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Maternal cortisol during pregnancy and offspring schizophrenia: Influence of fetal sex and timing of exposure

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ABSTRACT

Introduction: Maternal stress during pregnancy has been repeatedly linked to increased risk for schizophrenia; however, no study has examined maternal cortisol during pregnancy and risk for the disorder. Study aims were to determine whether prenatal cortisol was associated with risk for schizophrenia and risk for an intermediate phenotype—decreased fetal growth—previously linked to prenatal cortisol and schizophrenia. Timing of exposure and fetal sex also were examined given previous findings.
Methods: Participants were 64 cases diagnosed with schizophrenia spectrum disorders (SSD) and 117 controls from a prospective birth cohort study. Maternal cortisol was determined from stored sera from each trimester and psychiatric diagnoses were assessed from offspring using semi-structured interviews and medical records review.
Results: Maternal cortisol during pregnancy was not associated with risk for offspring schizophrenia. There was a significant interaction between 3rd trimester cortisol and case status on fetal growth. Specifically, cases exposed to higher 3rd trimester maternal cortisol had significantly decreased fetal growth compared to controls. In addition, these findings were restricted to male offspring.
Conclusions: Our results indicate that higher prenatal cortisol is associated with an intermediate phenotype linked to schizophrenia, fetal growth, but only among male offspring who developed schizophrenia. Findings were consistent with evidence that schizophrenia genes may disrupt placental functioning specifically for male fetuses, as well as findings that males are more vulnerable to maternal cortisol during pregnancy. Finally, results suggest that examining fetal sex and intermediate phenotypes may be important in understanding the mechanisms involved in prenatal contributors to schizophrenia.

1. Introduction

Maternal stress during pregnancy has been repeatedly linked with increased risk of offspring schizophrenia and other spectrum disorders, herein referred to as schizophrenia (Fineberg et al., 2016). In particular, exposure to a number of severe life events during pregnancy, such as war (Malaspina et al., 2008; Van Os and Selten, 1998), natural disaster (Selten et al., 1999; Watson et al., 1999), famine (Susser and St Clair, 2013), and death of a spouse or close relative (Huttunen and Niskanen, 1978; Khashan et al., 2008), has been associated with schizophrenia in offspring. Several of these findings have been complicated by use of population-level exposure data (Selten et al., 1999; St Clair et al., 2005; Susser and Lin, 1992; Van Os and Selten, 1998) and measures of extreme and uncommon environmental stressors that likely involve other processes beyond stress (e.g., malnutrition; Susser and Lin, 1992; St Clair et al., 2005). Additionally, the findings relating bereavement during pregnancy to increased schizophrenia risk (Huttunen and Niskanen, 1978; Khashan et al., 2008) have been somewhat mixed (Abel et al., 2014; Class et al., 2014). Nevertheless, studies using more common

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stressful life events during pregnancy, as well improved methodologies (e.g., prospective measures of maternal psychological stress), have found similar associations between prenatal stress and offspring schizophrenia. For example, studies examining maternal reports of unwantedness of pregnancy have found associations between maternal report and later development of offspring schizophrenia (Herman et al., 2006; McNeil et al., 2009; Myhrman et al., 1996). Furthermore, prospectively collected maternal reports of daily life stress during pregnancy (e.g., financial stress, marriage difficulties) have been associated with significantly increased odds of schizophrenia in male offspring (Fineberg et al., 2016).

Several mechanisms have been investigated to explain the adverse effects of maternal stress on fetal neurodevelopment (Corcoran et al., 2003; Rakers et al., 2017; Walker et al., 2008). Higher levels during pregnancy of the stress hormone cortisol have been identified as a possible mediator of the maternal stress effects on fetal development (Cottrell and Seckl, 2009; Moisiadis and Matthews, 2014). For instance, higher maternal cortisol during pregnancy has been consistently associated with obstetric complications (OCs) and premorbid difficulties found in the histories of schizophrenia patients. Specifically, higher maternal cortisol (particularly in the 2nd trimester) has been associated with decreased gestational age and decreased birth weight/fetal growth restriction, OCs that have been associated with schizophrenia (Abel et al., 2010; Bloom et al., 2001; Cannon et al., 2002; Eide et al., 2013; Ellman et al., 2008; Fineberg et al., 2013; French et al., 1999; Ichiki et al., 2000; Lane and Albee, 1966; Murphy et al., 2006; Reinisch et al., 1978; Trainer, 2002). In addition, we have previously found that both fetal hypoxia and exposure to maternal influenza during pregnancy are associated with decreased fetal growth, but only for infants that later go on to develop schizophrenia and not controls, indicating that vulnerability associated with schizophrenia may interact with these prenatal events to impair fetal growth (Fineberg et al., 2013). Also, in both human and preclinical studies (Glover et al., 2010; Kapoor et al., 2008; Lemaire et al., 2000; McArthur et al., 2005; Sandman et al., 2018), higher maternal prenatal cortisol has been associated with a variety of offspring brain abnormalities that have been linked to schizophrenia, such as hippocampal alterations (e.g., inhibited neurogenesis) and dopaminergic abnormalities. Cumulatively, these findings suggest that fetal exposure to maternal cortisol is associated with birth outcomes and long-lasting neuronal and cognitive alterations similar to those found among schizophrenia patients.

In addition, accumulating evidence suggests that males and females differ in their vulnerability to adverse influences of prenatal stress (Chan et al., 2018; Mueller and Bale, 2008; Sandman et al., 2013). A number of studies show increased risk of schizophrenia among male, but not female, offspring whose mothers experienced psychological stress during pregnancy (Chan et al., 2018; Fineberg et al., 2016; Khashan et al., 2008; Van Os and Selten, 1998). Similarly, as compared to females, males appear to display greater vulnerability for early mortality and morbidity, including developmental delays in important markers of neonatal maturity (such as decreased fetal growth), following prenatal exposure to elevated levels of stress hormones and maternal psychosocial stress (Ellman et al., 2008; Sandman et al., 2013). Second, there is some evidence, albeit mixed, to suggest that males with schizophrenia are more susceptible to adverse pre- and perinatal events and obstetrical complications compared to females (Cannon et al., 2002; Foerster et al., 1991; Goldstein and Walder, 2006; Matsumoto et al., 2001), possibly contributing to a form of schizophrenia that has stronger "neurodevelopmental" origins (Castle and Murray, 1991; Walker et al., 2002). Third, males may be more vulnerable to prenatal gonadal hormone disruptions than females, contributing to sexual dimorphisms in behavioral sequelae and risk for psychopathology (Walder et al., 2006).

Hence, the present study sought to determine whether fetal exposure to higher maternal cortisol was associated with increased odds of offspring schizophrenia. In addition, this study investigated whether timing of exposure to cortisol and fetal sex contributed to the findings. Although there has been some variability in previous results, most studies have linked 2nd trimester maternal stress with offspring schizophrenia and outcomes associated with schizophrenia (Bloom et al., 2001; Cannon et al., 2002; Ellman et al., 2008; Fineberg et al., 2013; French et al., 1999; Ichicki et al., 2000; Lane and Albee, 1966; Murphy et al., 2006; Reinisch et al., 1978; Trainer, 2002). Finally, the present study aimed to investigate whether higher maternal cortisol during pregnancy was associated with decreased fetal growth and whether this association was influenced by fetal sex and case status, as has previously been suggested (Chan et al., 2018; Ellman et al., 2008; Fineberg et al., 2016; Khashan et al., 2008; Mueller and Bale, 2008; Sandman et al., 2013; Van Os and Selten, 1998). This latter aim was explored given the strong possibility that higher maternal cortisol during pregnancy is associated with an intermediate phenotype associated with both schizophrenia and prenatal cortisol, instead of the full diagnostic criteria for the disorder (Abel et al., 2010; Bloom et al., 2001; Cannon et al., 2002; Eide et al., 2013; Ellman et al., 2008; Fineberg et al., 2013; French et al., 1999; Ichicki et al., 2000; Lane and Albee, 1966; Murphy et al., 2006; Reinisch et al., 1978; Trainer, 2002). We hypothesized that higher levels of 2nd trimester maternal cortisol would be associated with increased odds of schizophrenia and decreased fetal growth among cases. We also hypothesized that these associations would be restricted to males, given repeated associations suggesting that male fetuses are preferentially sensitive to the effects of prenatal cortisol (Ellman et al., 2008; Sandman et al., 2013). We hypothesized that maternal cortisol during pregnancy would not be significantly associated with schizophrenia risk and/or fetal growth among female cases, based on previous findings (Ellman et al., 2008; Fineberg et al., 2016).

2. Materials and methods

The study was approved by the Institutional Review Boards of the New York State Psychiatric Institute, the Kaiser Foundation Research Institute, and Temple University.

2.1. Description of the cohort

Participants were derived from the Prenatal Determinants of Schizophrenia (PDS) study, which ascertained cases of schizophrenia and other spectrum disorders from a large birth cohort described in detail previously (Susser et al., 2000). Briefly, the PDS study included pregnant women (n = 12,094 live births) receiving obstetric care from the Kaiser Permanente Medical Care Plan (KPMCP) in Alameda County, California, as part of the Child Health and Development Studies (CHDS). Maternal serum samples were collected throughout the pregnancies and were frozen and stored at −20 °C.

2.2. Ascertainment and diagnosis

Case ascertainment and screening were accomplished following computerized record linkage between the CHDS and KPMCP identifiers from inpatient, outpatient, and pharmacy registries of CHDS participants who belonged to KPMCP from 1981 to 1997 (corresponding to the initiation of KPMCP computerized psychiatric registries and to the end of follow-up). Potential cases were diagnosed using DSM-IV criteria following assessment with the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al., 1994), chart review, and consensus of 3 experienced research psychiatrists. A "case" was defined as an individual diagnosed with

a schizophrenia spectrum disorder (SSD; schizophrenia, schizoaffective disorder, schizotypal personality disorder, other nonaffective psychoses), as described elsewhere (Susser et al., 2000). The PDS study included 71 cases of SSD. PDS control matching has been described elsewhere, but briefly up to 8 controls were matched to cases based on length of membership in KFHP, gender, number and gestational timing of prenatal blood draws, and date of birth, while randomly selecting one sibling for each family (Susser et al., 2000). The present study included 64 cases, each of whom were matched to 1 or 2 controls who had available sera, except for one case who had no matched controls. Among cases with trimester 2 cortisol data, 6 had matched controls without trimester 2 cortisol data; among cases with trimester 3 cortisol data, 5 were matched to controls without trimester 3 cortisol data. Therefore, controls for the unmatched case cortisol samples in trimesters 2 and 3 were matched to 1 of the control samples from the remaining controls with available cortisol data; for each case sample, the control sample with gestational age at blood draw closest to that of the case was selected, given known increases in cortisol throughout gestation (Trainer, 2002). For cases who had more than one blood draw in a given trimester, the blood draw was selected that minimized the difference in gestational age at the time of blood draw for the matched set (i.e., closest in weeks gestation at the time of blood draw between the case and control). The process yielded 57 first trimester samples (SSD = 20), 113 second trimester samples (SSD = 45), and 165 third trimester samples (SSD = 59). Of the cases, 38 were diagnosed with schizophrenia, 15 schizoaffective disorder, 5 schizotypal personality disorder, 1 delusional disorder, 5 other nonaffective psychosis.

2.3. Cortisol analyses

Although diurnal variations of cortisol remain intact during pregnancy, they are substantially blunted due to rising levels of cortisol throughout gestation, with the main variation consisting of a spike during the first 30 min following awakening (de Weerth and Buitelaar, 2005). Although times of the blood draws are not known, blood was collected primarily in the morning while fasting at the study site, which reduces the possibility that blood samples were obtained directly following awakening. Further, data from the CHDS cohort and another similar birth cohort study (NCPP cohort) during the same period as the CHDS study (also with unknown collection times) found that maternal cortisol values were consistent with values from published studies of fresh samples collected at similar points in gestation, indicating minimal degradation of cortisol over time (Stroud et al., 2007).

Serum cortisol was measured in the Analytical Psychopharmacology Laboratory at Nathan Kline Institute. Cortisol was measured by radioimmunoassay after denaturation of the binding proteins by heat. Primary antibodies (raised in rabbit against cortisol-3-carboxymethyl oxime-bovine serum albumin) and ^{125}I-labeled cortisol were purchased from MP Biomedicals (Santa Ana, CA). The cortisol standard was purchased from Sigma Chemical Company (Saint-Louis, MO). Anti-rabbit globulin serum in conjunction with polyethylene glycol was used for separation of the bound and free fractions. Samples were assayed in duplicate. The intra- and inter-assay critical values were: 2.95% and 6.0% at 3.1 μg/dL level, 2.53% and 3.93% at 19.3 μg/dL level, and 2.00% and 2.91% at 32.7 μg/dL level.

2.4. Statistical analyses

All statistical analyses were performed using SAS software version 9.4 (Cary, NC). Cortisol distributions by trimester were inspected for the overall analytic sample and when stratifying by presence/absence of SSD by examining kurtosis and skewness values, as well as visually inspecting the distributions. Potential covariates were determined by conducting correlations between the main study variables (i.e., cortisol variables and SSD) and birthweight, gestational age (measured in weeks from last menstrual period to birth), maternal race (African-American versus not African-American), maternal age, and maternal education (HS degree or below vs. above HS). If these variables were associated with both the main IVs and DVs, then they were included in subsequent models. In addition, bivariate correlations in each trimester were tested for significance among cortisol and SSD.

Separate logistic regressions were conducted for the second and third trimesters to determine whether cortisol and/or the interaction between cortisol and infant sex were associated with increased odds of SSD. Cortisol, infant sex, and an interaction between cortisol and sex were included as independent variables in each model, conducted separately by trimester. If interaction variables were significant, logistic regressions were conducted stratifying by sex, in order to descriptively probe the significant interaction. Due to small sample sizes in the first trimester, a logistic regression was conducted with cortisol as the independent variable without a cortisol by sex interaction term, as the interaction would not be interpretable with such small cell numbers (i.e., when breaking down case status by sex). Separate regressions were conducted by trimester to determine if SSD, cortisol, and the interaction between SSD and cortisol were associated with birth weight. All regression analyses controlled for gestational age, to assess fetal growth accounting for variations in the length of the pregnancy and significant findings were probed by conducting regressions stratifying by case status. Additionally, any significant stratified case/control results were probed for sex differences by adding infant sex interaction terms (excluding the first trimester due to small sample sizes). For all other analyses, significance was based on two-tailed p-values<0.05.

3. Results

No major deviations from normality were found for cortisol levels, so analyses were performed using raw values. Demographic characteristics are listed in Table 1 (and Supplementary Table 1 for characteristics broken down by infant sex). Bivariate correlations indicated that one of the potential covariates, maternal education, was significantly associated with both cortisol and SSD (see Table 2). As such, maternal education was included as a covariate in logistic regression analyses of trimester 2 cortisol predicting schizophrenia. No additional covariates were included in analyses, as they were not significantly associated with both the predictor and outcome variables (see Table 2).

Logistic regression analyses indicated that cortisol did not significantly increase the odds of SSD in any trimester, and there were no significant sex by cortisol interactions (see Table 3). As Table 4 indicates, linear regression analyses indicated that SSD status significantly interacted with trimester 3 cortisol levels to predict birthweight while controlling for gestational age, such that higher third trimester cortisol levels were associated with lower birthweight in cases, but not in controls ($p = 0.011$). When stratifying by SSD status, for each unit increase in cortisol, there was a 12.83 g decrease in birthweight ($p = 0.029$) among those who later developed SSD, but not control infants, controlling for gestational age (see Table 5). Similarly, when stratifying by sex, the interaction between SSD status and trimester 3 cortisol was significantly associated with decreased fetal growth among males, but not females. In males, for each unit increase in cortisol, there was a 29.00 g decrease in birthweight ($p = 0.001$) among those who later developed SSD, but not control infants.

4. Discussion

This is the first study to determine that higher third trimester

Table 1
Demographics characteristics.

	Overall sample (n = 181)	Cases (n = 64)	Controls (n = 117)	*p*-Value (*t* or χ^2)
Cortisol (μg/dL): M (SD)				
Trimester 1	14.77 (5.12)	14.40 (5.44)	14.97 (5.00)	0.688
Trimester 2	23.23 (9.45)	21.79 (7.75)	24.19 (10.36)	0.163
Trimester 3	38.44 (12.17)	36.77 (11.44)	39.37 (12.51)	0.190
Gestational age at blood draw (weeks): M (SD)				
Trimester 1	10.92 (1.92)	11.19 (1.86)	10.77 (1.96)	0.443
Trimester 2	20.27 (3.61)	20.04 (3.69)	20.42 (3.58)	0.589
Trimester 3	34.57 (2.85)	34.68 (3.02)	34.51 (2.77)	0.708
Potential covariates				
Birth weight (grams): M (SD)	3322.43 (521.57)	3379.85 (552.52)	3291.02 (503.50)	0.275
Gestational age (weeks): M (SD)	40.16 (2.37)	40.48 (2.02)	39.99 (2.53)	0.183
Maternal age at childbirth: M (SD)	27.84 (6.27)	28.30 (6.24)	27.59 (6.30)	0.474
Maternal race: N (%)				
Caucasian	96 (53.93)	32 (50.79)	64 (55.65)	0.534
African American	69 (38.76)	27 (42.86)	42 (36.52)	0.407
Asian	9 (5.06)	1 (1.59)	8 (6.96)	0.118
Maternal education: N (%)				
High school or less	89 (54.94)	38 (66.67)	51 (48.57)	0.027*
More than high school	73 (45.06)	19 (33.33)	54 (51.43)	
Infant sex: %M (%F)	67.40 (32.60)	65.63 (34.38)	68.38 (31.62)	0.706

The following variables had missing data: For cases: maternal race (n = 4), maternal education (n = 7). For controls: gestational age (n = 1), maternal age at childbirth (n = 1), maternal race (n = 3), maternal education (n = 12). *p*-Values correspond to tests of differences between cases and controls (*t*-tests for continuous variables and chi-square tests for categorical variables).
* $p < 0.05$.

maternal cortisol is associated with decreased fetal growth among infants who later develop schizophrenia, but not control infants. Specifically, our findings suggest that liability associated with schizophrenia appears to render the fetus vulnerable to the influences of maternal cortisol with observable decrements in fetal growth. Contrary to our hypotheses, maternal cortisol during pregnancy was not associated with increased risk of offspring schizophrenia, but rather was associated with a phenotype, decreased fetal growth, that has been linked to schizophrenia and prenatal cortisol in previous studies. Our results highlight the importance of examining phenotypes that may be more proximal to risk factors for disorders, such as fetal growth, and may have more biological relevance than DSM criteria (Ellman et al., 2018).

Our findings also suggest that fetal sex and timing of exposure to maternal cortisol during pregnancy matter in terms of fetal growth. Specifically, maternal cortisol during the third trimester of pregnancy was associated with decreased fetal growth for male infants who later developed schizophrenia, but not for control infants or females. These findings are consistent with our previous results suggesting that maternal influenza during pregnancy and fetal hypoxia are associated with decreased fetal growth only for cases who develop schizophrenia and not control infants, indicating that vulnerability associated with schizophrenia renders the fetus more susceptible to these obstetric complications and leads to observable decreases in fetal growth (Fineberg et al., 2013). These findings are also consistent with a variety of studies that have found sex differences in fetal responses to maternal cortisol, with males more likely to exhibit decreases in fetal growth and maturation when exposed to higher maternal cortisol (Ellman et al., 2008; Sandman et al., 2013). Although we hypothesized that the 2nd trimester would be particularly important based on previous studies linking second trimester cortisol (including early and later second trimester) to reduced fetal growth and maturation (Ellman et al., 2008; Sandman et al., 2013), the present study was limited by including serum samples throughout the extent of the second and third trimesters; therefore, it remains possible that our significant

Table 2
Bivariate correlations between case status, cortisol by trimester, gestational age at blood draw, and potential covariates.

	Case status	Cortisol (T1)	GA at blood draw (T1)	Cortisol (T2)	GA at blood draw (T2)	Cortisol (T3)	GA at blood draw (T3)	Birth weight	Gestational age	Maternal age at childbirth	African-American	Maternal education
Cortisol (T1)	−0.05	–										
GA at blood draw (T1)	0.10	0.13	–									
Cortisol (T2)	−0.12	0.30	−0.31	–								
GA at blood draw (T2)	−0.05	−0.13	0.28	0.32***	–							
Cortisol (T3)	−0.10	0.44**	−0.08	0.53***	0.09	–						
GA at blood draw (T3)	0.03	0.06	−0.09	−0.09	0.11	−0.07	–					
Birth weight	0.08	0.14	0.08	−0.10	−0.05	−0.05	−0.02	–				
Gestational age	0.10	−0.22	0.15	−0.08	−0.07	−0.05	0.001	0.37***	–			
Maternal age at childbirth	0.05	−0.13	−0.01	−0.02	−0.11	−0.25**	0.05	−0.09	−0.02	–		
Race (African American)	0.06	0.11	−0.26*	−0.22*	−0.01	−0.02	0.01	−0.21**	−0.14	−0.13	–	
Maternal education	−0.17*	−0.12	0.10	0.22*	0.09	−0.01	0.15	0.06	0.01	0.20*	−0.22**	–
Male sex	−0.03	0.07	0.27*	−0.09	−0.12	−0.18*	0.07	0.10	−0.07	0.09	0.04	−0.08

[a]Abbreviations: GA: gestational age; T1: Trimester1; T2: Trimester 2; T3; Trimester3.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

Table 3
Logistic regression results for cortisol (μg/dL) by trimester predicting case status, with and without cortisol by sex interaction.

Cortisol by trimester	Without interaction			Cortisol by sex interaction
	OR	95% CI	*p*-Value	*p*-value
Trimester 1[a]	0.977	0.874–1.091	0.679	Underpowered
Trimester 2[b]	0.971	0.927–1.018	0.223	0.792
Trimester 3[a]	0.980	0.953–1.008	0.158	0.153

Table 3 includes logistic regression results for models that included a cortisol by sex interaction term, as well as models that did not include this interaction term to predict case status.
[a] Controlling for infant sex.
[b] Controlling for infant sex and maternal education.

findings were driven by early third trimester cortisol, a possibility that we were underpowered to examine. While cortisol is critical for fetal maturation during later parts of gestation (Murphy et al., 2006; Trainer, 2002; Welberg and Seckl, 2001), it has been repeatedly demonstrated that women receiving synthetic corticosteroids (with administration typically in late second and third trimesters) were more likely to deliver infants with fetal growth restriction and low birth weight, even when controlling for length of gestation, suggesting that high levels of glucocorticoids may be detrimental to fetal growth even in the third trimester (Bloom et al., 2001; Davis et al., 2011; French et al., 1999; Reinisch et al., 1978). Finally, decreased fetal growth has been associated with schizophrenia (Cannon et al., 2002), supporting the plausibility of our findings, and suggesting that higher maternal cortisol during pregnancy may be an additional factor contributing to this association.

As predicted, our findings were restricted to male offspring. Our findings are consistent with a variety of studies that have found increased vulnerability of male fetuses following maternal experiences of traumatic life events (e.g., 9/11) and stress during pregnancy, with a number of studies suggesting that male fetuses are less likely to survive, more likely to suffer from motor and cognitive difficulties, and more likely to have poor birth outcomes (e.g., preterm delivery/fetal growth restriction; Bruckner and Nobles, 2013; Sandman et al., 2013). Our findings also are consistent with studies that have linked higher levels of cortisol during pregnancy to adverse birth outcomes and premorbid difficulties commonly found among schizophrenia samples (Ellman et al., 2008). Nevertheless, our findings are inconsistent with our previous results linking maternal stress during pregnancy to male offspring with schizophrenia (Fineberg et al., 2016). We were unable to compare the current results to our previous findings, given that collection of maternal prenatal interviews that reported stress occurred before most of our blood draws (mean gestational age at time of interview = 15.85). However, some studies suggest that maternal reports of stress decrease as gestation progresses, even as cortisol levels become increasingly elevated (maternal cortisol increases throughout gestation partially as a function of a feedback loop between the mother's adrenal cortex and the placenta that releases corticotropin-releasing hormone [CRH]); therefore, elevations in cortisol may not fully reflect stress processes in pregnant samples (Glynn et al., 2004; Glynn et al., 2001; Trainer, 2002). In addition, although the variability in levels of cortisol in our study were consistent with previous studies (Ellman et al., 2008; Stroud et al., 2007), we combined samples throughout an entire trimester, potentially obscuring relevant findings. It is possible that higher maternal cortisol during specific periods within trimesters portends increased risk for schizophrenia, particularly among male offspring; however, to address this question would require a very large sample with multiple blood draws throughout pregnancy.

The mechanisms by which elevated maternal cortisol during the third trimester impact fetal growth are unclear; however, the third trimester is a period of rapid fetal growth (in length, weight, and most organ systems), so our findings fit with what is occurring developmentally (Pardi and Cetin, 2006; Prayer and Brugger, 2007). The preponderance of studies in community samples suggest that elevated cortisol in the 2nd trimester primes the placenta to release more CRH in the third trimester (particularly for males; Sandman et al., 2006), which is further associated with earlier parturition and reduced fetal growth, implicating placental functioning as one potential mediator of this association (Ellman et al., 2008; Sandman et al., 2013). In addition, there is evidence that human fetal testosterone (which is higher in male fetuses) increases fetal cortisol; therefore, maternal cortisol could alter fetal exposure to glucocorticoids in multiple ways (Gitau et al., 2005). Although there is an enzyme in the placenta that converts cortisol to its inactive form cortisone, (11β hydroxysteroid dehydrogenase 2, 11β-HSD2), expression of this enzyme decreases over the course of gestation (with the highest levels of cortisol getting to the fetus in the third trimester) and there is evidence of less activity in this enzyme in male placentas (Stark et al., 2009). Our findings also are consistent with recent reports that schizophrenia genes (using polygenic risk scores, PRS) are highly expressed in male placental tissue (primarily for genes involving cellular stress responses), and these genes are more expressed in placentas of fetuses with intrauterine growth restriction, indicating that genetic vulnerability associated with schizophrenia may render male fetuses particularly sensitive to a range of obstetric events, thus increasing the likelihood of decreased fetal growth (Ursini et al., 2018).

Our findings also may have been influenced by health-risk behaviors (e.g., substance use) during pregnancy that have been associated with stress and decreased fetal growth (Auerbach et al., 2014; Lobel et al., 2008; Pereira et al., 2017) In addition, although no other study (to our knowledge) using the current cohort has examined fetal growth among SSD cases and controls, a variety of other OCs (e.g., infections, inflammation, etc.) have been linked to SSD in this cohort (Brown et al., 2004b; Brown et al., 2004a). While many of the OCs that have been examined in this cohort have not

Table 4
Linear regression results with cortisol, case status, and a cortisol by case status interaction predicting birth weight (in grams), with and without controlling for gestational age.

	Cortisol		Case status		Cortisol x Case Status	
	Unstandardized coefficient	$p > \|t\|$	Unstandardized coefficient	$p > \|t\|$	Unstandardized coefficient	$p > \|t\|$
Without controlling for gestational age						
Trimester 1	3.71	0.818	−339.77	0.402	23.27	0.374
Trimester 2	−0.76	0.907	437.76	0.147	−16.31	0.194
Trimester 3	3.92	0.316	745.03	0.007**	−18.10	0.0099**
Controlling for gestational age						
Trimester 1	10.50	0.503	−378.79	0.328	10.50	0.503
Trimester 2	−0.04	0.995	298.50	0.269	−0.04	0.995
Trimester 3	4.47	0.228	691.50	0.0097**	−17.28	0.011*

* $p < 0.05$.
** $p < 0.01$.

Table 5
Linear regression results for trimester 3 cortisol predicting birth weight (in grams).

Without controlling for gestational age					
Overall sample					
Case status		Unstandardized coefficient	95% CI	*t* (SE)	$p > \|t\|$
Cases		−14.18	(−25.76, −2.60)	−2.45 (5.78)	0.017*
Controls		3.92	(−3.78, 11.62)	1.01 (3.89)	0.315
Stratified by sex					
Case status	Sex	Unstandardized coefficient	95% CI	*t* (SE)	$p > \|t\|$
Cases	Males	−32.18	(−46.45, −17.91)	−4.57 (7.04)	<0.0001***
	Females	14.14	(−4.07, 32.35)	1.62 (8.70)	0.121
Controls	Males	1.99	(−7.91, 11.89)	0.40 (4.96)	0.689
	Females	8.63	(−4.01, 21.25)	1.39 (6.20)	0.174
Controlling for gestational age					
Overall sample					
Case status		Unstandardized coefficient	95% CI	*t* (SE)	$p > \|t\|$
Cases		−12.83	(−24.30, −1.37)	−2.24 (5.72)	0.029*
Controls		4.49	(−2.78, 11.76)	1.22 (3.67)	0.224
Stratified by Sex					
Case status	Sex	Unstandardized coefficient	95% CI	*t* (SE)	$p > \|t\|$
Cases	Males	−29.00	(−45.34, −12.66)	−3.61 (8.04)	0.001**
	Females	13.84	(−9.35, 37.03)	1.25 (11.04)	0.226
Controls	Males	2.37	(−7.07, 11.80)	0.50 (4.73)	0.618
	Females	10.50	(−1.05, 22.06)	1.85 (5.66)	0.073

The table above includes linear regression analyses (with and without controlling for gestational age) stratifying by case status, as well as stratifying by cases status and sex. Only 3rd trimester results are included, given that the significant interactions were only found in trimester 3 analyses. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

been associated with decreased fetal growth, studies have linked prenatal cortisol and stress to higher incidences of infection and higher levels of inflammation (Coussons-Read et al., 2007; Coussons-Read et al., 2005). In addition, other parental factors that have been linked to decreased fetal growth and SSD (e.g., psychiatric disorders and paternal age) would be important to examine in future studies (Wallwiener et al., 2019). Therefore, future studies with larger samples should consider the possible additive and/or interactive effects of other pre- and postnatal influences in contributing to decreased fetal growth among cases and SSD risk.

There were several limitations of the present study that should be noted. Specifically, no information pertaining to time of day of blood collection was available; therefore, it is possible the diurnal variations in cortisol may have influenced our findings (Allolio et al., 1990). Nevertheless, any differences in blood collection times were minimized by the majority of samples being collected in the morning and that diurnal variations in cortisol are blunted during pregnancy (de Weerth and Buitelaar, 2005). In addition, it is unlikely that diurnal variations in cortisol would preferentially affect cases or controls. It also is possible that degradation of cortisol over time influenced findings; however, cortisol has a fairly long half-life, and we and others in a similar birth cohort have found cortisol levels consistent with fresh samples (Stroud et al., 2007). It also is unlikely that degradation of sera would influence one comparison group more than another. The small sample sizes in the first trimester also may have obscured findings that could be addressed in future studies; however, most human and animal studies linking prenatal cortisol to decreased fetal growth have focused on mid-to-late gestation which bolster our findings (Braithwaite et al., 2017; Fameli et al., 1994; Graham et al., 2018; Osterholm et al., 2012).

This study also had a number of strengths, including being the first study to examine the timing of exposure to maternal cortisol during pregnancy and risk for offspring schizophrenia and decreased fetal growth in a longitudinal, prospective, representative birth cohort. In addition, this study was unique in its continuous follow-up of offspring and well-validated diagnoses of SSD in a cohort with prospectively collected prenatal information.

The current study has the potential to further our understanding of prenatal contributors to schizophrenia, particularly those involving stress, trauma, and cortisol levels during pregnancy. As we have written previously (Ellman and Susser, 2009; Ellman et al., 2018), findings indicate that examining phenotypes that are more proximal to prenatal events, such as decreased fetal growth, have the potential to shed light on how obstetric events influence the course of schizophrenia. The present study also adds to our previous findings by suggesting that higher prenatal cortisol is one of multiple obstetric complications that results in decreased fetal growth in male infants who later develop schizophrenia, but not in male controls or females. However, it is important to note that there were no case/control differences in maternal cortisol levels; therefore, our findings suggest that variations in normal levels of cortisol may be influencing fetal growth only for male cases who develop schizophrenia. These findings are consistent with our previous findings and recent reports that suggest that liability for schizophrenia may render fetuses particularly sensitive to a range of obstetric events (Fineberg et al., 2013; Ursini et al., 2018). Nevertheless, our findings highlight that high maternal cortisol during pregnancy and genetic risk for schizophrenia may only increase risk for a phenotype associated with the disorder. Accordingly, we should view these risk factors within the context of an evolving developmental framework, in which exposure to high maternal cortisol levels in utero may increase vulnerability to schizophrenia, but only in conjunction with other developmental risk factors, such as genetic vulnerability for psychosis and exposure to other environmental risk factors (Ellman et al., 2018; Fineberg and Ellman, 2013). Our findings may facilitate the development of more precise prediction models that include a range of developmental risk factors, which is a first step towards identifying who is at the greatest risk for both psychosis and reduced fetal growth, a necessary step before developing early intervention and prevention strategies.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.07.002.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest to report.

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Contributors

Dr. Ellman came up with the idea for the manuscript and the present study, she was involved with the processes of cortisol analyses (i.e., interactions with the lab for serological analyses), she wrote the majority of the manuscript, she contributed to the statistical analyses (and supervised the statistical analyses of the data analyst in her lab), and she coordinated communication between all of the co-authors. Shannon Murphy contributed to writing the introduction and editing the manuscript. Seth Maxwell conducted most of the statistical analyses (under the supervision of Dr. Ellman), cleaned the data, provided descriptive statistics, and edited the manuscript. Evan Calvo created all of the tables for the manuscript, conducted some literature reviews, edited the manuscript, and checked the descriptive statistics for accuracy. Thomas Cooper conducted all of the serological analyses of cortisol in his lab and consulted on issues pertaining to cortisol analyses. Dr. Schaefer was integrally involved in data collection for the original PDS study, including locating potential cases and obtaining diagnoses through chart review and semi-structured interviews. Dr. Bresnahan was very involved in the original PDS study; including maintaining/creating the PDS databases and being involved with accurately documenting consensus call decisions. Dr. Susser was the PI of the original PDS study and was involved in every aspect of the study design and execution. Dr. Brown also was involved in the original PDS study, including participating on consensus calls, and was Dr. Ellman's postdoctoral mentor when she conceived of the present study; therefore, he advised her on every aspect of this study and funded the cortisol analyses. All authors contributed edits to the final manuscript.

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