1. Introduction

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines peripartum depression as the occurrence of a major depressive episode during pregnancy or in the first four weeks following delivery (American Psychiatric Association, 2013). However, the terms used until recently in the literature to describe depressive episodes associated with childbirth, such as “postpartum depression” (PPD) or “postnatal depression”, usually comprise the first 12 months postpartum. Period prevalence has been estimated to 19% for the first three months postpartum (Gavin et al., 2005). Point prevalence varies between 6.5–13% during the first year postpartum (Gaynes et al., 2005). These high prevalence rates, rendering peripartum depression among the most common psychiatric disorders associated with childbirth (Brockington, 2004), emphasize its importance, considering the potential consequences of depressive episodes on maternal health (Alder et al., 2007; Yim et al., 2015), fetal and neonatal wellbeing (Alder et al., 2007; Dennis and McQueen, 2009) as well as short-term and long-term adverse effects on child mental health (Deave et al., 2008; Goodman et al., 2011) and family environment (Brockington, 2004; Paulson and Bazemore, 2010).

The etiology of peripartum depression appears to be multifactorial (Skalkidou et al., 2012). Studies have associated peripartum depression with previous puerperal or non-puerperal episode of psychopathology (mainly depressive and anxiety disorders), stressful life events, inadequate social or partner support, and poor marital relationship (Bobo and Yawn, 2014; Milgrom et al., 2008; Skalkidou et al., 2012). Biological factors implicated in the pathophysiology of the condition include disturbances in reproductive, stress, and thyroid hormones as well as immunological and inflammatory factors (Skalkidou et al., 2012; Yim et al., 2015). Despite the relatively extensive literature on the biological background of peripartum depression, results are often
contradictory and have failed to fully explain the mechanisms leading to depressive symptoms through a simple endocrine model (Iliadis et al., 2015a). Some women appear to be differentially sensitive to the endocrine changes occurring in all childbirth and newly delivered women, suggesting that underlying factors other than those referring to hormonal levels may influence the individual susceptibility to mood changes in the perinatal period (Figueiredo et al., 2014).

Facing these facts, a growing body of studies has attempted to examine the role of genetic factors in postpartum depression. Twin and family studies suggest a familial component in postnatal depressive symptoms (Forty et al., 2006; Murphy-Eberenz et al., 2006; Treloar et al., 1999). Moreover, the genetic component in PPD has been suggested to be larger than that in major depression occurring in other points in life (Viktorin et al., 2015).

The association of single nucleotide polymorphisms (SNPs) in several genes implicated in the etiology of postpartum depressive disorders has been the focus of an increasing number of studies. Genetic variations in the serotonin transporter (5HTT), catechol-O-methyltransferase (COMT), monoamine oxidase A (MAOA), tryptophan hydroxylase 1 (TPH1), and tryptophan hydroxylase 2 (TPH2) genes have been associated with postpartum depression (Comasco et al., 2011a, 2011b; Couto et al., 2015).

Regarding the hypothalamic-pituitary-adrenal axis (HPA-axis), studies have demonstrated the implication of stress hormones, through HPA-axis dysregulation, in the pathophysiology of postpartum depression (Chrousos et al., 1998; Iliadis et al., 2015a). SNPs in HPA-axis related genes have been studied (e.g. glucocorticoid receptor [NR3C1], FK506 binding protein 5 [FKBP5], and corticotropin-releasing hormone receptor 1 [CRHR1]) (El-Ibiary et al., 2013; Engineer et al., 2013) in association to peripartum depressive symptoms, to elucidate the influence of genetic variations on depressive symptomatology during pregnancy and postpartum, with the results so far being equivocal (Costas et al., 2010; Schneider et al., 2014).

However, to date, only a fraction of HPA-axis genes, in terms of their influence on peripartum depression, has been examined. Based on a gene-set approach, haplotype tag SNPs of HPA-axis genes have been investigated in a large cohort. The top-hit rs12565406 was found to be associated with the occurrence of depressive symptoms in the postpartum period (Comasco et al., 2016, manuscript). This SNP is an intronic variant of the hydroxysteroid (11-beta) dehydrogenase 1 gene (HSD11B1) located in chromosome 1. The 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) catalyzes the conversion of inactive cortisone to active cortisol and has in recent studies been implicated in the pathophysiology of perinatal depression and offspring behavior (Raikonen et al., 2015). Dekker et al. reported a positive association between evening salivary cortisol levels, a genetic variant in HSD11B1, and depression, suggesting that the 11β-HSD1 is implicated in HPA-axis regulation and depression susceptibility (Dekker et al., 2012).

Intermediate phenotypes (endophenotypes) have been searched to dissect the etiology of diseases and complex phenotypes, such as depression (Gottesman and Gould, 2003). Neuroticism has been proposed as having the strongest support in the literature to be considered as a candidate intermediate phenotype of depression (Goldstein and Klein, 2014). The link between neuroticism and peripartum depression has been examined by a number of studies, pointing to an effect of neuroticism on the occurrence of depressive disorder by modulating vulnerability after major events such as childbirth (Iliadis et al., 2015b). One of the signaling systems that may have a central role in the biological background of neuroticism is the HPA-axis (Ormel et al., 2013). Altered stress-induced cortisol levels have been demonstrated in individuals scoring high on neuroticism (McClery and Goodwin, 2001; Oswald et al., 2006). Additionally, on a genetic level, twin studies have reported that around half of the genetic variance in depression is shared with neuroticism (Kendler et al., 2006). Genome-wide association studies (de Moor et al., 2015) (GWAS) have also demonstrated the influence of many genetic variants on neuroticism as well as major depressive disorder.

As mentioned above, peripartum depressive symptoms have been associated to the rs12565406 single nucleotide polymorphism in the hydroxysteroid (11-beta) dehydrogenase 1 gene as well as neuroticism. The aim of the present study was to examine the association between this polymorphism and neuroticism and the possible mediatory role of neuroticism in the association between the polymorphism and postpartum depressive symptoms, taking into account possible confounders.

2. Methods

2.1. Study population

The current study was conducted as a sub-study of a larger project, which examined the role of genotype of stress-regulatory genes in peripartum depression (Comasco et al., 2016, manuscript), using data from the BASIC-project. A detailed description of this project is provided elsewhere (Iliadis et al., 2015a). Self-administered questionnaires were sent to study participants, containing the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) at six weeks postpartum and questions on personal history, sociodemographic and pregnancy-related variables at pregnancy week 17 and 32 and at six weeks postpartum, as well as the Swedish universities Scale of Personality (SSP) (Gustavsson et al., 2000) at pregnancy week 32. Moreover, blood samples for genetic analyses were collected at some point between gestational week 17 and eight weeks postpartum. In total, 769 women were included in the present study.

2.2. Psychometric measures

The Swedish validated version of the EPDS, a 10-item self-reported questionnaire designed as a screening tool to identify depressive symptoms in the peripartum period, was used to assess postpartum depressive symptoms. Whenever the EPDS score was inserted in the models as a dichotomized variable, a cut-off of 12 points was used. This threshold is often used to screen for postpartum depression in clinical settings in Sweden and provides sensitivity between 72% and 77% and specificity between 88% and 92.5% (Murray and Carothers, 1990; Statens beredning for medicinsk utvärdering (SBU), 2012). Stressful life events (SLE), during the past 12 months, were assessed six weeks postpartum with a ten-item scale developed by Rosengren et al. (1993). An index 0–10 was created based on the following events: serious illness in family member, serious concern about family member, death of family member, divorce or separation, involuntary change of residence, involuntary change of work, feelings of redundancy, feelings of insecurity at work, serious financial trouble, and legal prosecution. When SLE was used as dichotomous variable, the cut-off for significant life events was set at three or more events. To assess personality traits, women were administered, during gestational week 32, the Swedish universities Scale of Personality, a personality-assessment instrument based on the Karolinska Scales of Personality (KSP) (Schalling et al., 1987). The SSP contains 91 statements (e.g. “I get tired and hurried too easily”) and the participants rate each item on a scale from 1 to 4, where 1 equals “does not apply at all” and 4 equals “applies completely”. The items form 13 scales or traits. These traits are usually grouped into three major factors, including neuroticism.

In the present study, these traits were grouped into three major factors: neuroticism (somatic trait anxiety, psychic trait anxiety, stress susceptibility, lack of assertiveness, detachment, embitterment, mistrust), aggressiveness (trait irritability, verbal trait aggression, physical trait aggression, inverted value of social desirability) and sensation seeking (impulsiveness, adventure seeking). Neuroticism often refers to the experience of negative affect upon frustration, threat or loss, and relates to measures of reactivity, vulnerability, hostility, irritability, sensitivity to criticism, and anger as well as feelings of
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