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Association of glucocorticoid and type 1 corticotropin-releasing hormone receptors gene variants and risk for depression during pregnancy and post-partum

Neelam Engineer [a], Lucy Darwin [b], Deole Nishigandh [a], Kandala Ngianga-Bakwin [c], Steve C. Smith [b], Dimitris K. Grammatopoulos [b,c,*]

[a] Dept of Obstetrics and Gynaecology, UHCW NHS Trust, Coventry, UK
[b] Dept of Clinical Biochemistry, UHCW NHS Trust, Coventry, UK
[c] Division of Metabolic and Vascular Heallth, Warwick Medical School, University of Warwick, Coventry, UK

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ABSTRACT

Women with postnatal depression (PND) appear to have abnormal hypothalamic pituitary adrenal (HPA) axis responses to stress, which might involve a genetic variability component. We investigated association of genetic variants in the glucocorticoid receptor (GR, NR3C1) and corticotropin releasing hormone receptor 1 (CRHR1) genes with increased risk for PND. Two hundred pregnant women were recruited prospectively and PND risk was assessed by the Edinburgh Postnatal Depression Scale (EPDS) during pregnancy and again 2–8 weeks post-natally (CW-GAPND study). The BclI and ER22/23EK single nucleotide polymorphisms (SNPs) of the GR and the haplotype-tagged rs1876828, rs242939 and rs242941 SNPs of the CRHR1 associated with genetic risk to depressive disorders were genotyped. A cut-off score of 10 was used to detect increased risk of PND. Association analysis was carried out in 140 patients that completed the study protocol. The BclI and rs242939 SNPs were over-represented in women with postnatal EPDS score $\geq$10 with significant allele association (p = 0.011 and <0.001, respectively) and risk ratios of 2.9 (95% CI: 1.2–6.9) for BclI, 4.9 (2–12) for rs242939 and 5.48 (2.13–14.10) for both. The rs242939 SNP was also associated with increased EPDS values during pregnancy. Moreover, the G-G-T haplotype of the CRHR1 was significantly over-represented in patients with high EPDS scores, with risk ratio of 3.22 (95% CI: 1.91–5.42). This is the first evidence that specific SNPs of genes involved in 'stress' responses might contribute in the genetics of high-risk for depression during pregnancy and postpartum.

1. Introduction

In Western countries postnatal depression (PND) affects approximately 1 in 7 women, whereas in non-Western populations prevalence ranges between 5 and 60% (O'Hara and Swain, 1996; Cooper et al., 1999; Klainin and Arthur, 2009). If left untreated, PND has profound consequences on the quality of family life, social functioning as well as in the long-term emotional and cognitive development of the baby (Grace et al., 2003; Payne, 2007). Most importantly, severe forms of PND, such as puerperal psychosis, which affects 0.1–0.2% of new mothers, are linked to suicide and infanticide (Spinelli, 2009).

Despite detailed prevalence statistics, high probabilities of re-experience with future pregnancies, and well documented consequences of the disorder, PND remains difficult to identify. Routine assessment for either prenatal depression or PND is not universal. Screening guidelines for PND assessment across healthcare institutions are inconsistent. As a result fewer than half of PND cases are detected by primary healthcare professionals in routine clinical practice (Hearn et al., 1998) and in the UK screening policies rely on opportunistic case finding. The Edinburgh Postnatal Depression Scale (EPDS) which detects high levels of PND symptoms, is a widely used screening tool, however, it cannot be used for prospective identification of women at risk and is not considered to be cost-effective (Paulden et al., 2009). Clearly, PND management and outcomes would benefit substantially from early identification of women at risk and clinically effective treatments available. There is also inconclusive data about the long-term outcome of PND patients; most cases last around 3 months and resolve spontaneously without

* Corresponding author. Warwick Medical School, The University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL, UK. Tel.: +44 2476 968661; fax: +44 2476 574637.
E-mail address: d.grammatopoulos@warwick.ac.uk (D.K. Grammatopoulos).

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treatment. However, several studies demonstrated the presence of depression, with over 50% lasting over 6 months and some still being present up to 24 months postpartum (Goodman, 2004).

Several psychosocial risk factors for PND have been identified: the strongest predictors are past history of depression and psychological disturbance during pregnancy, as well as poor marital relationship and low social support, and stressful life events (O'Hara and Swain, 1996). A family history of depression is another risk factor for PND (Murphy-Eberenz et al., 2006), in agreement with the view that depressive illnesses are associated with high heritability, although individual episodes are frequently triggered by stressful life events. The later implicates stress-driven hormonal responses in disease pathogenesis (Spijker & van Rossum, 2009). The maternal hypothalamic-pituitary-adrenal (HPA) axis undergoes gradual changes during pregnancy because of an increasing production of placental corticotrophin-releasing hormone (CRH) (Chrousos et al., 1998). The abrupt withdrawal of placental CRH at birth results in a re-equilibration of the maternal HPA axis in the days post-delivery. Indeed, women with PND appear to have abnormal hypothalamic pituitary adrenal (HPA) axis responses to stress, possibly due to enhanced sensitivity to gonadal steroids during pregnancy (Magiakou et al., 1996; Bloch et al., 2005). It has been hypothesized that in women with symptoms of postpartum "blues" or depression, the HPA axis function fails to return to normal post-delivery and exhibits blunted adrenocorticotropic hormone (ACTH) responses to CRH challenge at 6 and 12 weeks postpartum suggesting prolonged HPA suppression (Magiakou et al., 1996; Rich-Edwards et al., 2008). Recent studies (O'Keane et al., 2011) investigating hormonal changes in the HPA axis in the days after delivery in relation to daily mood changes suggest that postpartum 'blues' positively correlated with ACTH; and negatively correlated with oestriol levels during the postpartum days, and with the reduction in CRH concentrations from pregnancy. These findings support the hypothesis that the 'reactivation' of hypothalamic ACTH secretagogue peptides may be involved in the aetiology of the disease.

Impaired signalling of key molecules of the HPA axis such as the glucocorticoid receptor (GR) and corticotrophin releasing hormone receptor type 1 (CRH-R1) has been implicated in the pathogenesis of various depressive disorders including PND (Wisner and Stowe, 1997; Kammerer et al., 2006; Brummelte and Galea, 2010). HPA dysfunction has been identified in a wide spectrum of postpartum psychiatric disorders; for example it has been shown that increased circulating ACTH levels but not CRH or cortisol, are associated with the presence of postpartum thoughts of harming the infant (Labad et al., 2011). Measurement of maternal circulating CRH levels at mid-pregnancy has been proposed as a specific biomarker of maternal depression (Rich-Edwards et al., 2008) and this was supported by other studies suggested that the activity of the HPA axis during pregnancy is associated with maternal HPA responsiveness to stress postpartum (Meinlschmidt et al., 2010). However, recent studies yielded contradictory results with positive or no association with either prenatal or postpartum depression (Yim et al., 2009; Meltzer-Brody et al., 2011).

The functional anomalies of the HPA axis in depressive disorders appear to include an inherited component due to genetic variability (Spijker & van Rossum, 2009). The genetic contribution to PND and postpartum psychosis is strongly supported by family and twin studies and genome-wide linkage analysis in conditions such as bipolar disorder and history of mood or anxiety disorder (Jones and Craddock, 2001; Forty et al., 2006; Jones et al., 2007; Kumar et al., 2007; Payne, 2007; Friedman, 2009; Mahon et al., 2009). While there has been much interest in the identification of genes responsible for psychiatric illness, there remains a paucity of information relating to molecular markers and detection of PND risk.

The objective of our study was to investigate association between genetic variations (single nucleotide polymorphisms-SNPs) in the GR and CRHR1 genes, previously shown significant correlation with depression (Liu et al., 2006; Claes, 2009; Spijker & van Rossum, 2009), and increased risk for PND as determined by a raised EPDS score. To address this, a prospective cohort study was designed involving a secondary care University Hospital setting. To our knowledge, this represents the first prospective investigation of genetic variation of genes involved in HPA activity and PND risk.

2. Materials and methods

2.1. Patients-study design

For the Coventry and Warwickshire Genetic Risk for PostNatal Depression (CW-GAPND) study, 200 Caucasian women were recruited during antenatal clinic visits. The study focused on Caucasians to ensure ethnic background homogeneity of the cohort since ethnicity-related differences in PND prevalence have been reported (O'Hara and Swain, 1996; Patel et al., 2002). Symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS) questionnaire, which was completed upon the hospital visit between 20 and 28 weeks gestation (mean 25.4 ± 1.9) and again 2–8 weeks post-delivery (mean 4.6 ± 2.1). The choice of this time-period was based on previous studies suggesting that incidence of PND peaks at around 4–6 weeks (Cox et al., 1993; Evans et al., 2001; Verkerk et al., 2003). From the 200 women invited to participate, questionnaires were obtained from 140 subjects for a return rate of 70%. There was no significant difference in the socio-demographic characteristics (educational qualification, marital status, employment, support from partner, subsequent pregnancy) of responders and non-responders. Following current clinical practice, there was no follow-up of women who returned EPDS scores below the cut-off of 10.

Recruited patients were assessed for risk factors such as family history (first degree) of depression, personal history of depression, and depressive symptomatology at recruitment using the EPDS, however, there was no stratification to high or low-risk groups in accordance with current clinical practice. According to standard clinical practice all women were assessed for presence of anaemia (by full blood count and haemoglobin measurement) and thyroid disease (by TSH measurement) and women with abnormal results were excluded from the study. Women with a history of depression before pregnancy are especially vulnerable to depressive symptoms during or after pregnancy (Rich-Edwards et al., 2006). Therefore, in order to ensure pregnancy-specific and exclude non-pregnancy related depressive illness, women with pre-existing mental illnesses or on antidepressant medications or any other medications that can influence risk of developing PND were excluded from the study. A cut-off EPDS score of 10 was used for the identification of high-risk patients for PND. This reported performance characteristics at this cut-off point is: sensitivity of 0.81 and specificity of 0.86 for detection of both major and minor depression and a sensitivity of 0.917 and specificity of 0.77 for major depression only (Hewitt et al., 2009). The study was approved by the local ethics committee and informed consent was obtained from all subjects.

Similar to previous studies (Fasching et al., 2012; Mehta et al., 2012), the CW-GAPND study protocol included antenatal use of the EPDS questionnaire to assess depressive symptoms during pregnancy between 20 and 28 weeks gestation. Several studies validated the use of EPDS as a pre-screening tool for depression during pregnancy especially in the research setting (Rubertsson et al., 2011; Milgrom et al., 2008) although, it is not currently used in routine antenatal care in the UK. In this study it was used exclusively as a research instrument to screen for symptoms of PND