Elevated Serum Levels of Interleukin-15, Interleukin-16, and Human Chorionic Gonadotropin in Women With Preeclampsia

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Abstract

Objectives: We sought to investigate the relationship between serum levels of interleukin 15 (IL-15), interleukin 16 (IL-16), and human chorionic gonadotropin (β-hCG) in women with a normal pregnancy and with preeclampsia, and their association with disease severity. We also wished to calculate the accuracy of these markers in diagnosing the disease and predicting its severity.

Materials and Methods: The study was conducted at Al Fayoum University in Cairo between December 2006 and September 2007. Thirty-two primigravid women with preeclampsia (preeclamptic group) scheduled for Caesarean Section were recruited and matched for age and duration of pregnancy with 35 normotensive primigravid women (control group). Of the preeclamptic women, 18 had severe preeclampsia, and 14 had mild preeclampsia. Blood sampling was performed for assays of serum IL-15, IL-16, and β-hCG.

Results: Serum concentrations of IL-15, IL-16, and β-hCG were significantly greater in preeclamptic women than in normotensive pregnant women ($P < 0.001$). Moreover, they were significantly higher in women with severe preeclampsia than in mild cases ($P < 0.001$). There was a positive correlation between serum IL-15, IL-16, and β-hCG among all groups. The sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of serum β-hCG in predicting preeclampsia were 56.25%, 91.43%, 85.71%, 69.57%, and 74.63%, respectively. These values for IL-15 were 94.44%, 89.8%, 77.27%, 97.78%, and 91.04%, respectively, and for IL-16, the values were 88.89%, 95.92%, 88.89%, 95.92%, and 94.03%, respectively.

Conclusion: Serum levels of IL-15, IL-16, and β-hCG were significantly increased in preeclamptic women compared with normotensive women, and these levels correlated with disease severity. However, serum IL-15 and 16 had a greater overall accuracy than β-hCG in diagnosing severe preeclampsia.

Key Words: Interleukin-15, interleukin-16, chorionic gonadotropin, preeclampsia, Caesarean section

Competing Interests: None declared.

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Résumé

Objectifs : Nous avons cherché à explorer la relation entre les taux sériques d'interleukine 15 (IL-15), d'interleukine 16 (IL-16) et de gonadotrophine chorionique (β-hCG) chez les femmes présentant une grossesse normale et une prééclampsie, ainsi que leur association avec la gravité de la maladie. Nous souhaitions également calculer la précision de ces marqueurs dans le diagnostic de la maladie et la prévision de sa gravité.

Documents et méthodes : L'étude a été menée à l'Université Al Fayoum au Caire entre décembre 2006 et septembre 2007. Trente-deux primigravides présentant une prééclampsie (groupe « prééclampsie ») qui devaient subir une césarienne ont été recrutées et appariées en fonction de l'âge et de la durée de la grossesse avec 35 primigravides normotendues (groupe témoin). Au sein du groupe « prééclampsie », 18 femmes présentaient une prééclampsie grave et 14, une prééclampsie bénigne. Du sang a été prélevé aux fins du dosage des taux sériques d'IL-15, d'IL-16 et de β-hCG.

Résultats : Les concentrations sériques d'IL-15, d'IL-16 et de β-hCG se sont avérées significativement plus élevées chez les femmes prééclamptiques que chez les femmes enceintes normotendues ($P < 0,001$). De surcroît, ces concentrations étaient considérablement plus élevées chez les femmes qui présentaient une prééclampsie grave que chez celles qui présentaient une prééclampsie bénigne ($P < 0,001$). Une corrélation positive a été constatée entre les taux sériques d'IL-15, d'IL-16 et de β-hCG parmi tous les groupes. La sensibilité, la spécificité, le coefficient de prévision d'un test positif, le coefficient de prévision d'un test négatif et la précision globale du taux sérique de β-hCG dans la prévision de la prééclampsie étaient de 56,25 %, de 91,43 %, de 85,71 %, de 69,57 % et de 74,63 %, respectivement. Pour ce qui est de l'IL-15, ces valeurs étaient de 94,44 %, de 89,8 %, de 77,27 %, de 97,78 % et de 91,04 %, respectivement, tandis que pour l'IL-16, elles étaient de 88,89 %, de 95,92 %, de 88,89 %, de 95,92 % et de 94,03 %, respectivement.

Conclusion : Les taux sériques d'IL-15, d'IL-16 et de β-hCG étaient considérablement accrus chez les femmes prééclamptiques, par comparaison avec les femmes normotendues, et étaient en corrélation avec la gravité de la maladie. Cependant, les taux sériques d'IL-15 et d'IL-16 présentaient une plus grande précision globale que la β-hCG dans le diagnostic de la prééclampsie grave.

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INTRODUCTION

Preeclampsia is a relatively common syndrome that is unpredictable in its onset and progression. It is untreatable except by terminating the pregnancy and is an important cause of fetal and maternal mortality and morbidity.[1] It is estimated that it affects from 3% to 8% of nulliparous women.[2] Despite improvements in prenatal care and intense efforts to identify the mechanisms and the molecules that induce preeclampsia, no specific etiological factors have been identified. It is currently believed to result from a combination of immunologic, environmental, and genetic factors that lead to the failure of normal trophoblastic invasion and remodelling of the uterine spiral arteries.[3,4]

Hemsteiner et al. believe that human chorionic gondotropin (hCG) is an important embryonic signal that could trigger adaptive cardiovascular changes in early pregnancy, simultaneously preserving sufficient uteroplacental perfusion during the entire gestation period by an endothelial-independent mechanism.[5] Since trophoblastic abnormalities play a central role in the pathophysiology of preeclampsia and precede its clinical manifestations, it is conceivable that some placental hormone profiles such as an increased secretion of hCG are modified in the maternal circulation, pointing to the defect of placental function.[6] Several studies have reported an association between unexplained elevation of maternal second trimester serum hCG levels and the development of preeclampsia.[6–8] Some believe that hCG secretion may be increased as a result of abnormal placental invasion or placental immaturity.[9] Production of hCG may also be linked to the trophoblast response to hypoxia,[6] with the development of a hypersecretory state.

Moreover, in vitro studies have reported a relationship between several cytokines and hormone production by the placenta.[7] For example, interleukin-1β (IL-β) induces release of hCG in vitro in first trimester human trophoblast and choriocarcinoma cell lines by activating the IL-6 and IL-6 receptor system.[10,11]

In addition, in women with preeclampsia there is a bias towards Th1 immunity, while IL-16 alters the Th1/Th2 balance by inhibiting Th2 immunity.[12–14] IL-16 stimulates the production by monocytes of pro-inflammatory cytokines such as IL-6, tumour necrosis factor alpha (TNF-α), IL-1α and IL-15, and up-regulation of IL-2 receptor alpha (IL-2R α) on T cells.[15,16] IL-16 inhibits IL-4 and IL-5 release from T cells and thus impairs Th2 immunity.[14] These findings strongly suggest that both IL-15 and IL-16 levels may increase in preeclampsia, although the relationship between IL-15, IL-16, and hCG during the third trimester of pregnancy has not been evaluated.

None of the laboratory tests developed to predict the occurrence of preeclampsia have been generally accepted because of their low specificity or sensitivity, complexity, the time needed to perform them, and cost. The present study was conducted to investigate the relationship between serum levels of IL-15, IL-16, and hCG in women with normal pregnancy and with preeclampsia, the association of these serum levels with disease severity, and to calculate the accuracy of these markers in diagnosing the disease and its severity.

MATERIALS AND METHODS

The study was conducted at Al Fayom University between December 2006 and September 2007. Sixty-seven pregnant women with gestational age 38 to 40 weeks who were scheduled for Caesarean section were included in the study. Gestational age was calculated by menstrual dates in women with a known last menstrual period, or by early ultrasonographic dating of pregnancy in women with uncertain menstrual dates. Thirty-two primigravid women with preeclampsia (preeclamptic group) were recruited and matched for maternal age and gestational age with 35 normotensive primigravid women who served as the control group. Among the preeclamptic women, 18 had severe preeclampsia, and 14 had mild preeclampsia.

Preeclampsia was diagnosed and classified according to strict criteria recommended by the American College of Obstetricians and Gynecologists in 2002[17]: a systolic blood pressure of 140 mmHg or higher or a diastolic blood pressure of 90 mmHg or higher on two occasions at least six hours apart, occurring after 20 weeks of gestation in a pregnant woman with previously normal blood pressure, and detectable proteinuria (≥ 1+ by dipstick or ≥ 0.3 g/24 h). Severe preeclampsia was defined as a blood pressure greater than or equal to 160 /110 with either a urine dipstick showing 3+ or 4+ in a random urine sample or greater than 5.0 g of proteinuria over 24 hours. Other evidence of severe disease included elevated serum creatinine, eclampsia, pulmonary edema, oliguria (less than 500 mL/24 h), fetal growth restriction, oligohydramnios, and symptoms suggesting significant end-organ involvement (headache, visual disturbance, or epigastric or right upper quadrant pain). Women who met the criteria of preeclampsia but not severe preeclampsia were diagnosed as having mild preeclampsia.

The control subjects had no evidence of gestational complications or fetal distress, and all delivered healthy neonates of appropriate size for gestational age. The common indications for Caesarean section among the control group included dystocia, antepartum hemorrhage, being an elderly primigravida, and malpresentation such as breech. Exclusion criteria were cigarette or illicit drug use, multiple