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Research paper

Plasma adiponectin and depressive symptoms during pregnancy and the postpartum period: A prospective cohort study

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ABSTRACT

Background: Some authors have described an inverse association between adiponectin and depression, but this association has not yet been investigated during the perinatal period.
Objective: To evaluate the association between the plasma adiponectin levels and symptoms of depression in women from early pregnancy to 30–45 days postpartum.
Methods: A prospective cohort of 235 women was analyzed, with four waves of follow-up: 5–13th, 22–26th, and 30-36th gestational weeks and 30–45 days postpartum. Depressive symptoms were measured using the Edinburgh Postnatal Depression Scale (EPDS; cutoff ≥ 11). The plasma adiponectin concentrations were measured using an enzyme-linked immunosorbent assay. The statistical analyses included linear mixed effects regressions to model the association between these time-dependent variables.
Results: The prevalence of depressive symptoms was 35.5%, 22.8%, 21.8%, and 16.9% and the median (μg/mL) adiponectin levels were 4.8, 4.7, 4.4, and 7.5 in the 1st, 2nd, and 3rd trimesters and the postpartum period, respectively. Women who remained non-depressed throughout the study tended to have higher values of adiponectin throughout pregnancy and the postpartum period compared to those who had depressive symptoms at least once, but this difference was not statistically significant ($\beta = -0.14$; $p = 0.071$). There was no statistically significant association between the plasma adiponectin levels and the EPDS scores in the multiple model ($\beta = -0.07$; $p = 0.320$).
Limitations: Losses to follow-up, different procedures for the blood draws at the prenatal and postpartum visits, and the presence of a nested clinical trial with omega-3 supplementation.
Conclusion: The plasma adiponectin levels were not associated with depressive symptoms during the perinatal period.

1. Introduction

It is estimated that 18.4% of pregnant women become depressed during their pregnancies, and 19.2% of new mothers may have major or minor depression in their first 3 months postpartum (Gavin et al., 2005). Perinatal depression is particularly problematic due to the negative effect on the health of both the mother and child (Gross et al., 2013; Jensen et al., 2013) and is associated with negative outcomes, such as preeclampsia, preterm birth, low birth weight, and others (Grote et al., 2010; Hu et al., 2015). In addition, pharmacological treatment becomes more complicated due to the risk of drug transfer to the fetus via the umbilical cord and placenta and absorption from the amniotic fluid or transfer to the infant via the breast milk (Lanza di Scalea and Wisner, 2009; Sit et al., 2011).

The etiology of perinatal depression is complex and is not yet completely elucidated. Among the factors associated with depressive symptoms in this period, we can highlight the history of the occurrence of major depressive episodes or depressive symptoms at any time prior to pregnancy, low socioeconomic status, domestic violence, lack of social and financial support, multiple pregnancies and obstetrical complications (Dennis and Vigod, 2013; Patel et al., 2012). Moreover, recent studies have shown that the proliferation of hippocampal cells is involved in the physiological function of this structure and, consequently, in the development of mental disorders (Hill et al., 2015). This form of neurogenesis can be stimulated by cytokines, such as adiponectin (Zhang et al., 2011)

Adiponectin, a 244 amino acid protein, is a hormone that is

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primarily secreted by the white adipose tissue (Nedvídková et al., 2005). Among the well-established functions of adiponectin, we can highlight its role in the regulation of energy homeostasis by participating in the metabolism of glucose and fatty acids (Berg et al., 2002; Dridi and Taouis, 2009). Adiponectin has also been associated with beneficial liver functions, such as improved insulin sensitivity, the prevention of steatosis and anti-fibrinogen properties (Gao et al., 2013; Kamada et al., 2003; Turer et al., 2012), and has an important role in inhibiting the inflammatory cascade by preventing oxidative stress (Gustafsson et al., 2013; Indulekha et al., 2012).

There is a growing body of evidence regarding the association between adiponectin and mental disorders. Some authors have indicated that adiponectin is admittedly involved in the pathophysiology of depression (Wędrychowicz et al., 2014). However, recent systematic reviews and meta-analyses have shown little evidence of this behavior, with heterogeneous and inconsistent results (Carvalho et al., 2014; Hu et al., 2015). Many studies found inverse associations between the adiponectin concentrations and depression or the severity of depression (Cizza et al., 2010; Diniz et al., 2012; Lehto et al., 2010; Leo et al., 2006; Narita et al., 2008; Zeman et al., 2009). Others reported a lack of association (Barbosa et al., 2012; Einvik et al., 2013; Hung et al., 2007; Jeong et al., 2012; Mamalakis et al., 2006; Pan et al., 2008). The majority of these studies were conducted with adults (both sexes) and did not consider the use of antidepressant drugs, which may be a source of confounding factors (Narita et al., 2006). None of them were conducted on women during the perinatal period.

In this way, the search for new strategies to prevent and treat perinatal depression is a topic of great relevance and adiponectin concentrations may be a key marker to advance this field. Therefore, considering the need for more evidence regarding the association between adiponectin and depression, the lack of studies about pregnant and postpartum women in this area, and the impact of depression on maternal and child health, the aim of the present study is to evaluate the association between the plasma adiponectin levels and symptoms of depression on a prospective cohort of women followed from early pregnancy to 30–45 days postpartum. We hypothesized that women with lower adiponectin concentrations have a higher risk of developing symptoms of depression.

2. Methods

2.1. Study design and protocol

A prospective cohort with four follow-up visits was conducted in Rio de Janeiro, Brazil. Pregnant women were recruited in a low risk prenatal care unit when they accessed the service for the first time or as soon as they received a positive result for the immunological pregnancy test. The study employed a convenience sample that was formed as the participants enrolled and remained open for 24 months (November 2009–October 2011). To be eligible for the study, the women should be 20–40 years of age, be free of chronic, non-communicable (except obesity), or infectious diseases, and present a singleton pregnancy. Women who used antidepressant drugs were excluded. The final sample was comprised of 235 subjects: 211 attended the first wave of follow-up (baseline, 5–13th gestational weeks); 193 participated in the second trimester interview (22–26th gestational weeks); 202 were evaluated at the third trimester (30–36th gestational weeks); and 177 attended the fourth follow-up wave (30–45 days postpartum). The process of recruitment and follow-up, exclusions and losses are detailed in Fig. 1.

After the second trimester interview, a subsample of 41 women participated in a nested clinical trial. The inclusion criteria were: being at risk for postpartum depression, as evidenced by a history of depression according to the American Psychiatric Association (2000) or by a score greater than or equal to 9 on the Edinburgh Postnatal Depression Scale (EPDS) at the baseline interview. The nested clinical trial objective was to test the efficacy of omega-3 supplementation during late pregnancy (3rd trimester) and the early postpartum period in preventing depressive symptoms in the postpartum period. The women participating in this sub-study randomly received gelatin capsules containing either omega-3 (fish oil) or placebo for 16 weeks. The capsules of omega-3 contained a total dose of 1.8 g per day (1.08 g of Eicosapentaenoic acid and 0.72 g of Docosahexaenoic acid). For both groups, the capsules were vacuum deodorized and supplemented with 0.2 mg/g of vitamin E as an antioxidant. The inclusion of these women in the study was conditional upon the outcome of a sensitivity analysis (more details are provided in the statistical analysis section).

The study protocol was approved by the research ethics committee of the National School of Public Health (Protocol number: 33635313.9.0000.5240) and the Municipal Secretary of Health of Rio de Janeiro Municipality (Protocol number: 0139.0.314.000-09). The participants signed informed consent, which was obtained freely and spontaneously after all necessary clarifications had been provided. All ethical procedures of this study related to research involving human beings followed Brazilian Resolution 466/2012. The participants did not receive any type of compensation.

2.2. Depressive symptoms

The symptoms of depression were measured in the subjects in all follow-up waves using a validated Portuguese version of the EPDS, which was applied by trained interviewers. The scale consists of 10 items with four response options each (scored from 0 to 3, according to the presence and intensity of depressive symptoms), with higher scores indicating more symptoms of depression.

The EPDS scale was first developed by Cox et al. (1987) and its Portuguese version was translated and validated by Santos et al. (2007) on a sample of mothers from Pelotas, Brazil. According to this study, scores of ≥ 11 had a sensitivity of 83.8%, a specificity of 74.7% and a positive predictive value of 45% for screening for moderate and severe postpartum depression. The Brazilian version of the EPDS has not yet been validated during pregnancy. However, a meta-analysis provided evidence that the EPDS is a valid screening tool during pregnancy across different cultures. The investigation of 11 EPDS validation studies in the antenatal period showed that the sensitivity and specificity for major depression varied from 70% to 100% and from 74% to 97%, respectively (Kozinszky and Dudas, 2015).

2.3. Plasma adiponectin levels

Blood samples were collected in tubes containing Ethylenediamine tetraacetic acid (EDTA) by a trained nurse technician at all follow-up visits (four repeated measures). The women were scheduled between 6:50 and 7:50 am and must have fasted for at least 12 h for the prenatal waves. The postpartum blood collection was usually scheduled between 10 and 11 am and fasting was not required. The samples were centrifuged (5000 rpm/5 min) and the supernatant was separated, stored in cylinders containing liquid nitrogen and transported weekly to a -80°C freezer, where they were stored until further analysis. The plasma adiponectin concentrations (μg/ml) were measured with an enzyme linked immunosorbent assay (ELISA) using commercial kits (Millipore, St. Charles, MO, USA) with a sensitivity of 0.78 ng/mL. The measurements were performed in duplicate and the inter- and intra-assay