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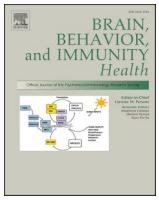

Depression in pregnant Hispanic women: Risk factors, pregnancy outcomes and plasma cytokines

Maureen E. Groer [a,*], Kelley Baumgartel [b], Cary Springer [a], Tina Mutka [b], Teodor T. Postolache [c,d]

[a] University of Tennessee Knoxville, USA
[b] University of South Florida, USA
[c] Department of Psychiatry, University of Maryland School of Medicine, Rocky Mountain MIRECC for Suicide Prevention, Aurora, CO, USA
[d] VISN 5 MIRECC, Baltimore, MD, USA

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ABSTRACT

Background: Maternal depression is considered a major contributor to morbidity and mortality in pregnancy. A population at risk are U.S. born or immigrant Hispanic women, and few prenatal depression or immune studies have focused on this population.
Objective: The research questions for the study were 1) What are the occurrences, risk factors and outcomes associated with depression in Hispanic pregnant women in the United States and 2) What are the associations of plasma immune cytokines and prenatal depression in this population.
Study design: Women of self-reported Hispanic ethnicity were born in the continental United States or foreign-born. Screening of potential participants (n = 690) at a first prenatal clinic visit consisted of antibody testing for Toxoplasma gondii antibodies in a larger grant, and only the women with antibody levels below the cutoff for *T. gondii* positivity (N = 536) were included in the present study. All participants completed a health and demographic questionnaire, the Edinburgh Postpartum Depression (EPDS) scale, the Perceived Stress Scale (PSS), and the Medical Outcomes Study Social Support (MOS) scale. We surveyed electronic health records (EHR) for risk factors and adverse pregnancy outcomes in the sample. We further measured physical and mental health and seven plasma immune cytokines at four study visits during pregnancy in a longitudinal subsample (N = 128).
Results: The frequency of EPDS scores of 10 (depression risk) or above was 18.6 % at the time of enrollment. Socioeconomic factors such as less education, greater unemployment, and U.S. born nativity were associated with greater depression risk, but these relationships became insignificant when we corrected for false discovery rate. Depression scores were not associated with adverse birth and pregnancy outcomes. The inflammatory cytokine TNF-α was significantly higher across pregnancy in women with depression risk ($p < 0.03$). Other inflammatory cytokines were higher in depressed women, but only at one time point in mid-pregnancy.
Conclusions: Prenatal depression occurs in early pregnancy and then declines in Hispanic women. The frequency of depression and stress were higher in U.S. born compared to immigrant Hispanic women. There was an elevation in plasma levels of TNF-α through the pregnancy in depressed women, and elevations in other cytokines, at midpregnancy. The adverse pregnancy outcomes, including preterm delivery, known to be associated with prenatal depression were not present in this cohort.

1. Introduction

We had collected data from a large sample of Hispanic pregnant women. The research questions asked for the study were 1) What are the occurrences, risk factors and adverse pregnancy outcomes associated with depression in Hispanic pregnant women in the United States and 2) What are the associations of plasma immune cytokines and prenatal depression in this population.

Depression during pregnancy (prenatal depression) has a prevalence of 10–20% in U.S. women, with potential short- and long-term health risks to both mothers and infants (Grigoriadis et al., 2013). Up to 30% of women have depressive mood during pregnancy, but major prenatal

* Corresponding author. University of Tennessee, Nursing Education Building, 1412 Circle Dr, Knoxville, TN, 37996, USA.
E-mail address: mgroer@utk.edu (M.E. Groer).

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depression during pregnancy occurs in only 6–9%, with highest symptom reports in early pregnancy (Banti et al., 2011). Maternal depression is considered a major contributor to morbidity and mortality in pregnancy (Gelaye et al., 2016). There is controversy about mechanisms by which prenatal depression is associated with adverse pregnancy outcomes (miscarriages, preterm birth, small or large for gestational age infants, gestational diabetes mellitus, preeclampsia, and hypertension). Depression may alter maternal behavior and lifestyle, which could then impact adverse outcomes (Surkan et al., 2016). Treatments for prenatal depression vary widely across the world, which could also affect association with adverse outcomes if effective in reducing the depression (Gelaye et al., 2016).

Preterm birth appears to be the most reported adverse outcome associated with depression. The results of a systematic review showed small relationships between prenatal depression and premature delivery, and the recommendation was for research of higher methodological quality (Grigoriadis et al., 2013). Depression that worsened over the course of pregnancy in nulliparous women was associated with increased odds of preterm birth in a secondary study of 8784 women (Miller et al., 2022). A scoping review found associations of secondary maternal mental illnesses and low birth weight with preterm birth (Montagnoli et al., 2020).

There are few large studies of prenatal depression in women of Hispanic ethnicity, although acculturation through living in the United States is known to increase both adverse pregnancy outcomes (D'Anna-Hernandez et al., 2012) and prenatal depression (D'Anna-Hernandez et al., 2015). Factors that appear to influence the risk for prenatal depression include adverse social determinants of health, racial/ethnic minority status, unplanned pregnancy and domestic violence (Fortner et al., 2011; Field, 2017). Prenatal depression incidence is reported to be higher in both immigrant and U.S.-born Hispanics living in the United States, compared to Caucasians, with reported ranges between at 11% and 50% (Kuo et al., 2004; Lara et al., 2009). Incidence of prenatal depression (using the EPDS) in Hispanic women in a large New Mexico population was 12.7% for Spanish compared to English speaking pregnant women (de la Rosa et al., 2021). In another study in late pregnancy, there were nearly a third of the Hispanic women with EPDS scores above the cutoff for probable depression, but the birth origins were not provided (Lara-Cinisomo, D'Anna-Hernandez, Fujimoto and Pedersen, 2019). The concerns of particular importance for pregnant women of Hispanic ethnicity include stress related to stigma, discrimination and acculturation factors (Harris et al., 2022; Lara-Cinisomo et al., 2018). One consideration is that there may be cultural influences that limit a mother's reporting of mood states in the Hispanic population, in that the culture prioritizes motherhood and family above personal issues (Callister et al., 2011). There may also be a fear of reporting severe mood disturbances by poor Hispanic mothers without documents required for legal immigration or residence (undocumented), who fear that their children might be taken if they disclose depression to health care providers (Lara-Cinisomo et al., 2019). Understanding the risks for prenatal depression in the growing U.S. Hispanic population is very important and has not been well studied. More than half of the 44 million yearly immigrants to the United States are from Mexico or Latin America and Hispanic women accounted for nearly 24% of U.S. births in 2021. The number of Hispanic childbearing women (15–44) has doubled since 2000 and 50% of all U.S. immigrant women's births were in Hispanic women (https://pewrsr.ch/2YzvLa8). It is projected that by 2060, the population of Hispanics will increase by 30% (www.mckinsey.com/featured-insights/sustainable-inclusive-growth/the-economic-state-of-latinos-in-america-the-american-dream-deferred). This population experiences many social disparities, including discrimination, poverty, unemployment, and low social support.

We included exploration of the relationships of plasma cytokines across pregnancy with depression in the longitudinal subsample. There is a large body of literature that supports links between the immune system and the neurobiology of *non-prenatal* depression (Zorrilla et al., 2001). Higher levels of IL-6 and TNF-α have been found in non-pregnant patients with major depressive disorder compared with non-depressed controls (Dowlati et al., 2010). TNF-α, an inflammatory cytokine, can increase permeability of the blood brain barrier in animal models, which could permit metabolites and cytokines to enter the brain (Cheng et al., 2018). A meta-analysis of 82 studies of cytokines and non-prenatal depression reported higher levels of TNF-α, IL-6, IL-13, IL-18, IL-12, IL-1RA, and sTNFR2, along with a decrease in IFN-γ in depression (Köhler et al., 2017). With regard to postpartum depression, many studies also show relationships between inflammation and depression, as reviewed recently (Zhu et al., 2022). Pregnancy depression studies are more difficult to interpret, as the immune system and cytokines in pregnancy vary along the course of the pregnancy. We studied longitudinal relationships between EPDS, PSS and MOS scores, and plasma cytokines throughout pregnancy in a cohort of Hispanic women.

2. Materials and methods

The University of South Florida Institutional Review Board approved the study, and all women gave written informed consent, in either English or Spanish. Women were screened and enrolled at their first prenatal visits in clinics in Tampa, Florida. These clinics offered prenatal care to all low income, uninsured pregnant persons. Early pregnancy, self-identification of Hispanic ethnicity, and *T.gondii* negative antibody levels were the inclusion criteria for the current study. Participants allowed access to their electronic health record (EHR) to provide data for the current study. Exclusion criteria included age under 18 years old, HIV infection, drug and/or alcohol dependency, autoimmune disease or cancer, steroid medications, BMI<20, plans to terminate the pregnancy, or presence of congenital anomalies. All screened women provided a 15 mL venous blood sample at the first prenatal visit. Blood was collected in tubes with EDTA as anticoagulant and kept cold until brought to the lab for processing within 24 h. This blood was then screened for *T. gondii* IgG levels to determine presence of latent toxoplasmosis. Only those negative for this *T. gondii* screening were enrolled in the current study of prenatal depression. Blood samples were taken at every prenatal visit for the longitudinal cohort. Plasma aliquots were stored at −80 °C and used for cytokine assays.

2.1. Demographics

Many of the study participants spoke only Spanish, and it is possible that a significant number were undocumented, although this was not a study variable. There were 536 eligible women with data collected at the first prenatal visit who gave consent for access to the EHR for information related to their health, pregnancy, and labor and delivery. There were 207 born in the United States and 329 foreign born immigrants. For the latter group, the range of years living in the United States was 2 months to 35 years. Twenty-one women had been in the United States less than 2 years and 74 less than 5 years.

There were 128 of these 536 women who were randomly selected to enroll in a smaller prospective study. The range of weeks of pregnancy for the prospective study was 4–14 at visit 1, 15 to 23 at visit 2, 24 to 30 at visit 3, and 31 to 38 at visit 4. All women in the sample had data through birth so statistical analysis for the first research question involved the larger sample size. For the prospective study of cytokines and EPDS (research question 2) the sample size was from the prospective study, 113 at visit 1 (4–14 weeks), 125 at visit 2 (15–23 weeks), 109 at visit 3 (24–30 weeks), and 110 at visit 4 (31–38 weeks).

2.2. Instruments

Demographic, psychosocial and health data were obtained at study visit 1 for all participants and at each study visit in the prospective cohort. The three psychosocial instruments were the Edinburgh Postpartum Depression Scale (EPDS), Cohen's Perceived Stress Scale (PSS),

and the Medical Outcomes Social Support Survey (MOS). The EPDS is a validated 10-item questionnaire that evaluates feelings and satisfaction with regular activities and behaviors in the prior 7 days. The EPDS is not a diagnostic tool and is used to evaluate possible risk for both prenatal and postpartum depression symptoms. While originally designed to measure postpartum depression, the EPDS is widely used during pregnancy. In a large Icelandic sample of pregnant women (Lydsdottir et al., 2019), the EPDS was validated at weeks 16, 25 and 36 of pregnancy by comparing results against other depression and anxiety scales and also with use of a mini-international neuropsychiatric interview. The internal reliability, discriminant validity, and convergent validity were all deemed very acceptable for use of this scale in pregnancy. The score cutoff identifying women at risk differs by country, but most U.S. studies use scores above 11. We used the Spanish language version of the EPDS, depending on women's choices, and chose a score of 10 or greater to classify the women into non-depressed or risk of depression. This was based on work with Mexican women which found the appropriate cutoff in pregnancy to be 10 or greater for classifying women at risk for depression. At this cutoff there was a sensitivity of 75.7%, a specificity of 74.4%, and the area under the curve was 0.89 (95% confidence interval: 0.71–1.06) (Alvarado-Esquivel et al., 2014). The PSS is a 10-item widely used questionnaire which evaluates the degree to which life experiences are deemed unpredictable, uncontrollable, and overwhelming (Cohen et al., 1983). The MOS is a 19 item survey of emotional/informational, tangible, affectionate, and positive social interactions and includes and overall functional social support index (Sherbourne and Stewart, 1991).

2.3. Health and pregnancy data

For both the large cohort of screened women and for the prospective sample, the EHR provided details about health, pregnancy complications, adverse events, and labor and birth data. Demographic and health history data were gathered from an investigator developed questionnaire administered at the first visit.

2.4. Plasma cytokines

In the prospective study a multiplex panel of plasma biomarkers was done at each of the four visits in plasma samples preserved at −80 °C. Cytokines (IFN-γ, TNFα, IL-2, IL-6, IL-10, IL-12, IL-17) were measured in plasma aliquots in duplicate using the Luminex MagPix multiplexing system. Coefficients of variation were under 10, and cytokines under the limit of detection (LOD) were assigned as undetectable.

2.5. Analysis

Descriptive statistics included frequencies, means, t-tests, chi squares, and Pearson correlations for the normally distributed measures. Spearman correlations were used for the measures that were not normally distributed. EPDS scores were compared across visits using a linear mixed model with an autoregressive covariance structure with subject as a random effect. Contrasts were run comparing mean EPDS scores at visit 1 to each of the other visits. The EPDS was split into two groups, with the scores of 10 or above being the group considered at risk for prenatal depression, and below 10 indicating little evidence of depressive symptoms. The cytokines were measured at each pregnancy visit and were highly positively skewed. The only cytokines that could be log transformed to achieve normal distributions were IFN-γ, IL-10, and TNF- α. The other cytokines were not analyzed due to non-normal distributions and a large number (over 30%) were undetectable. Therefore, linear mixed models with an autoregressive covariance structure were used to examine differences in log transformed values of IFN-γ, IL-10, and TNF- α by EPDS group over time with subject as a random factor. We also examined relationships of levels of all cytokines with EPDS scores at visit 3 by Mann-Whitney U analyses. Demographic comparisons and linear mixed models were run in SPSS 29.0. Repeated measures correlations were run using the rmcorr package in R.

3. Results

3.1. Demographics

Retention in the study was maintained for the great majority throughout the pregnancy, as only 50 out of 740 women dropped out. The reasons for dropout from the study were related to moving out of the area for most of these women, as agricultural workers often migrated to other parts of the country depending on available work.

Continental U.S. born women constituted 38.1% of the sample. In immigrant women (61.9%), most were born in Mexico (47.4%), followed by Puerto Rico (22.4%) and Cuba (11.8%), with the remaining countries of Columbia, Venezuela, Honduras, Guatemala, El Salvador, Peru, Costa Rico, and Brazil constituting 18.8%. The mean number of years living in the United States was 13 years. The majority (64%) of the sample chose the Spanish versions of the consent forms and psychosocial instruments, suggesting that their language of preference was likely Spanish.

Comparing the women below or above the EPDS cutoff at the initial visit, the women at risk for depression had statistically significant lower levels of education and employment. They were more likely to be single, and more likely to have been born in the continental United States. Women above the EPDS cutoff were also significantly more likely to report a history of previous preterm births and abortions and had higher scores on both the PSS and the MOS (See Table 1). If the p values for demographics are adjusted by the Holm-Bonferroni adjustment, only employment ($p = 0.008$) remained significant.

The scores on the EPDS, PSS and MOS at the first prenatal visit were compared by country of origin in the larger sample and were significantly different by EPDS score cutoffs and remained significant at adjustment. First trimester EPDS means were significantly higher in women born in the continental United States compared to foreign-born ($t = 3.1$, $df = 561$) $p < 0.002$). The PSS mean scores were also higher in the U.S. born compared to foreign born ($t = 3.0$, $df = 560$, $p = 0.002$). The MOS average scores indicating total social support were higher for the U.S. born compared to the foreign-born ($t = 3.5$, $df = 561$, $p < 0.001$). U.S. born Hispanic pregnant women at their first prenatal visit thus had better social support, but greater stress and depression than foreign born Hispanic pregnant women.

In the longitudinal cohort, the EPDS mean scores ($F(3,228) = 4.43$, $p = 0.005$) and the PSS mean scores ($F(3,329) = 2.99$, $p = 0.03$) declined significantly over the course of pregnancy. Fig. 1 shows the pattern of EPDS, PSS and MOS scores in the longitudinal cohort over time. The percentage of scores of 10 or greater on the EPDS was 18.6% at the initial visit and remained high in the prospective participant sample at visit 2 (19.4%) then declined to 13.9% at visit 3 and 8.2% at the last pregnancy visit. PSS scores also were highest at the initial visit 12.1 ± 0.29 and declined to 10.3 ± 0.60 at the last visit. MOS scores did not vary across pregnancy.

At the initial visit, EPDS and PSS scores were highly correlated ($r = 0.64$, $p < 0.001$) and EPDS and MOS scores were significantly inversely correlated ($rho = -0.40$, $p < 0.001$). Number of years living in the United States for immigrant women was positively correlated with PSS scores at initial visit ($r = 0.20$, $p = 0.02$), but was not correlated with EPDS scores ($r = 0.09$, $p = 0.3$) or MOS scores ($rho = 0.15$, $p = 0.08$).

3.2. Health and adverse pregnancy outcomes

In the large, screened sample we examined whether EPDS scores at the initial visit were associated with later adverse pregnancy outcomes (miscarriage, preterm birth, small or large for gestational age infants, gestational diabetes mellitus, hypertension, preeclampsia, labor complications such as hemorrhage.anemia, other mental health disorders). There were no relationships between the EPDS cut scores and the

Table 1
Overall sample demographics measured at initial visit 1 by t-tests or Chi Square analysis; Values are Means or Frequencies, and Standard Errors of the Means.

	EPDS <10	EPDS 10 or >	Significance	Holm-Bonferonii Adjusted Significance*
Variable (Mean or Percentage ± Standard error of the Mean)				
Age	28.84 ± 0.29	28.34 ± 0.61	NS	NS
BMI	30.7 ± 0.33	31.03 ± 0.77	NS	NS
Total number of children	1.61 ± 0.064	1.70 ± 0.15		
Number of people, living in the home	3.92 ± 0.08	4.03 ± 0.15	NS	NS
Number of full term pregnancies	1.38 ± 0.06	1.70 ± 0.15	NS	NS
Number of abortions	0.14	0. 31	p = 0.02	NS
Percent of births that were preterm	13.9%	26.1%	p = 0.01	NS
Infant gender	48.5% male, 51.5% female	53.8% male 46.25 female	NS	NS
Ethnicity			p = 0.03	NS
Hispanic white	89.7%	85.2%		
Hispanic Black	3.3%	4.5%		
Other Non White Hispanic	5.1%	9.1 %		
Unknown	1.8%	1.1%		
Educational (Graduate)			p = 0.03	NS
Grammar school	2.2%	4.5%		
Middle school	19.4 %	11.4%		
High school	60.0%	73.9%		
College	15.0%	10.2%		
Post-Graduate	3.3%	0.0%		
Household Income			NS	NS
<$4999	18.9%	25.6.4%		
$5000-$14,99	20.5%	23.3%		
$15,000-$24,999	29.7%	27.9%		
$25,000-$39,999	21.5%	15.1%		
$40,000-$69,999	8.7%	8.1%		
>$70,000	0.7%	0.0%		
Marital status			p = 0.05	NS
Single	60.0%	70.5%		
Married	36.6%	23.9%		
Separated/ Divorced	3.3%	5.7%		
Employment			p = 0.002	p = 0.008
Part time	17.3%	8.0%		
Full time	30.8%	19.5%		
Unemployed	51.9%	72.4%		
Country of Birth			p = 0.02	NS
Continental United States	78.6%	21.4%		
All Other countries	86.3%	13.5%		
PSS mean	10.56 ± 0.27	20.23 ±0 .58	p < 0.001	p < 0.001
MOS mean	83.99 ± 0.70	69.81 ± 1.99	p < 0.001	p < 0.001
EPDS mean	3.30 ±0 .0.12	13.85 ±0 .0.37	P < 0.001	P < 0.001

adverse health outcomes in the current pregnancy except for report of "other mental health diagnoses", which was more frequent in women above the EPDS cutoff (24% compared to 9.2%) ($\chi^2 = 11.99$, df = 1, p < 0.001). We also found that women at risk of depression had significantly more abortions and premature births in their health histories. We divided the sample by the U.S. born vs foreign born and observed that a higher percentage of U.S. born women were in the higher depression group. We did not find any difference in relationships of EPDS with adverse disorders and outcomes by country of birth.

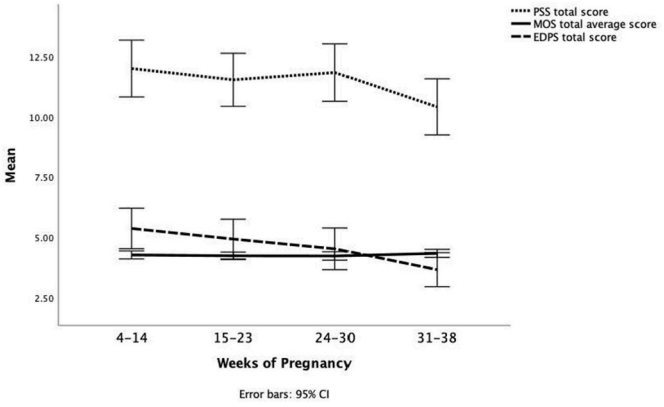

Fig. 1. The PSS and EPDS scores across pregnancy show a gradual decline, while the MOS score remains stable.

3.3. Immune differences

Fig. 2 depicts all plasma cytokines across pregnancy. Plasma cytokine levels were positively skewed and there were many levels below the limit of detection (LOD). Common logarithm transformation normalized IFN-γ, TNF-α and IL10. Linear mixed models were employed to explore relationships between the EPDS over time through pregnancy for these three cytokines. TNF-α was significantly higher across pregnancy in women with EPDS scores of 10 or greater (F (1,352) = 4.82, p = 0.03) (Fig. 3).

Neither IFN- γ (F (1,379) = 1.28, p = 0.26) nor IL-10 (F (1,380) = 0.747, p = 0.39) differed significantly by EPDS cut scores (Figs. 4 and 5). Plasma cytokine levels also did not differ significantly across pregnancy by ethnicity.

The trajectories of most cytokines over time in women with risk for depression generally showed peaks at mid-pregnancy, and there were significant differences in cytokines and at this time of gestation. A Mann-Whitney *U* test was performed to evaluate whether cytokines at 24–30 weeks differed by EPDS scores. IL-10 (z = [−2.4], p = [0.015] was significantly lower in the higher EPDS cut scores while IL-12 (z = [−2.38], p = [0.019], IL-2 (z = [−2.6], p = [0.009] and TNF-α [z = −2.64], p = 0.008] were significantly higher and IL-17 (z = [−1.9], p = [0.05] marginally higher in the higher EPDS cut scores.

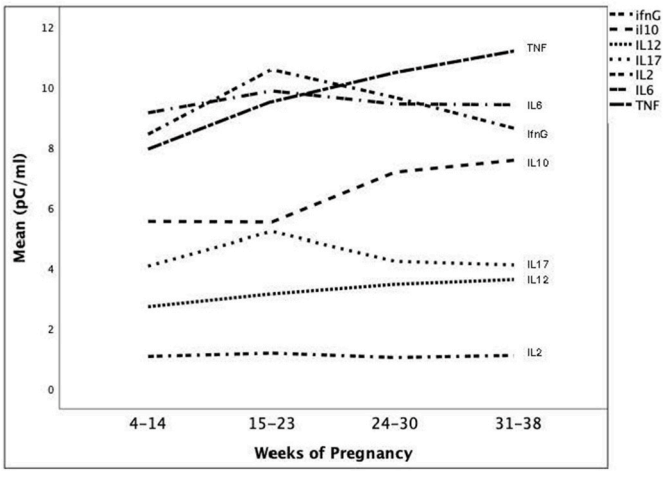

Fig. 2. Plasma cytokines across pregnancy have differing trajectories, with TNF rising across pregnancy, and several cytokines peaking at mid pregnancy.

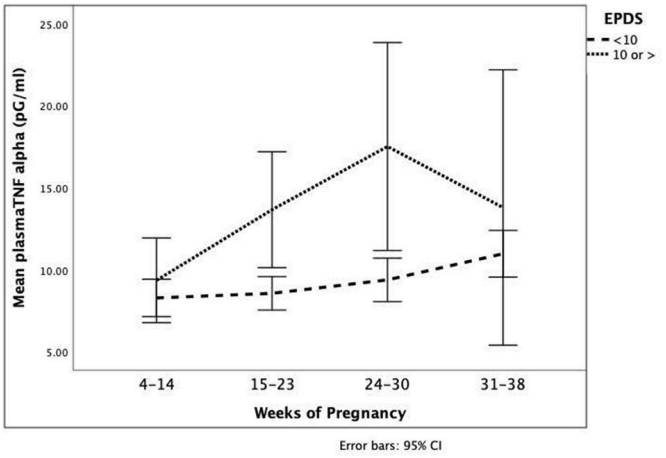

Fig. 3. TNF alpha is significantly higher in depressed women across pregnancy.

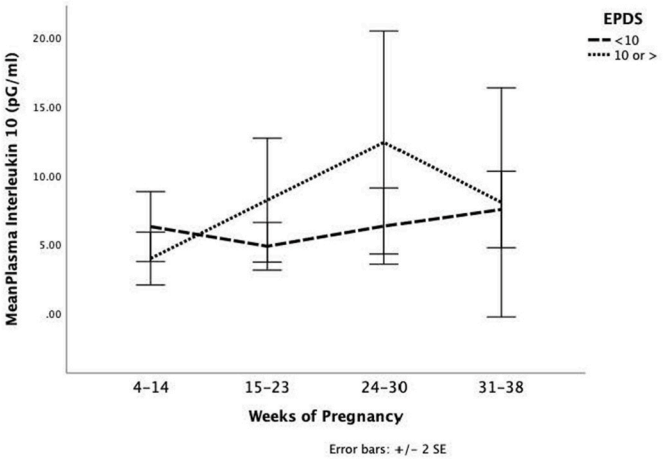

Fig. 4. IL10 trajectory shows a non significant increase in depressed women across pregnancy.

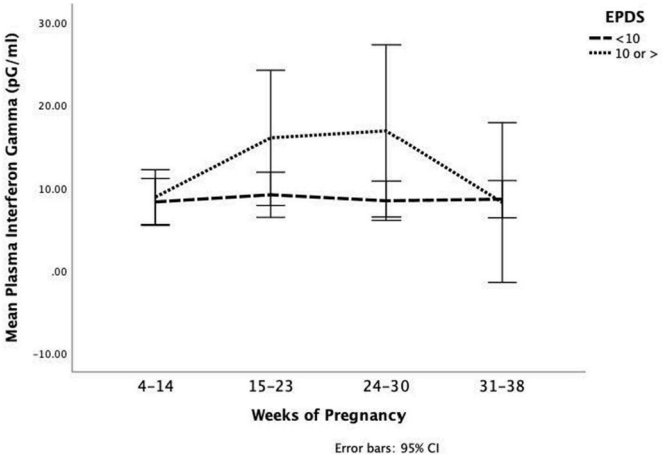

Fig. 5. Interferon gamma shows a nonsignificant increase in depressed women across pregnancy.

4. Discussion

4.11 In response to research question 1, we found that 1) depression mean scores were generally low, 2) certain socioeconomic factors increased frequency of prenatal depression, 2) depression scores declined over the course of pregnancy, 3) Hispanic women born in the United States had higher depression and stress scores than immigrant women, but better social support, and 4) there were few adverse pregnancy outcomes in women with higher scores on the EPDS.

The EPDS mean scores in our sample were low, but we had a nearly 19% incidence of depression risk based on EPDS scores in the early weeks of pregnancy (Fig. 1). Others have reported higher levels of prenatal depression in the second and third trimester (Okagbue et al., 2019), but we found that mean EPDS scores dropped across pregnancy. The higher early scores may be related to pregnancy hormones, economic worries, or unanticipated or unwanted pregnancy (Lundsberg et al., 2020; Wenzel et al., 2021). U.S. born Hispanic women had higher mean prenatal depression scores and were more likely to have EPDS scores of 10 or greater than foreign-born women. This relationship was also true for perceived stress, but social support was better in the U.S. born compared to foreign-born women. The sample had disparities in education, income, employment, marital status, and country of birth. Women with depression scores above the EPDS cutoff were more likely to have less education and income and were more likely to be unmarried (Table 1). They had increased numbers of previous preterm pregnancies and more abortions. Surprisingly, the high and low groups on the EPDS did not differ on individual disorders and adverse outcomes during pregnancy, other than an increased incidence of mental health disorders and past histories of abortions and premature births in the higher EPDS group. Hispanic identity may protect against some adverse pregnancy events (Seage et al., 2022), and our lack of associations between depression scores and many adverse pregnancy outcomes corroborates this. Considering the likely stressors and difficulties Hispanic women, especially immigrant women, have suffered, their resiliency is potentially an important factor that buffers the depression-adverse outcomes relationships (Montoya-Williams et al., 2021).

4.12 In response to research question 2, we did discover immune differences in that TNF-α was higher across pregnancy and several inflammatory cytokines were higher and an anti-inflammatory cytokine lower at midpregnancy in depressed women (Figs. 2–5) These differences could not be explained by ethnicity as cytokines did not differ across pregnancy by country of origin. Cytokines are messenger molecules secreted by immune cells which have multiple effects on other cell types and on effectiveness of immune responses. However, many cytokines in healthy individuals are at extremely low levels in the plasma, and by most ELISA assays are essentially undetectable (Wu et al., 2017). This was true for the current sample for all the cytokines except TNF-α, which had no undetectable values, and which was significantly higher in those with EPDS scores of 10 or greater. TNF-α is considered a Th-1 proinflammatory cytokine with many functions in both normal and inflammatory conditions. TNF-α is purported to increase across pregnancy and postpartum (Christian and Porter, 2014), and we observed this as well. High levels of this proinflammatory cytokine may be associated with adverse pregnancy outcomes (Peraçoli et al., 2007). In pregnant women with inflammatory diseases the exposure of the trophoblast to high levels of circulating TNF-α could be potentially damaging to the placenta and the conceptus, and anti-inflammatory mechanisms appear to respond to TNF-α exposure through release of protective cytokines (Romanowska-Próchnicka et al., 2021). TNF-α along with other proinflammatory biomarkers is also known to be associated with major (non-prenatal) depression (Nobis et al., 2020). The role of TNF-α in depression pathophysiology may be related to regulation of serotonergic neurotransmission or through activation of the indoleamine-2,3- dioxygenase enzyme which steals tryptophan from serotonin synthesis through the kynurenine pathway (Yao et al., 2020). A recent systematic review (van Zundert et al., 2022) identified several studies, including one by our team (Groer et al., 2018) which found prenatal depression to be associated with lower tryptophan levels. This may indirectly be related to high levels of inflammatory cytokines such as IFN-γ, IL-6 and TNF-α.

A few other studies have shown relationships between prenatal depression and immunity. In a sample of 120 Thai women, several clusters of cytokines, representing separate immune profiles, were associated with prenatal depression (Maes et al., 2023). In a U.S. study of 114 pregnant women measured at each trimester, IL-1β and IL-6 levels were predictive of third trimester depression (Sha et al., 2022).

The trajectories show significant elevations of one inflammatory cytokine, TNF-α, across pregnancy and elevations in 4 other inflammatory cytokines and decreases in one anti-inflammatory cytokine (IL-10) at 24–30 weeks gestational age in women with EPDS scores of 10 or above. This phase in pregnancy for healthy women is usually a time of immune quiescence preceding the later pregnancy responses in preparation for labor and birth. In mid-pregnancy successful implantation and fetal organogenesis is completed, so fetal growth is the major hallmark of mid-pregnancy. Stress and depression during pregnancy may increase inflammation which is known to affect fetal growth (White and Yates, 2023; Kaya et al., 2023). We did not see this relationship in the current study, although we did see a significantly increased frequency of *previous preterm* births in mothers at current risk for depression.

The significance of elevated TNF-α and other inflammatory cytokines in depressed Hispanic pregnant women is not immediately clear, as it does not seem to be related to current pregnancy events and outcomes that were measured. There may be effects of this inflammation on other variables not measured in the study, or the actual circulating cytokine levels may not be physiologically significant.

The well-known epidemiological advantage for prenatal outcomes in people of Hispanic ethnicity is believed to be true for recently arrived foreign-born Hispanic women in the United States and for certain nationalities and subgroups (Montoya-Williams et al., 2021). The lack of relationships between depression scores and many adverse pregnancy outcomes is surprising and may reflect, to some degree, the Hispanic paradox that Hispanic women have better health outcomes than other similarly marginalized and economically disadvantaged groups. The protective effect of ethnicity may have genetic, epigenetic and immune roots as well as environmental influences (Özdemir and Dotto, 2017). It is also possible that depressed immigrant women reporting previous preterm births may have been deprived of routine medical care during previous pregnancies and births in their countries of origin. Access to health care in Tampa, Florida was available to all the low-income pregnant women, but this was likely to not be common in the past for recent immigrants and even true for U.S. born, marginalized, poor Hispanic women. The general absence of relationships of adverse health outcomes with depression may be partially biased by access to the excellent health care being offered in the clinics. The care currently available to them in the Tampa clinics was likely superior to their previous experiences and decreased the risks of adverse outcomes. For example, pregnant women with anxiety or depression were referred to social services or to other mental health providers when signs and symptoms were observed during their clinic visits. Women were routinely tested for GDM and treated appropriately. However, we did not study outcomes or relationships in a population without adequate access to pregnancy health care, which is a limitation of the study.

The current study has the advantages of prospective measurements during pregnancy, a sample of single ethnicity, and comparisons of the longitudinal trajectories of measurable cytokines in women with and without risk for depression as determined by EPDS scores. The common Hispanic ethnicity makes this study unique, but these women did not come from monolithic cultures, and bring multiple cultural influences and attitudes with them that are likely important to their pregnancies and motherhoods.

4.1. Limitations

The sample size for the longitudinal study visits was too small to discern more subtle effects of depression trajectory effects on pregnancy outcomes and adverse events. The EPDS is not a diagnostic instrument, and the lack of association of higher EPDS scores with adverse pregnancy outcomes may be related to transient mood disturbances rather than true major prenatal depression. Further studies would be improved using an acculturation measure, high sensitivity cytokine assays, and increased sample sizes to reflect multiple, different Hispanic birthplaces and cultures.

CRediT authorship contribution statement

Maureen E. Groer: Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Kelley Baumgartel:** Writing – review & editing, Investigation, Conceptualization. **Cary Springer:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Tina Mutka:** Writing – review & editing, Methodology, Data curation. **Teodor T. Postolache:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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