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Treatment with serotonin reuptake inhibitors during pregnancy is associated with elevated corticotropin-releasing hormone levels

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Abstract Treatment with serotonin reuptake inhibitors (SSRI) has been associated with an increased risk of preterm birth, but causality remains unclear. While placental CRH production is correlated with gestational length and preterm birth, it has been difficult to establish if psychological stress or mental health problems are associated with increased CRH levels. This study compared second trimester CRH serum concentrations in pregnant women on SSRI treatment ($n = 207$) with untreated depressed women ($n = 56$) and controls ($n = 609$). A secondary aim was to investigate the combined effect of SSRI treatment and CRH levels on gestational length and risk for preterm birth.

Women on SSRI treatment had significantly higher second trimester CRH levels than controls, and untreated depressed women. CRH levels and SSRI treatment were independently associated with shorter gestational length. The combined effect of SSRI treatment and high CRH levels yielded the highest risk estimate for preterm birth.

SSRI treatment during pregnancy is associated with increased CRH levels. However, the elevated risk for preterm birth in SSRI users appear not to be mediated by increased placental CRH production, instead CRH appear as an independent risk factor for shorter gestational length and preterm birth.

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1. Introduction

During pregnancy a significant proportion of women suffer from depressive symptoms and 3—5% are diagnosed with major depressive disorder (Andersson et al., 2003; Gavin et al., 2005). When antidepressant treatment is needed during pregnancy, selective serotonin reuptake inhibitors (SSRIs) are the most widely prescribed as they are considered to be efficient, safe, have relatively few side-effects, and are not associated with gross teratogenic effects (Myles et al., 2013). Over the past years a substantial increase in the use of SSRIs during pregnancy has been noted (Alwan et al., 2011), and the proportion of women in Europe who are being treated with SSRIs during their pregnancy is approximately 2—3% (Kieler et al., 2012). Although generally considered safe, SSRIs have been shown to cross the placenta, and are detected in the amniotic fluid and in umbilical cord blood (Hendrick et al., 2003). SSRI treatment has been associated with an increased risk of poor pregnancy outcomes including preterm birth, impaired fetal placental function and decreased fetal body and head growth, however, these outcomes are also found in offspring of mothers with antenatal depression (reviewed by (Olivier et al., 2013)). Because pharmaco-epidemiological studies tend to be confounded by indication, i.e. the reason for treatment, it remains unclear which effects are caused by the antenatal depression *per se* and what is caused by the pharmacological treatment of the depression. We have previously shown that placental gene expression and nerve growth factor (NGF) signaling is differentially regulated in SSRI-treated and untreated depressed women (Kaihola et al., 2015; Olivier et al., 2014). However, besides these studies few attempts have been made to describe the SSRI-induced biological effects on placental function or the potential biological mechanisms that might explain why SSRI treatment is associated with an increased risk for preterm birth.

One factor of relevance for preterm birth is placental corticotropin-releasing hormone (CRH). The human placenta secretes large amounts of CRH resulting in 100—1000-fold increased CRH levels in maternal serum during pregnancy (Campbell et al., 1987). Beginning in the late second trimester CRH levels starts to increase exponentially to reach approximately 800 pg/ml during the final weeks of gestation, with a final peak during labor (Campbell et al., 1987; Goland et al., 1986; Sasaki et al., 1987). Factors modulating CRH release in the placenta are mostly identical to those regulating its release in the brain. Prostaglandins, norepinephrine, acetylcholine, angiotensin II, arginine, vasopressin, and interleukin 1 (IL-1) all stimulate CRH secretion from cultured placental cells *in vitro* and placental CRH production is decreased by progesterone and nitric oxide (Petraglia et al., 2010). However, in contrast to the hypothalamic CRH system, the production of CRH by the placenta is positively up-regulated by glucocorticoids (Robinson et al., 1988), and shows no diurnal variation (Latendresse and Ruiz, 2008).

It is generally established that maternal serum CRH concentrations are correlated with gestational length and are elevated in women who subsequently deliver preterm (Petraglia et al., 2010; Smith and Nicholson, 2007). However, at the same time because of low sensitivity and poor predictive value, there is little support for the clinical use of CRH alone as a predictor of preterm delivery in low risk (Hill et al., 2008; Holzman et al., 2001; Inder et al., 2001; Leung et al., 1999; Smith et al., 2009) or high-risk populations (Sibai et al., 2005). Relevant to antenatal depression, it has been assumed that psychological stress stimulates placental CRH release, however, the evidence to support this assumption is thus far weak. While some studies have demonstrated a significant positive correlation between psychosocial stress level and CRH levels in mid-pregnancy (Hobel et al., 1999) others have found no difference (Harville et al., 2009; Himes and Simhan, 2011; Kramer et al., 2009), except in certain ethnic groups (Tse et al., 2012), or lower CRH levels in women with chronic stressors (Guendelman et al., 2008). Similar findings are at hand when depressive symptoms have been evaluated in relation to mid-pregnancy CRH levels; symptoms of maternal antenatal depression have been found to be associated with lower (Chen et al., 2010; Schmeelk et al., 1999; Susman et al., 1999), unchanged (Meltzer-Brody et al., 2011; Yim et al., 2009), or higher CRH serum concentrations (Rich-Edwards et al., 2008). Although the discrepancies in these studies may depend on sample sizes, ethnic background or use of different instruments to assess stress or depressive mood, it is also possible that the severity of depression may play a role. Indeed, in a relatively small study of subjects with major depressive disorder, second trimester CRH concentrations were found to be significantly higher in the depressed women than in the controls (O'Keane et al., 2011). SSRI treatment has only been assessed in one study, again with a very limited sample size, reporting no association between SSRI use and CRH levels (Latendresse and Ruiz, 2011).

Because of the lack of studies investigating SSRI-induced biological effects on placental function this study aimed to compare CRH serum concentrations in pregnant women on SSRI treatment, in women with untreated depressive symptoms and in controls. A secondary aim was to investigate the combined effect of SSRI treatment and CRH levels on gestational length and risk for preterm birth.

2. Materials and methods

Data for this study were derived from two different studies at the Department of Women's and Children's Health, Uppsala University hospital.

Information about depressed mood during pregnancy was collected from the BASIC project (Biology, Affect, Stress, Imaging, Cognition), which is a population-based, longitudinal study of psychological wellbeing during pregnancy and the postpartum period in Uppsala County, Sweden. All women attending the routine ultrasound examination are invited to participate in the study. Exclusion criteria for the BASIC study are (1) inability to adequately communicate in Swedish, (2) women whose personal data were kept confidential, (3) women with pathologic pregnancies as diagnosed by routine ultrasound (miscarriages or malformations leading to termination of pregnancy), and (4) women younger than 18 years. The study subjects complete web-based self-administrated structured questionnaires containing questions on demographic variables, prior psychiatric history, ongoing medication, and the Swedish validated version of the Edinburgh Postnatal