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Infection and higher cortisol during pregnancy and risk for depressive symptoms in adolescent offspring

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Abstract

Prenatal infection, particularly at mid-gestation, has been associated with various psychopathological outcomes in offspring; however, findings linking prenatal infection to offspring depression outcomes have been mixed. Previous research indicates that it may be the co-occurrence of prenatal adversities (e.g., infection and stress) that are associated with depression outcomes in offspring. Nevertheless, no study to date has investigated whether higher levels of biomarkers linked to prenatal stress (e.g., cortisol) in the presence of infection may account for these outcomes. Participants were drawn from the Child Health and Development Studies (CHDS), a prospective, longitudinal study of pregnant women and their offspring. The present study included mother-offspring dyads from the Adolescent Study, a subsample of the CHDS cohort, whose offspring were assessed in adolescence and whose mothers also provided sera to be assayed for cortisol (n = 695). Hierarchical multivariable regressions were conducted to examine whether maternal cortisol during the first and second trimesters of pregnancy interacted with maternal infection to predict increased risk for symptoms of depression in adolescent offspring. There was a significant interaction of second trimester infection and higher cortisol on offspring depression scores during adolescence, controlling for maternal education ($p = 0.04$). Findings suggest that higher maternal cortisol may sensitize mothers and their offspring to the

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disruptive influences of infection during mid-pregnancy, conferring greater risk of depressive symptomatology in offspring.

Keywords

pregnancy; cortisol; infection; adolescent depression; prenatal stress

1. Introduction

Incidence of maternal infection during pregnancy repeatedly has been linked to psychopathological outcomes in offspring, such as schizophrenia, autism spectrum disorder, and depression (Brown, 2012; Simanek and Meier, 2015). Although maternal prenatal infection has been associated with elevated risk for depression in offspring, findings are mixed across samples (Simanek and Meier, 2015). A handful of studies to date directly link infection during pregnancy to depression outcomes, particularly associating influenza and infection requiring hospitalization during pregnancy to increased risk for affective disorders in offspring (Al-Haddad et al., 2019; Machón et al., 1997). Nevertheless, several other studies identify no such direct link (Brown et al., 1995; Mino et al., 2000; Morgan et al., 1997; Pang et al., 2009).

There also is growing evidence of a relationship between prenatal stress and depression in exposed offspring. Several types of prenatal stress have been directly linked to depression in offspring, including experience of an ecologic stressor during pregnancy (e.g., famine) (Brown et al., 2000), stressful life events (Khashan et al., 2011), as well as antenatal depression and anxiety (Betts et al., 2014; Pawlby et al., 2009). Furthermore, prenatal stress has been linked to a number of intermediate phenotypes for depression symptoms, such as childhood anxiety (Davis and Sandman, 2012), externalizing problems (e.g., ADHD, conduct problems) (MacKinnon et al., 2018), and difficult temperament (Davis et al., 2007). Prenatal stress also is a risk factor for obstetric complications, such as preterm birth and low birthweight, that also have been linked to depression specifically in adolescence (Coussons-Read et al., 2012; Patton et al., 2004).

There are methodological inconsistencies in studies of prenatal infection and stress that may account for some of the variability in findings across samples. Many studies of prenatal infection and offspring outcomes do not examine the variability of outcomes across different types of infection, utilize self-report of infection versus clinical diagnostic information or serologic confirmation, and do not have information about the timing of exposure (Khandaker et al., 2013; Simanek and Meier, 2015). Studies examining prenatal stress and offspring outcomes also suffer from similar quandaries. For example, ecologic studies of prenatal stress in pregnancy (e.g., being present during a famine, war or natural disaster) are useful and unique opportunities to examine the impact of a traumatic event on offspring outcomes; however, there is limited generalizability of these findings due to the anomalous nature of the stressor (Brown et al., 2000; Watson et al., 1999). Furthermore, the traumatic impact of these types of events likely is confounded by other prenatal insults also linked to psychopathological outcomes in offspring, such as malnutrition and

exposure to environmental contaminants (Lipner et al., 2019). The type of stressor and timing of exposure have been underscored as key moderators of the relationship between prenatal stress and offspring psychopathology and remain important factors to consider in understanding developmental origins of disease (Kim et al., 2015). Additionally, there is evidence that several postnatal factors, some as a result of prenatal insults, may further confer risk for offspring depression (Maxwell et al., 2018). Not all of these studies have examined these key moderators and additive factors, leaving conclusions about the direct relationship between prenatal infection, stress, and depression outcomes variable and inconclusive across samples.

Existing literature may point to the importance of examining various prenatal adversities (e.g., stress, infection) in concert with each other as they relate to offspring neuropsychiatric outcomes. Our prior study identified that only the co-occurrence of prenatal stress and infection in the second trimester increased risk for depressive outcomes in adolescence (Murphy et al., 2017). There also is evidence from the work of others that prenatal stress and elevated stress hormones, including cortisol, have been associated with elevations in immune markers and subsequent increased risk of infection in pregnancy, demonstrating the transactional endocrine-immune relationship during pregnancy (Coussons-Read, 2013). Overall, these findings underscore the importance of examining the co-occurrence of prenatal stress and infection/inflammation and its impact on offspring outcomes.

One mechanism through which prenatal maternal stress is likely to confer risk to offspring is through increased activation of the hypothalamic-pituitary-adrenal (HPA) axis and elevations in maternal cortisol levels (Coussons-Read, 2013; Wadhwa et al., 2011). Elevated cortisol also has been linked to other developmental risk factors for depression, including difficult infant temperament (Davis et al., 2007) and alterations in infant stress responses (Davis et al., 2011a). Furthermore, there is evidence of the role of elevated glucocorticoids in brain changes associated with depression, such as alterations in the limbic system (Buss et al., 2012) and the HPA axis (Davis et al., 2011b).

Given our previous study identifying that the co-occurrence of stress and infection is associated with depressive symptoms in adolescent offspring (Murphy et al., 2017), further exploration of this interaction is warranted. The main aim of this study is to explore the relationship between prenatal maternal cortisol levels, infection, and depressive symptoms in adolescent offspring. Consistent with findings from our previous study, we hypothesized that maternal cortisol levels would moderate the association between maternal infection during pregnancy and risk for offspring depressive symptoms during adolescence. Furthermore, we examined prenatal cortisol and infection in the first (T1) and second (T2) trimesters of pregnancy to identify the role of timing of these prenatal adversities, expecting that T2 cortisol and infection would be significantly associated with higher depressive symptoms in adolescence, consistent with our previous findings.

2. Materials and Methods

2.1 Description of the Cohort

Participants were mother-offspring dyads derived from a prospective, longitudinal study of pregnant women called the Child Health and Development Studies (CHDS) (N = 19,044 live births) (van den Berg et al., 1988). The CHDS included pregnant women seeking prenatal care using the Kaiser Permanente Health Plan and living in Alameda County, California, between the years of 1959–1966. A portion of these dyads subsequently enrolled in the Adolescent Study, a subsample of CHDS, whose offspring were assessed in childhood and adolescence (n = 2,020). Offspring enrolled in the Adolescent Study, compared to the original CHDS cohort, were more likely to be White and high school graduates (van den Berg et al., 1988). Mother-offspring dyads included in the current analyses were among 736 mothers from whom archived maternal serum samples and cortisol data were available from the first (T1) and/or second trimesters (T2). Among these dyads, there were 41 offspring missing depressive symptom data in adolescence, resulting in a final analytic sample of 695 dyads (see Table 1). Although offspring included in the present study were significantly younger than the rest of the Adolescent Study subsample ($p < 0.001$), the present sample did not differ in maternal race, maternal education at time of birth, or offspring sex from the rest of the Adolescent Study subsample. A sample size of over 377 participants is sufficiently powered to identify small-medium sized effects between the predictors and outcomes of interest in the present study.

The present study analyses were approved by Institutional Review Boards (IRBs) at Temple University, UCLA, and the Public Health Institute. The initial recruitment of the CHDS cohort predated the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008; however, all participants provided assent after receiving a complete description of the study.

2.2 Demographics and Maternal Variables

Demographic data were collected via maternal report during prenatal study visits. Maternal education was used as a proxy for socio-economic status (SES) given that maternal education was correlated with other measures of SES, such as income, in previous studies of this cohort (Fineberg et al., 2016). Maternal education is also used as a proxy variable for postnatal adversity (Schlotz and Phillips, 2009), which is related to increased risk for disease across development. Maternal education was categorized as ‘Did not complete HS,’ ‘Completed HS’ or ‘Completed more than HS.’ Maternal race was categorized as ‘White/Non-Hispanic,’ and ‘Non-White,’ given a very small number of Asian participants (n = 38). The ‘Non-White” group was comprised of African American, Asian, and Mexican mothers. Of note, information on ethnicity separate from race is not available within this sample and is a limitation of this work. Offspring sex was categorized as ‘Male’ or ‘Female’ and examined as a potential covariate due to evidence of sex-differentiated pathways to psychopathology in offspring from prenatal adversity (Sandman et al., 2013). Maternal parity was also examined as a potential covariate, given the relationship between parity and fetal growth, which may be an intermediate phenotype for risk for offspring psychopathology (Shoham-Vardi et al., 1994).

2.3 Maternal Infection

Presence and timing of a variety of infections were abstracted from women's Kaiser medical records. Infection variables were dichotomous to indicate presence or absence of infection in each trimester. Genital-reproductive, upper respiratory, other viral, and other bacterial infections were collapsed for the sake of the present analyses, with genital-reproductive (T1 = 34, T2 = 44) and upper respiratory infections (T1 = 59, T2 = 81) being the most common types of infection within our sample. Further details about the abstraction and inclusion of maternal infections for the present analyses can be found in prior CHDS studies (Murphy et al., 2017).

2.4 Cortisol Analyses

Maternal serum samples were collected at the CHDS study site during the first and second trimesters of pregnancy, primarily in the morning, while fasting (see Table 1 for gestational timing of blood draws). Samples were then frozen and stored at −20°C. ELISA kits (Parameter Cortisol Assay, R&D Systems, Inc., Minneapolis, MN) were used according to the manufacturer's protocol, with a fifty-fold serum sample dilution, to determine cortisol levels. Cortisol concentrations were reported in micrograms/dL, taking the sample dilution into account; lower and upper limits of detection were 0.8 and 50 micrograms/dL, respectively. Comparisons with similar birth cohorts (e.g., NCPP cohort) demonstrated that there was not significant degradation of the cortisol over time (Stroud et al., 2007). All samples were tested in duplicate; an internal quality control sample (pooled sera) was included on every assay plate, with a mean inter-assay CV of 10.8% and mean intra-assay CV of 5.5%. All intra-assay CVs were < 15% (range = 0 – 14.4%).

2.5 Adolescent Depressive Symptoms

Offspring (mean age = 16.4 years, SD = 0.7) responded to a 130-item, self-report questionnaire at the Adolescent Study follow-up that inquired about different aspects of their lives and beliefs about themselves. Fifteen of these items assessed current cognitive symptoms of depression (e.g., worthlessness, inadequacy, failure) and elicited responses on a 4-point Likert scale. Responses to these items were summed and examined continuously, with possible scores ranging from 15 to 60. Prior examinations of this scale of depressive symptomatology demonstrated high internal consistency, high predictive validity of clinical interview diagnosis in adulthood, and concurrent validity (Maxwell et al., 2018; Murphy et al., 2017).

2.6 Maternal Depressive Symptoms at Adolescent Follow-Up

Mothers also completed a self-report inventory of depressive symptoms, similar to the inventory completed by the offspring, at the Adolescent Study follow-up. The scale previously has demonstrated high internal consistency (Murphy et al., 2017). Given the genetic contributions to risk for major depressive disorder, maternal depressive symptoms were used as a proxy for genetic risk, consistent with prior studies of this cohort (Murphy et al., 2017). Maternal depressive symptoms were examined continuously and were also explored as a potential covariate.

2.7 Data Analysis

Bivariate correlations between adolescent depressive symptoms, maternal cortisol, maternal infection, and demographic and maternal variables were examined using Pearson correlations. Cortisol was log-transformed to achieve normality. Variables significantly associated with both the independent (infection) and dependent (offspring depressive symptoms) variables, or with sufficient theoretical link to the proposed analyses, were included as covariates.

Hierarchical multivariable regressions were conducted using R (v 4.0.3), examining the influences of maternal cortisol in T1 and T2, presence of maternal infection in T1 and T2, and their interaction, on depressive symptoms in adolescence. In the first step of the model, main effects of infection and cortisol on adolescent depressive symptoms were examined. Cortisol was mean-centered, and infection was treated as a factor variable for the analyses. The second step of the model included the interaction between infection and cortisol by trimester, computed as the product of the variables. Interaction terms were based on mean-centered predictors. Covariates (maternal education) were categorical and treated as a factor variable. Simple slope analyses are reported to indicate whether the association of the predictor and the outcome variable differs from zero at a given level of the moderator (e.g., presence or absence of infection). All tests were two-tailed with $p < 0.05$ indicating significance.

3. Results

There were 736 mothers for whom there was serum cortisol data at T1 and/or T2, but 41 dyads were missing adolescent depressive symptom data, resulting in a final sample of 695 dyads with both maternal cortisol and offspring adolescent depression data. This included 608 mothers who were assayed for cortisol at T1, with serum cortisol levels ranging from 1.42 to 21.57 micrograms/deciliter (mean [SD] = 6.69 [3.01]), and 610 mothers who had sera assayed for cortisol at T2 (range 1.90 – 21.75 micrograms/dL, mean [SD] = 8.93 [3.02]). Of the 695 mothers, 523 contributed serum cortisol data at both T1 and T2. There was a total of 89 (12.8%) mothers who experienced prenatal infection in T1 and 127 mothers who experienced infection in T2 (18.3%).

Bivariate correlations between all examined variables are presented in Table 2. Maternal education, race, parity, and offspring sex all showed no significant associations with depressive symptoms in adolescence; however, T2 cortisol was significantly correlated with maternal race and parity ($p < 0.01$). Maternal depressive symptoms at the adolescent interview were significantly associated with offspring adolescent depressive symptoms ($p < 0.01$) and female offspring ($p < 0.05$); however, maternal depressive symptoms at the adolescent interview were not significantly associated with maternal cortisol in either trimester during pregnancy. T1 infection was significantly associated with T2 cortisol ($p < 0.01$).

Adjusted and unadjusted multivariable regression analyses, predicting to offspring adolescent depressive symptoms, are reported in Table 3. Adjusted analyses controlled for maternal education at offspring birth as a proxy for the incidence of postnatal adversity

(Schlotz and Phillips, 2009). There were no observed significant main effects of infection or cortisol in either T1 or T2 on adolescent depressive symptoms. There was, however, a significant interaction between T2 maternal cortisol and T2 maternal infection in predicting offspring depressive symptoms. Inclusion of the interaction term in T2 significantly increased the percentage of variance accounted for in adolescent depressive symptoms in both the adjusted [$\Delta R^2 = 0.07$, $F(1, 115.84) = 4.17$, $p = 0.04$] and unadjusted models [$\Delta R^2 = 0.07$, $F(1, 126.65) = 4.52$, $p = 0.03$].

To further understand the significant interaction, we estimated the simple slopes of T2 maternal cortisol on offspring adolescent depressive symptoms in the presence and absence of T2 maternal infection. The interaction effect is displayed in Figure 1. In the absence of T2 infection, T2 cortisol was not significantly associated with adolescent depressive symptoms (b = −0.66, SE = 0.67, $t = -0.99$, $p = 0.32$); however, in the presence of T2 infection, T2 cortisol was trending towards an association with adolescent depressive symptoms (b = 2.74, SE = 1.52, $t = 1.80$, $p = 0.07$). This effect was similar in the unadjusted model for T2 (no infection, b = −0.65, SE = 0.68, $t = -0.97$, $p = 0.33$; infection, b = 2.90, SE = 1.53, $t = 1.90$, $p = 0.06$).

Discussion

To our knowledge, this is the first human study to examine the interactive effects of a biomarker for prenatal stress with prenatal infection on depressive symptoms in adolescence, utilizing a longitudinal, prospectively examined cohort. These findings suggest that the co-occurrence of higher levels of the stress hormone, cortisol, with maternal infection, increases risk for depressive symptoms in offspring during adolescence. Furthermore, findings show this interaction only reached significance during the second trimester of pregnancy. These findings are consistent with a previous study from this cohort that found that maternal reports of stress during pregnancy were associated with offspring adolescent depressive symptoms, only in the presence of second trimester infection (Murphy et al., 2017). Higher levels of maternal stress hormones, perhaps as a consequence of prenatal stress, likely impact the development of the offspring's brain and HPA axis, as well as placental functioning, constituting mechanisms that may partially underlie the neuropsychiatric impact on offspring (Monk et al., 2019). Nonetheless, after stratifying findings based on infection status, the results only approached significance, likely due to a reduction in power from stratifying the sample. Even so, the stratified results highlight that the significant interaction between T2 cortisol and T2 infection is likely driven by the co-occurrence of infection and higher cortisol, given that cortisol exhibited no association with offspring depressive symptoms in the absence of T2 infection. Future studies utilizing larger sample sizes should seek to determine if these findings replicate.

Animal models of maternal immune activation utilize lipopolysaccharide (LPS) or Polyinosinic–polycytidylic acid (Poly I:C) to mimic prenatal infection, which in turn induce increased levels of inflammatory markers and corticosterone, the rodent equivalent of cortisol in humans (Meyer, 2014). These models substantiate the role of inflammatory insults in the emergence of depressive-like behaviors, such as prepulse inhibition and latent inhibition, and neurodevelopmental changes, in rodent offspring in a strain- and timing-

dependent manner (Babri et al., 2014; Depino, 2015; Ronovsky et al., 2017). Animals models of maternal immune activation also demonstrate the presence of interactions between the HPA axis stress response and inflammation, which is likely at work in the preponderance of psychiatric outcomes in human offspring as well (Coussons-Read, 2013).

Furthermore, findings from the present study mirror our previous findings that the presence of infection, concurrent with prenatal stress, confers risk for depression in offspring when it occurs in mid-gestation (Murphy et al., 2017). Previous studies that examine the relationship between prenatal infection and offspring depression that specify infection timing have identified that infection occurring in the second trimester increases risk for offspring for affective disorders (Machón et al., 1997; Murphy et al., 2017; Watson et al., 1999). Animal studies also have highlighted mid-gestation as a sensitive period for the impact of inflammatory agents like LPS or Poly I:C on depressive-like behavior in offspring (Boksa, 2010); however, translational comparisons of timing-specific endocrine and immune changes should be executed with caution due to differences in neurodevelopment between rodents and humans (Brown and Meyer, 2018). Finally, it is of note that the co-occurrence of higher cortisol and T1 infection was associated with *lower* levels of depressive symptoms in adolescent offspring ($p < 0.1$); however, this association was not significant. Future studies with larger sample sizes may seek to further explore differences in directionality in these relationships by timing of prenatal exposures. Shifts in the inflammatory milieu during pregnancy, as well as changes in glucocorticoid-immune regulation across gestation make it plausible that directionality of findings may not be consistent across pregnancy (Hantsoo et al., 2019); however, interpretation of our finding should be viewed with caution, given that it did not reach significance.

It is important to consider why there was no independent main effect of higher serum levels of maternal cortisol on depressive symptomatology in offspring adolescence in either trimester. It is possible that these higher levels are not deleterious in isolation, but rather in the ways they potentiate other dysregulation *in utero* to ultimately confer risk to offspring. There is evidence that experiencing stress during pregnancy can increase risk for infections (Culhane et al., 2001). Furthermore, cortisol can both stimulate and inhibit the inflammatory response, which becomes both critical during a period of rapid development such as the prenatal period, and complicated due to the fluctuating nature of the inflammatory milieu in pregnancy (Zen et al., 2011). In the present study, T2 cortisol was significantly correlated with incidence of T1 infection. Incidence of infection is linked to activation of the HPA axis, increasing production of corticotropin releasing hormone and stimulating cortisol production (Coussons-Read, 2013). As such, the directionality of the relationship between stress and infection is not yet clarified and is likely a complex reciprocal relationship that changes over the course of pregnancy. Although the present study examines the moderating effect of cortisol on the relationship between maternal infection and offspring depressive symptoms, infection may also plausibly moderate the relationship between cortisol and offspring symptomatology. Simultaneous presence of higher cortisol levels and maternal infection itself may confer risk for offspring; however, increased stress and/or increases in maternal glucocorticoids, may increase risk for maternal infection in a transactional manner that is ultimately harmful to offspring. Future studies utilizing precise, timing-specific longitudinal

measurement of psychosocial stress, infection, and related biomarkers (e.g., inflammatory cytokines and glucocorticoids) can help to further clarify this cascade of risk.

Limitations of this study must be considered. First, the self-report questionnaire used to evaluate depressive symptoms only addresses cognitive symptoms of depression (e.g., hopelessness, worthlessness). Our measure of depressive symptoms in adolescence was strongly predictive of future depression diagnoses that included all symptoms of depression (Murphy et al., 2017). Other domains of depressive symptoms (e.g., motivation, energy, sleep) have been associated with alterations in biomarkers of stress (Freed et al., 2018). It is possible that inclusion of these symptom clusters would impact the nature of these results; however, we would expect that it would only strengthen these findings. Future research may seek to include a well-validated, standardized, and comprehensive assessment of depression in offspring to study the impacts of prenatal infection and stress. Nonetheless, the ability to use a dimensional measure of depressive symptoms in this valuable prospective cohort with adequate psychometrics serves as a strength of the present study.

Additionally, the manner in which infection was categorized and examined may have obscured unique influences of specific infections. Future research may seek to examine variability across types of infection while using serological information to confirm infection. Nevertheless, the present study's use of a prospectively collected, population-based cohort enables the examination of the developmental precedents of alterations in adolescent health and serves as a notable strength of this research. Moreover, given that all the maternal infections included in this study do not appear to cross the placenta (Murphy et al., 2017), and all infections relied on a confirmed diagnosis from medical records, it is more likely that our infection variable included incidences of infection that involved an inflammatory response (common in symptomatic infections), which is a key pathway that has been found to be involved in the association between infections during pregnancy and offspring psychopathology (Ellman and Susser, 2009). Follow-up data through pregnancy and into offspring's adolescence is a strength of the present study and is a valuable tool in examining these themes.

Finally, it is important to note that our study utilizes a single point measurement of cortisol collected primarily in the morning. We do not have precise information about the timing of this blood draw and are unable to control for it in the present analyses. Although cortisol awakening and stress response are blunted during pregnancy (de Weerth and Buitelaar, 2005; Sandman et al., 2011), future studies may seek to explore the relationship between these diurnal rhythms in tandem with other co-occurring obstetric complications and their relationships to offspring psychiatric outcomes. The literature examining the relationship between maternal prenatal cortisol and offspring outcomes contains substantial heterogeneity in the measurement of cortisol (i.e., biological material collected, gestational age/time of collection), perhaps accounting for the variability in findings across studies (Zijlmans et al., 2015). Moreover, there is evidence that blood cortisol measures in pregnancy may be more associated with various biological (e.g., maternal age, body mass index, infection, inflammation) and lifestyle factors (e.g., smoking behavior) than psychosocial factors, unless the prenatal stress is severe (Bleker et al., 2017; Ruiz et al., 2001). Although maternal stress during pregnancy was measured in this sample (Murphy et

al., 2017), these data were not collected at the same time point as maternal blood draws, making it difficult to interpret associations between these variables. As such, we cannot conclusively claim that higher levels of cortisol were a result of increases in acute or chronic stress during T1 and/or T2. It is also important to note that cortisol levels naturally increase, beginning in the second trimester through the end of pregnancy, although maternal perceptions of stress decrease over the course of pregnancy (Glynn et al., 2004; Trainer, 2002), and also may vary dependent on the fetus' sex (Bleker et al., 2017).

A robust body of literature supports the role of various prenatal risk factors (e.g., stress, inflammation, nutrition) for neuropsychiatric illness in offspring and further clarification of these prenatal factors facilitates a better understanding of intervention and prevention efforts even earlier in the lifespan. Nonetheless, it is important to note that effect sizes for these findings are often small and not all fetuses that face prenatal adversity will go on to develop a psychiatric illness later in development (Ellman et al., 2018). These points are both substantiated by the present study. As such, our understanding of prenatal risk factors for psychiatric outcomes is even more impactful when understood in the full scope of the developmental trajectory to disease (Lipner et al., 2019). There is evidence from animal and human studies that postnatal factors (e.g., parenting factors, postnatal stress) may also interact with the adverse effects of prenatal stress or infection in the pathway to psychiatric illness and its correlates, serving in either protective or exacerbating roles (Debost et al., 2017; Giovanoli et al., 2013). Future research may seek to explore outcomes of the endocrine-infection interaction more proximal to childbirth, such as obstetric complications and dysregulation in childhood temperament, cognitive function, and language acquisition, that are also predictive of adolescent psychopathology (Ellman et al., 2018).

5. Conclusions

The present study serves to further our understanding of endocrine-infection interactions during pregnancy that may confer risk for depressive symptoms in adolescent offspring. It is important to consider whether this interaction of glucocorticoids and the presence of an acute documented infection is instrumental only in the emergence of depressive symptoms, or whether it is also predictive of other psychiatric symptomatology (Huizink and Rooij, 2018). Animal models of maternal immune activation, in response to/or mimicking infection, provide a glimpse into the transdiagnostic role of both stress and immune insults to the fetus (Brown and Meyer, 2018; Ronovsky et al., 2017). Given that prenatal stress, elevations in cortisol, and prenatal infection have also been linked with schizophrenia, autism spectrum disorder, and attention deficit/hyperactivity disorders (Estes and McAllister, 2016; Kim et al., 2015), further multidisciplinary research is needed within models of prenatal stress and responses to prenatal infections (Brown and Meyer, 2018).

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Highlights

- Co-occurrence of higher cortisol with maternal infection associated with higher depressive symptoms in adolescent offspring.
- This association is significant only in second trimester.
- No direct association between higher cortisol or maternal infection with offspring symptoms.

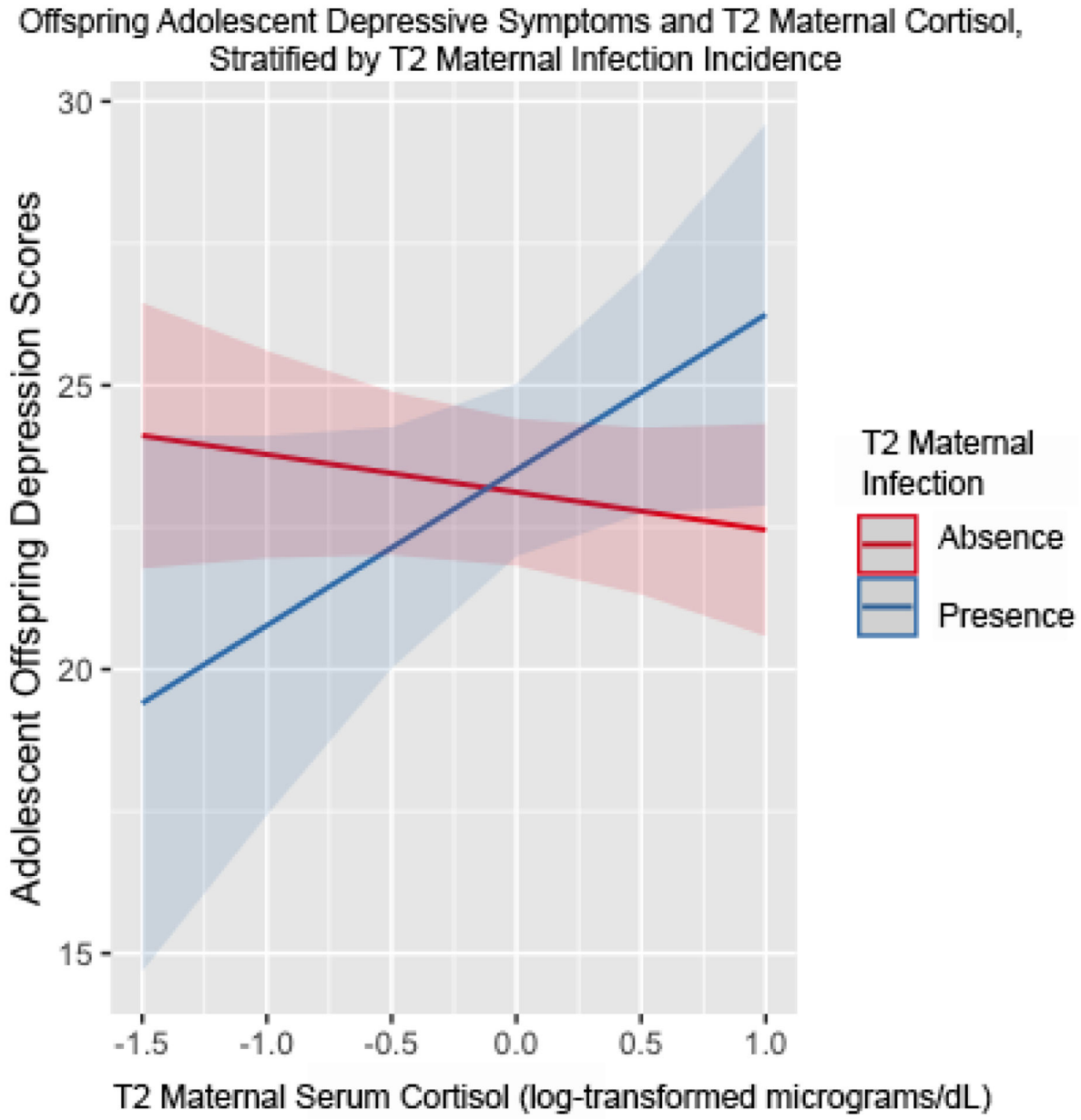

Figure 1.

Offspring adolescent depression scores are plotted against simple slope estimates of log-transformed maternal serum cortisol levels in the second trimester (T2), stratified by presence (blue line) and absence (red line) of maternal infection during T2. Shaded areas indicate confidence intervals of slope estimates. Moderation analyses controlled for maternal education at offspring birth.

Table 1.

Demographic characteristics of the sample (N = 695 dyads)

	N	%	Mean	SD	Missing (n)
Maternal Variables					
Maternal race					
White	497	71.5			0
African American	138	19.9			
Asian	38	5.5			
Mexican	22	3.2			
Maternal education					0
< High school	72	10.3			
= High school	249	35.8			
> High school	374	53.8			
Maternal age at offspring birth (years)			28.8	5.8	1
Maternal parity			2.1	2.0	0
Gestational age at blood draw (weeks)					
Trimester 1			12.2	2.6	84
Trimester 2			23.7	3.0	86
Cortisol (micrograms/dL)[a]					
Trimester 1			6.7	3.0	87
Trimester 2			8.9	3.0	85
Infection during trimester					
Trimester 1	89	12.8			0
Trimester 2	127	18.3			0
Maternal depressive symptoms score at offspring adolescence			14.7	3.3	74
Offspring Variables					
Offspring sex					
Male	360	51.8			0
Female	335	48.2			
Birth weight (oz.)			118.3	17.6	0
Gestational age at birth (weeks)			39.9	2.1	5
Adolescent depressive symptoms score			23.5	5.3	0

[a]Raw cortisol values presented here.

Table 2.

Bivariate correlations (N = 695)

Variable	1	2	3	4	5	6	7	8	9
1. Offspring Dep									
2. T1 Cortisol	0.02								
3. T2 Cortisol	−0.01	0.26**							
4. T1 Infection	−0.03	−0.05	−0.11**						
5. T2 Infection	0.02	0.01	−0.02	0.08*					
6. Maternal Dep	0.15**	−0.01	0.01	−0.01	0.01				
7. Maternal ed	−0.06	0.02	0.00	−0.09*	−0.05	−0.03			
8. Maternal race	−0.03	−0.07	−0.15**	0.04	−0.02	0.07	−0.12**		
9. Parity	0.03	−0.04	−0.12**	−0.01	−0.03	0.04	−0.19**	0.16**	
10. Offspring Sex	0.02	−0.06	0.01	0.04	−0.01	−0.09*	−0.01	−0.02	−0.02

Values presented are bivariate Pearson correlations.

* indicates $p < 0.05$,

** indicates $p < 0.01$

Serum cortisol levels were log-transformed prior to all analyses.

Reference groups: Maternal ed = < HS; Maternal race = White; Offspring sex = Male

Abbreviations: Offspring Dep = offspring adolescent depressive symptoms; T1 = Trimester 1; T2 = Trimester 2; Maternal Dep = maternal depressive symptoms at adolescent interview; Maternal ed = maternal education at offspring birth

Table 3.

Hierarchical multivariate regression models predicting to offspring depressive symptoms in adolescence from (i) maternal cortisol and infection, and (ii) interaction of maternal cortisol and infection.

	Adjusted[a]		**Unadjusted**	
	Trimester 1	**Trimester 2**	**Trimester 1**	**Trimester 2**
	b[b] **(SE)** ***P***	**b (SE)** ***p***	**b (SE)** ***p***	**b (SE)** ***p***
Infection	−1.03 (0.63) *0.10*	0.35 (0.55) *0.52*	−0.91 (0.63) *0.15*	0.35 (0.55) *0.52*
Cortisol[c]	0.17 (0.52) *0.74*	−0.11 (0.62) *0.86*	0.21 (0.52) *0.69*	−0.07 (0.62) *0.91*
R^2	1.4%	1.1%	0.4%	0.07%
Cortisol*Infection	−2.53 (1.47) *0.09*	**3.40 (1.67)** ***0.04***	−2.32 (1.47) *0.11*	**3.55 (1.67)** ***0.03***
R^2	1.9%	1.8%	0.8%	0.8%
df	602	604	604	606

[a]Adjusted analyses controlled for maternal education at offspring birth.

[b]All estimates are unstandardized.

[c]Cortisol is log-transformed.