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Roles of Inflammation and Depression in the Development of Gestational Diabetes

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Abstract

Inflammation, the body's response to harmful external agents, has long been found to be associated with depressive symptoms. The relationship between inflammation and depression is well established in the general population of people with depression, but is less so among perinatal women. Depression in the perinatal period is a common disorder, however available data do not indicate that there is a specific inflammatory picture associated with perinatal depression. We suggest that perinatal depression may be a heterogeneous construct, and that inflammation may be relevant to it in the context of other inflammatory morbidities of pregnancy. In this review we explore the available support for the hypothesis that inflammation associated with depression can represent a precipitating insult for the development of gestational diabetes, a known inflammatory morbidity of pregnancy.

Keywords

Inflammation; gestational diabetes; perinatal depression; postpartum depression; cytokine; insulin

Introduction

Inflammation is the body's physiological response to harmful external agents. Depression is a clinically heterogeneous mental disorder that can also have far-reaching negative effects on physical health[1]. Despite a lack of apparent superficial similarity between these phenomena, the past two decades of research have established far-reaching connections between inflammatory pathophysiological states and the manifestations of clinical depression. The mechanisms and directions of this relationship are still under study, and many open questions remain.

Inflammation is a broad term that can cover a variety of physiological states with distinct expression profiles of the many mediators involved in proinflammatory responses. Likewise, depression is a heterogeneous disorder that may represent a final common pathway for cumulative insults at the genetic, psychosocial, endocrinological, and neurochemical

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levels[2,3]. It is possible that distinct subtypes of depression may be associated with particular inflammatory profiles, which could explain some of the conflicting or negative data obtained by some researchers in the field.

Perinatal depression is a subtype of depression that is marked by onset during pregnancy or the postpartum period. It has been suggested that perinatal depression may represent an inflammatory morbidity of pregnancy[4,5]. On the other hand, evidence for a unique profile of inflammatory markers in pregnancy remains mixed. One possible explanation for the heterogeneity in the literature could be hidden heterogeneity in the patient population, such that different subpopulations of perinatal women with depression may have distinct inflammatory profiles, potentially corresponding to other, comorbid inflammatory states. Gestational diabetes, which has itself been associated with a unique profile of elevated inflammatory markers, may be one such comorbidity.

In this review we will discuss the hypothesis that women with gestational diabetes represent a distinct subpopulation whose specific inflammatory profile may have unique associations with depressed mood that are not observed in the larger population of perinatal women.

Depression and inflammation in the general population

As several thorough reviews on this topic are available[6–8], we will offer only a brief summary here. As a broad overview, the model asserts that depression is associated with dysfunctional signaling through the glucocorticoid receptor. This disrupts the delicate negative feedback system of the hypothalamic-pituitary-adrenal axis (HPA), resulting in HPA hyperactivity[6]. Proinflammatory cytokines promote this state of glucocorticoid resistance in part via direct effects on the glucocorticoid receptor, impairing its translocation to the nucleus and thus preventing glucocorticoid-induced gene transcription[9]. Ultimately this leads to unchecked pituitary stimulation and excess release of cortisol from the adrenal cortex[10]. Chronically elevated cortisol can again perpetuate the development of glucocorticoid resistance. This impairs the normal downregulatory effect of cortisol on the inflammatory response[11], thus creating a mutually reinforcing feedback loop of increased inflammation and increased glucocorticoid resistance. (See Figure 1 for diagram of relationships between depression, inflammation, and metabolic impairment.)

The molecular inflammatory signature most reliably associated with depression in the general population involves elevation of C-reactive protein (CRP), tumor necrosis factor alpha (TNFα), and interleukin-6 (IL6), and possibly depression of transforming growth factor beta (TGFβ)[8,12,13]. TNFα and IL6 are proinflammatory cytokines that are released in the acute stress response, and act directly on hypothalamic and pituitary cells to trigger the cortisol response pathway[14]. TNFα directly antagonizes the actions of insulin by blocking the tyrosine phosphorylation of the insulin receptor[15]. CRP, which is under the regulatory control of IL6, is a component of the acute stress response that identifies necrosed or pathogenic cells for destruction[16]. TGFβ comprises a superfamily of signaling molecules that stimulate gene expression in a wide variety of contexts[17]. TGFβ is a master regulator of adaptive immunity, suppressing inflammatory responses in multiple ways, including direct

inhibition of Th1 and Th2 responses, upregulation of Tregs, inhibition of effector T cell function, and inhibition of B cell proliferation[17].

Metabolic impairment is also strongly and bidirectionally associated with depression[18], a relationship which reflects the diabetogenic effect of chronic glucocorticoid excess[13]. Evidence for a causal relationship can be adduced from studies demonstrating a positive benefit of insulin-sensitizing agents on mood[19,20], as well as for positive effects of improved mood on metabolic control[21,22].

Alterations in the expression of adipokines, inflammatory mediators associated with metabolic function, have also been documented among depressed individuals. Adiponectin, an anti-inflammatory cytokine, is associated with enhanced phosphorylation of the insulin receptor[23], and exists in negative feedback balance with TNFα[24]. Adiponectin has been found by many groups to be lowered among depressed individuals[25–27], although negative results exist also[28,29], and recent meta-analyses have suggested the effect may be restricted to certain populations[30] or significantly modified by other biometric factors[31]. While effective treatment of depression has not been definitively linked with recovery of serum adiponectin levels[32], exogenous administration of adiponectin has been found to have antidepressant-like benefits in animal models[33]. Leptin, a negative feedback regulator of fat tissue, is reliably reduced in chronic stress levels[32], although any association with depression may be complexly moderated by other factors such as body weight, metabolic function[34], and depression subtype[35]. To date, other adipokines such as chemerin or vaspin have not been studied for potential associations with depression.

In addition to the evidence that depressive states and inflammatory states co-occur, studies of pharmacotherapy provide evidence for a bidirectional causal connection between inflammatory profiles and depressive symptoms. Antidepressant treatment is associated with reductions in the expression of the proinflammatory cytokines IL-10, TNFα, and CCL2[36]. Conversely, antidepressant effects of anti-inflammatory medications have also been demonstrated[37]. Thus, the association between depressive and inflammatory symptoms appears to be integrated and bidirectional.

It has been argued that the links between depression and inflammatory responses are a key reason why alleles conferring risk for depression have been maintained in the population[38]. This model posits that depressive symptoms are an inextricable facet of physiological responses to infection that have been selected because they reduce infectious mortality. Under this hypothesis, biological and behavioral manifestations of major depression such as social withdrawal, anorexia, hypervigilance, elevated body temperature and hypoferremia all have specific functional roles in host defense against pathogens. This model would explain the observed functional link between depressive symptoms and inflammatory states, and also has interesting implications for the study of depression in the perinatal period, a time in which immune function is reoriented in complex and temporally variable ways.

Depression and inflammation in the perinatal period

Pregnancy requires the immune system to balance the requirement for continued defense against pathogens with the need for maternal tolerance of the immunologically foreign fetus[39]. Levels of pro- and anti-inflammatory cytokines differ from the nonpregnant baseline and also vary in a predictable pattern over the course of the pregnancy. Thus, studies of depression and inflammation in the nonpregnant state do not yield information that can be applied to pregnant women, because the immunological baseline in pregnancy is distinct from that in non-perinatal women, and also because it varies over the course of the pregnancy, creating distinct functional phases as required by the differing needs of the embryo and fetus over the course of gestation.

Alterations to immune function in healthy pregnancy

Healthy pregnancy requires that maintenance of immune function be balanced with the requirement for fetal tolerance. During normal pregnancy, an expanded population of regulatory T cells (Treg, CD4+ CD25+) arises to orchestrate immune responses, dampen immune reactions and support fetal tolerance[40–42]. The balance of T helper cells (CD4+) is globally shifted from a proinflammatory Th1 phenotype to an anti-inflammatory Th2 phenotype[43]. Thus, in concert with the increases in cortisol that are observed over the course of normal pregnancy[44], autoimmune reactions are under tighter control and inflammatory responses are reduced.

Mor and colleagues[39] have further divided pregnancy into three immunological phases with distinct inflammatory profiles: an early, proinflammatory phase which supports implantation and placentation[45], a mid-pregnancy anti-inflammatory phase that supports rapid fetal growth and development, and an acute return to a more proinflammatory balance to facilitate parturition[46], with a gradual return to nonpregnant immune status over the postpartum period. Periods of increased inflammatory activity, at the beginning of pregnancy and around the time of parturition and the early postpartum, tend to coincide with lower maternal well-being. Conversely, maternal well-being is generally highest mid-pregnancy, corresponding to a time of anti-inflammatory activity and dampening of immune responses. This offers an interesting parallel to the observations that depressive behaviors are linked with proinflammatory responses, and in fact function to promote effective defense against pathogens[38].

The observed changes in circulating inflammatory markers during pregnancy also reflect these functional shifts. Several different patterns have been observed. One common pattern is a monotonic increase over the course of the pregnancy, with a maximum observed around delivery. This pattern has been observed for both TNFα, a pro-inflammatory, Th1-associated cytokine, and IL-6, a Th2-associated cytokine with both pro-and anti-inflammatory properties[47–49]. A similar pattern has been observed for the counter-regulatory receptor molecules TNF RII and IL-1 Ra, which promote the expansion of Tregs and dampen inflammatory responses[50]. A complementary pattern is monotonic reduction over the pregnancy. The inflammatory acute-phase reactant CRP follows this pattern[49,50], albeit with an acute peak in the first 1 to 3 days after delivery[51]. Other patterns include a nadir in the second trimester with a maximum around delivery, as observed for the pro-inflammatory,

neutrophil-recruiting cytokine IL-8[49,52] , and the Th2-promoting cytokine MCP-1[50,53]. The adipokine chemerin, a proinflammatory chemoattractant that recruits immune cells to sites of injury, also rises over the course of pregnancy, while the anti-inflammatory adipokine adiponectin does not show obvious changes throughout most of the pregnancy[54] but exhibits a sharp rise in the postpartum period[55]. (See Figure 2 for a schematic diagram of the trajectories of selected pro- and anti-inflammatory cytokines over the course of pregnancy and the postpartum period.)

Thus, cytokine expression in pregnancy follows complex temporal patterns that support the distinct requirements of each phase of pregnancy, delivery, and the puerperium, and any investigation of changes in immune function must be assessed against this dynamic background.

Changes in cytokine expression in perinatal depression

The available studies of changes in cytokine expression with perinatal depression have yielded a complicated mixture of results (Table 1).

A number of studies have addressed those inflammatory mediators that had previously been associated with depression in the general population, including CRP, TNFα, IL-1, and IL-6[56]. However, results from women in pregnancy and the postpartum period have been less clear-cut than those in the general population of people with depression.

Albacar and colleagues[57] found no difference in CRP concentrations between 87 women with and 966 without depression at 8 weeks postpartum. Cassidy-Bushrow and colleagues[58] similarly did not find any association between CRP concentrations and depressive symptoms in a sample of 187 pregnant women who were between 13–28 weeks gestation. Of two smaller studies, one with an N of 27[59] found an increase in CRP with depressive symptoms at both 35–38 weeks gestation and at 1–5 days postpartum, though not at 5–6 weeks postpartum; while another with an N of 31[60] found no association of CRP with depressive symptoms, either at 26+ weeks gestation or at 12 weeks postpartum. Given the disparate timeframes within which these studies were conducted, it is difficult to draw any solid conclusions; however taken together they suggest that CRP elevation is not a consistent feature of perinatal depression.

A larger number of studies have examined IL-6 concentrations with respect to perinatal depression, though again with a mixed set of results. Several available studies did produce an association of IL-6 concentration with depressive symptoms or with negative affect, including Maes et al. (N=113, postpartum)[61], Christian et al. (N=60, mean 15 weeks gestation)[62], Cassidy-Bushrow et al. (N=187, 13–28 weeks gestation)[58], Boufidou et al. (N=33, postpartum, observed in CSF but not serum)[63], and Fransson et al. (at delivery, observed only for preterm group, N=27)[64]. However the majority of studies, including most of the larger ones, found no association (Groer et al., 4–6 weeks postpartum, N=200[65]; Blackmore et al., 18 and 32 weeks gestation[66], N=145; Okun et al., postpartum, N=33[67]; Skalkidou et al., at delivery, N=347[68]; Corwin et al., 3rd trimester and multiple postpartum timepoints, N = 152[69]; Simpson et al., 26+ weeks gestation and 12 weeks postpartum, N=31[60]; Shelton et al., 16–26 weeks gestation, N=105[70]). Simpson et al. (N=31)[60] found

that lower IL-6 in pregnancy was predictive of postpartum but not concurrent depressive symptoms. Taken together, these studies do not suggest any consistent association of IL-6 concentration with depressive symptoms, either during pregnancy or the postpartum period.

IL-1α and IL-1β were examined by four groups. Cassidy-Bushrow et al. (13–28 weeks gestation, N=187)[58] found a positive association of IL-1β with depressive symptoms. Shelton et al. (16–26 weeks gestation, N=105)[70] found an inverse association of IL-1β with depressive symptoms. Corwin et al. (3rd trimester and multiple postpartum timepoints, N=152)[69] found no association of IL-1β with depressive symptoms. Fransson et al. (at delivery, N=64)[64] found no association of IL-1α in cord serum with maternal depressive symptoms. (This group attempted to measure both IL-1α and IL-1β in maternal serum at delivery as well but found both below the limit of detection of their assay.)

Similarly mixed results were obtained among the seven studies that examined levels of TNFα in relation to depressive symptoms. Two studies reported a positive association (N=60, mean 15wk gestation[62]; and N=56, postpartum[63]). Two studies reported a negative association (N=105, 16–26 weeks gestation[70];and N=152, significant at all six postpartum timepoints measured[69]). Three studies reported no association (N=31, 26+ wk gestation and postpartum[60]; N=18, 13–28 weeks gestation[58]; N=145, 18 and 32 weeks gestation[66]).

Regarding adipokines in perinatal depression, lower adiponectin levels have been associated with postpartum depression by at least one group[71]; however a second group that followed women throughout pregnancy and the postpartum period did not observe this association[55]. While the first of these two studies[71] also examined leptin levels and found no concurrent relationship with postpartum depression, others have reported that reduced serum leptin after delivery predicts the later development of postpartum depression[72].

In general the heterogeneous results in the current literature suggest either that there is no reliable relationship between immune activation and perinatal depression, or that there is a complex relationship that either is variable over the course of the pregnancy, or else is affected by unmeasured factors in the available datasets, precluding the discovery of reliable associations.

Variability in immune activation over pregnancy could possibly explain the disparate results obtained by different investigators. Most of the available studies included only a single timepoint, which often covered a range of gestational ages, and thus their results may not be directly comparable to each other. However even investigators examining overlapping gestational ages have produced conflicting results, as for the opposite sign of the association between IL-1 β and depressive symptoms found by Cassidy-Bushrow et al.[58] and Shelton et al.[70], who examined populations of similar gestational age.

Unmeasured covariates are also a plausible explanation for these heterogeneous results. Obesity has been raised as one such potential interacting factor[58], especially given the complex associations of increased body weight with immune activation, trauma, depression, and diabetes; but many others are possible. External stressors and trauma histories are other factors that have been associated with increased inflammatory biomarkers, and indeed some of the studies discussed above that did not find significant associations between depressive

symptoms and cytokine markers of inflammation, did find such associations between the cytokine markers and measures of stress or trauma[66].

In general, it is likely that perinatal depression, like non-perinatal depression, is a pathophysiologically heterogeneous disorder. This is an idea that has garnered increasing support on the basis of observable clinical characteristics[73,74]: a class analysis of phenotypic heterogeneity in women with postpartum depression identified three distinct subtypes that differed in timing of onset, severity, and comorbidities[73]. Thus if there is a relationship between perinatal depressive symptoms and inflammatory status, the specific profile of inflammatory markers might differ among different subsets of women with depression. Such a mixed picture could explain the highly variable results obtained by different investigators in this area.

If this is true, one way to disentangle the picture could be to explore depressive symptoms in subsets of pregnant women with existing proinflammatory disruptions, controlling for phase of pregnancy. For example, gestational diabetes, pre-eclampsia, preterm birth, and history of early life adversity are all conditions that have been associated both with proinflammatory physiological states and with increased risk for depression in pregnancy[4]. Addressing the question of inflammatory contributions to depression in the context of women who all have a similar identified proinflammatory condition may permit the disentanglement of pathophysiologically distinct subgroups.

To explore whether such an approach could be effective, the following portion of this review will focus on the subgroup of women with gestational diabetes. We will discuss the profile of inflammatory markers associated with gestational diabetes and cover literature relevant to the nexus of gestational diabetes, inflammation, and perinatal depression.

Inflammatory Mediators: Parallels Between Gestational Diabetes and Perinatal Depression

Gestational Diabetes and Perinatal Depression

Gestational diabetes mellitus (GDM) and depression are both common disorders in pregnancy. Many cross-sectional analyses have found significant degrees of comorbidity between the two conditions, particularly when glucose tolerance is examined as a scale variable[75,76]. However, other cross-sectional studies have suggested that depression in pregnancy is associated with pre-existing diabetes rather than with diabetes of gestational onset[77,78]. Thus this observation could represent the known association between diabetes and depression in the general population, rather than any specific association of perinatal depression with GDM.

More recently, longitudinal studies examining the effects of depression prior to pregnancy or present in early pregnancy have found that it is associated with greater rates of onset of GDM[79,80]. Racial disparities may also play a role, with Hispanic populations less likely than Caucasian populations to display this association[79,81]. Conversely, the available studies examining GDM as a risk factor for postpartum depression have either not found an association[75,82] or else found that when a relationship is present, it is explained by

adjustment for medical comorbidities[83,84]. Gestational weight gain and Caesarean delivery, both complications of GDM, were particularly strongly associated with postpartum depressive symptoms[83], suggesting that increases in body weight may be an important mediator in those cases where GDM does predate depressive symptoms.

Taken as a whole, there is somewhat more evidence for a forward causation, where pre-existing depression predisposes women to develop GDM, rather than the reverse. In those cases where GDM does precede depression, excessive maternal weight gain and Caesarean delivery may be important mediating factors.

This suggests that, if inflammatory processes are indeed involved in this cascade, the mechanism could be such that the early development of depressed mood, in concert with a proinflammatory physiological state , contributes to impaired insulin secretion and leads to gestational diabetes.

Inflammatory Activity in Gestational Diabetes

Reductions in the sensitivity to insulin are a feature of healthy pregnancy[85]. Unlike general adult-onset diabetes, which is associated initially with increases in peripheral resistance to insulin, GDM is associated with a failure of insulin secretion to compensate for this reduced sensitivity, resulting in impaired ability to metabolize ingested sugars[85].

GDM is accompanied by a disruption to the normal pregnancy balance of pro- and anti-inflammatory mediators[86,87]. T cell subsets expressing markers of activation are increased in women with GDM compared to healthy controls, while T cells expressing CTLA-4, a downregulator of immune response that is constitutively expressed in Tregs, are reduced[88,89]. Shifts in subpopulations of Tregs suggest a reduction in the suppressive capacity of the Treg pool in GDM[90]. These findings indicate a deficiency in the processes that downregulate immune activation in order to support maternal-fetal tolerance. Conversely however, the Toll-like receptors TLR2 and TLR4, which promote activation of inflammatory mediators, are increased in peripheral blood mononuclear cells of women with GDM[91,92].

Some of the inflammatory mediators implicated in depression among the general population are also elevated in women with GDM. TNFα is perhaps the most extensively studied cytokine in this context, with most studies finding a positive association with GDM[93–96, and for reviews see 86,87]. While some others have reported no changes in TNFα with GDM[91,97,98], overall the literature suggests a fairly reliable association of elevations in TNFα with GDM[87]. CRP elevation in GDM is a consistent finding also[98–102]. IL-6 has also been found elevated in GDM by a number of investigators[97,99,103–106]. While some others have failed to find this association[107–109], the magnitude of the difference is not large in any case, suggesting it could be easily missed in smaller study cohorts, and it has been suggested that the negative results in some studies could be due to methodological differences[87]. TGFβ has not been as well studied in this context: one group examined plasma of women with or without GDM and detected no difference in TGFβ levels (N=28)[110], while another found elevated levels of TGFβ mRNA in the placentas of women with GDM (N=60)[111].

Another set of cytokines of particular interest in the context of both pregnancy and diabetes is the adipokines, including adiponectin, leptin, chemerin, and vaspin[112,113]

GDM is associated with lower plasma levels of adiponectin[94–97,114–116]. Interestingly, a study of mRNA expression in placenta found increases in adiponectin mRNA in placentas from women with GDM[111]. This could possibly suggest a compensatory response by the fetus to an impaired maternal metabolic environment, although the methods section of this paper does not detail whether the placental tissue obtained was of fetal or maternal origin.

Leptin is increased in GDM[96,117,118]. Vaspin has also been documented to be increased in GDM by most authors who have studied this[119–121], though a report of no association also exists[122]. Results of investigations into the association between serum chemerin and gestational diabetes have been mixed, with the majority of studies finding no effect[123–126], while two studies reported an elevation[118,127], and at least one small study described a reduction in chemerin among women with GDM[128]. Many of the above authors reported that obesity was a stronger determinant than GDM of serum chemerin.

Available evidence suggests that the increases in certain inflammatory markers predate frank GDM; for example, higher CRP[99] (Maged et al. 2014) and lower adiponectin[112,113,129,130] in early pregnancy predict the later development of GDM. This order of events supports the model suggested above, i.e. that depression is associated with an inflammatory picture that then interacts with other risk factors to increase the likelihood of developing metabolic impairment and gestational diabetes.

Comparison of Inflammatory Profiles of Gestational Diabetes and Perinatal Depression

As outlined above, there is noticeable overlap in the profiles of inflammatory markers that characterize GDM and those that characterize depression in the general population. Gestational diabetes is particularly associated with elevations in TNFα, CRP, and IL-6, as well as lower levels of adiponectin. TNFα, CRP, and IL-6 are also the markers that are most reliably elevated in studies of non-perinatal depression. Several studies have found adiponectin to be reduced in depression in the general population as well, although not as reliably as in gestational diabetes.

As discussed, a clear pattern of inflammatory markers reliably associated with perinatal depression has not emerged; nonetheless, the overlap between the inflammatory profile of GDM with that of depression more generally suggests that this could be an important area for future research. The implication that depression may precede GDM, derived from epidemiological work, is consistent with the hypothesis that depression occurs in association with a proinflammatory milieu, characterized by elevations in TNFα, IL-6, and CRP, which then precipitates impairments in insulin secretion and, ultimately, the development of GDM.

Such a hypothesis would imply that the proinflammatory milieu precedes the GDM, which is generally in agreement with the results from those studies that have used a longitudinal design to examine the time course of elevation in inflammatory markers and the onset of GDM[99,112,113,129]. This model is also supported by *in vitro* work showing that the precipitaton of an inflammatory response by introduction of a viral dsRNA analogue impairs

insulin-mediated glucose uptake in tissues cultured from pregnant women[131]. Thus, while no study has yet demonstrated a direct causal progression from depression-associated inflammation to gestational diabetes, it has been shown that depression and elevation of inflammatory markers generally precede the development of GDM.

Inflammation, Depression, and GDM: Potential Molecular Mechanisms of Cytokine Action

It is important to note that, while proinflammatory cytokine activity has been shown to contribute to glucocorticoid resistance via direct effects on the glucocorticoid receptor[9], the mechanism of GDM is not mainly related to pathological levels of insulin resistance, but rather to a failure of the appropriate compensatory insulin response to the physiological increase in insulin resistance that is present in normal pregnancy. Control of insulin sensitivity in pregnancy is mediated by factors such as estrogen, progesterone, and human placental lactogen (hPL)[132]. Thus it is not clear whether increased inflammatory activity should precipitate GDM by mechanisms analogous to those involved in its pro-diabetic action in the general population.

At least one study has addressed this concern directly: McLachlan et al.[133] explored associations between proinflammatory cytokines, insulin sensitivity, and insulin secretion in 40 pregnant women with and without GDM. This group found that TNFα levels were inversely related to insulin secretion in pregnancy, supporting the hypothesis that TNFα could indeed have a direct influence on the development of GDM. However, none of the studied factors (TNFα, adiponectin, leptin, and CRP) correlated with insulin sensitivity in pregnancy. TNFα, adiponectin, and leptin all had associations with insulin sensitivity in the same group of women when retested at 4 months postpartum. This suggests that while the mechanisms of diabetogenesis may differ from the nonpregnant to the pregnant state, TNFα may facilitate diabetogenesis in both contexts, albeit by distinct mechanisms.

As to the question of whether the observed associations are causal in nature, it has been established that impairments in insulin response can result from an inflammatory stressor, via an *in vitro* study of the effects of a viral dsRNA analogue on insulin-mediated glucose uptake in skeletal muscle cultured from pregnant women[131]. It was not clear from this work whether the inflammatory cascade mediated the relationship between the stressor and the metabolic impairment or whether these were parallel pathways. Furthermore, any potential contribution of depression to inflammation could not be examined in this model. Nonetheless, given the established bidirectional associations between inflammatory responses and depression in the general population, it is reasonable to speculate that a rise in depression-associated inflammatory factors could have metabolic effects that parallel those of the viral analogue.

Thus, existing work suggests that inflammatory pathways indeed contribute to metabolic impairment in pregnancy, and that TNFα, a factor that is reliably increased among the general population of people with depression, may be a crucial mediator in this process. While available mechanistic evidence for a link with depression is scant, epidemiological evidence suggests that depression could provide the initial inflammatory insult that predisposes to the development of GDM.

Conclusions

Activation of inflammatory pathways features in many physiological processes, both those that are healthy, including host defense as well as embryo implantation and parturition, and those that are pathological, including depression as well as inflammatory morbidities of pregnancy such as preterm birth and gestational diabetes. In many of these contexts, the adaptive and pathological facets of inflammation are two faces of the same coin, and are not readily disentangled.

While inflammation and depression in the general population are clearly related, questions remain about the relationships of these two processes in the context of pregnancy and the postpartum period, where inflammatory processes take on new and important roles that are crucial for the healthy development of the fetus and safe delivery of the newborn; and at the same time, risk for depression is increased. The small collection of studies to date that have examined inflammatory markers in pregnancy in relation to depressive symptoms have yielded disparate and inconsistent results.

We suggest that if perinatal depression has a relationship to inflammation, this relationship may be complex and could be moderated either by the specific phase of pregnancy and its corresponding inflammatory profile, or by the presence of inflammatory comorbidities such as gestational diabetes, trauma history, pre-eclampsia, or preterm birth, each of which might present a distinct profile of immune activation and, potentially, a correspondingly distinct relationship with the expression of depressive phenotypes.

Our examination of the available evidence has disclosed a general correspondence between the most commonly elevated inflammatory mediators in depression and those typically associated with gestational diabetes, including CRP, TNFα, and IL-6. Furthermore, epidemiological evidence indicates that depression and inflammation may precede gestational diabetes, suggesting a pathway where pre-existing depression is associated with a proinflammatory milieu that raises risk for metabolic impairment in pregnancy.

While these findings are intriguing, they remain circumstantial, as to date no study has explored the causal relationship between markers of inflammation and depressive symptoms specifically with respect to the development of gestational diabetes. We suggest that separating out populations of women with distinct inflammatory comorbidities may be key to disentangling the complex relationship between immune function and depressive symptoms in the perinatal period.

Recommendations for Future Study

At present, none of the available studies of inflammatory markers in perinatal depression have attempted to separate out distinct populations of women with inflammatory comorbidities. We suggest that study designs that take this into account may prove more fruitful in dissecting the contributions of inflammatory cascades to the development of depression in the perinatal period.

Thus, studies which consider women with perinatal depression *en bloc*, as most of the studies conducted to this point have done, may continue to yield inconclusive results. We suggest instead that inflammatory markers in perinatal depression should be studied with attention to both the metabolic and psychiatric context. This would permit investigators to establish whether depression severity is related to the metabolic dysfunction and inflammatory activity of GDM. Similar approaches examining women with other inflammatory morbidities of pregnancy, including pre-eclampsia, trauma history, and preterm birth, would also be exceedingly informative.

In order to establish whether depression can act as the precipitating insult for the chain of events leading from inflammation to metabolic impairment, longitudinal clinical studies would be needed. An observation that elevation of depressive symptoms and inflammatory cytokine activity in pre-pregnancy or early pregnancy is associated with the later development of GDM would offer support for the hypotheses advanced here.

From a mechanistic standpoint, studies are needed that explore whether TNFα, IL-6, and CRP can produce impairments in insulin secretion such as are present in GDM. This could be done with in vitro study designs that examine insulin secretion after exogenous application of inflammatory cytokines in cultured cells.

A clinical population that is of particular interest with respect to these questions is women with PCOS and/or diabetes who are treated with metformin during pregnancy[134]. Metformin is an effective treatment for pre-existing as well as gestational diabetes[135] and has been documented to reduce serum concentrations of inflammatory markers including CRP[136], yet to our knowledge no research examining the effect of metformin in pregnancy on maternal mental health exists. A comparison of mental health outcomes and inflammatory profiles in women using metformin as compared to insulin would be a very useful addition to the existing literature.

We hope that future research in the suggested directions will contribute to our ability to disentangle the complex relationships between inflammatory processes and psychiatric dysfunction in the perinatal period.

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Griffith OW, Chavan AR, Protopapas S, Maziarz J, Romero R, & Wagner GP (2017). Embryo implantation evolved from an ancestral inflammatory attachment reaction. Proceedings of the National Academy of Sciences, 201701129.This work provides molecular evidence that ancient inflammatory signals were repurposed to facilitate the process of embryo implantation in mammals.

Consortium PACT (2015). Heterogeneity of postpartum depression: a latent class analysis. The Lancet Psychiatry, 2(1), 59–67. [PubMed: 26359613] This study analyzes the clinical characteristics of a large number of women with postpartum depression, identifying three subtypes with distinct patterns of onset, timing, and severity.

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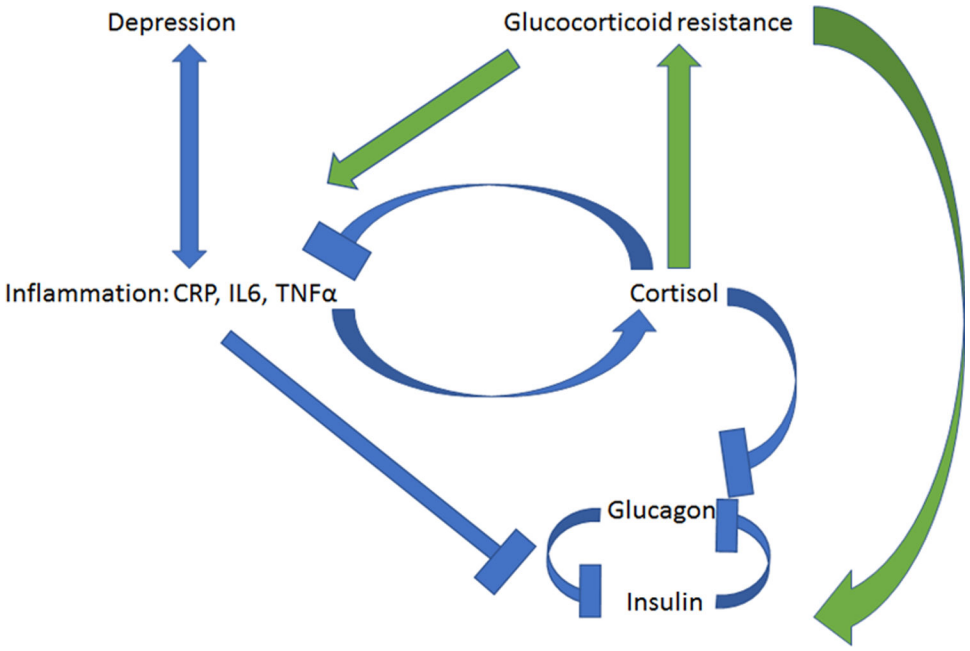

Figure 1.

Relationships between depression, inflammation, HPA axis activity, and metabolic function. Blue indicates short-term or acute effects, green indicates chronic or homeostatic effects.

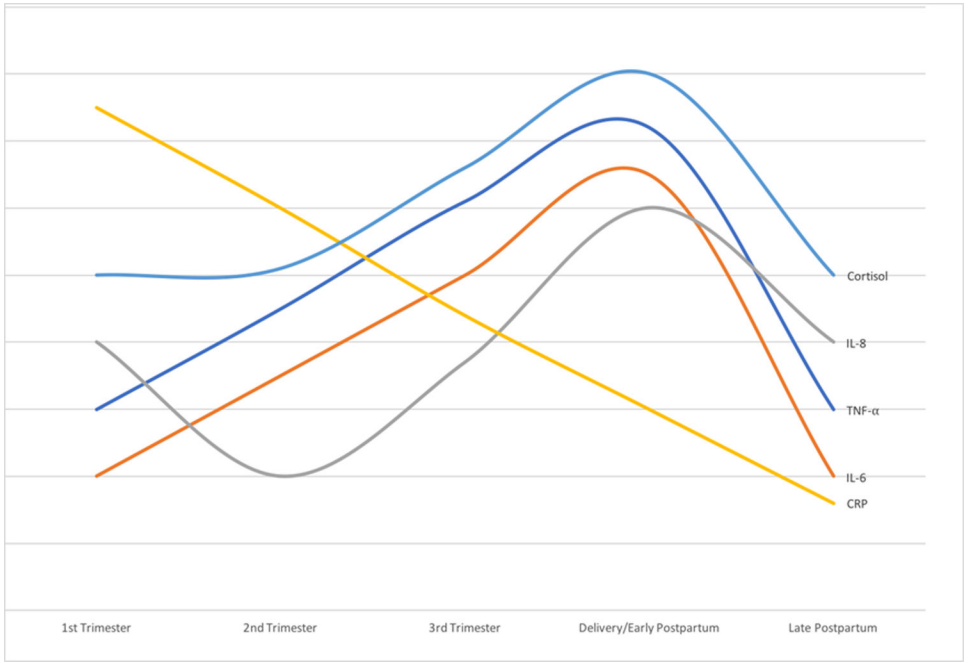

Figure 2.

Schematic diagram showing trajectories of selected cytokines over the course of pregnancy and the postpartum period[44,49,50].

Table 1.

Summary of changes in pro- and anti-inflammatory cytokine expression in perinatal depression.

Studies finding reductions in inflammatory markers in women with perinatal depression			
Citation	**Study Details**	**Markers/cytokines examined**	**Direction of association with depressive symptoms**
Simpson, W., Steiner, M., Coote, M., & Frey, B. N. (2016). Relationship between inflammatory biomarkers and depressive symptoms during late pregnancy and the early postpartum period: a longitudinal study. Revista Brasileira de Psiquiatria, 38(3), 190-196.	-N= 31 -Serum (Blood) -time points at 26 wk gestation and 12 wk postpartum	IL-6 (antepartum) IL-10 (antepartum) CRP (antepartum) TNF-α (antepartum) IL-6 (postpartum) IL-10 (postpartum) CRP (postpartum) TNF-α (postpartum)	↓ ↓ ~ ~ ~ ~ N/A ~
Shelton, M. M., Schminkey, D. L., & Groer, M. W. (2015). Relationships among prenatal depression, plasma cortisol, and inflammatory cytokines. Biological research for nursing, 17(3), 295-302.	-N= 105 -Plasma (Blood) -16-26 wk gestation	IL-1β TNF-α IL-7 IFN-γ, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, and IL-13	↓ ↓ ↓ ~

Edvinsson, Å., Brännn, E., Hellgren, C., Freyhult, E., White, R., Kamali-Moghaddam, M., ... & Skalkidou, A. (2017). Lower inflammatory markers in women with antenatal depression brings the M1/M2 balance into focus from a new direction Psychoneuroendocrinology, 80, 15-25.	-N= 159 -Plasma/Serum (Blood) -Antepartum	TRAIL, CSF1, CX3CL1, CST5, DNER, VEGFA, STAMPB, CD5, CD244, TNFRSF9, TNFB, IL10RB, CD40, IL15RA, Hgdnf, ST1A1, CCL11, ADA, CCL25, Upa, AXIN1, SLAMF1, IL17C (These markers were lower in women with antenatal depression or on SSRI treatment versus healthy controls, however, none of the markers had sufficient discriminatory power as a diagnostic marker for antenatal depression)	~
Corwin, E. J., Pajer, K., Paul, S., Lowe, N., Weber, M., & McCarthy, D. O. (2015). Bidirectional psychoneuroimmune interactions in the early postpartum period influence risk of postpartum depression Brain, behavior, and immunity, 49, 86-93.	-n= 152 (27 of them depressed) -Plasma (Blood) -32-36 wk gestation, and 1wk, 2wk, 1mo, 2mo, 3mo, 6mo postpartum	TNF-α IL-6, IL-1β , IL-8, IFN-γ,IL-10 Ratio of pro-inflammatory/anti-inflammatory cytokines	↓ ~ ~
Groer, M. W., & Davis, M. W. (2006). Cytokines, infections, stress, and dysphoric moods in breastfeeders and formula feeders. Journal of Obstetric, Gynecologic, & Neonatal Nursing, 35(5), 599-607	-n= 181 -Serum -Postpartum	-IFNγ -serum Th1/Th2	↓ ↓
Groer, M. W., & Morgan, K. (2007). Immune, health and endocrine characteristics of depressed postpartum mothers. Psychoneuroendocrinology,	-n= 200 (25 of them depressed) -Postpartum	- IFN-γ *(serum and ex vivo)* -IFN-γ/IL-10 (serum and whole	↓ ↓

32(2), 133-139		blood) -IL-6 (serum)	~
Maes, M., Ombelet, W., Libbrecht, I., Stevens, K., Kenis, G., De Jongh, R., ... & Bosmans, E. (1999). Effects of pregnancy and delivery on serum concentrations of Clara Cell Protein (CC16), an endogenous anticytokine: lower serum CC16 is related to postpartum depression. Psychiatry research, 87(2), 117-127	-n=53 -3–5 days before the anticipated date of delivery and 1 and 3 days after delivery -Serum (blood)	-CC16	↓
Studies finding increases in inflammatory markers in women with perinatal depression			
Christian LM, Franco A, Glaser R, Iams JD. Depressive symptoms are associated with elevated serum proinflammatory cytokines among pregnant women. Brain Behav. Immun. 2009 Aug; 23(6):750-4	-n= 60 -Serum (Blood) -15 ± 7.8 wk gestation	-IL-6 -TNF-α	↑ ↑
Christian, L. M., Franco, A., Iams, J. D., Sheridan, J., & Glaser, R. (2010). Depressive symptoms predict exaggerated inflammatory responses to an in vivo immune challenge among pregnant women. Brain, behavior, and immunity, 24(1), 49-53	-n= 22 -Serum (blood) -Antepartum	-MIF	↑
Cassidy-Bushrow, A. E., Peters, R. M., Johnson, D. A., & Templin, T. N. (2012). Association of depressive symptoms with inflammatory biomarkers among pregnant African-American women. Journal of reproductive immunology, 94(2), 202-209.	-n= 187 -Serum (blood) -13-28 wk gestation	IL-6 IL-10 (but only elevated in women with lower BMI, in higher BMI women the relationship was reversed)	↑ ↑

		IL-1β TNF-α CRP	↑ ~ ~
Boufidou, F., Lambrinoudaki, I., Argeitis, J., Zervas, I. M., Pliatsika, P., Leonardou, A. A., ... & Nikolaou, C. (2009). CSF and plasma cytokines at delivery and postpartum mood disturbances. Journal of affective disorders, 115(1), 287-292.	-n= 56 total (n=33 for CSF, n=56 for serum, blood) -At delivery (postpartum)	-IL-6 (CSF) -TNF-α (CSF) - TNF-α (Serum, blood) -Il-6 (Serum, blood)	↑ ↑ ↑ ~
Fransson, E., Dubicke, A., Byström, B., Ekman-Ordeberg, G., Hjelmstedt, A., & Lekander, M. (2012). Negative emotions and cytokines in maternal and cord serum at preterm birth. American Journal of Reproductive Immunology, 67(6), 506-514.	-n= term 37, preterm 27 -At delivery -Serum (blood)	*Preterm Group* Negative Affect: Maternal levels of IL-6 and cord levels of IL-6, IL-8, IL-10, IL-13, and IL-18 Depressive symptoms: maternal levels of IL-8 and cord levels of IL-18 IL-1a, IL-1b IL-2, IL-4, IL-12 p70, IL-17, IFN-γ *Term Group* IL-1a, IL-1b IL-2, IL-4, IL-6, IL-8, IL-10, IL-12 p70, IL-13, IL-17, IL-18, IFN-γ	↑ ↑ ~ ~
Kondo, N., Suda, Y., Nakao, A., Oh-Oka, K., Suzuki, K., Ishimaru, K., ... & Yamagata, Z. (2011). Maternal psychosocial factors determining the concentrations of transforming growth factor-beta in breast milk. Pediatric Allergy and Immunology, 22(8), 853-861.	-n= 29 -postpartum -Breast milk	- TGF-b2	↑

Okun, M. L., Luther, J., Prather, A. A., Perel, J. M., Wisniewski, S., & Wisner, K. L. (2011). Changes in sleep quality, but not hormones predict time to postpartum depression recurrence. Journal of affective disorders, 130(3), 378-384.	-n= 33 -postpartum -Plasma (blood)	-IL-6	~
Skalkidou, A., Sylvén, S. M., Papadopoulos, F. C., Olovsson, M., Larsson, A., & Sundström-Poromaa, I. (2009). Risk of postpartum depression in association with serum leptin and interleukin-6 levels at delivery: A nested case–control study within the UPPSAT cohort. Psychoneuroendocrinology, 34(9), 1329-1337	-n= 347 -antepartum -Serum (blood)	-IL-6	~
Studies with mixed or equivocal results			
Blackmore, E. R., Moynihan, J. A., Rubinow, D. R., Pressman, E. K., Gilchrist, M., & O'Connor, T. G. (2011). Psychiatric symptoms and proinflammatory cytokines in pregnancy. Psychosomatic medicine, 73(8), 656.	-n= 145 -antepartum -Serum (blood)	-IL-6 - TNF-α (There was only a significant effect between TNF-α and trauma, but not depression)	~ ~
Maes, M., Lin, A. H., Ombelet, W., Stevens, K., Kenis, G., De Jongh, R., ... & Bosmans, E. (2000). Immune activation in the early puerperium is related to postpartum anxiety and depressive symptoms. Psychoneuroendocrinology, 25(2), 121-137	-n=113 -3–5 days before the anticipated date of delivery and 1 and 3 days after delivery -Serum (blood)	IL-6 (lower in anxiety) IL-6R Gp130	~ ↑ (end of pregnancy and in the early puerperium) ~

		IL-1RA (Higher in anxiety) LIFR (Lower in anxiety)	~ ~
Maes, M., Ombelet, W., De Jongh, R., Kenis, G., & Bosmans, E. (2001). The inflammatory response following delivery is amplified in women who previously suffered from major depression, suggesting that major depression is accompanied by a sensitization of the inflammatory response system. Journal of affective disorders, 63(1), 85-92	-n= 66 - 3 to 5 days before the anticipated date of delivery and 1 and 3 days after delivery -Serum (blood)	IL-6 sIL-6R sgp130 sIL-1RA IL-6×sIL-6R	↑ ~ ~ ↑ ↑
Scrandis, D. A., Langenberg, P., Tonelli, L. H., Sheikh, T. M., Manogura, A. C., Alberico, L. A., ... & Boteva, K. (2008). Prepartum depressive symptoms correlate positively with C-reactive protein levels and negatively with tryptophan levels: a preliminary report. International journal of child health and human development: IJCHD, 1(2), 167	-n=27 -antepartum, early postpartum, late postpartum -Serum (blood)	CRP IL-6 TRP KYN KYN/TRP	↑ ~ ↓ ~ ~
Corwin, E. J., Pajer, K., Paul, S., Lowe, N., Weber, M., & McCarthy, D. O. (2015). Bidirectional psychoneuroimmune interactions in the early postpartum period influence risk of postpartum depression. Brain, behavior, and immunity, 49, 86-93	-n= 152 -antepartum, early postpartum, late postpartum -Plasma (blood)	IL-6 IL-1β TNF-α IL-8 IFN-γ IL-10 Cortisol	 ↓

		(overall: lower individual cytokine levels but higher pro- to anti-inflammatory ratios in women symptomatic of PPD)	↑