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Preliminary communication

Breastfeeding, retinoids, and postpartum depression: A new theory

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ABSTRACT

Postpartum depression (PPD) is an international public health problem affecting at least 1 in 8 mothers. Known risk factors include: giving birth to a preterm or low birth weight infant, babies with greater symptoms of illness at age 4–6 weeks, formula feeding, younger maternal age, smoking, and fatigue. Prolonged breastfeeding is associated with a reduced risk of PPD but the mechanisms are not well understood. Interventions for PPD focusing on psychosocial risk factors have been largely unsuccessful, suggesting that the condition has a mainly biological basis. The hypothesis proposed for consideration is that breastfeeding protects against PPD by maintaining endogenous retinoids (vitamin A-related compounds) below a threshold concentration. In fact, breast milk is rich in retinoids; pregnant women accumulate retinoids in liver and breast in preparation for lactation; there is increasing evidence that retinoids in higher concentration are associated with cognitive disturbances and mood disorders, including depression and suicide; and prolonged lactation reduces maternal stores of retinoids. Consistent with this hypothesis, it is estimated that an amount of vitamin A is transferred from mother to infant during the first six months of exclusive breastfeeding equivalent to 76% of a dose known to cause acute vitamin A poisoning in an adult. Breastfeeding may thus have evolutionary-adaptive functions for both mother and infant, transferring vital nutrients to an infant unable to feed itself, yet at the same time providing a natural means of reducing potentially toxic concentrations of retinoids in the mother.

1. Introduction

Mood disorders are common in the postpartum period and form a continuum of severity. Up to 80% of postpartum women experience a mild form of depression ("maternal blues") (Workman et al., 2012) and from 10% to 15% are diagnosed with postpartum depression (PPD) (O'Hara, 2009). Postpartum psychosis occurs in 1–2 per 1000 childbirths (Spinelli, 2009). A well-established instrument for identifying women at high risk is the Edinburgh Postpartum Depression Scale (EPDS) (Cox et al., 1987; McCoy et al., 2006). Women with PPD are at risk for addictive behaviors, self-injury, intimate partner abuse (Fitelson et al., 2011), violence (Kornfeld et al., 2012), and violence against children (Chandra et al., 2002; Kauppi et al., 2008).

2. Risk factors and mechanisms

Known risk factors for PPD include: a history of depression before or during pregnancy; anxiety and higher perceived stress in pregnancy; negative life events during pregnancy; low levels of social support and low socioeconomic status; younger age; formula feeding; tobacco smoking; babies with greater symptoms of illness at 4–6 weeks postpartum; obstetric complications, and smaller birth weight infants (McCoy et al., 2006; Groër and Morgan, 2007; Milgrom et al., 2008). Mothers of preterm and low birth weight infants report rates of PPD of up to 40% (Vigod et al., 2010). Additional risk factors include postpartum anemia (Corwin et al., 2003) and fatigue (Bozoky and Corwin, 2002; Corwin et al., 2005; Corwin and Arbour, 2007).

Human studies and animal models have suggested a role for hormonal dysfunction, abnormalities in the hypothalamic–pituitary–adrenal axis, and genetic factors in perinatal mood disorders (Meltzer-Brody, 2011). A role for low levels of long-chain polyunsaturated fatty acids in PPD, in particular docosahexaenoic acid, has been proposed (Keim et al., 2012). Another suggestion is that PPD is due to perinatal stress-induced systemic inflammation (Groër and Morgan, 2007).

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3. Role of breastfeeding

Breastfeeding is a protective factor for several diseases in women, including type 2 diabetes (O'Reilly et al., 2011), breast and ovarian cancer, metabolic syndrome and myocardial infarction (Ip et al., 2009; Stuebe, 2009). Although the role of breastfeeding in PPD has been less clear, a comprehensive review of the evidence relating to breastfeeding and maternal health outcomes in developed countries concluded that early cessation of breastfeeding or its absence was associated with an increased risk of PPD (Ip et al., 2009). Other reports have similarly suggested that not breastfeeding or ceasing to breastfeed in the first weeks or months is associated with an increased risk of PPD (McCoy et al., 2006; Taveras et al., 2003; James, 2009; Misri et al., 1997; Fergerson et al., 2002; Abou-Saleh et al., 1998). Support for the hypothesis that lactation itself is associated with a lower incidence of PPD (rather than breastfeeding difficulties or stress) is the observation that in countries where exclusive breastfeeding is the norm the incidence of PPD peaks at 9 months postpartum whereas in countries where formula-feeding is the norm, the incidence of PPD peaks at 3 months postpartum (Labbok, 2001).

Evidence for a causal relationship between breastfeeding and reduced risks of PPD has remained inconclusive because the data have been obtained mostly from cross-sectional studies. Negative experiences associated with a failure to breastfeed may contribute to or induce depression in mothers (Watkins et al., 2011; Gagliardi et al., 2012), and antenatal or postpartum depression may contribute to adverse infant-feeding outcomes, including breastfeeding difficulties and reduced breastfeeding duration (Hatton et al., 2005; Nishioka et al., 2011; Dennis and McQueen, 2009). In fact, both effects could occur concurrently; that is, breastfeeding may protect against depression, and depression may cause women not to breastfeed. Other factors may also contribute to the decision to begin or cease breastfeeding (Ip et al., 2009). Formula feeding itself is a major predictor of PPD (Hamdan and Tamim, 2011), suggesting that non-lactation rather than negative feelings associated with the inability to breastfeed is critical for the development of PPD.

Given that lactation reduces the risk of PPD, what could be the basis of the protective effect? Based on evidence of an increased inflammatory response in mothers with PPD (Maes et al., 2004, 2009), one suggestion is that breastfeeding protects against PPD by attenuating stress and modulating the inflammatory response (Kendall-Tackett, 2007). The question remains as to how breastfeeding attenuates stress and modulates the inflammatory response. Interventions for PPD focusing exclusively on psychosocial risk factors have been largely unsuccessful, suggesting an important role for biological factors in PPD (Corwin and Pajer, 2008).

4. Hypothesis

PPD may be due to an endogenous form of hypervitaminosis A caused by the accumulation of retinoids (vitamin A and its congeners) to toxic concentrations in breast, liver, and brain. Although vital for numerous biological functions, retinoids in higher concentration can be cytotoxic and teratogenic. Retinoids are associated with cognitive disturbances and mood disorders, including depression and suicide. Breast milk is rich in vitamin A, and pregnant women accumulate the vitamin in liver and breast in preparation for lactation. Prolonged lactation also reduces body stores of the vitamin. Based on known concentrations of vitamin A in breast milk and daily amounts of breast milk consumed by an infant (see below), we estimate that during the first six months of exclusive breastfeeding a quantity of vitamin A is transferred to the infant that would be sufficient to cause acute vitamin A intoxication if consumed by an adult. It is hypothesized, therefore, that non-lactation or the early cessation of breastfeeding contributes to the pathogenesis of PPD due to the retention and accumulation of retinoids in brain and other tissues that would normally be transferred to the infant for its nutrition.

5. Retinoids and retinoid toxicity

Retinoids are mainly dietary-derived fat-signaling molecules, stored principally (about 80%) in the liver, and in sufficient quantity to last the average adult for about two years without the need for additional intake. Retinoids are essential for multiple biologic functions, including normal cellular homeostasis, embryonic development, tissue differentiation, growth and mucus secretion (Maden et al., 2002; Blomhoff and Blomhoff, 2006; D'Ambrosio et al., 2011). Retinoic acid (RA), the major active form of vitamin A, binds to and activates specific retinoic acid receptors (RARs) and retinoid X receptors (RXRs), which regulate the transcription of numerous target genes (Litwack, 2007). RA is produced from free retinol in a process that involves the hydrolysis of retinyl esters in the liver, the release of retinol into the circulation and its delivery to the target tissues bound to retinol-binding protein (RBP). The subsequent oxidation of retinol to retinaldehyde occurs via an alcohol dehydrogenase, followed by the oxidation of retinaldehyde to RA via the enzyme retinaldehyde dehydrogenase. Serum retinol levels are closely regulated by the liver and remain relatively stable despite major fluctuations in dietary intake (Blomhoff and Blomhoff, 2006).

Many neuronal genes are responsive to retinoids, suggesting that retinoid-responsive gene transcription has a significant impact on adult brain function. At normal physiological concentrations RA acts as a growth factor, participates in locomotor behavior and modulates dopamine pathways (Lane and Bailey, 2005). On the other hand, large single or short-term doses of preformed vitamin A can induce a condition of acute toxicity characterized by nausea, vomiting, headache, fatigue, vertigo, blurred vision, increased intracranial pressure, irritability and lack of muscular coordination. The symptoms of chronic vitamin A poisoning are varied and can be manifested by central nervous system effects, liver abnormalities, growth arrest in children, bone and skin changes, and other adverse effects. Even low intakes of vitamin A in early pregnancy (7800 mcg/day) are associated with congenital malformations (National Research Council, 2001; Allen and Haskell, 2002).

Vitamin A toxicity can occur exogenously, due to excessive dietary consumption or treatment with retinoids, as well as endogenously due to medical conditions related to liver and kidney function (Penniston and Tanumihardjo, 2006). Acute vitamin A poisoning can occur after administration of 150 mg retinol in adults and 100 mg in children (Bendich and Langseth, 1989), whereas chronic vitamin A intoxication occurs in adults ingesting 15–30 mg/day over several months (Ross, 1999; Russell, 2000). Even single doses of 30–60 mg were reported to cause nausea, vomiting, headache, diarrhea and fever in some children enrolled in supplement programs (Florentino et al., 1990). In adults, symptoms of acute vitamin A toxicity can occur with single or short-term doses of 15 mg (Bendich and Langseth, 1989).

6. Retinoids and mood disorders

Retinoids have been linked to neuropsychiatric symptoms including depression, psychosis and violence (Bremner and McCaffery, 2008). Hypervitaminosis A was unwittingly induced in early Arctic explorers by consuming the livers, kidneys and fat