

An Examination into the Relationship Between Iron Deficiency and Postpartum
Depression

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Abstract

Postpartum depression is recognized as the most common complication of childbearing; however, its etiology remains fairly undetermined. Many different influences have been hypothesized as to what may cause postpartum depression, including changes in levels of various hormones (such as estrogen and progesterone), a decrease in serotonin, low levels of vitamin D, social factors, and iron deficiency. The lack of strong evidence for one specific cause makes it fairly clear that there are many factors that play a role in the development of postpartum depression. Iron deficiency is one issue that is thought to contribute to the development of postpartum depression due to iron's role of oxygenating the brain, as well as in the synthesis of some neurotransmitters and enzymes in the nervous system. Therefore, iron deficiency can result in decreased oxygenation of the brain tissue, which can result in depression symptoms, and it can also decrease the number of certain neurotransmitters that are linked to depression.

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Postpartum Depression

Postpartum depression (PPD) is the commonly-known name for a depressive mood disorder that develops in women during pregnancy or following childbirth.

According to Delrosario, Chang, and Lee (2013), PPD is the most common complication of childbearing as it occurs in about 15% of women in the postpartum period. Despite PPD's prevalence in postpartum women, its exact etiology remains unknown. Many causes have been speculated and examined including changes in levels of various hormones (such as estrogen and progesterone), a decrease in serotonin, low levels of vitamin D, social factors, and iron deficiency (Delrosario et al., 2013).

Clinical Manifestations and Diagnosis

The 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* is the official manual used to diagnose mental health issues. Oddly enough, PPD does not exist in the *DSM-5*. The *DSM-5* instead diagnoses PPD as a “major depressive disorder (MDD) with peripartum onset” (American Psychiatric Association, 2013). The previous edition of the *DSM*, the *DSM-IV*, used the specifier of “postpartum onset,” but the *DSM-5* made the change in time specifier as a result of acknowledging that half of major depressive episodes occur prior to delivery (Segre & Davis, 2013). The use of the new peripartum onset specifier allows for the inclusion of major depressive episodes that develop during pregnancy as well as during the four weeks following delivery (Black & Grant, 2014). The diagnostic criteria for MDD provided by the *DSM-5* are when a patient meets five or more symptom criteria from a list including depressed

mood, loss of interest or pleasure, significant weight loss or weight gain, insomnia or hypersomnia, psychomotor agitation, fatigue or loss of energy, feelings of worthlessness, diminished ability to think or concentrate, and suicidal ideation (Black & Grant, 2014).

Despite the *DSM-5* setting the time frame for MDD with a peripartum onset to be during pregnancy and up to four weeks following delivery, in clinical practice, many women are not diagnosed until six weeks to three months postpartum (Ellsworth-Bowers & Corwin, 2012). In fact, the prevalence of PPD is about 7% in women during the first 3 months postpartum (Albacar, 2011). Although the *DSM* does not recognize PPD as its own diagnosis, the use of the term “postpartum depression” is accepted throughout the medical community, and in clinical practice, it is usual to have an onset past the timeframe set by the *DSM* (Bozoky & Corwin, 2002).

It is also important to note that PPD is not the same as “baby blues” or postpartum psychosis. “Baby blues,” which are essentially mood swings, are common in many women in the early postpartum period. These mood swings are mild, often resolve within ten days, and are never associated with suicidal ideation. Postpartum psychosis, on the other hand, is to be taken extremely seriously. It rapidly occurs in the postpartum period and is associated with delusions, confused thinking, and disorganized behavior. The safety of the mother and baby is at risk in postpartum psychosis and hospitalization is often required (Delrosario et al., 2013).

The Edinburgh Postnatal Depression Scale (EPDS) is a widely used, ten question screening tool for PPD in pregnant or postpartum women (Cox, Holden, & Sagovsky, 1987). According to Bunevicius, Kusminskas, and Bunevicius (2009), the internal

consistency of the EPDS is 0.83 by means of the Chronbach alpha coefficient, which suggests adequate reliability.

Some examples of the types of questions asked are whether or not there has been a change in the woman's ability to find humor in her day-to-day life or whether or not she looks forward with enjoyment to things. The questions assess for feelings of anxiousness, unhappiness, insomnia, crying, and suicidal thoughts. The woman is to complete the questionnaire by herself and check which of the four responses most closely relates to how she has been feeling in the past seven days. The healthcare provider then grades the responses with a score of 0, 1, 2, or 3. The scores attributed to each response are then added together. A woman who has a total score of 10 or greater has possible depression and women who score above 13 are likely to be suffering from a depressive illness. It is of especially great importance to look at the woman's answer to the last question. The last question is a statement that says "the thought of harming myself has occurred to me" and the patient is to respond with "Yes, quite often", "sometimes", "hardly ever", and "never". Because this assesses for suicidal ideation, it is important to note the patient's response, regardless of the total score (Cox et al., 1987).

Treatment

Traditional first-line therapy for treating PPD is the use of medications and/or psychotherapy. Psychotherapy--which may also be referred to as counseling-- is considered an appealing option especially to women who are breastfeeding in order to avoid any potential side effects on the baby. Selective serotonin reuptake inhibitors (SSRIs) are first line medication choices for the treatment of PPD and are considered effective in treating depressive symptoms. There is not a large body of evidence to

contraindicate the use of antidepressants while breastfeeding; however, there are not many long-term studies to examine the effects they could potentially have on the baby. A common psychotherapy method used with PPD patients is cognitive behavior therapy. This type of therapy encourages patients to change their thought patterns, as well as improve their coping behaviors (Delrosario et al., 2013).

Iron Homeostasis

Due to iron's role in oxygenation of the brain, as well as the function it plays in the synthesis of some neurotransmitters and enzymes in the nervous system, a deficiency in iron is hypothesized to have a responsibility in the development of PPD. It is therefore important to discuss how iron is absorbed in the body, factors that prevent absorption, and a more in depth look at the pathophysiology behind iron deficiency.

Iron is derived from the diet in two forms known as heme iron and non-heme iron. Heme iron is derived from food of animal sources whereas non-heme iron comes from all other sources. Molecularly, the difference between heme iron and non-heme is that heme iron is tightly bound to a porphyrin ring structure (heme), whereas non-heme iron is not. Heme iron is able to absorb into the bloodstream more easily than non-heme iron and is not as affected by components of the diet like non-heme iron is. Phytate, polyphenols, and tannic acid all inhibit the absorption of non-heme iron by binding to iron while it is in the gastrointestinal tract, thus making it unable to be absorbed from the gastrointestinal tract into the bloodstream. Citric acid, certain amino acids, and ascorbic acid are all known to help promote the absorption of non-heme iron into the bloodstream. Citric acid promotes non-heme iron absorption by chelating iron, while certain amino acids and ascorbic acid convert ferric iron (the form the non-heme iron takes in the gastrointestinal

tract) into a more soluble ferrous form. Due to the number of factors necessary to promote non-heme iron absorption, as well as the factors that antagonize non-heme absorption, the absorption of heme iron is considered more efficient than non-heme iron (Beard & Han, 2009).

Once iron is released into the body's circulation, it immediately binds with a β -globulin called apotransferrin. Together, these two molecules form transferrin. It is with transferrin that iron can be transported in the plasma. Transferrin can also transport iron to the bone marrow and bind to membrane receptors there in order to have the developing RBCs take up the iron and use it for the synthesis of hemoglobin (Grossman, 2014a).

According to Grossman (2014a), women normally have about 2 grams of iron in their bodies with the majority of this (about 80%) used to create hemoglobin. A small amount of iron is found in the muscle (the myoglobin), the cytochromes, and some iron-containing enzymes. The remaining iron is stored in the bone marrow, liver, spleen, and some other organs (Grossman, 2014a).

Iron's Role in Hemoglobin

Because iron is a component of heme, iron deficiency leads to decreased hemoglobin synthesis. On the RBC, hemoglobin functions as the carrier of oxygen to the body tissues. Because of this, when iron and hemoglobin are decreased, there is a resulting impairment of oxygen delivery to the body cells. The hemoglobin molecule has two pairs of alpha and beta polypeptide chains. Each of these chains consists of a globin (which is a protein) and a heme unit. Each polypeptide chain can carry one molecule of oxygen; so one hemoglobin molecule has the ability to carry four oxygen molecules. The

rate at which hemoglobin is formed is dependent on the availability of iron in the body readily available for that function (Grossman, 2014a).

As previously discussed, hemoglobin within the RBC is the primary transporter of oxygen in the body as oxygen is relatively insoluble in the plasma. Within the lungs, oxygen moves from the alveoli to the pulmonary capillary and then into the red blood cells to bind to hemoglobin. Once oxygen binds to hemoglobin, the hemoglobin is known as oxyhemoglobin. Once all four units of heme are bound to oxygen, the hemoglobin is considered 100% saturated. When a blood cell enters a tissue capillary where the partial pressure (PO_2) is less than that of the arterial blood, the hemoglobin dissociates from the O_2 . The O_2 dissolves in the plasma and then moves into the tissues where it can be taken up into body cells so that they can perform metabolic functions (Grossman, 2014b).

Iron's Role in the Brain

Iron plays a role in the oxygenation of brain parenchyma (due to the function it has in the synthesis of hemoglobin), but it also acts as an enzyme to synthesize neurotransmitters, including serotonin, norepinephrine, and dopamine (Beard, 2001). According to Hallgren and Sourander (1958), in the study of about 100 autopsied brains, “the globus pallidus, the red nucleus, the substantia nigra and the putamen contain the greatest amounts of iron”. Also, according to Kim and Wessling-Resnick (2014), iron is especially concentrated in the basal ganglia, which is heavily influenced by dopamine and GABA metabolism. Within these areas, the microglia and the oligodendrocytes are the types of brain cells that contain ferritin (an iron storage protein), with the predominant cell being the oligodendrocyte, which is responsible for the production of myelin (Beard, 2003).

Alterations in the functioning of oligodendrocytes are associated with hypomyelination. Because of the high concentration of ferritin in oligodendrocytes, there is an interest as to whether or not iron plays a role in the myelination of neurons. For that reason, a large amount of research has been focused on the relationship between iron deficiency and cognitive function in infants and young children through the study of rat brains. It is thought that if iron deficiency had any impact on the under myelination of neurons, it could cause developmental delays. While many studies provide evidence for cognitive alterations in children developing potentially from iron deficiency, the number of studies on adults is much more limited. Nonetheless, because myelination is mostly completed in late adolescence and early adulthood, iron's role in myelination is likely less relevant for the purpose of discussing it in regards to women who are childbearing and therefore at risk for PPD.

Iron deficiency's effect on the brain. It has been demonstrated in studies that the brain is sensitive to dietary iron intake (Beard, 2001). Iron is a cofactor for enzymes involved in the synthesis of serotonin, norepinephrine, and dopamine (Bodnar, Cogswell, & McDonald, 2005). Serotonin (5-HT) is suspected to play a role in the control of appetite, sleep, mood states, hallucinations, pain perception, and vomiting and underactivity of serotonin is believed to predispose to depression and anxiety disorders (Wheeler & Grossman, 2014). Norepinephrine is proposed to function in learning and memory and attribute value in reward systems (Wheeler & Grossman, 2014). Depending on the area of the brain in which norepinephrine acts in, it can be either an inhibitory or excitatory neurochemical, and its underactivity is thought to be involved in depression in some people (Wheeler & Grossman, 2014). Dopamine is involved in mood, pleasure in

reward systems, judgment, reasoning, and insight (Wheeler & Grossman, 2014).

Therefore, low levels of dopamine are associated with depression (Wheeler & Grossman, 2014).

Given that iron is a factor needed for the synthesis of certain neurotransmitters, one would expect a nutritional iron deficiency to result in a lower brain concentration of those neurotransmitters. Yet, in studies of rats, whole-brain concentrations of norepinephrine and dopamine remained unchanged by iron deficiency (Beard, 2001). However, according to Kim and Wessling-Resnick (2014), the activity of monoamine oxidase is lower in humans with iron deficiency anemia. Monamines are “involved in the regulation of mood, neuronal activity, and anxiety” (Kim & Wessling-Resnick, 2014, p. 1101), so if iron is involved in their activity and metabolism, iron deficiency may be indirectly affecting mood.

In studies, the only neurotransmitter that is consistently affected by iron deficiency is dopamine (Beard, 2001). In studies performed by Youdim (1990), it was found that whole brain levels of dopamine were not affected in rats undergoing dietary iron depletion. Dopamine receptor densities in these same rats were shown to be significantly lowered in the striatum and nucleus accumbens. Because of this association, it is believed that the biological and behavioral alterations that are observed when iron status significantly drops are related to changes in the dopaminergic system.

Dopamine’s possible link to depression. Serotonin levels in the brain are most traditionally associated with depression. Selective serotonin reuptake inhibitors (SSRIs) are one of the most common antidepressants used in the treatment of depression and PPD; yet, there are a number of people who take an SSRI and still maintain symptoms of

anhedonia, loss of interest, fatigue, and a lack of energy (Fulmer, 2010). Because of these untreated symptoms, researchers began to look more into the role of dopamine in depression as it often is found in brain regions associated with pleasure, drive, reward, and motivation (Fulmer, 2010). Because lack of pleasure and lack of motivation are two of the core clinical manifestations of depression, dopamine is suspected to share a responsibility in its development. Some clinical studies have shown certain dopamine agonists, including bromocriptine, pramipexole, and ropinirole, exhibit antidepressant properties (Nutt et al., 2007). Dopamine agonists' antidepressant effects may further give evidence of dopamine's role in depression. To review, iron has a function in the synthesis of dopamine and clinical testing shows that iron deficiency results in a significant decrease in dopamine receptors in the brain. If alterations in the brain's dopamine system play a role in PPD, then iron deficiency could be the underlying factor.

Iron deficiency's impact on cognitive function. Beard et al. (2005) collected data on young South African women and the effect of iron deficiency anemia on maternal emotions and cognition. The study was a double-blind randomized controlled interventional trial of three groups of mothers. One group was iron-deficient and was given a daily dose of 25 mg of vitamin C plus 10 µg of folic acid. The second group of anemic mothers was given 125 mg of FeSO₄, 25 mg of Vitamin C, and 10 µg of folic acid. The control group was comprised of non-anemic mothers who received no supplements. The Raven's Colored Progressive Matrices test was administered to subjects in order to assess nonverbal intelligence at 10 weeks and 9 months postpartum. At the end of the trial, the anemic subjects who had been given iron supplements had a 25% improvement in scores on the Raven's test and the nine-month scores were almost

the same between the anemic iron supplemented subjects and the control group. The anemic mothers who did not receive iron supplementation did not experience a significant change in scores between 10 weeks and nine months and the scores were lower than the other two groups. According to Beard et al., at 9 months postpartum, women who were in the control group (non-anemic and did not receive supplementation) had a mean score on the Raven's test of 20.3 ± 1.0 , and anemic mothers who received supplementation had a mean score of 20.4 ± 1.0 . Conversely, anemic mothers who did not receive supplementation had a mean score of 16.7 ± 1.0 on the Raven's test. The results of this study show that iron deficiency may, in some scenarios, take part in the poor cognitive functioning of adults; nevertheless, the exact mechanism is unclear.

Iron Deficiency

Iron deficiency is the most common nutrient deficiency in the world as it affects greater than 50% of women of reproductive age (Beard et al., 2005). The term "iron deficiency" is a term that encompasses iron deficiency anemia as well as tissue iron deficiency. The latter, tissue iron deficiency, is commonly referred to as "depleted iron stores" and iron deficiency anemia is a reflection of the later stages of this (Grossman, 2014a). Iron is a necessary component in oxidative metabolism and immunity as well as the synthesis of monoamine neurotransmitters and the myelination of axons (Albacar et al., 2011). It is also necessary for the functioning of many biochemical processes, such as electron transfer reactions, gene regulation, the binding and transport of oxygen, and the regulation of cell growth and differentiation (Beard, 2001). Probably iron's most notable role in the body is as a building block for hemoglobin, the oxygen-carrying molecule vital for the function of the red blood cell (RBC). Because of its function in hemoglobin,

when there is a deficiency of iron in the body, oxygen delivery to the body cells is impaired.

Etiology of iron deficiency. In general, iron deficiency results from inadequate intake of iron, an excessive turnover of RBCs, or an excessive loss of blood. The body is efficient at recycling hemoglobin; when RBCs become too old (RBCs have a lifespan of about 120 days), the spleen destroys them and releases iron into the circulation so it can go to the bone marrow and be used in the creation of new RBCs (Grossman, 2014a). Despite this recycling, there is a loss of about 1 mg of iron per day (Beard & Han, 2009). This loss of iron is a normal occurrence, and it generally occurs through the gastrointestinal tract (Beard & Han, 2009). Because of this regular loss of iron through the feces, iron balance is maintained by absorbing 1-2 mg of iron daily (Grossman, 2014a). Blood loss that exceeds what the body normally excretes is what can result in iron deficiency if there is not adequate absorption to compensate for the loss. Women who are menstruating lose an additional 1.5-2.1 mg of iron per day, but this number increases when an intrauterine device is in place (Beard & Han, 2009). Pregnant women eliminate a source of this blood loss through ceasing to menstruate monthly; nevertheless, due to increasing iron requirements, iron deficiency can result. Postpartum women are also able to generally stop menstruating monthly if they choose to breastfeed, because cessation of menstruation is frequently associated with the hormones released during lactation. The cessation of menstruation associated with lactation is beneficial as it can be a time to restore some depleted iron stores (Grossman, 2014a). If a woman makes the decision not to breastfeed though, she is more likely to begin her menstrual cycle sooner than a woman who does breastfeed (Grossman, 2014a). By restarting her menstrual cycle

sooner, she will consequently lose more iron, which could potentially make the replenishing of iron stores in the postpartum period more difficult (Grossman, 2014a).

With inadequate intake of iron through the diet, excessive turnover of RBCs (as in hemolytic anemia where the excess hemoglobin in the blood may be excreted from the body), or any of the conditions previously discussed, there will be a decrease in body iron levels, and deficiency will result. With a decrease in body iron levels comes a decrease in the amount of hemoglobin that can be synthesized. Subsequently, this results in smaller red blood cells as they do not carry as much hemoglobin and cannot carry oxygen as well to the body cells.

Development of iron deficiency in pregnancy. Iron deficiency is especially common in pregnancy as it becomes difficult to balance increased iron requirements with dietary intake (Consigli, 2016). Iron requirements during pregnancy increase due to the growth of the fetus, placenta, and maternal blood volume (Consigli, 2016). Blood volume increases in pregnancy in order to continue to supply oxygen to the mother's body cells as well as transfer oxygen to the developing fetus through the placenta. In order to compensate for this increased oxygen demand, the mother's iron requirement increases so that the body can create more circulating RBCs. Increased demands for iron from the fetus also contribute to the development of iron deficiency. The fetus begins to store iron in the liver, especially during the third trimester of pregnancy in order to compensate for low levels of iron found in breast milk for the first four months of life (Consigli, 2016).

Recommended intake of iron during pregnancy is 27 mg per day, and although the rate of absorption increases during pregnancy, the most iron that can be reasonably obtained from the average American diet is 15 to 18 mg per day (Consigli, 2016). Not

meeting the recommended iron intake can result in low iron stores for the fetus and also anemia for the mother well into the postpartum period (Consigli, 2016). For this reason, all pregnant women should be taking a daily prenatal vitamin that includes iron and they should also continue taking it well into the postpartum period.

Clinical manifestations. Patients with iron deficiency anemia may report feeling tired, having difficulty concentrating, being less productive at work or home, or feeling like they are lacking in energy (Beard, 2001). Assessment of the patient may reveal palpitations, dyspnea, and tachycardia (Grossman, 2014a). In iron deficiency anemia, tachycardia is a compensatory mechanism to increase oxygen transport to the body cells. Because oxygen binding to hemoglobin is a quick process, when the body has an increased heart rate, there can be more RBCs that reach the pulmonary capillaries and have hemoglobin bind with oxygen for transport. Tachycardia also results in more RBCs reaching the body tissues carrying oxygen. So in short, while the RBCs may be able to carry less oxygen per cell, in order to compensate, there is a greater number of RBCs reaching the tissues in the same amount of time. Iron deficiency can also result in impaired thermoregulation, immune function, mental function, and physical performance (Beard, 2001). These findings are all related to impaired oxygen transport and a lack of hemoglobin. Findings will be dependent on how severe the anemia in the patient is. Other physical symptoms may be brittle hair and nails, a smooth tongue, sores in the corners of the mouth, or a spoon-shaped deformity of the fingernails known as koilonychia (Grossman, 2014a).

Testing and diagnosis. Serum ferritin level is the most sensitive and specific test used for the identification of depleted iron stores. According to the standards set by the

World Health Organization (2011), a serum ferritin less than 15 $\mu\text{g/L}$ generally indicates depleted iron stores. Ferritin is a protein-iron complex that is used to store iron in the liver but can also return it to the circulation easily (Grossman, 2014a). Serum ferritin is a helpful indicator of iron status in the body because decreased levels generally indicate decreased body stores (Grossman, 2014a).

A transferrin saturation level of less than 16% indicates an iron supply that is insufficient to support normal erythropoiesis. Hemoglobin may be examined but this value will only be depressed in iron deficiency anemia and not in tissue iron deficiency (Camaschella, 2015). A hemoglobin test is performed in order to determine the hemoglobin content of the blood. Normal values differ between men and women, with men having a slightly higher range. Women ought to have a hemoglobin level within the range of 12-15 g/dL (Grossman, 2014a). Hematocrit is also examined to determine the presence of anemia. Hematocrit measures the percentage of RBCs in 100mL of plasma. In men, hematocrit should be 40-50% and in women, it should be 37-47%. A low hematocrit may indicate anemia (that there are not enough RBCs), so examining this with other labs can determine anemia, as well as the cause (whether or not is related to iron deficiency).

Iron deficiency will alter RBC size and shape as well as the number. Red blood cell count will decrease and cells will be microcytic and hypochromic. RBC size and shape can be determined through the laboratory tests for mean corpuscular hemoglobin concentration (MCHC) and mean corpuscular volume (MCV). Mean corpuscular hemoglobin concentration examines the concentration of hemoglobin in the RBC and MCV examines the size of the RBC. Normal MCHC is 31-35 g/dL and lower than

normal levels are seen with iron-deficiency anemia. A low MCHC results in hypochromic RBCs meaning that they are paler than normal due to a decreased hemoglobin level in the cell (hemoglobin is what gives RBCs the red color). Normal MCV levels are 85-100 fL. Low levels of MCV are seen with iron-deficiency anemia as it means that the RBCs are microcytic (smaller than normal) (Grossman, 2014a).

Testing in pregnant and postpartum women. Ferritin in the postpartum period is expected to be low due to the decrease in iron stores in pregnancy and from blood loss in delivery. Sometimes, however, this is not found to be the case. According to Muñoz, Villar, and Garcia-Erce (2009), delivery produces an inflammatory response in women, which can alter ferritin concentrations. The two acute inflammatory response proteins to be noted in this case are C-reactive protein (CRP) and α_1 -acid-glycoprotein (AGP) (World Health Organization, 2011). If these proteins are elevated, in order to account for the resulting increase in ferritin, the cut-off for defining iron deficiency can be raised to a ferritin concentration of less than 30 $\mu\text{g/L}$ (World Health Organization, 2011).

According to Krafft, Huch, and Breyman (2003), even when iron stores are actually depleted in the postpartum period, ferritin levels will be elevated as a result of inflammation. Consequently, although ferritin is considered to be the most reliable marker of iron status in the general population, it is less reliable in the postpartum period.

Treatment. In general, the goal for treatment for iron deficiency in both adults and children is to treat the cause if there is chronic blood loss involved, increase intake of iron through the diet, and administer supplemental iron. Because iron deficiency in pregnancy is almost always due to inadequate intake of iron, the goal of treatment would be to increase iron intake through the use of supplements.

Rapid restoration of an iron-depleted state can be achieved by administering 125-250 mg of ferrous sulfate orally daily (Beard & Han, 2009). In severe anemia of pregnancy, doses of greater than 250 mg twice a day is common practice; however, this further increases the common side effects of iron supplementation (Beard & Han, 2009). Constipation and black stool are common side effects and may complicate patient compliance (Beard & Han, 2009). Patients should be instructed that if they can tolerate it, iron supplements should be taken between meals in order to enhance absorption (Beard & Han, 2009). The negative of this advice is that iron supplements often cause gastrointestinal discomfort on an empty stomach (Consigli, 2016). If possible, it may be beneficial to begin supplementation in the second trimester once the nausea and vomiting associated with the first trimester subside (Consigli, 2016). Using ferrous sulfate supplements can replenish iron stores in a few months and once iron levels have reached normal levels, the normal RDA dietary guidelines for iron intake should be maintained (Beard & Han, 2009).

There could also be potential benefit in looking deeper into treatment options of iron deficiency that are more efficient than traditional oral iron repletion. A study performed by Becuzzi, Zimmerman, and Krafft (2014), found that intravenous iron therapy was beneficial in replenishing depleted iron stores. Subjects in the experimental group received a single infusion of 500 mg iron carboxymaltose 24-48 hours postpartum and then took iron supplements daily for 6 weeks. Subjects in this group reported no adverse effects to the intravenous iron. The control group subjects took iron supplements for 6 weeks but received no intravenous iron. The average ferritin at 6 months was significantly lower in the control group versus the experimental group; 32.9 µg/L versus

57.7 µg/L respectively. This study was consistent with others that intravenous iron replenishes iron stores more efficiently than oral iron but this particular study established its long-term effect on iron levels. Intravenous iron therapy also provides the benefit of less gastrointestinal side effects that may affect patient compliance in traditional oral iron supplementation.

Patient education. Because phytate, polyphenols, and tannic acid (all found in cereals and high fiber foods) can hinder iron absorption, patients should be educated to avoid consuming foods with high levels of these along with iron supplementation (Beard & Han, 2009). Caffeine can also hinder iron absorption, so patients should be told to avoid taking iron supplements with drinks like coffee or soda. Patients should be educated on what may help with iron absorption such as ascorbic acid and citric acid, which can be found in citrus fruits (Beard & Han, 2009). For example, patients should be encouraged to take iron supplements with something like a glass of orange juice. Patients should also be encouraged to include good food sources of iron into their diet, such as meat (specifically beef) as well as iron-fortified cereal and bread, lentils, beans, and spinach. If, however, elevated cholesterol is a problem for the patient, he or she should be taught to limit their consumption of red and organ meats and instead eat more fish and poultry products. As vegetarian and vegan diets increase in popularity, it is also important to address the dietary concerns associated with those diets. Vegan and vegetarian diets do not include any meat products, which are good sources of iron. Patients who do not consume meat products should be educated about other good sources of iron that follow their dietary preferences. Patients should also be cautioned to limit their consumption of cured meats (such as jerky) as sodium nitrate is often used to cure them (Grossman,

2014a). Large amounts of nitrates can react with hemoglobin and cause it to have a lower affinity for oxygen, meaning that less oxygen may combine with the hemoglobin molecule for transport (Grossman, 2014a).

As previously stated, constipation and black stool are common side effects of iron supplementation therapy. In order to alleviate some of the discomfort associated with these side effects, the woman should be consuming adequate fluid and fiber in her diet (Consigli, 2016). Pregnant women should be consuming at least 64-96 ounces of fluid each day and avoiding caffeinated beverages due to their diuretic effect which can be counterproductive when trying to increase fluid intake (Consigli, 2016).

Relationship Between Iron Deficiency and Postpartum Depression

As previously stated, it is extremely unlikely that iron deficiency is the single cause of postpartum depression. Research regarding the subject is sometimes inconclusive which further points to the deduction that iron deficiency does not solely cause PPD. For example, Armony et al. (2012) published a study of 567 Chinese women in a rural area of northern China and found no relationship between the maternal iron status and postpartum depression. While this was a large study, it was completely observational and it stopped screening subjects for PPD using the EPDS after six weeks postpartum. As previously discussed, according to Ellsworth-Bowers and Corwin (2012), in clinical practice, most women are not diagnosed until six weeks to three months postpartum, so it could be argued that this study's time frame was cut too short. Future studies should take this consideration into account and evaluate blood levels for ferritin and screen for PPD up to three months postpartum. This study also mainly was assessing subjects' hemoglobin as a way to screen for iron deficiency. The downfall of focusing on

a subject's hemoglobin status is that it is not the best indicator of iron status and it can be affected by residential altitude above sea level and smoking (World Health Organization, 2011).

Despite the study concluding that there was no relationship between iron deficiency and PPD, there are a number of other studies that have found a relationship. While it is unknown why exactly there are different findings between studies, most likely, it is another example of the complexity of PPD due to the many confounding factors involved. Many factors take part in the development of postpartum depression, and iron deficiency is likely a probable contributor. The lack of relationship found in the study by Armony et al. does not mean that there is definitively a lack of a relationship between iron deficiency and PPD. That specific study's findings could boil down to a number of confounding factors such as the rural location of the subjects, cultural differences, differences in social support, a biological/genetic factor, or even an unaccounted shortcoming of the study. One example of a likely confounding factor not addressed by this study is that the majority of new Chinese mothers often are taken care of and receive lots of positive support specifically from their mother or mother-in-law for about the first 30 to 40 days postpartum (Cheng & Pickler, 2009). This time frame is commonly referenced as "doing-the-month" and allows the new mother to follow cultural practices to promote health and prevent disease while relatives take over many of the house responsibilities and food preparation (Cheng & Pickler, 2009). Studies show that Chinese mothers with limited family support often have a high level of depressive symptoms, while those who receive the most support have lower incidences of depressive symptoms (Cheng & Pickler, 2009). "Doing-the-month" is a cultural ritual for the

Chinese and the level of support that family gives to women in the early postpartum period is not often seen in western cultures. American culture often values independence more and women often do not receive nearly as much support as Chinese women. Stress is a predictor for PPD and because “doing-the-month” relieves many of the new stresses for the new Chinese mother, it places Chinese mothers at lower risk for PPD (Cheng & Pickler, 2009). Therefore, this could be a reason why the results of this study were not similar to other past studies and the high levels of support could have been a confounding factor.

Another example as to why this study may have a different outcome than others that are similar is regarding cesarean sections. The article mentions that 60% of the births in the study were by elective caesarean section, which according to the article, is common practice in China (Armony et al., 2012). As mentioned previously, inflammation alters serum ferritin levels. If a non-traumatic vaginal birth results in an elevated CRP that alters ferritin readings, then a caesarean section, which is much more traumatic, is likely going to result in a greater inflammatory reaction. The study by Armony et al. did not assess for any markers of inflammation in the blood testing of subjects, which means the ferritin levels of the subjects could not be accurately assessed nor could the researchers throw out any subjects who had extremely high levels of inflammatory markers that could skew their results and statistical analysis. Because ferritin is the most valuable assessment of iron stores, this study’s basis of iron deficiency mostly on subject’s hemoglobin values is probably not the most accurate.

A study of 729 Spanish women by Albacar et al. (2011) sought to find an association of depleted iron stores and PPD. This study assessed multiple markers for

iron depletion but focused on serum ferritin as this is a more sensitive and specific test for iron deficiency and decreased levels (<30 µg per liter) indicates decreased body stores. Blood tests were taken on subjects only once in the study at 48 hours following delivery. This study also screened participants for PPD over a longer time frame than the Chinese study by Armony et al. While it did not screen subjects for PPD during pregnancy, it screened using the EPDS at 48 hours, eight weeks, and 32 weeks postpartum. It also used a lower cutoff score on the EPDS than the Chinese study by Armony et al. For the study of Spanish women by Albacar, the cutoff score was set for 9. According to Navarro et al. (2007), lowering the cutoff score to 9 increases sensitivity for PPD to 100% and the specificity to 89%. Women who scored above a 9 on the EPDS were then evaluated using the criteria set by the *DSM-IV* for PPD to confirm a diagnosis. This study found an association between PPD and low ferritin levels. In the group of women who developed PPD, 38.5% met the criteria for depleted iron stores set by the World Health Organization and of the non-PPD women, 23.3% had depleted iron stores (Albacar et al., 2011).

One of the reasons why iron deficiency was examined to be related to postpartum depression in the first place is because of the overlap between some of the symptoms seen between the two. These overlapping symptoms include diminished ability to think or concentrate and fatigue or loss of energy. In studies, early postpartum fatigue was found to be a predictor of postpartum depression (Bozoky & Corwin, 2002). This idea was studied due to the fact that fatigue is a common symptom in all forms of depression (Bozoky & Corwin, 2002). Since fatigue is a common symptom in many forms of depression, and it is considered a predictor of postpartum depression, it raises interest in the relationship between fatigue and PPD. Because the symptom of fatigue seen with iron

deficiency is directly related to a deficiency in hemoglobin and thus a deficiency in oxygen transport, it raises the question as to whether or not a potential lack of oxygen plays a significant role in postpartum depression.

Iron's function in hemoglobin is not the only role of significance, though. Because it also has a job in the synthesis of neurotransmitters, clinical evidence shows that iron status has a part in affecting cognitive function (Beard et al., 2005), seemingly independent of its role with hemoglobin. The potential link between iron levels and the brain's dopamine system was discussed earlier, and because dopamine is thought to play a part in feelings of pleasure, drive, reward, and motivation (Fulmer, 2010) it is thought that lower levels of dopamine receptors could be hampering these feelings and playing a position in the development of PPD, thus linking iron levels to PPD.

Implications

If there is a connection between maternal iron status and PPD, even if it is just one of the number of contributing factors, then health professionals need to be better educating pregnant patients about iron deficiency. Specifically, this education can include: how patients can make better diet choices; how to take iron supplements so that they will be best absorbed; and actions they can take to decrease the side effects of supplementation (so that compliance will be increased). Taking the extra time to educate patients on the topic is a small price to pay when compared to the social and economic consequences of PPD. Treatment for iron deficiency should be re-evaluated if the patient does not respond or act on patient education. As previously discussed, intravenous iron has shown promising results in replenishing iron stores. Also, because it is administered

as a single infusion, patient compliance is not an issue with this treatment option like it is with oral supplementation.

Conclusions

American culture generally sees the birth of a new child as a happy time in a mother's life, so in the past, when a woman struggled with PPD, it was almost never discussed. Postpartum depression can cause a new mother to face a lack of energy, depressed mood, and have negative thoughts, which is contrary to what culture somewhat expects new mothers to experience in the postpartum period. When a mother has these feelings, she may feel afraid to discuss them as she may feel as if she is wrong to feel the way she does. She may not be aware that those feelings are a part of a mental disorder and that she is not alone in experiencing it. Thus, it is vital for healthcare providers to build a trusting relationship with their patients so that mothers will feel safe enough to express their thoughts and feelings and can receive the help they need. Postpartum depression has the potential to negatively affect the maternal-child relationship and potentially even the child's development (Delrosario et al., 2013). The social impact that this disorder can have should drive medicine to investigate this disorder more deeply so that more links can be made to PPD and it can be better prevented. Clinical evidence appears to point to a relationship between iron deficiency and PPD, but there are many confounding variables to take into account. Regardless of the sometimes blurry connection between iron status and PPD, all pregnant patients should be encouraged to consume adequate iron through diet and daily prenatal vitamins throughout pregnancy as well as into the postpartum period in order to prevent iron deficiency or lessen its potential severity and consequently decrease the risk of developing PPD in the process.

The importance of the relationship between PPD and iron deficiency ought to alter the way PPD is viewed. Instead of seeing it as a disorder that is treatable once diagnosed, thinking can be shifted and, ideally, it can instead be seen as having potentially preventable factors. With proper patient education and treatment of preventable factors, the prevalence of PPD could be reduced, having a monumental impact on women's health.

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