced for several present or later occurring gestational or fetal pathologies. For pre-eclampsia (PE), increased concentrations of inhibin and activin with decreased levels of placenta growth factor (PLGF) were found in the second-trimester. While maternal smoking does not influence the serum levels of many markers, its effects on activin A and PLGF, and hence on the risk assessment result, has never been studied. Sera, obtained at 17 pregnancy weeks from 42 smokers and 47 non-smokers, were analyzed for inhibin A, activin A and PLGF, together with eight other markers. PLGF, but not activin A was increased at 17 weeks in the smokers. Previously reported elevations in inhibin A levels were confirmed. These new findings indicate that PLGF and inhibin A, but not activin A, will require the smoking status to be taken into account in screening tests for PE and other gestational pathologies.
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MOTS CLÉS
Tabagisme ;
PLGF ;

Résumé Le calcul de risque à base de marqueurs sériques, en première moitié de grossesse, est devenu pratique courante pour un certain nombre de pathologies gestationnelles et fœtales. Dans le cas de la prééclampsie, des concentrations élevées pour l'inhibine et l'activine, accompagnées de taux réduits pour le facteur de croissance placentaire (PLGF), ont été décri-

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tes. La consommation régulière de cigarettes n'influence pas la concentration sérique d'une majorité de marqueurs testés mais son effet sur les taux d'activine A et PLGF et, en conséquence, sur le résultat d'un test de dépistage, n'a pas été publié. Nous avons étudié un groupe de 89 femmes, toutes en 17e semaine de grossesse et composé de 42 fumeuses et 47 non-fumeuses en examinant les taux sériques de l'inhibine A, l'activine A, du PLGF et d'autres marqueurs par méthode immunometrique enzymatique sur microplaques. Contrairement à l'activine A, la concentration du PLGF s'est avérée être augmentée chez les consommatrices de cigarettes. En même temps, une élévation de l'inhibine A, déjà rapportée, a été confirmée. Nous concluons qu'il sera nécessaire, dans l'application de tests de dépistage basés sur le PLGF et l'inhibine pour pathologies de grossesse, de tenir compte de la consommation de cigarettes de la femme enceinte.
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Introduction

Non-invasive, biochemical risk assessment using the concentrations of various serum protein markers in the second and now increasingly in the first trimester of pregnancy has been proposed and gradually introduced for several gestational pathologies. Fetal chromosomal abnormalities (e.g. trisomy 21) and pre-eclampsia (PE) are the most frequent of these. Such screening protocols are based on a precisely known gestational age and the exact quantitative determination of the marker in question. These values are then introduced, together with the maternal age and often with the weight, into a mathematical formula which returns a risk ratio for the pathology to be present (such as trisomy 21) or to occur later in gestation (such as PE). This is done by comparison with median values from a large number of healthy, unaffected pregnancies. The result from such a calculation is of great importance to the patient since the decision to perform (or not to perform) an invasive diagnostic procedure or close surveillance of the pregnancy may depend on them.

As a consequence the obtained, calculated risk ratios are extremely sensitive to the result from the laboratory. The effect of smoking on the levels of some of these markers has been investigated; and though most of them were found not to be greatly influenced by the smoking pattern, this was found to be the case for some others yielding significant quantitative differences and thus falsely increased or reduced risk ratios between smokers and non-smokers presenting otherwise identical clinical parameters. Inhibin A, which has been suggested to be potentially useful in both fetal trisomy [1] and PE [2] screening, is a hormone in part produced by the placenta and for which such an effect due to smoking has been observed [3]. Placenta growth factor (PLGF) is a recently described protein sharing structural and functional features with vascular endothelial growth factor (VEGF). In patients with PE its serum levels were found to be reduced [4]. On the other hand, activin A, inhibin A, and pregnancy-associated plasma protein A (PAPP-A) [5,6] were increased in these patients. These markers have thus been suggested to be potentially useful for PE risk assessment in the first or second-trimester, i.e. before the occurrence of the maternal symptoms which can only be treated by the delivery of the placenta. Inhibin A [7,8] and activin A [9] were indeed found to be increased over healthy controls in earlier gestation while, interestingly, PAPP-A was recently suggested to be reduced in these pregnancies before the onset of symptoms [10,11] as it was the case for PLGF [12].

In pregnancy, while smoking was suggested to influence the serum concentrations of inhibin A [3], no studies on a possible effect on activin A and PLGF levels are available in the literature. As it is precisely these two serum markers which show the most significant differences between pregnancies subsequently affected by PE (elevation for the former and reduction for the latter) and healthy ones, the aim of this project was to investigate, in a pre-existing sample of smokers and non-smokers at precisely defined gestational ages, whether light or heavy smoking would influence the serum levels of these proteins. This would not only have an effect on the result of the risk assessment for PE, but may further influence biochemical screening protocols for a number of gestational pathologies.

Materials and methods

This study was based on the Scandinavian part (Trondheim, Bergen, Uppsala) of an international, prospective multicentre trial originally aimed at the identification of causes and consequences of being born small for gestational age [13]. Only Caucasian women with parity 1 or 2 were recruited initially, and for each of them a detailed follow-up was available. A total of 89 women had a serum available at precisely 17 weeks of pregnancy. Twenty-five of them were cases who subsequently developed mild PE as defined in a previous study [11]. No cases of fetal growth restriction were included. Our sample consisted in 42 (of which 11 with PE) smokers and 47 (of which 14 with PE) non-smokers; a chi-square test showed no association between smoking and PE in our groups ($P = 0.89$). The fraction of smokers was comparatively large as a consequence of a strict definition (smoker = one or more cigarettes per day). No difference in maternal and infant characteristics were observed between the smokers and non-smokers. The maternal age in our smoking and non-smoking groups was 26.7 ± 3.5 (S.D.) and 29.8 ± 4.3 years, and the body mass index 21.7 ± 2.7 and 22.1 ± 3.1 kg/m^2, respectively.

Non-fasting blood samples were centrifuged at room temperature within 60 min of venipuncture, and the obtained serum stored at –70 °C before performing the assays, which was done in batches. PLGF was determined using matched-pair antibodies from R&D systems Europe (Oxford, England) in a microplate immunometric ELISA developed in our laboratory and described elsewhere [11].

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