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Antenatal depression, psychotropic medication use and inflammation among pregnant women

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Abstract

Purpose—To evaluate the association between psychotropic medication and inflammatory biomarkers in women with antenatal depressive symptoms (ADS).

Methods—In this cross-sectional secondary analysis of a prospective multicenter observational study, 723 pregnant women underwent a depression screen using the Center for Epidemiologic Studies Depression Scale (CES-D) between 12 and 21 weeks gestation. Self-reported use of medications for depression and/or anxiety was corroborated with the medical record to document exposure to pharmacotherapy. Serum was collected and inflammatory biomarkers (IFN γ , IL13, IL6, IL8, TNF α , CRP) were measured concomitantly. Women were included if they fell into one of three categories: ADS responsive to treatment (CES-D < 16 with medication), ADS not responsive to medication (CES-D \geq 23 despite medication), and untreated ADS (CES-D \geq 23 with no medication). Levels of inflammatory biomarkers were compared among groups and multivariable regressions performed.

Results—Of the 85 women studied, 16 (19%) had ADS responsive to treatment, 12 (14%) had ADS not responsive to medication, and 57 (67%) had untreated ADS. TNF α concentrations significantly differed ($P = 0.016$) across the cohorts. Post-hoc bivariate analyses demonstrated that

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women with ADS responsive to treatment had lower serum TNF α than non-responders ($p=0.02$) and women with untreated ADS ($p=0.01$). There were no differences in IFN γ , IL13, IL6, IL8 or CRP among the groups. Regressions demonstrated that, compared to women with ADS responsive to treatment, non-responders or women with untreated ADS had higher TNF α levels ($\beta=0.27$, 95% CI 0.02-0.52 and $\beta=0.23$, 95% CI 0.02-0.44, respectively).

Conclusions—Pregnant women on pharmacotherapy who respond to treatment for ADS have lower TNF α compared to women not responsive to medication or women with untreated ADS. These data suggest the possibility that either the therapeutic response in the context of pharmacotherapy is accompanied by modulation of the immune system, or that pre-existing higher levels of TNF α may be associated with a poorer response to traditional pharmacotherapy.

Keywords

antenatal depression; perinatal depression; inflammation; anti-depressants; selective serotonin reuptake inhibitors

Introduction

Perinatal depression remains one of the most common complications of pregnancy, affecting over half a million women in the United States annually.(Gaynes et al. 2005; Wisner et al. 2013) When treated, women with perinatal depression often utilize pharmacotherapy targeting the monoamine pathways, such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), or tricyclic antidepressants (TCAs). However only 50-70% of individuals utilizing anti-depressant pharmacotherapy, even at adequate doses, will achieve a therapeutic response.(Fava 2009; Rush 2007) This modest efficacy calls into question whether subtypes of depression can be identified that are a result of other pathophysiologic underpinnings and could be more effectively treated by other modalities.

There are data that suggest that monoaminergic changes may not solely mediate the effects of antidepressants. For example, levels of serotonin are unchanged in individuals with depression compared to those without depression and experimental models that rapidly deplete serotonin and/or norepinephrine do not reliably induce depressive symptomatology. (Lacasse and Leo 2005) Furthermore, while antidepressants have a near-immediate impact on serotonin transmission (Felton et al. 2003), clinical improvements in depressive symptomatology lag behind by weeks.(Andrews and Nemeroff 1994)

Patients with major depressive disorder outside of pregnancy are consistently show to have increased plasma inflammatory cytokines, most consistently IL-1 β , IL-6, TNF α , and CRP. (Dowlati et al. 2010; Howren et al. 2009) As blockade of the production of these cytokines reduces depressive symptoms (Abbott et al. 2015; Kohler et al. 2014; Raison et al. 2013; Tyring et al. 2006) and administration of anti-inflammatory agents has been associated with a reduction in depressive symptomatology (Lin and Su 2007; Pasco et al. 2010; Stafford and Berk 2011; Tyring et al. 2006), a causal relationship is suspected. More recent meta-analytic data have suggested that perinatal depression, or at least subtypes of perinatal depression,

may have an underlying inflammatory etiology.(Dowlati et al. 2010; Howren et al. 2009; Liu et al. 2012; Osborne and Monk 2013; Raison et al. 2013)

Given these promising findings, some have questioned whether anti-depressants exert their effects through modulation of inflammation. Indeed clinical data support an anti-inflammatory effect of anti-depressant pharmacotherapy in the general population with observed reductions in multiple cytokines including TNF α , IFN γ , IL1 β , and IL6. (Hannestad et al. 2011; Janssen et al. 2010; Musselman et al. 2001) Yet, it is not known whether antidepressants have an anti-inflammatory effect during pregnancy or if women with higher levels of inflammation are more refractory to conventional treatment. To our knowledge, only one study has examined this relationship. Latendresse et al and identified that IL1 β , IL6, and IL10 were lower among women who took at SSRI during pregnancy compared to those untreated.(Latendresse et al. 2013). However, while these authors were able to examine the relationship between psychological distress and inflammatory cytokines after controlling for SSRI use, they did not compare inflammatory markers in women who did and did not respond to treatment. Thus, our objective was to evaluate the association between psychotropic medication and maternal serum inflammatory biomarkers in women with antenatal depressive symptoms (ADS) in the mid-trimester. We hypothesized that, among women with ADS, those who respond to psychotropic medications would have lower levels of peripheral inflammatory biomarkers than women who were untreated or treated without a response in symptomatology.

Materials and Methods

This is a secondary analysis of the Measurement of Maternal Stress (MOMS) study, a multi-center prospective cohort study of pregnant women with singleton gestations who delivered between June 2013 and May 2014.(Ross et al. 2016) Between 12 weeks 0 days and 20 weeks 6 days women underwent a self-reported screen for depression using the Center for Epidemiologic Studies Depression Scale (CES-D). The CES-D is a reliable 20-item measure of depressive symptomatology (Radloff 1977) that has been validated against a psychiatric interview (Nabbe et al. 2017). Women also completed self-reported surveys about sociodemographic characteristics and medical co-morbidities. They also were asked to report any ongoing medication use, including endorsement of any medications used for treatment of depression and/or anxiety. Medical charts were reviewed to confirm self-reported medications and medical diagnoses and only women with confirmed data were included. Women were included in the analysis if they fell into one of three categories: untreated ADS (CES-D ≥ 23 with no reported medication), ADS not responsive to medication (CES-D ≥ 23 despite medication), and ADS responsive to treatment (CES-D <16 with medication). A cut off score of 16 was represent women without ADS given the high sensitivity at this threshold (Lewinsohn et al. 1997). A score above 23 was used to represent clinically significant ADS. Women who were non-depressed (CES-D <16) and not on medications were not considered further for this analysis. Sociodemographic characteristics were compared across these groups in bivariate analyses.

Concomitant with administration of the CES-D, maternal serum was collected and inflammatory biomarkers were measured (IFN γ , IL13, IL6, IL8, TNF α , CRP). The

cytokines were chosen for inclusion for the primary study aims given their hypothesized relationship with antenatal stress and were measured by electrochemoluminescent immunoassay on a Meso Scale Discovery instrument (SECTOR Imager 2400; Gaithersburg, MD USA) as previously described (Ross et al. 2016). Intra-assay coefficients of variation for each of the measured cytokines averaged 5.4, with a range from 2.2 (IL8) to 8.9 (IL-13). The concentration of CRP in each sample was determined using the Beckman Coulter UniCel® DxC 800 System (Beckman Coulter, Inc., Brea, CA). The analytical measuring range of CRP was 0.2 – 80.0 mg/L. Samples with CRP concentrations higher than 80.0 mg/L were diluted with saline and re-analyzed. The highest CRP concentration reportable was 380.0 mg/L. Low and high control samples were included with each assay, and the percent coefficient of variation (%CV) between assays was 5.3 and 3.2, respectively.

Levels of inflammatory biomarkers were compared between groups in bivariable analysis. Biomarkers that significantly differed among the three groups were considered for analysis in multivariable linear regression analyses. In a small sample like this, the risk of over fitting regression models is high. Thus, we limited the models to a small panel of key covariates identified in previous research including race/ethnicity, income, and marital status.

ANOVA, Kruskal-Wallis, or Fisher's exact tests were used, as appropriate, for bivariable analyses. Post-hoc analyses were performed using the Bonferroni correction. Statistical analyses were performed using Stata version 14.0 (StataCorp, College Station, TX). A two-tailed alpha of 0.05 was used to define statistical significance. Adjustments were not made for multiple comparisons given the exploratory nature of this study. The primary study was IRB approved at each participating institution prior to its initiation and all women included provided informed consent. Data utilized for this analysis were de-identified and considered IRB exempt.

Results

Of the 723 women in the original study, 85 (12%), had evidence of ADS (based on either CES-D score or treatment) from 12-21 weeks gestation. Of these women, 16 (19%) had ADS responsive to treatment, 12 (14%) had ADS not responsive to medication, and 57 (67%) had untreated ADS. Characteristics of the sample are shown in Table 1. Compared to women being treated pharmacologically for ADS (with or without a response), women with untreated ADS were more likely to be from a racial/ethnic minority group, to have a lower household income, to be publically insured, to have a lower educational level, and were less likely to be married. Women with untreated ADS were more likely to be employed compared to women with ADS not responsive to medication but were less likely to be employed compared to women with ADS responsive to treatment.

There were no differences across ADS and medication strata in maternal serum levels of IFN γ , IL13, IL6, IL8, or CRP (Table 2). However, TNF α concentrations significantly differed among the groups. Post-hoc analyses demonstrated that non-responders ($p=0.02$) and women with untreated ADS ($p=0.01$) had lower concentrations of TNF α compared to women with ADS responsive to treatment. There was no difference in TNF α concentrations between untreated women and non-responders ($p=0.76$).

In multivariable linear regression controlling for race/ethnicity, income, and marital status, both women with ADS who were non-responders and women with untreated ADS had higher TNF α levels ($\beta=0.27$, 95% CI 0.02-0.52 and $\beta=0.23$, 95% CI 0.02-0.44, respectively) compared to women with ADS responsive to treatment.

Discussion

In this cross-sectional analysis of a prospective cohort of women assessed for ADS between 12 and 21 weeks, pharmacotherapy coupled with evidence of remission of antenatal ADS is associated with lower TNF α levels compared to pharmacotherapy with continued ADS or untreated ADS. While the other examined inflammatory biomarkers were not statistically significantly different among groups, point estimates for each were lower in women with ADS responsive to treatment compared to women on pharmacotherapy but with continued ADS or untreated women. These data support one of three theories: 1) the therapeutic response in the context of pharmacotherapy is accompanied by modulation of inflammatory activity, 2) women with elevated levels of TNF α have a poorer response to pharmacotherapy, or 3) there is unmeasured confounding in the quality, timing or amount of treatment for ADS, the severity or subtype of ADS, other psychosocial adversity or pregnancy complications that co-vary with depression and inflammation and may influence the trajectories of perinatal depression.

Our findings in pregnant women corroborate findings from the general psychiatric population. TNF α is a cell signaling protein involved regulation of the immune response and is a potent activator of sickness behavior. Data from non-pregnant individuals with depression consistently demonstrate they have elevations in TNF α levels.(Dowlati et al. 2010; Liu et al. 2012) Furthermore, data outside of pregnancy also has established that SSRIs (Diamond et al. 2006; Maes et al. 1999) and other anti-depressants (Martensson and Nassberger 1993; Xia et al. 1996a; Xia and Eneroth 1996) have anti-inflammatory properties, with several studies indicating an inhibition specifically of TNF α release associated with anti-depressant use.(Taler et al. 2007; Xia et al. 1996b)

The absence of an association between other inflammatory cytokines and pharmacotherapy response deserves discussion. One prior study has demonstrated IL1 β , IL6, and IL10 are lower in women taking SSRIs compared to untreated women (Latendresse et al. 2013), however these authors did not stratify their treated group by response. One explanation for our lack of observed differences in the other cytokines between women exposed and not exposed to pharmacotherapy could be the limited response to treatment seen in our study. Indeed of the 28 women on pharmacotherapy, only 16 (57%) had sub-clinical depression scores. Alternatively as our sample was limited to only women with ADS, the modest decrease in inflammation observed in association with SSRI use may have been masked by the pro-inflammatory contribution of ADS.

These findings may hold important clinical implications. If inflammation mediates depressive symptomatology in the antenatal period and reductions in inflammatory profiles are associated with a remission in symptoms, anti-inflammatory agents, anti-inflammatory diets (Griffiths et al. 2016), or exercise (with its anti-inflammatory properties) (Kasapis and

Thompson 2005) may augment response to treatment. Indeed, the use of anti-inflammatory medications for psychiatric illness has begun to receive attention outside of pregnancy. Tying et al. demonstrated that, in patients with psoriasis, administration of etanercept (an anti-TNF α agent) reduced symptoms of depression independent of its effect on psoriatic symptomatology.(Tying et al. 2006) Pasco et al. showed that women on aspirin and statins have a significantly greater chance of remaining free of depression than non-exposed women.(Pasco et al. 2010) Mueller and colleagues have shown that the addition of celecoxib (a nonsteroidal anti-inflammatory drug) to reboxetine (a serotonin-norepinephrine reuptake inhibitor type of anti-depressant medication) was more effective in improving depressive symptoms than reboxetine alone.(Muller et al. 2006) And, finally, Raison et al demonstrated infliximab (an anti-TNF α agent) reduced depressive symptoms in treatment-resistant depression associated with high inflammatory biomarkers.(Raison et al. 2013) To our knowledge, no study has examined the clinical effect of any of these anti-inflammatory agents in antenatal depression.

Another notable finding from this study is that the majority (68%) of women with an elevated CES-D score were not on pharmacotherapy. While this study was unable to identify whether women were receiving psychotherapy or other therapeutic modalities, the high scores on their depression screen suggest that a therapeutic intervention was not taking place. These data are supported by current epidemiologic literature; only half of pregnant women identified as depressed accept a mental health care referral and fewer than 10% remain in treatment at six months after the initial diagnosis.(Miller et al. 2009) Thus, these findings highlight the continued care gap in perinatal depression support services.

Limitations of this study must be noted. First, despite a large sample size of the overall cohort, the number of women meeting inclusion criteria for this specific analysis was limited. While we were able to identify a significant difference in levels of TNF α across ADS/treatment strata, the absence of differences in other biomarkers could be a result of type 2 error. Alternatively, given the multiple comparisons performed, the finding of a significant association between ADS/treatment strata and TNF α could represent type 1 error. It is notable that point estimates for each maternal serum biomarker was lower in the treated cohort compared to those untreated or inadequately treated. Furthermore, depression was not clinically diagnosed, but rather depressive symptomatology was reported via the CES-D. However, we would anticipate that the decreased specificity resultant from utilization of a screen versus clinical diagnosis would bias the results toward the null. Additionally, we do not have granular detail of the specific psychiatric medications or psychotherapeutic interventions being utilized. However, as SSRIs are the most widely utilized depression medication in pregnancy (Huybrechts et al. 2013), we anticipate our data were driven by effects of this class of pharmacotherapy. Any impact of adjuvant psychotherapy or anxiety in the absence of depressive symptoms being treated with pharmacotherapy cannot be assessed using these data. Finally, the cross-sectional study design as well as our inability to define the timing of initiation of pharmacotherapy are further limitations to our ability to attribute causality to the observed association.

Conclusion

In summary, in this cohort of pregnant women with symptoms of depression during the antenatal period, decreased symptomology in conjunction with pharmacotherapy treatment is associated with lower levels of TNF α . These data provide support to the findings in non-pregnant individuals that anti-inflammatory properties may be one potential mechanism of action of psychotherapeutic agents. In addition, these data support the need for future work examining the role of more targeted anti-inflammatory agents in the setting of antenatal depression.

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Table 1

Maternal characteristics stratified by depressive symptomatology and medication use

	ADS responsive to treatment n=16	ADS not responsive to medication n=12	Untreated ADS n=57	p-value
Maternal age (years)	31 ± 4	31 ± 7	28 ± 7	0.168
Gestational age at CES-D (weeks)	17 ± 2	16 ± 2	16 ± 3	
Race/ethnicity (n=729)				<0.001
Non-Hispanic white	15 (93.8%)	9 (75.0%)	19 (33.3%)	
Non-Hispanic black	0 (0.0%)	0 (0.0%)	18 (31.6%)	
Hispanic	0 (0.0%)	3 (25.0%)	18 (31.6%)	
Other	1 (6.3%)	0 (0.0%)	2 (3.5%)	
Household income (n=76)				0.004
Below \$15K	1 (6.7%)	2 (20.0%)	21 (41.2%)	
\$15K–29,999	0 (0.0%)	0 (0.0%)	8 (15.7%)	
\$30K–49,000	2 (13.3%)	4 (40.0%)	10 (19.6%)	
\$50K–100K	7 (46.7%)	3 (30.0%)	8 (15.7%)	
>\$100K	5 (33.3%)	1 (10.0%)	4 (7.8%)	
Insurance (n=84)				<0.001
Private	15 (93.8%)	4 (33.3%)	13 (23.2%)	
Public	0 (0.0%)	6 (50.0%)	39 (69.6%)	
Other	1 (6.3%)	1 (8.3%)	3 (5.4%)	
None	0 (0.0%)	1 (8.3%)	1 (1.8%)	
Education level (n=84)				0.002
High school or less	2 (12.5%)	4 (33.3%)	25 (44.6%)	
Some college/associates degree	4 (25.0%)	5 (41.7%)	24 (42.9%)	
College or more	10 (62.5%)	3 (25.0%)	7 (12.5%)	
Employed	13 (81.3%)	3 (25.0%)	28 (49.1%)	0.011
Married (n=84)	12 (75.0%)	4 (33.3%)	15 (26.8%)	0.002
BMI at 1st prenatal visit	29 (24–34)	33 (24–36)	28 (23–35)	0.758

Data presented as mean ± standard deviation or n (%)

ADS = antenatal depressive symptomatology; CES-D = Center for Epidemiologic Studies Depression Scale; BMI = body mass index

Table 2

Inflammatory biomarker concentrations stratified by depressive symptomatology and medication use

	ADS responsive to treatment n=16	ADS not responsive to medication n=12	Untreated ADS n=57	p value
IFN γ (pg/mL)	2.51 (2.16–5.20)	3.37 (2.89–5.24)	3.03 (2.22–4.41)	0.347
IL13 (pg/mL)	1.89 (0.74–4.40)	2.75 (1.56–8.06)	2.07 (0.88–5.38)	0.509
IL6 (pg/mL)	0.47 (0.35–0.68)	0.57 (0.36–0.81)	0.60 (0.40–0.97)	0.483
IL8 (pg/mL)	1.50 (1.25–2.01)	2.34 (1.54–2.65)	1.61 (1.19–2.06)	0.108
TNF α (pg/mL)	0.74 (0.60–0.96)	1.06 (0.88–1.25)	0.98 (0.83–1.14)	0.016
CRP (mg/dL)	4.20 (3.10–9.80)	6.60 (1.90–12.05)	7.30 (3.10–13.00)	0.514

ADS = antenatal depressive symptomatology; IFN = interferon; IL = interleukin; TNF = tumor necrosis factor; CRP = C-reactive protein

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