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Increased systemic microbial translocation is associated with depression during early pregnancy

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ABSTRACT

Plasma level of microbial translocation is a marker of mucosal permeability. Increased mucosal permeability ignites elevated microbial translocation and as a consequence of systemic inflammation. Pregnant women with depression have higher levels of inflammatory markers relative to pregnant women without depression, however, no studies have reported whether systemic microbial translocation will change in depressed women during pregnancy. In this study, we examined the plasma LPS level of depressed women during pregnancy. The results showed that the plasma LPS level was significantly increased in depressed mothers during their 8–12 weeks gestation compared to healthy controls. Compared to 8–12 weeks gestation, the plasma LPS levels were significantly decreased at 24–28 weeks gestation and 6–8 weeks postpartum in both depressed subjects and healthy controls. Furthermore, the plasma levels of pro-inflammatory cytokines (TNF-α and MCP/CCL2) associated with microbial translocation were significantly increased in depressed subjects during 8–12 weeks gestation compared to healthy controls. These results indicate that the level of microbial translocation is increased in depressed women during early pregnancy.

1. Introduction

Peripartum depression is a debilitating mood disorder that occurs in 8–15% of childbearing women (Byatt et al., 2016; Robakis et al., 2015). Although several psychosocial risk factors have been identified, a substantial proportion of the risk for the disorder remains unexplained and biological contributors are unclear (Babb et al., 2015). Dysregulation of the innate immune system is thought to be important in the etiology of major depression (Miller et al., 2009). Pregnant women with depression have higher levels of inflammatory markers during pregnancy, compared to non-depressed pregnant women (Osborne and Monk, 2013) but it is unclear what may be triggering this inflammatory cascade.

The passage of bacterial products from the gastrointestinal tract to extraintestinal sites is a process known as microbial translocation (Brenchley and Douek, 2012). Microbial translocation ignites a pro-inflammatory cytokine milieu and systemic immune activation that is thought to be important in the pathogenesis of a number of diseases (Brenchley et al., 2006; Costa et al., 2016; Jiang et al., 2009). Plasma lipopolysaccharide (LPS) is considered to be a representative biological marker of microbial translocation, stimulates immune cells through the toll like receptor 4 pathway and contributes to the pro-inflammatory cytokine milieu and systemic immune activation (Brenchley and Douek, 2012), and may contribute to several disease states including depression. Here, we tested the hypothesis that microbial translocation is associated with depression during pregnancy.

2. Methods and materials

2.1. Study subjects

These studies were approved by the Institutional Review Boards for Human Research (IRB#Pro00021511) at the Medical University of South Carolina. Participants (Table 1) were pregnant women receiving routine obstetrical care and were recruited into the study during their first prenatal visit (8–12 weeks gestation). Women were excluded if they were younger than 18 years of age, more than 12 weeks of

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Table 1
Clinical characteristics.

	Healthy controls	Depressed patients	P value [a]
Numbers of subjects	14	14	
Age (years) median [b]	30 (25–32)	29 (23–33)	0.61
Maternal BMI at visit 1 (kg/m^2) [b]	33.0 (26.3–38.3)	32.5 (25.5–37.3)	0.92
Gravidity [b]	2.0 (2.0–3.3)	2.5 (1.0–4.0)	0.97
Parity [b]	1.0 (0.8–1.0)	0.5 (0.0–1.3)	0.33
Total gestation weeks [b]	39.0 (37.8–40.0)	39.5 (38.0–40.3)	0.39
Baby birth weight (oz) [b]	115.5 (108.8–130.3)	122.5 (107.5–136.3)	0.46
Therapies of depression	No	No	
Previous psychiatric disorders	No	No	
Alcohol drinking (past 12 h)	No	No	
Systemic antibiotic treatment (past 6 months)	No	No	
Fetal sex (%)			> 0.99
Male	35.7	42.9	
Female	64.3	57.1	
Delivery type (%)			0.33
Vaginal	85.7	70.0	
Cesarean	14.3	30.0	
Ethnicity (%)			> 0.99
Caucasian	50.0	50.0	
Africa American	42.9	42.9	
Asian	7.1	7.1	
Education (%)			0.97
Less than high school +	7.1	21.4	
High school	28.6	42.9	
Some college	35.7	28.6	
College or higher	28.6	7.1	
Family income (%)			> 0.99
Less than $20,000 +	14.3	28.6	
$20,000–$49,999	35.7	35.7	
$50,000–$74,999	35.7	35.7	
$75,000 or more	14.3	0.0	
Smokers (%)			0.80
Never	92.9	71.4	
Former	7.1	21.4	
Current	0.0	7.1	

[a] P values compared between the two study groups were analyzed by Mann Whitney test (non-paired).
[b] Data are median (interquartile range) values.

gestation, or unable to provide informed consent. Participants provided demographic information, and were screened for depression using the Edinburgh Postnatal Depression Scale (EPDS) (Osborne and Monk, 2013). Blood samples were collected at 8–12 weeks gestation (visit 1), 24–28 weeks gestation (visit 2), and 6–8 weeks postpartum (visit 3). During these visits, participants who scored 10 or greater on the EPDS were considered depressed subjects (n = 14) and participants scored less than 9 on the EPDS were considered healthy controls (n = 14) (Table S1).

2.2. Plasma levels of LPS

Plasma were stored in a 1.5 mL microtube at 80 °C until they were thawed for study. LPS level in Plasma was then quantified using limulus amebocyte lysate QCL-1000 kit (Lonza, Walkersville, USA) as described in our previous studies (Jiang et al., 2009). Data were shown in median (interquartile range [IQR]).

2.3. Plasma levels of TNF-α, IL-6, IL-1β and MCP/CCL2

Plasma cytokines levels (TNF-α, IL-6, IL-1β and MCP/CCL2) were measured using the Bio-Plex Pro™ Human Chemokine Panel, 40-plex (Bio-Rad Laboratories, Hercules, CA, USA) according to the manufacturer's instruction.

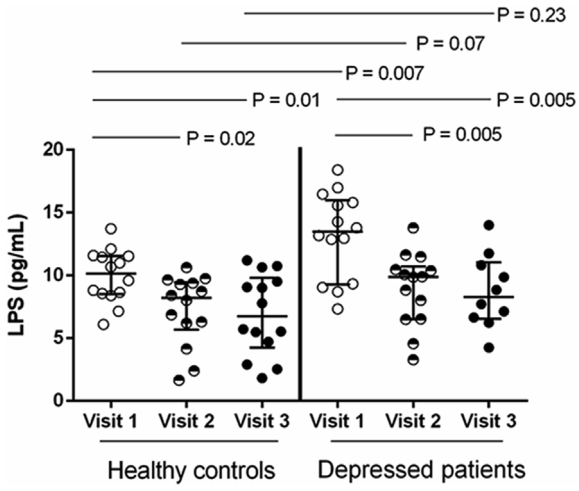

Fig. 1. Increased plasma levels of LPS in depressed women during early pregnancy compared to healthy controls. Plasma LPS levels in healthy control women and depressed women during pregnancy (median ± IQR). Mann Whitney *U* test.

2.4. Statistical analysis

In the pre-specified hypothesis, we were interested in the comparisons of results from depression versus from healthy controls; therefore, *p*-values from comparing depression to each of control groups were not adjusted for multiple comparisons (Rothman, 1990). Therefore statistical significance was assessed using Mann Whitney U tests. A multivariable linear regression model was used to analyze the differences in plasma LPS after adjusting age, race and BMI using SAS (Version 9.3, Cary, NC, USA). $P \leq 0.05$ was considered statistical significance.

3. Results

In order to assess systemic microbial translocation, we examined the plasma LPS level. Compared to visit 1, the plasma LPS level was significantly decreased at visit 2 and visit 3 in both healthy controls (P = 0.02 and P = 0.01) and depressed subjects (P = 0.005 and P = 0.005) (Fig. 1). Notably, the plasma LPS level was significantly increased in depressed subjects at visit 1 compared to healthy controls (P = 0.007), even after controlling age, race, and BMI (P = 0.01). The plasma LPS levels at visit 2 and visit 3 in depressed subjects were marginally increased compared to health controls (P = 0.07 and P = 0.23) but did not achieve statistically significant differences (Fig. 1).

To further verify our finding, we compare the levels of pro-inflammatory cytokines in early pregnancy (Fig. 2). The results showed that the plasma TNF-α and MCP/CCL2 levels were significantly increased in depressed subjects at visit 1 compared to healthy controls (P = 0.02, and P = 0.04). Interestingly, plasma IL-6 level was increased in depressed subjects at visit 2 but not at the other visits compared to healthy controls (P = 0.02). However, plasma levels of IL-6 and IL-1β at visit 1 were similar among depressed and healthy women.

4. Discussion

Elevated plasma LPS level, which is translocated from impaired mucosal barriers, will lead to the production of pro-inflammatory cytokines and a state of aberrant immune activation (Brenchley and Douek, 2012; Brenchley et al., 2006). Research has demonstrated that women with depression may have higher levels of inflammatory markers (IL-6 and TNF-α) related to microbial toll-like receptor signaling pathway in early pregnancy (Haeri et al., 2013). Recently, study showed that plasma IgA and IgM against commensal gram-negative