Putting theory into preliminary practice: neuroinflammatory models of postpartum depression

K Brogan*

Abstract
Introduction
Understanding of underlying risk, predisposing factors and effective treatments with high-safety profile for breastfeeding mothers with postpartum depression continues to evolve. As investigation into neuroinflammatory models of depression becomes more the focus of mainstream medicine, research into pathological patterns of immune adaptation in late pregnancy and postpartum has begun to emerge in the literature. Alternatives to medication are highly sought after by this patient population, and natural agents such as probiotics, melatonin and tryptophan, omega-3 fatty acids, folate, curcumin and behavioural interventions such as dietary modification, exercise, mindfulness meditation, and cranial electrical stimulation present appealing considerations. Inflammatory lifestyle factors, appropriate diagnostics and environmental modification are addressed. This article discusses neuroinflammatory models of postpartum depression.

Conclusion
Although exercise, relaxation response and targeted supplementation of the postpartum patient with anti-inflammatory nutrients (such as turmeric, probiotics, folate, omega-3s and melatonin) have not been formally studied, they hold promise for low-risk, potentially high-yield interventions of benefit to the mother and the infant.

Beyond ‘chemical imbalances’
Today’s pregnancies are not those of our ancestors. We have ever-increasing incidences of maternal and infant mortality and morbidity, particularly in America. The changes in chronic illness in our paediatric population cannot be accounted for by Mendelian genetics, and we must look to our environment for its role in adverse epigenetic effects. Today’s mother-to-be suffers from a toxic burden through everyday exposures, and there is reason to believe that these largely unstudied exposures are cumulative in their risk. Additives such as dyes and preservatives in prenatal vitamins, metals and adjuvants in vaccines1 and industrial chemical exposures through cosmetics, furniture, paints, cars, and pollution all bioaccumulate in the very top of the food chain, the foetus. These factors conspire to modulate endocrine and immune responses while simultaneously rendering the body less capable of managing and supporting metabolic processes of detoxification. This is known as oxidative stress, or the inability of the products of aerobic respiration to be effectively neutralized by endogenous antioxidant agents prior to causing damage to cellular machinery and membranes.

What are these toxins?
Environmental toxic exposures include pesticides, most notably glyphosate; industrial chemicals such as polybrominated diphenyl ether (PDBE) flame retardants, phthalates, bisphenol A (BPA); neurotoxic metals such as mercury and aluminium; and carcinogens such as dioxins. With 80,000 registered agents in the Toxic Substances Inventory, a mere 200 have been studied for human safety.

*Corresponding author
Email: drbrogan@kellybroganmd.com
New York University/Bellevue Hospital Center, 280 Madison Avenue, Suite 702, New York, NY 10016, USA

Licensee OA Publishing London 2013. Creative Commons Attribution Licence (CC-BY)

parameters. An important case series supported by the Environmental Working Group and the Red Cross examined umbilical cords, identifying 287 toxic chemicals, 217 of which are known neurotoxins. PDBE and BPA have been associated with adverse cognitive, endocrine and motor outcomes in children, and while ubiquitous, may represent a modifiable exposure in our immediate environment.

Between the years 1948 and 1971, treatment of pregnant women treated with a synthetic oestrogen, diethylstilbestrol (DES), demonstrated epigenetically driven reproductive effects two generations later, leading to its ban in 1971. Similarly, Skinner et al. have looked at germ cell inheritance of chronic disease phenotypes (tumours, kidney disease, immune dysfunction) in fourth-generation rats born of pesticide-exposed ancestors, demonstrating that these non-DNA-sequenced-related phenotypes could be passed down. This research serves to sound the alarm on understudied environmental toxins and their role in consideration of pregnancy exposures.

A recent report on the potential harm associated with the most ubiquitously applied pesticide, glyphosate, typically applied to ‘roundup-ready’ genetically modified crops (soy, corn, sugar beets etc.) discusses the potential role of this chemical in depleting tryptophan and altering gut flora functioning related to the pesticide’s bactericidal effects on gut microbiota. Alteration of microbes in gut ecology may have deleterious effects independent of the depletion of this essential amino acid. The role of healthy gut microbial balance will be discussed in the following, but the integrity of colonic enterocytes rely on healthy balance of bacteria and fungi for nutrient absorption, vitamin production and immune protection.

These exposures may be driving inflammatory responses and perturbations of the antenatal immune system in ways that deleteriously affect the foetus and put the mother at greater risk for postpartum mood pathology.

**The greatest defence compromised**

The experience of pregnancy is one that draws heavily on a woman’s native nutrient stores and involves fluctuations in hormone levels and immunologic parameters. The anabolic state of pregnancy demands a synergy of nutrients not only to nourish the growing foetus but also to support the tissues of reproduction (mammary, placental) and metabolism. Some theorise that the relative deficiencies of certain critical nutrients may make some women more vulnerable to postpartum psychiatric symptoms. A study of pregnant American women found that the majority were consuming below recommended amounts of iron, zinc, calcium, magnesium, folate and vitamins D and E and that selenium supplementation may protect against the development of postpartum depression.

In addition, elements of our modern diet, including high sugar (fructose) content and trans fats rendered from heat-labile vegetable oils, contribute to free radical production and a drive on behalf of the body, to manage these perceived sources of inflammation. Two studies have raised questions about the role of foods such as gluten and dairy in the development of postpartum depression and psychosis, finding that plasma/cerebrospinal fluid morphine-like fragments derived from casein and gluten may have an association with maternal psychopathology and, potentially, mental illness in the child.

**Inflammatory underpinnings**

Several years of preliminary work have focused on the premise that these affected women experience suppression of the hypothalamic-pituitary axis (free cortisol and corticotrophin-releasing hormone) more severely and extensively than ‘normal’ controls and that postpartum blues may represent the activation of inflammatory response system. In states of relative hypocortisolemia (or low hypothalamic activity), inflammation, infection and autoimmune are more likely. Specifically, studies have noted that macrophages are activated and TH1 cells are suppressed, suggesting that this aberrant immune response may be a significant driving force in the presentation of altered mood states.

A relatively recent discovery is the psychoneuroimmunologic bridge—the kynurenine pathway. In animal and clinical research, the kynurenine:tryptophan ratio has been used as a marker of inflammation correlated with postpartum depressive behaviours and states. Inflammatory messengers, or cytokines IL6 and TNF-alpha, have been demonstrated to be elevated in the cerebrospinal fluid of women at the time of their childbirth, who then presented with depression at 6 weeks postpartum. Similarly, elevated levels of IL-1B predicted depressive symptoms at 1 month postpartum. In the non-pregnant population, inflammatory underpinnings of depressive illness (cytokines, chemokines, reactive proteins, adhesion molecules) have been well-established, and anti-inflammatory interventions have been explored. Among other disruptive effects, these inflammatory agents induce the enzyme indoleamine 2,3-dioxygenase (IDO), which ‘steals’ tryptophan in the production of kynurenine, resulting in a net decrease of serotonin. Cortical cells appear to specifically convert kynurenine to kynurenic acid, which acts to decrease activity through acetylcholine antagonism. Meanwhile, in the amygdala, primitive impulses may go unchecked secondary to N-methyl-D-aspartate
(NMDA) receptor agonism by quinolinic acid. A brilliant review of this theory proposes that this sequence of unfortunate events may account for the intrusive violent images and impulses that often accompany postpartum mental pathology. In addition, an excellent review of the literature highlights seven studies examining postpartum depression and its association with inflammatory modulators, the best studied of which are IL1, IL6, c-reactive protein (CRP), TNF-alpha, further supporting the association between mood states and inflammation. Macrophage-driven cytokine production is an area of ongoing investigation in this population.

**Screening**

These models remain theoretical, and so are serotonergic theories of depression; hence, the consideration of individualized screening and low-risk interventions is appropriate. The monoamine hypothesis of depression and anxiety and associated pharmacologic interventions have fallen short of expected treatment responses and one reason for this may be the underlying aetiology continues largely unabated in treated patients. Assessing for individual parameters of a highly heterogeneous diagnosis serves to optimize benefit and minimize risk. Screening for the following markers is recommended to assess for drivers of inflammation:

- Homocysteine
- CRP
- Fasting insulin/glucose
- HgA1C
- Vitamin D 25 OH and 1,25
- Methylmalonic acid
- TSH, free T3, free T4 and thyroid antibodies
- Celiac panel
- Methylene tetrahydrofolate reductase (MTHFR) genetic profile.

Consideration of alternative treatment and non-medication alternatives is discussed in a review by this author; however, the following will focus on theoretical anti-inflammatory interventions.

**Looking to nature for support**

Targeted lifestyle recommendations around minimization of personal care products, home, and food-based toxins as well as a focus on whole, organic, unprocessed food may serve to protect the interests of the mother and the growing infant. It is recommended that women:

- filter their air and water
- purchase products free of known carcinogens and endocrine disruptors such as parabens, TEA, fragrance (pthalates), sodium lauryl/laureth sulphate and triclosan
- eat organic produce, pastured meat/dairy
- make their own cleaning products from household vinegar, baking soda, tea tree oil or purchase similarly simple products
- avoid eating or drinking from heated plastics
- avoid cell phone use
- avoid processed foods and sugar, consume low-mercury fish
- carefully consider the risks and benefits of any elective medical interventions.

**Probiotics**

Our most important interface between self and the environment is the gut. The vagus nerve appears to be the primary conduit between the 200 to 600 million nerve cells in our enteric or intestinal nervous system and our central nervous system. Stimulation and function of these cells is directly affected by the population of bacteria that nourish the enterocytes, promote immune tolerance and alert us of danger. While our intestinal microbiome is determined by our mode of birth delivery (c-section vs vaginal birth), whether we were breastfed and early exposures through environment and diet, it is ever modifiable through macro- and micro-nutrients, stress, and lifestyle. 

![Figure 1: Metabolism of Tryptophan Is Skewed By Stress and Inflammation](image-url)
and supplementation. In fact, clinical investigation into the beneficial effects of probiotics (lactobacillus and bifidobacterium) on mood and anxiety have suggested that probiotics may promote anti-inflammatory responses through IL-10 activation and alleviate anxiety\textsuperscript{17}.

**Melatonin and tryptophan**

An area of innovative speculation is looking at the role of melatonin as a treatment intervention in the third trimester and postpartum\textsuperscript{18}. If serotonin is compromised by inflammation or dietary insufficiency of tryptophan, melatonin will be as well. Melatonin plays a pivotal role in sleep onset and maintenance, but perhaps of equal importance, as a powerful antioxidant line of defence.

Tryptophan has been studied in the general population as an antidepressant and augmentation strategy with sleep-promoting and anxiolytic properties. One study investigated its efficacy for hormonally related pathology in luteal phase dysphoria and anxiety in early peperium have higher kynurenine:tryptophan ratios indicating tryptophan degradation secondary to inflammatory stimuli.

**Omega-3 fatty acids**

Omega-3 fatty acids come under the umbrella of essential polyunsaturated fatty acids, which refers to their dietary requirement and to their unique carbon/hydrogen structure. The best-studied representatives are docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). EPA is a relatively minor structural component of nerve cell membranes influencing fluidity but a major prostaglandin precursor, whereas DHA is a primary component of brain grey matter. Humans are assumed to be relatively inefficient at converting essential linoleic acid and alpha-linolenic acid precursors into highly unsaturated fats and eicosanoids such as the omega-6 fatty acids—dihomogammalinolenic acid (DGLA) and arachidonic acid (AA)—and the omega-3 fatty acid, EPA, which is derived primarily from fish and pastured meat. A high-carbohydrate diet and associated elevation in insulin and glucose levels may upregulate phopholipase A2, which cleaves fatty acids from phospholipids, disturbing membrane structure. Given the prevalence of refined vegetable oils in the American diet, some researchers posit that omega-6 fatty acids dominate dietary sources of omega-3s (a point of question is whether these vegetable oils in commercial foods represent trans or distorted fats when incorporated into human phospholipids). The anti-inflammatory effect of omega-3 fatty acids may be related to their interference with key inflammatory cytokines and competitive inhibition of the cyclo-oxygenase pathway, but there may also be a role in neurotrophic growth, genetic expression and neurotransmitter production and function.

Currently, the only means of assessing individual fatty acid needs is through erythrocyte analysis, and the optimal dietary omega-6:omega-3 ratio ranges from 4:1 to 1:1, depending on the source consulted. Disparity in benefit with omega-3 supplementation may relate to a lack of individual assessment for need. There is a risk that chronic oversupplementation of omega-3 from flax and/or fish oil may impair the production of omega-6 highly unsaturated fatty acids, such as gamma linolenic acid (GLA), DGLA, and AA (precursors to prostaglandin E1 [PGE1] and prostacyclin) and contribute to imbalance through competitive inhibition of desaturase enzymes\textsuperscript{20}. The effect of GLA administration can be simplisticly attributed to structural membrane support and production of eicosanoid DGLA, which serves to regulate AA (promoting its retention in the membrane) through its conversion to PGE1. At least three randomized, placebo-controlled trials of evening primrose oil (0.5–2 mg) in premenstrual syndrome suggest that GLA is an effective intervention potentially related to its potentiation of PGE1 and attenuation of prolactin sensitivity at the receptor site in the membrane\textsuperscript{21}. The importance of individual biochemical profile is an essential consideration.

Epidemiologic data suggest that prevalence of perinatal depression is inversely associated with fish consumption\textsuperscript{22} and breast milk levels of DHA\textsuperscript{23}.

In the postpartum period, there is concern for the maternal reservoir of essential nutrients having been largely depleted by the needs of growing fetus. Without appropriate repletion, these deficits may represent an underlying aetiology of postpartum depression and anxiety. Immediately following delivery, omega-3 fatty acids are lower and omega-6:omega-3 ratios higher in women who develop depressive symptoms at 6 to 10 months postpartum\textsuperscript{24}. One study demonstrated that recovery of maternal DHA levels at 32 weeks postpartum was slower in women with postpartum depressive symptoms\textsuperscript{25}, potentially reflecting reduced membrane fluidity. A prospective cohort study demonstrated that women with dietary ratios of omega-6:omega-3 fats greater than 9:1 (unclear whether adequate control for trans fat intake) had a higher incidence of postpartum depression as assessed by the Edinburgh Postnatal Depression Scale (EPDS). Given concerns over pollutants and mercury contamination of marine sources, many patients may benefit from considering a molecularly distilled, third-party-checked supplement.

**Folate**

Folate (B9) is found in leafy greens, lentils, broccoli and sunflower seeds...
and is an important cofactor in the synthesis of monoamines, reduction of homocysteine and slowing brain breakdown of tryptophan. The relationship between folate and depression has been explored in studies linking low serum levels to poor treatment response, elevated homocysteine, depression incidence and augmentation to increased likelihood of remission. There are four transformation steps required to render folic acid a biologically available form of folate that can cross the blood–brain barrier to participate in the production of neurochemicals. One of these metabolites, 5-MTHF or l-methylfolate, is required for the production of biotin, a cofactor for neurotransmitter production, and of methionine/S-adenosylmethionine from homocysteine (with B12 as a cofactor), influencing the production and function of neurotransmitters, DNA and enzymes. Recent literature has focused on the role of genetic polymorphism for MTHFR in the metabolism of folate and associations with depressive illness.

For individuals with variants in one of the two known genes, C677T and 1298C, efficiency of conversion of folate or folic acid to l-methylfolate is compromised to varying extents. Maternal MTHFR polymorphisms are associated with antenatal depression and may influence the foetal programming of serotonin transporter methylation and future functioning. A recent study in the postpartum population demonstrated benefit with regard to EPDS scores at 21 months postpartum for women with C677TT polymorphism who supplemented with folic acid during pregnancy. Bypassing this enzymatic conversion with supplementation of bioactive folate appears to be a potentially important treatment option. Thus, it is important to assess individual risk factors in terms of dietary/supplement intake in the first trimester and biomarkers for methylation.

**Turmeric**

Taking the multiple potential pathways to postpartum depression and anxiety into account—hypothalamic-pituitary-adrenal axis, dysregulated inflammatory pathways, increased oxidative stress, mitochondrial dysfunction, nutrient depletion—the multi-modal effects of curcumin, the principal cucuminoid of the Indian spice turmeric are very appealing. Although much of the data are animal-based at this point, curcumin has demonstrated anti-inflammatory modulation of cytokines, including COX-2 inhibition, and inhibition of IDO expression, neurotransmitter-supportive through monoamine oxidase (MAO) inhibition mechanisms, and protective against oxidative stress on a mitochondrial and tissue level. When used as a culinary spice or as a concentrated curcumin supplement, absorption is enhanced with pepper (Figure 2).

**Cranial electrical stimulation**

Cranial electrical stimulators are FDA-approved patient-administered devices. They are indicated for the treatment of anxiety, depression and insomnia. A low-intensity alternating current is transmitted across the skull for 20 minutes once or twice daily to promote alpha-wave activity and to modulate neurotransmitters, endorphins and cortisol.

The five meta-analyses include 67 human studies (n = 2,910) and demonstrate the efficacy of devices without report of adverse events. There are no perinatal studies of the device; however, given the relative safety of electroconvulsive treatments in the pregnant population, adverse effects are unlikely. This device may represent a first-line option for women, given that it is non-invasive with a low-side-effect profile.

**Exercise**

Perhaps the most potent health elixir, exercise is never more important than in our sedentary, technology-driven societies. It has been demonstrated to have resonant clinical benefits, such as those evidenced by a controlled trial that looked at 3 hours of weekly exercise in depressed postpartum women and found that they
improved significantly relative to controls. Perhaps one of the putative mechanisms of this improvement is the effect of exercise on inflammatory cytokines, such as IL6 and TNF-alpha. The practice of yoga has been demonstrated in the Treatment with Exercise Augmentation for Depression (TREAD) study, where depressed patients, partially treated with an antidepressant were found to have clinical improvement that correlated with decrease in THF-alpha.

Yoga and mindfulness
As was demonstrated in a pilot study looking at mindfulness-based yoga practice in an antenatally depressed population, interventions that are based on ancient practices of parasympathetic nervous system support may also present a feasible option for non-medication treatment. The practice of yoga has been demonstrated in the general and chronically ill population to have a favourable impact on cortisol, endorphins and inflammatory cytokines such as IL6 and TNF-alpha in as short a time as 10 days. A recent study examined the immediate and long-term epigenetic effects of meditation finding that within 15 minutes of relaxation response practice, genomic benefits were apparent at centres thought to be responsible for inflammatory control (downregulation of NF-KB), insulin release and mitochondrial function.

Stress and breastfeeding
It is now appreciated that science has not been able to replicate the complexity of breast milk and the myriad essential benefits it confers to an infant and baby and that formula feeding may have negative repercussions for the mother as well. An interesting perspective in addition to psychotherapy and group support.

Conclusion
Although exercise, relaxation response and targeted supplementation of postpartum patient with anti-inflammatory nutrients (such as turmeric, probiotics, folate, omega-3s and melatonin) have not been formally studied, they hold promise for low-risk, potentially high-yield interventions of benefit to the mother and the infant. Promoting immune system balance through minimization of lifestyle-related sources of inflammation (i.e. sugar, trans fats, stress, poor sleep, sedentariness, toxic chemical exposures) represents a powerful commonsense tool for health and wellness in the reproductive years and beyond. For the patient at risk for postpartum depression (based on personal, family history or sociodemographics), implementation of lifestyle modification as prophylaxis would be beneficial. In the setting of active symptoms, the patient who elects not to take psychiatric medication should be offered alternatives in addition to psychotherapy and group support.

References
10. Maes M, Verkerk R, Bonacorso S, Ombelet W, Bosmans E, Scharpé S. Depressive and anxiety symptoms in the early puerperium are related to increased degradation of tryptophan into kynurenine, a phenomenon which is related to immune activation. Life Sci. 2002 Sep 6;71(16):1837–48.


