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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

Depression Scale (EPDS) (Cox et al., 1987) at gestational week 17 and 32. The Edinburgh Postnatal Depression Scale is an internationally used 10-item self-reported questionnaire, designed as a screening tool to identify depressive symptoms in the peripartum period (Cox et al., 1987). A cut-off point of 13 for depression during pregnancy is often used in clinical settings (Rubertsson et al., 2011), and was also used to define depressed mood in this study. While the sensitivity of the instrument is not impressive, typically ranging between 0.47 and 0.71, the specificity as regards depressive disorders is excellent (pooled specificity 0.94—0.98) (NICE guidelines [CG 192], 2014).

Blood samples for this study were collected as part of the population-based Uppsala Biobank of Pregnant Women, where blood samples are collected in conjunction with the routine ultrasound screening. Eligible women are (1) 18 years or older, (2) Swedish-speaking, and (3) without blood-borne disease (HIV, hepatitis C and hepatitis B). For this sub-study, we also excluded duplex pregnancies. In Sweden, all pregnant women are invited to an ultrasound examination at 16—20 weeks of gestation and approximately 97% of the Swedish pregnant population participate. In Uppsala County, all routine ultrasound examinations are performed at Uppsala University Hospital, which is also the only available delivery ward within the county. Hence, the Biobank subjects represent a population-based sample. Invitation to participate in the Biobank is done at random, when a research nurse is available. Approximately 30% of the respondents decline participation, and it is estimated that the Biobank covers approximately half of the pregnant population of Uppsala County (Granfors et al., 2013). Upon inclusion, brief demographic data are collected, including ongoing chronic disorders, ongoing medication (including use of SSRI), smoking, height, and weight. Following written informed consent, a plasma sample is collected. The sample is centrifuged within two hours and stored at −70 °C. Both of these studies have been approved by the Independent Ethical Review Board of Uppsala, Sweden.

By June 1, 2013, 711 women of the BASIC cohort had donated a blood sample in the Uppsala Biobank of Pregnant Women. Of these, 56 women had EPDS scores ≥13 in gestational week 17 but no pharmacological treatment for their symptoms (women with untreated depressive symptoms) and 31 reported that they were using SSRI treatment. To increase the number of SSRI users we also included 183 women who reported they were on SSRI treatment upon inclusion in the Uppsala Biobank of Pregnant Women. For the latter group, no information on depressive symptoms were available. Hence, the study population consisted of 894 women.

The medical records of all women were reviewed to ascertain important information on obstetric and perinatal variables, and somatic and psychiatric history as reported at first antenatal booking. In addition, the medical records of the 214 women who were on SSRI treatment were reviewed between December 2013 and February 2014 to verify the self-reported SSRI use, establish brand and dose at the time of blood sampling, and to ensure that SSRI treatment had been used during the entire pregnancy. We also recorded the reason for SSRI use, as reported by the women at the first antenatal visit. Standard dose of SSRI was defined as 20 mg daily for fluoxetine, citalopram, and paroxetine, 10 mg daily for escitalopram, and 50 mg daily for sertraline. Doses below these were defined as sub-normal whereas, doses exceeding the standard dose were defined as high-dose treatment.

2.1. Radioimmunoassay

Radioimmunoassay (RIA) was performed using a Corticotropin Releasing Factor (CRF) (Human, Rat Mouse, Canine, Feline) RIA Kit with a 10—1280 pg/ml range from Phoenix Pharmaceuticals, Inc. (Burlingame, CA, USA). 100 μl of pure and undiluted plasma samples were pipetted in polystyrene tubes. Controls, standards and reagents were diluted and used according to the kit's protocol. Incubation times and temperatures were 21 h at 4 °C for rabbit anti-CRH antibody, 24 h at 4 °C for ^{125}I-CRH tracer solution and 90 min at room temperature for goat anti-rabbit antibody and normal rabbit serum. Tubes were subsequently centrifuged at 3500 rpm for 15 min at 4 °C. The supernatant was carefully poured off so that only a pellet was left. Samples were analyzed using a WIZARD automatic gamma counter from Perkin-Elmer (Waltham, MA, USA). A standard curve was automatically generated by plotting the standard sample concentration against the ^{125}I-CRH binding relative to the maximum binding (B/B_{max}) in that particular sample. B_{max} was calculated by subtracting the counts per minute (cpm) value of a non-specific binding control from the cpm value of a total binding sample, in which all ^{125}I-CRH was bound to the available antibody. Subsequently, CRH concentration in the tested samples was automatically derived from the standard curve. The intra-assay variability in the first 100 cases was 1.7%. Due to this low variability, we decided to test the remainder of the samples in mono. A total number of eight RIAs were performed, and positive controls from normal pregnancies were analyzed in each RIA to assess the inter-assay variability (inter-assay variability 3.0%). In order to nullify the effect of inter-assay variability on our final results, samples from every group were present in each RIA.

2.2. Statistics and power

Because no attempt had previously been made to compare CRH levels between SSRI-treated and untreated pregnant women, and as most previous studies on CRH had used samples taken between 24 and 29 weeks of pregnancy, the power analysis was based on Rich-Edwards and colleagues (Rich-Edwards et al., 2008), in addition assuming that the mean difference in CRH levels would be half of that detected in gestational week 24—29. Hence, the study had sufficient power to detect a mean difference in logCRH of 0.10, with a standard deviation of 0.15. Notably, the study did not have power to discriminate between the effect of SSRI use (or CRH levels) on spontaneous preterm birth and medically indicated preterm birth. However, as samples were taken before gestational week 20 when complications associated with increased CRH (and medically indicated preterm birth) such as preeclampsia (Perkins et al., 1995) and intrauterine growth restriction (Goland et al., 1993) presumably had not yet developed, and as the consequence for participating women on SSRI treatment would be similar (whether

preterm birth would be spontaneous or not), we assumed it to be reasonable at this stage to combine spontaneous and medically indicated preterm birth.

Sociodemographic and clinical variables were compared between groups by use of ANOVA with post hoc Tukey HSD, or Chi-square tests. Multivariable linear regression and multivariable logistic regression analyses were performed to elucidate the influence of CRH (continuously by standard deviations) and SSRI treatment on gestational length and preterm birth, respectively. Delivery was categorized as preterm if it occurred before 37 gestational weeks (36 + 6). Covariates for these analyses include variables that were associated ($p < 0.1$) with case-control status or CRH levels (in addition to their known influence on preterm birth in Scandinavia (Cnattingius et al., 2013), and included parity (nulliparous vs. parous), Body Mass Index (BMI) (continuous), maternal birth place (Scandinavia or outside Scandinavia), smoking during pregnancy (yes vs. no), and pre-pregnancy history of hypertension. In addition, gestational age at blood sampling was always included as a covariate in all analyses. Interaction analyses on the combined effect on SSRI use and CRH levels on gestational age was conducted by two-way ANOVA. The interaction effect on preterm birth was evaluated by logistic regression in which controls and SSRI users were dichotomized according to above or below median CRH levels.

CRH levels were normally distributed in our sample. However, as previous studies had used log-transformed values we also repeated all analyses by use of log-transformed CRH, without any change of results.

3. Results

Among the 894 women included in this study, nine were excluded due to multiple gestations, one was a duplicate, and 12 were excluded, as blood samples had been taken outside of the stipulated time-frames. Hence, the final study population consisted of 872 women, among whom 207 used SSRI treatment at the time of the blood sampling. Nine SSRI users later discontinued treatment but have been kept in the analyses on gestational length and preterm birth. Eighteen women delivered outside of Uppsala County, leaving 854 subjects available for analyses on gestational length and preterm birth.

According to the EPDS scores filled out by women in gestational week 17, 56 women suffered from depressed mood but received no pharmacological treatment for their symptoms. The EPDS scores of these 56 women with untreated depressive symptoms and SSRI users, for whom EPDS scores were also available due to their participation in the BASIC study ($n = 31$), were 14.2 ± 2.3 and 8.4 ± 5.0 respectively, $p < 0.001$. Corresponding figures for women with untreated depressive symptoms ($n = 70$) and SSRI-treated women in gestational week 32 were 14.6 ± 3.5 and 7.8 ± 4.8, respectively.

The demographic and clinical variables of SSRI-treated, untreated depressed and controls are displayed in Table 1. Women on SSRI treatment were more often parous and smokers, and they tended to be more obese ($p = 0.077$). They also more often developed preeclampsia, had shorter gestational length and more often delivered preterm. In addition, while the proportion of small-for-gestational age children did not differ between groups, the birth weight of offspring to SSRI-treated women tended to be lower than in controls ($p = 0.068$). In contrast, untreated depressed women had very few pregnancy complications and did not differ from controls in any of the perinatal outcomes. The reported reasons for SSRI treatment were depression ($n = 122$, 68.9%), bipolar disorder ($n = 4$, 1.9%), anxiety disorder ($n = 23$, 11.1%), depression with comorbid anxiety disorder ($n = 22$, 10.6%), depression or anxiety with other psychiatric comorbidities ($n = 24$, 11.6%), or not reported ($n = 12$).

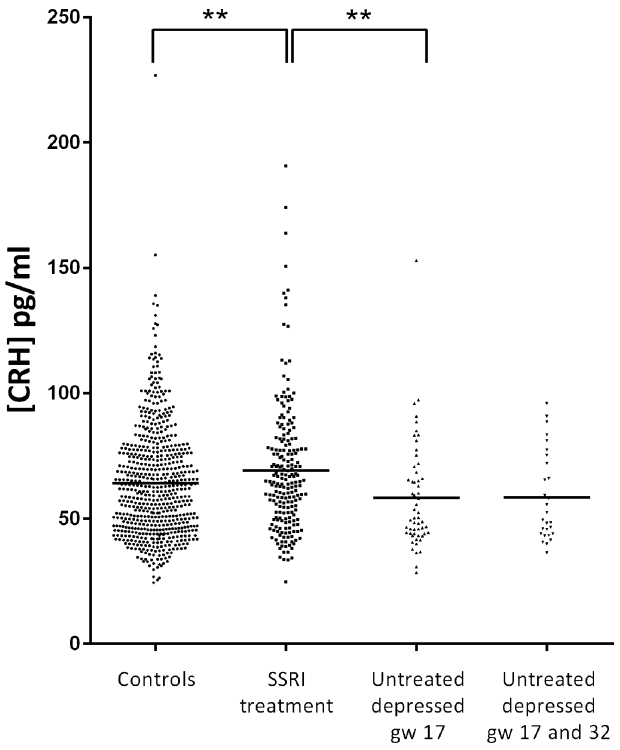

Figure 1 CRH concentrations at gestational week 17—19 in controls ($n = 609$), women on SSRI treatment ($n = 207$), women with untreated depressive symptoms in gestational week 17 ($n = 56$), and women with untreated depressive symptoms in gestational week 17 and 32 ($n = 28$). Women on SSRI treatment had significantly higher CRH levels than controls and women with untreated depressive symptoms in gestational week 17, $p < 0.01$ and $p < 0.01$, respectively. These findings remained unchanged when adjusted for gestational age at time of blood sampling according to ultrasound. gw = gestational week. ** $p < 0.01$ One-way ANOVA with post hoc Tukey HSD.

CRH serum concentrations at gestational week 16—20 in SSRI-treated, untreated depressed, and control women are displayed in Figure 1. Women on SSRI treatment had significantly higher CRH levels (69.2 ± 25.9 pg/ml) than controls (63.5 ± 22.4 pg/ml), and women with untreated depressive symptoms (58.3 ± 21.4 pg/ml), $p < 0.01$ and $p < 0.01$, respectively. These findings remained unchanged when adjusted for precise gestational age at time of blood sampling, according to the ultrasound estimation. Furthermore, women who continued to have high depression scores also in gestational week 32 ($n = 28$) did not differ from those

Table 1 Demographic data and clinical variables of the study population ($n = 872$).

		Controls ($n = 609$) mean ± SD or n (%)	Untreated depressive symptoms ($n = 56$) mean ± SD or n (%)	p-value	SSRI treated ($n = 207$) mean ± SD or n (%)	p-value
Age, years		31.0 ± 4.6	29.6 ± 4.5	1.0	30.6 ± 5.0	0.6
BMI, kg/m^2		23.8 ± 4.2	23.6 ± 4.4	1.0	24.6 ± 5.4	0.092
Parity, n (%)	No previous children	338 (55.6)	29 (51.8)	0.3	93 (44.7)	0.01
	1–2 children	250 (41.1)	27 (48.2)		98 (47.1)	
	3 or more children	20 (3.3)	0		17 (8.2)	
Smoking during pregnancy, n (%)		20 (3.3)	5 (8.9)	0.05	17 (8.3)	0.01
Alcohol use during pregnancy, n (%)		2 (0.3)	0		1 (0.5)	
Somatic disease, n (%)	Hypothyroidism[a]	29 (4.8)	4 (7.1)	0.5	15 (7.2)	0.3
	Inflammatory diseases	15 (2.5)	2 (5.4)	0.3	5 (2.4)	1.0
	Chronic hypertension	11 (1.8)	1 (1.8)	1.0	0	0.052
	Rheumatoid disorders	6 (1.0)	2 (3.6)	0.2	1 (0.5)	0.5
	Obesity	66 (10.9)	7 (12.5)	0.8	32 (15.4)	0.077
Previous psychiatric history, n (%)[c]		84 (13.8)	13 (23.2)	0.1	207 (100%)	0.001
Pregnancy complications, n (%)	Gestational hypertension	36 (5.9)	0	0.1	7 (3.4)	0.2
	Preeclampsia	21 (3.5)	3 (5.4)	0.5	14 (6.7)	0.05
	Gestational diabetes	6 (1.0)	0	n.c	5 (2.4)	0.2
	Preterm birth	27 (4.5)	0	n.c	17 (8.4)	0.05
	Spontaneous preterm birth	20 (3.4)	0	n.c	11 (5.4)	0.2
	Medically indicated preterm birth	7 (1.2)	0	n.c	6 (3.0)	0.2
Gestational age at blood sampling, days		127 ± 7	126 ± 7	0.8	127 ± 7	1.0
Gestational age at delivery, days		279 ± 12	281 ± 9	0.6	274 ± 16[b]	0.001
Birth weight, g		3600 ± 574	3674 ± 504	0.7	3492 ± 649	0.068
Small for gestational age, n (%)		5 (0.5)	0	1.0	4 (2.0)	0.3
Large for gestational age, n (%)		24 (4.1)	0	0.3	7 (3.4)	0.7

P-values are given in relation to controls, except where indicated by superscript letter. Missing values evident in 0–2.8% of cases, percentages are given in relation to available information. Eighteen women gave birth outside of Uppsala, hence only limited information available on offspring in these cases. n.c. = not calculated

[a] Hypothyroidism includes cases with hypothyroidism and subclinical hypothyroidism, treated with levothyroxine during pregnancy.

[b] Also significantly different from untreated depressed women, $p < 0.01$

[c] As reported at the first antenatal booking.

who only displayed high scores in gestational week 17 (58.5 ± 17.8 pg/ml vs. 58.1 ± 24.7 pg/ml, $p = 1.0$), Figure 1. No difference in CRH levels was noted between women with untreated depressive symptoms and controls.

As seen in Table 2, sertraline was the most commonly used SSRI, whereas paroxetine, on the other hand, was rarely used. No differences in CRH serum concentrations or gestational length were noted between the different SSRIs (Table 2). Similarly, no difference in CRH levels was noted between women using sub-normal (67.6 ± 20.2 pg/ml, $n = 35$), standard (68.2 ± 27.1 pg/ml, $n = 112$), or high doses of SSRI (70.6 ± 24.8 pg/ml, $n = 56$). Finally, seven women had additional psychotropic drugs that were used on a daily basis. These women did not differ in their CRH

Table 2 CRH concentration according to SSRI ($n = 207$).

	Number of cases	CRH concentrationmean ± SD	Gestational agemean ± SD
Sertraline	81	68.5 ± 22.4	276 ± 14
Citalopram	67	70.1 ± 24.9	272 ± 21
Fluoxetine	35	71.0 ± 36.1	273 ± 13
Ecitalopram	21	67.9 ± 24.2	276 ± 9
Paroxetine	3	57.1 ± 13.0	272 ± 6

No significant differences according to specific SSRI were found.

levels from women on SSRI monotherapy (71.4 ± 14.7 vs. 69.1 ± 26.2 pg/ml).

As expected, both the linear multivariable regression analysis on gestational length and the logistic multivariable regression analysis on preterm birth confirmed an association between CRH levels and short gestational length and preterm birth, respectively (Tables 3 and 4). SSRI use was independently associated with shorter gestational length, but the association with preterm birth was only borderline significant (Tables 3 and 4). The combined effect of SSRI treatment and above median CRH levels yielded the highest risk estimate for preterm birth, with a preterm incidence of 9.3% (Table 5). However, no interaction between SSRI use and CRH levels were noted for gestational age $F(1,211) = 1.27$; $p = 0.13$ or preterm birth, $p = 0.2$, Table 5.

Table 3 Multivariable linear regression analyses of gestational length in relation to CRH serum concentrations, SSRI treatment or untreated depressive symptoms in women with complete birth records ($n = 854$).

	Unadjusted β	*p*-value	Adjusted β[a]	*p*-value
SSRI treatment ($n = 207$)				
SSRI treatment	−0.16	0.001	−0.14	0.001
CRH, SD	−0.11	0.01	−0.09	0.05
Parity, *n*			−0.09	0.01
Smoking			−0.06	0.078
BMI, kg/m^2			0.09	0.05
Chronic hypertension			−0.07	0.062
Maternal country of origin outside Scandinavia			−0.02	0.7
Untreated depressive symptoms ($n = 56$)				
Untreated depressive symptoms	0.04	0.3	0.04	0.3
CRH, SD	−0.11	0.01	−0.10	0.05
Parity, *n*			−0.06	0.2
Smoking			−0.04	0.3
BMI, kg/m^2			0.08	0.05
Chronic hypertension			−0.08	0.05
Maternal country of origin outside Scandinavia			−0.02	0.7

[a] Adjusted for parity, smoking, BMI, chronic hypertension, maternal country of origin, and gestational age at sampling.
SD = by standard deviation.

4. Discussion

The major finding of the present study was that women on SSRI treatment during pregnancy had higher CRH levels in gestational week 16–20 than controls and women with untreated depressive symptoms. Secondly, SSRI treatment and CRH were independent explanatory factors for gestational length, and women who were on SSRI treatment and also had high CRH levels, were at increased risk of preterm birth in comparison with controls that had normal CRH levels.

While these findings clearly suggest that SSRI treatment is associated with increased placental CRH production, it is not entirely clear from the present study whether the CRH increase seen in SSRI-treated women is due to the underlying psychiatric disorder, being the reason for treatment, or whether it is an effect of the treatment *per se*. The most compelling evidence for a differential effect of untreated depression and SSRI treatment on CRH levels is obviously the finding that women with untreated depressive symptoms, in fact, had significantly lower CRH levels than women on SSRI treatment. If it is presumed that SSRI treatment would be a representative of more severe depression, as could be predicted from the fact that only 25% of women who use antidepressants at the time of conception continue treatment during pregnancy (Ververs et al., 2006), we would at least have expected a severity-dependent increase in CRH levels, with CRH levels in women with untreated depressive symptoms somewhere in-between the controls and the SSRI treated women, instead of a U-shaped relationship. Furthermore, although we did not have access to depression scores in most of our SSRI-treated women, the available data suggested that SSRI-treated women had a clear benefit from treatment, as their scores of depressed mood were significantly lower than those of the women with untreated depressive symptoms. Clearly, it is a limitation that we did not have access to a control group with untreated depressive disorder, but the high specificity of the EPDS for depressive disorder (NICE guidelines [CG 192] 2014), together with the finding that CRH levels were similarly low in women who continued to display high depression scores in both gestational weeks 17 and 32 give us some indication that findings in this group were valid.

On the other hand, there are also findings, which speak against a clear-cut relationship between the SSRI treatment itself and the CRH levels. First, as expected we found no difference in CRH levels between different SSRI drugs, but we also found no SSRI dose-dependent differences in CRH levels and no effect of polytherapy (although cases were few). However, although the SSRI dose is usually linearly related to the measured serum concentrations (Bjerkenstedt et al., 1985), SSRI pharmacokinetics vary hugely between individuals during pregnancy (Freeman et al., 2008). Consequently, while a dose-dependent relationship would have strengthened the relationship between SSRI treatment and CRH,

Table 4 Multivariable regression analysis of risk factors for preterm birth, including SSRI treatment, untreated depressive symptoms, and CRH serum concentrations, among women with complete birth records ($n = 854$).

Variable		*n*	Preterm birth%	Unadjusted odds ratio	95% Confidence interval	*p*-value	Adjusted odds ratio[a]	95% Confidence interval	*p*-value
CRH, SD				1.34	1.06—1.70	0.05	1.30	1.02—1.69	0.05
Untreated depressive symptoms		0/56		n.c.			n.c		
SSRI treatment		17/203	8.4	1.92	1.02—3.61	0.05	1.86	0.94—3.69	0.074
Parity	≥1 child	22/406	5.4	1.16	0.70—1.94	0.6	1.08	0.63—1.86	0.8
BMI, continuous				1.02	0.96—1.09	0.5	1.01	0.94—1.08	0.8
Smoking		3/39	7.1	1.51	0.45—5.11	0.6	1.33	0.38—4.69	0.7
Chronic hypertension				3.81	0.91—17.94	0.091	4.51	0.88—23.11	0.071
Maternal country of birth	Outside Scandinavia	4/47	7.8	1.62	0.56—4.73	0.4	2.16	0.72—6.53	0.7

[a] Also adjusted for gestational age at blood sampling.
Smoking status was lacking in six women, otherwise no missing data was evident. n.c. = not calculated, SD = by standard deviation.

such relationships may be particularly difficult to discern in pregnancy. Secondly, it was also clear from the medical records review that a substantial proportion of SSRI-treated women were on treatment not only for depression, but also for anxiety disorders and more than 20% had some form of psychiatric co-morbidity. In contrast, less than 25% of women with untreated depressive symptoms reported a psychiatric history at the first antenatal visit, suggesting that their depressive symptoms in most cases may have evolved during the actual pregnancy. Taken together, these observations suggest that the SSRI-treated women had an overall greater burden of mental health problems than the women with untreated depressive symptoms that were used as controls for the CRH analysis. Furthermore, in light of the fact that untreated depressed women also had fewer obstetric and perinatal complications than expected from the literature (Grote et al., 2010), these two groups may not be entirely comparable as to the severity, duration, or early placental influence of their underlying mental health problems.

Even though the plasma samples of this study were taken at a relatively early stage of pregnancy, we were able to confirm previous reports of an association between placental CRH and gestational length on the one hand and preterm delivery on the other (Petraglia et al., 2010; Smith and Nicholson, 2007), albeit of limited impact. Similarly, in the bivariate analysis, SSRI treatment was associated with shorter gestational length and increased risk of preterm birth (Olivier et al., 2013). Following adjustment for a number of relevant confounders, the association between SSRI and gestational length remained whereas the association with preterm birth no longer was significant. However, women who were on treatment with SSRI and had high CRH levels in gestational week 16—20 had more than two times

Table 5 Risk for preterm birth in relation to CRH level and SSRI treatment.

Variable	*n*	Preterm birth%	Gestational length, days	Unadjusted odds ratio	95% Confidence interval	*p*-value	Adjusted odds ratio[a]	95% Confidence interval	*p*-value
Controls with below median CRH	13/291	4.3	279 ± 11	1			1		
Controls with above median CRH	14/277	4.8	279 ± 13	1.13	0.52—2.45	0.8	1.27	0.57—2.81	0.6
SSRI treated with below median CRH	6/79	7.1	275 ± 12	1.70	0.63—4.62	0.3	2.01	0.70—5.70	0.2
SSRI treated with above median CRH	11/107	9.3	272 ± 13	2.30	1.00—5.29	0.05	2.48	1.01—6.08	0.05

[a] Adjusted for parity, smoking, BMI, chronic hypertension, maternal country of origin, and gestational age at sampling. $P = 0.2$ for trend across CRH and SSRI strata.

increased odds of delivering preterm. Very few studies have attempted to relate SSRI use and CRH levels to gestational length, but our findings are in line with one study reporting that women with high CRH levels and high maternal prenatal anxiety delivered earlier than women with lower CRH levels and lower maternal prenatal anxiety (Mancuso et al., 2004). The exact mechanisms by which placental CRH production increases in SSRI treated pregnant women and how this later translates into an increased risk of preterm birth can only be speculated upon. Previous studies have suggested that stress, anxiety and depression could influence CRH levels in pregnant women, but findings are far from unanimous (Chen et al., 2010; Guendelman et al., 2008; Harville et al., 2009; Himes and Simhan, 2011; Hobel et al., 1999; Kramer et al., 2009; Meltzer-Brody et al., 2011; Rich-Edwards et al., 2008; Susman et al., 1999; Tse et al., 2012), and as previously mentioned, we cannot be entirely sure whether the effect we see is due to the SSRI treatment in itself, or the causes for treatment. In addition to that, while CRH is a likely determinant of gestational length and onset of delivery, the exact pathways that mediate this effect remain unclear (Smith and Nicholson, 2007). In addition to elevated placental production of CRH, preterm birth may also be a consequence of infection, premature rupture of the membranes, retroplacental hemorrhage, or it may be medically indicated due to preeclampsia or intrauterine growth restriction. Women who deliver preterm spontaneously have been shown to have a more rapid rate of CRH rise, which is detectible already early on in the second trimester (Petraglia et al., 2010; Smith and Nicholson, 2007). This finding has led to the hypothesis that the gestational length is determined early in pregnancy by a biological clock, somehow linked to the placental production of CRH (McLean et al., 1995). However, in many situations of fetal distress, such as intrauterine growth restriction (Goland et al., 1993) and reduced umbilical artery blood flow (Giles et al., 1996), CRH production is elevated, ultimately suggesting that fetal placental signaling may influence placental CRH production, and potentially also the timing of birth (Smith and Nicholson, 2007). Finally, preeclampsia being one of the most common causes for medically indicated preterm birth is also associated with elevated CRH levels (Perkins et al., 1995). Hence, as this study did not have power to discriminate between the effect of SSRI use on spontaneous preterm birth and medically indicated preterm birth, for individual women, any of the above mechanisms could be relevant. However, what can be said from the results is that the increased risk of preterm birth associated with SSRI treatment appear not to be mediated by increased placental CRH production. Instead, these two factors appear to act as independent explanatory variables for gestational length, and merely the additive effect of SSRI treatment and elevated CRH was associated with the greatest risk of preterm birth.

Besides the lack of a control group of women with untreated depressive disorder, and the insufficient power to evaluate spontaneous preterm birth only, this study is also limited by the single assessment of CRH in second trimester of pregnancy, and by lack of methods to protect from interference by CRH binding protein. However, it represents one of the first attempts to elucidate the direct biological effects of SSRI treatment on placental function, with a sample size sufficient for its primary aim.

In conclusion, our findings suggest that SSRI treatment during pregnancy is associated with increased mid-pregnancy CRH levels, although it remains unclear if this effect is due to the mental health problems women are suffering from, or whether it is due to the medication they need in order to cope with their mental symptoms. Nevertheless, the elevated risk for preterm birth in SSRI users appear not to be mediated by increased placental CRH production, rather do both of these factors appear as independent mechanisms influencing gestational length.

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Conflict of interest

The authors are alone responsible for the content and writing of the manuscript. I Sundstrom-Poromaa serve occasionally on advisory boards or act as invited speaker at scientific meetings for MSD, Bayer Health Care, Novo Nordisk, and Lundbeck A/S. The other authors have nothing to disclose.

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