Maternal infection and stress during pregnancy and depressive symptoms in adolescent offspring

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\textbf{A B S T R A C T}

Maternal infection during pregnancy has been linked to increased risk of offspring depression. Additionally, maternal stress during pregnancy has been consistently linked with adverse offspring outcomes associated with depression. Relatedly, stress has been associated with increased risk of infection; however no study has investigated stress-infection interactions during pregnancy and risk for offspring depression. Participants were drawn from the Child Health and Development Studies (CHDS), a prospective, longitudinal study that enrolled pregnant women from 1959 to 1966. Maternal health and birth outcome information were collected, as well as open-ended interviews about worrisome events during pregnancy. The present study included participants from a subsample of women whose offspring (n = 1711) completed self-reports of depressive symptoms during adolescence. Results indicated that maternal infection during only the second trimester was associated with higher scores on adolescent offspring depressive symptoms, while controlling for maternal education at birth, adolescent age, and maternal depressive symptoms at adolescence. Maternal experiences of daily stress during pregnancy moderated this association, such that mothers diagnosed with second trimester infection and who experienced daily stress had offspring with significantly higher depression scores than mothers of adolescents diagnosed with an infection alone. Findings have potential implications for prevention and intervention strategies.

\textbf{1. Introduction}

Increasing evidence suggests that maternal infection during pregnancy is implicated in risk for offspring depression (reviewed in (Bilbo and Schwarz, 2009; Markham and Koenig, 2011; Simanek and Meier, 2015)). Specifically, two studies found associations between being pregnant during influenza epidemics and unipolar depression in adult offspring (Cannon et al., 1996; Machón et al., 1997). The first study, utilizing an Irish cohort, found that maternal self-report of influenza at any time during pregnancy was associated with a 1.59 times increased risk of a depressive disorder among adult offspring (Cannon et al., 1996). The second ecologic study, using a Finnish cohort, also found a significant increase in the proportion of psychiatric hospital admissions for unipolar major depressive disorder among individuals whose mothers were pregnant during the second trimester of an influenza epidemic (Machón et al., 1997). However, these studies were complicated by use of hospital admission data and/or familial report of offspring health to determine depression diagnoses. As such, findings from both studies may be representative of more severe mood disorders and lack generalizability to more moderate, but nonetheless clinically significant, diagnostic profiles of depression. However, a number of other studies have identified no associations between fetal exposure to maternal influenza and offspring depression (Brown et al., 1995; Mino et al., 2000; Morgan et al., 1997; Pang et al., 2009; Takei et al., 1993). Research findings utilizing a cohort of 3076 individuals born to mothers who were clinically diagnosed with various viral infections (e.g., influenza, rubella, mumps, measles, varicella, herpes zoster, hepatitis, cytomegalovirus) in the United Kingdom between 1946 and 1980 found no associations between individual viral infections and offspring depression (Pang et al., 2009). Surprisingly, this is the only study to our knowledge that has examined the link between maternal infection other than the influenza virus and offspring depression (Simanek and Meier, 2015). However, several studies in rodents using translational models of maternal immune activation (MIA) during pregnancy have
demonstrated connections between prenatal infection and depressive-like alterations in offspring development (Bitanihirwe et al., 2010; reviewed in (Ronovsky et al., 2016)). Still, given the dearth of literature examining the role of prenatal infections in the etiology of depression, especially as it relates to adolescent psychopathology outcomes, further research is necessary.

Relatively, emerging data indicate that maternal stress during pregnancy is implicated in risk for offspring depression. For instance, an ecologic study examining prenatal exposure to a severe earthquake in the city of Tangshan, China, in 1976 found that 18-year-old offspring whose mothers were pregnant during the earthquake had increased levels of severe depression and overall depressive symptoms compared to controls (Watson et al., 1999). Similarly, another ecologic study of prenatal exposure to the 1944–1945 Dutch “Hunger Winter,” a period during World War II in which several cities in the Western Netherlands experienced famine, found that maternal exposure to famine during the second and third trimesters increased offspring risk of developing both unipolar and bipolar affective disorders in adulthood (Brown et al., 2000a, 2000b). However, the results likely reflect, at least in part, the adverse effects of long-term maternal malnutrition on offspring development. Moreover, both this study and that of Watson et al. (1999) are limited in their generalizability, given that “stress” was never measured but rather presumed based on severe life events. However, another study that prospectively followed mothers and their children for a period of more than 20 years, found that high levels of maternal depression, anxiety, and stress symptoms (assessed via a 4-item, self-report inventory) during pregnancy were associated with offspring internalizing behavior problems in adolescence (Betts et al., 2014) and adulthood (Betts et al., 2015). These results were consistent with findings from another prospective population-based cohort that demonstrated an association between maternal exposure to stressful life events during early pregnancy and an increased risk for depression and elevated depressive symptoms in 17 to 18-year-old offspring (Kingsbury et al., 2016).

Similarly, maternal stress during pregnancy has been related to childhood outcomes associated with later development of depression (Koenen et al., 2009). In particular, accumulating research suggests that maternal stress during pregnancy is related to childhood cognitive difficulties frequently seen in the histories of depressed populations (Hofstra et al., 2002; Wood et al., 2013), such as lower scores on tests of intellectual functioning and language abilities (Laplante et al., 2008; Slykerman et al., 2005), problems of attention/concentration (Brouwers et al., 2001; Gutteling et al., 2006), and difficulties in academic performance (Niederhofer and Reiter, 2004). Additionally, prenatal maternal stress has been shown to associate with increases in offspring behavioral/emotional problems during childhood that are linked to risk of later depression (Zahn-Waxler et al., 2000), such as childhood anxiety (Davis and Sandman, 2012; Loomans et al., 2011), parental report of behavioral maladjustment (Gutteling et al., 2005; O’Connor et al., 2002), internalizing problems (Howland et al., 2016; Park et al., 2014), and temperaments associated with increased frustration, crying, and negative reactivity (Davis et al., 2007; Gutteling et al., 2005; Werner et al., 2007). Evidence also suggests sex differences in fetal exposure to prenatal stress with females showing an increased risk for later affective problems compared to males, following fetal exposure to maternal stress (Quarini et al., 2016; Sandman et al., 2013). Further, there is substantial evidence that psychosocial stress is associated with increased risk of infection and increases in inflammation in both pregnant and non-pregnant populations (Coussons-Read et al., 2007, 2005; Culhane et al., 2001; Glaser and Kiecolt-Glaser, 2005; Wadwha et al., 2001). Despite these findings, no studies have examined the potential interactions between maternal stress and infection during pregnancy and later risk for offspring depression.

Utilizing a prospectively collected, large birth cohort study with follow-up data through adolescence, the aim of the present study was to investigate whether maternal infection and/or stress during pregnancy was associated with risk of adolescent depression among offspring. Based on known associations between maternal infection and stress during pregnancy and negative developmental outcomes in offspring (reviewed in (Markham and Koenig, 2011; Richetto and Riva, 2014; Simanek and Meier, 2015)), we predicted that the presence of maternal infection and/or stress during pregnancy would be associated with higher scores on adolescents’ self-reported ratings of current depressive symptomology. Gestational timing of infection also was examined, given evidence that insults during specific gestational time periods may confer increased risk for adverse offspring outcomes (Brown et al., 2004). Specifically, the second trimester of pregnancy has been hypothesized to be a critical period of time for the influence of maternal stress and infection on fetal neurodevelopment and risk of offspring depression (Brown, 2006; Ellman et al., 2008). Gestational timing of maternal stress could not be examined, as interviews were conducted primarily during the second trimester of pregnancy. The second important consideration in the present study was whether stress during pregnancy moderated the association between infection and offspring adolescent depressive symptoms, given the potential for stress to increase susceptibility to infection (Coussons-Read et al., 2007; Howerton and Bale, 2012). We hypothesized that mothers who reported experiences of daily stress during pregnancy and were diagnosed with an infection during pregnancy would have offspring with significantly higher depression scores than mothers of adolescents who experienced stress or infection alone.

2. Methods

2.1. Participants

Study procedures were approved by the following Institutional Review Boards: Columbia University, Public Health Institute, University of California-Los Angeles (UCLA) and Temple University. The Child Health and Development Studies (CHDS) is a prospective cohort study that enrolled pregnant women from 1959 to 1966 in Alameda County, California (van den Berg et al., 1988). The CHDS recruited almost all pregnant women receiving prenatal care through the Kaiser Foundation Health Plan (KFHP) at its clinics in the area (N = 19,044 live births; for review see van den Berg et al., 1988).

The Adolescent Study included offspring and mothers from the original CHDS cohort (who gave birth from 1960 to 1963, and resided in the San Francisco Bay Area). Offspring of the mothers (N = 2020) were followed from birth to adolescence. Mothers and offspring completed a series of interviews and questionnaires regarding health, health behaviors (e.g. exercise, smoking/drinking), and family relationships. Compared to the original CHDS cohort, the Adolescent subsample included a greater proportion of participants who were married and living with a husband at the original intake, who were white, and who were high school graduates; it also included a smaller proportion of first-born offspring (Keyes et al., 2011). Nevertheless, these differences were small and the demographic characteristics of the Adolescent Study still reflect a diverse and representative study sample (Keyes et al., 2011). Maternal interview data from pregnancy was available for 1976 of the 2020 adolescents (97.8%) participating in the study. As there were multiple offspring from the same mother in the sample, the present study randomly selected one member of each sibling set (n = 255) for removal to eliminate non-independent observations. An additional 10 participants had missing adolescent interview data, resulting in a final analytical sample of 1711 mothers (see Table 1 for demographic characteristics).

2.2. Prenatal exposure data

2.2.1. Maternal interviews and stress measurement

The maternal interviews in this study were conducted primarily during the second trimester of pregnancy (mean weeks gestation =
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