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THE EFFECT OF IRON DEFICIENCY ANEMIA DURING PREGNANCY ON BREASTFEEDING AND MATERNAL MENTAL WELL-BEING

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In this study we will collect and analyze scientific publications that review the correlation between anemia and breastfeeding, and anemia and maternal mental well-being both prepartum and postpartum. The risks concerning iron deficiency anemia during pregnancy and postpartum are widely known; anemia increases the morbidity of both mother and child. Our aim is to review whether iron deficiency anemia affects the initiation and duration of breastfeeding and, on the other hand, whether it increases maternal depression and anxiety.

According to our study, consensus whether anemia affects the initiation and duration of breastfeeding has not been reached. There are only a few studies of the association between postpartum anemia and duration of breastfeeding, and none of the association between anemia during pregnancy and duration of breastfeeding. Further research on the subject is needed.

The association between anemia and mental well-being, on the other hand, has been studied widely in the past. The studies concern mostly the association of anemia and postpartum depression. The evidence suggests that especially postpartum anemia is a major risk factor for postpartum depression.

We suggest that promotion of maternal health by means of treatment of iron deficiency anemia during pregnancy and postpartum by adequate iron supplementation could be one of the key factors in the prevention of maternal postpartum depression, anemia and possibly also cessation of breastfeeding.

Key words: iron deficiency anemia, breastfeeding, postpartum depression

Aim of the study

In this study we will collect and analyze scientific publications that review the correlation between anemia and breastfeeding, and anemia and maternal mental well-being. We will evaluate the effect of both prepartum and postpartum anemia on the subjects. Since mental well-being is hard to define and measure, we have outlined the mental well-being to include studies that view the association between anemia and depression or anxiety.

1.1 Anemia

In anemia, the number of red blood cells does not meet the body's physiological needs[1]. Other way to define anemia is trough hemoglobin level; in anemia, the blood hemoglobin concentration is low[2,3]. Common symptoms of anemia include fatigue, dyspnea and dizziness. Depending on how low the hemoglobin level is and how fast it has gone down, the symptoms tend to be more severe.[4]

Globally, iron deficiency is the most common cause behind anemia[1]. Other causes can be folate, vitamin B_{12} and vitamin A deficiency; inflammations; parasitic infections; and disorders affecting hemoglobin synthesis, red blood cell production or red blood cell survival[1]. In World Health Organization's (WHO) report of the prevalence of anemia in 2011, it was estimated that globally 38 % of pregnant women and 29 % of non-pregnant women in fertile age had anemia, affecting 32 million pregnant women and 496 million non-pregnant women altogether[2].

In Finland, the most common causes of anemia are iron deficiency and secondary anemia[5]. Secondary anemia, or anemia of chronic disease, is an inflammatory response to a chronic disease in which erythropoiesis attenuates and the utilization of iron decreases due to inflammatory transmitters and hepcidin.[6] In WHO Global Database on Anaemia (2005), the prevalence of anemia in different populations in Finland varied between 3.4 and 59.0 % when anemia was considered hemoglobin level below 120 g/l. When only non-pregnant women were taken into consideration, the prevalence was from 3.4 % to 11 %. Among pregnant women, the prevalence was 10-19 % before giving birth and 41-59 % after birth.[7]

According to WHO, for non-pregnant women, the normal hemoglobin level is 120 g/l or higher, and for men 130 g/l or higher[1], but the diagnostic levels may vary in different countries; in Finland, the normal hemoglobin level for non-pregnant women is set at 117 g/l and for men at 134 g/l[4,8]. For pregnant women, WHO recommends using 110 g/l or higher as a diagnostic level for anemia[1]; the same level is used in Finland[8]. The severity of anemia can be further assessed in three different diagnostic groups according to the level of hemoglobin: mild (100-109 g/l for pregnant women), moderate (70-99 g/l) and severe (< 70 g/l)[1].

1.2 Anemia in pregnancy and postpartum

In every pregnancy, the level of hemoglobin decreases due to hemodilution. In hemodilution, the volume of circulating blood increases 40-50 % to ensure blood flow to the uterus. At the same time, the erythropoiesis accelerates, but because the increase in the amount of plasma is greater than the increase in the amount of red blood cells, the blood gets diluted.[9-11] Hemodilution might cause anemia. In pregnancy, anemic level of hemoglobin is considered to be 110 g/l or lower[1,8,9]. The hemodilution starts already in the first trimester, but the increase in volume is steepest at the second trimester, after which the rate of increase slows down in the third trimester[10].

Anemia during pregnancy has been seen to increase the risk for prematurity[12-14], low birth weight of the infant[14,15], cesarean delivery[12,14], infant's admission to a neonatal unit[12], fetal intrauterine death[16], and maternal death[14,17]. To prevent anemia during pregnancy and postpartum, WHO recommends a daily oral iron supplementation of 30-60 mg of elemental iron. If side-effects prevent taking iron supplementation daily,

intermittent oral iron supplementation with 120 mg of elemental iron once a week is recommended.[18] In Finland, it is recommended by Finnish institute for health and welfare that if the hemoglobin level of the expectant mother is under 115 g/l after 12 gestational weeks, she should start taking an iron supplementation of 50-100 mg of iron daily[19].

The prevalence of postpartum anemia is high worldwide; 50 % of the mothers who were anemic in the third trimester had also postpartum anemia, and 25 % of mothers who did not have anemia in the third trimester developed anemia postpartum[20-22]. For postpartum anemia, the main cause is anemia during pregnancy combined with heavy bleeding during and after childbirth[23,24], with other risk factors being the lack of regular postpartum iron supplementation and young maternal age[24,25]. In addition to being one of the leading causes of postpartum anemia, heavy bleeding during and after childbirth remains the most common cause of pregnancy-related cause of death and morbidity, with uterine atony, trauma and prolonged second stage of labor increasing the risk[26-28]. There are multiple definitions of significant postpartum hemorrhage. American Congress of Obstetricians and Gynecologists define early postpartum hemorrhage as significant if the cumulative volume of lost blood is 1000 ml or higher, or if there are signs or symptoms of hypovolemia within 24 hours of giving birth[29]. WHO's definition of significant hemorrhage is 500 ml or more within 24 hours of giving birth.[27] In Finland, the blood loss is considered normal if it is less than 500 ml after vaginal delivery and less than 1000 ml after cesarean section[30].

1.3 Breastfeeding

The advantages of breastfeeding are widely known. For the infant, breastfeeding benefits the health and survival, enhances the intellectual and motor development, and reduces the risk for chronic diseases, while simultaneously increasing the health of the mother[31,32]. Breastfeeding has a positive effect on maternal mental well-being by inducing a calmer psychological state and by decreasing stress and anxiousness. These are believed to be mediated by oxytocin interaction with cortisol pathway.[33] Interplay between oxytocin and other regulators of human lactation (e.g. estrogen, progesterone and prolactin) influences human behavior and mental well-being in terms of sexual behavior, maternal behavior, friendly social interactions, stress and anxiety alleviation and attenuation of nociception, learning and memory[34]. World Health Organization (WHO) recommends that mothers breastfeed infants exclusively until the age of six months. WHO also recommends that the breastfeeding continues up to the age of two years or beyond, whilst simultaneously nutritious complementary foods are administrated.[35]

In Finland, 92 % of infants under the age of one month are breastfed, and 47 % of these infants exclusively. The amount of exclusively breastfed infants tends to decrease when the infant gets older; at the age of 5-6 months, only 9 % of infants are exclusively breastfed, while 57 % are partially breastfed and 34 % are not breastfed at all. Out of over 11 months old infants, 1 % is exclusively breastfed, 33 % partially breastfed and 66 % not breastfed at all. The median point to stop breastfeeding for Finnish mothers is at 2.3 months, and the average at 3.1 months.[36]

There are multiple factors that influence the initiation and continuity of breastfeeding. According to studies, women with higher level of education, marriage, stable financial

status and attendance to prenatal classes are more likely to initiate breastfeeding, and women with higher level of education, older age, commitment to non-smoking and participation in a home visitor program are more likely to continue breastfeeding[37,38]. Postpartum fatigue is one of the main causes of ceasing to breastfeed[22,39], and it can be associated not only with reduced amounts of sleep but also with low levels of ferritin and hemoglobin[40]. Self-reported insufficient milk and delayed onset of breastfeeding are interconnecting factors most commonly leading to cessation of breastfeeding[41]. Stress indicators including longer labor duration, maternal exhaustion, increased stress hormones and unscheduled cesarean section are associated not only with difficulties in breastfeeding[41] but also with iron deficiency anemia during pregnancy[12]. Furthermore, since breastmilk has a low iron concentration and the concentration cannot be altered through maternal supplementation, restoration of mother's iron status during pregnancy or even before seems to be important[42].

1.4 The effect of iron deficiency on fetus

When considering the effect of iron deficiency on fetus, it has been proven that iron is essential for central nervous system development (myelination, neurotransmitter function, neuronal energy metabolism and dendritogenesis). Several studies have shown an association between iron deficiency anemia and iron depletion in infancy and poor cognitive and behavioral performance.[43] Evolutionary conserved mechanisms of active iron transport from the mother to the fetus ensure normal neurodevelopment in mild or moderate maternal iron deficiency anemia, and the fetus is mostly protected from significant iron deficiency anemia in European settings. Accordingly, iron supplementation of pregnant women is not believed to improve infant's iron status in Europe in general.[44] However, in the developing countries with high frequency of malnutrition associated severe maternal iron deficiency anemia, iron supplementation seems to have beneficial effects on infant's iron status[45,46]. To improve infant's iron status, late cord clamping has been shown to be effective both in high and low income countries[47,48].

1.5 Mental well-being postpartum

Most women are mentally more sensitive after giving birth, a period which is also known as "baby blues" or "postpartum blues". This is considered a normal part of becoming a mother; up to 80 % of new mothers experience the symptoms. Postpartum blues usually goes by without other interventions than psychological support. Symptoms include crying, mood swings, headache, irritation, lack of appetite, and insomnia. The symptoms are usually worst at 3-5 days postpartum, but can last for several weeks. Though baby blues as a condition is considered harmless, it is important to remember that it increases the risk for postpartum depression.[49,50]

Postpartum depression (PPD) is defined as depression that occurs after giving birth[51]. Usually, the symptoms appear within 3 months of delivery, but may occur up to 6 months after giving birth[49,50]. As many as 10-20 % of mothers get PPD. Depressive symptoms prior to pregnancy and PPD in earlier pregnancies increase the risk. Other risk factors are antenatal depression, first pregnancy, marital problems, unmarried life, cesarean section, mental illnesses in the family, stress, negative experiences during pregnancy, lack of social support, and mother's bipolar disorder. The symptoms of PPD include insomnia, joylessness, flightiness, feelings of inadequacy, and excessive worrying over the newborn.[49-51]

PPD results in a diminished ability to take care of the infant and endangers the normal development of a healthy maternal-infant bond, as well as increases the later morbidity to mental illnesses for the whole family. The infants of mothers who have PPD are also more likely to have delays in cognitive and language development. Therefore, it is important to evaluate maternal mental well-being.[49,51] The use of screening tools for postpartum depression, such as Edinburgh Postnatal Depression Scale (EPDS), may help with early detection of the disease and reduce the adverse effects[50]. PPD can be treated the same way as any other depression: antidepressive medication, social support, and psychotherapy[49-51]. However, if medication is initiated, it is important to take into account the secretion of the chosen drug into breast milk[49].

Postpartum psychosis is a psychotic form of PPD. It is the least common mental illness occurring postpartum but also the most severe one; it is considered a psychiatric emergency and requires hospitalization. The symptoms usually start emerging 3-14 days after delivery and include restlessness, insomnia, agitation, mood swings, confusion, manic psychotic episodes and hallucinations. The mother is in danger of committing suicide as well as harming the baby.[49,50] Postpartum psychosis can be treated with antipsychotics, psychotherapy, and sometimes electrotherapy[49,50]. Social support of both the mother and the family is important. Prognosis is good after the first episode, but psychosis tends to recur in later pregnancies.[49]

2. Anemia and breastfeeding

2.1 The effect of anemia during pregnancy on breastfeeding

No studies of the association between prepartum anemia and the duration of breastfeeding could be found, though as stated earlier, prepartum anemia is a main factor in the development of postpartum anemia[23,24].

However, as is reviewed earlier, iron status of the infant is important when considering the development of central nervous system[43]. Mello-Neto et al (2013) have studied the effect of iron supplementation during pregnancy on the iron quantity of lactating human milk. They found in their study that in 45 % of breastmilk from an anemic mother the concentration of iron is low.[52] However, others have shown that there is no correlation between the mother's blood iron parameters and the concentration of iron in breastmilk[53,54]. These findings suggest that the concentration of iron in breastmilk is controlled by a mechanism that prioritizes the needs of the baby.

Pérez-Escamilla et al (2019) questioned the WHO recommendation of exclusive breastfeeding of all infants for 6 months. They discovered that iron deficiency in infancy could be reduced by delayed cord clamping in all infants. However, for low birth weight infants who are born to mothers with iron deficiency anemia during pregnancy, it is recommended that iron supplementation is started at the age of 2-3 months, since there is a risk of early infancy iron deficiency anemia and associated neurodevelopmental problems. In others, delayed cord clamping has been considered to be sufficient to ensure adequate iron storages in the early infancy.[41]

2.2 The effect of postpartum anemia on breastfeeding

Only a few studies have been made concerning the relationship between postpartum anemia and duration of breastfeeding. According to Rioux et al. (2006), postpartum anemia seems to be related to the duration of breastfeeding. In their study, they aimed to recruit retrospectively all the mothers who had given birth between April 23, 1998 and February 25, 1999 in the Dr. Georges-L. Dumont Regional Hospital in Moncton, Canada. The study had 76 subjects. They asked the mothers to visit the hospital when their baby was 9 months old to partake in a questionnaire and to determine blood hemoglobin level. The hemoglobin level after giving birth could be found in the records since it is one of the routine tests taken from every mother two days postpartum in Canada. They asked about breastfeeding in the questionnaire and considered the baby to be breastfed if it had received only breastmilk and possible complementary foods but no commercial formulas. 82.9 % of mothers initiated breastfeeding, but only 73.7 % breastfed for more than 7 days. The amount of breastfeeding mothers decreased over time; 68 % of mothers breastfed for over a month, while 43.4 % breastfed their infants for over 4 months. Only 22.4 % of mothers continued to breastfeed the recommended 6 months, and at the 9 month check-in, only 9 % were still breastfeeding. In the study, they found that postpartum hemoglobin level of under 95 g/l was associated with earlier cessation of breastfeeding ($p<0.02$).[38]

Henly et al (1995), on the other hand, studied the correlation between anemia and insufficient milk in first-time mothers. They studied 630 first-time mothers that had given birth in a private urban hospital in United States. Out of these mothers, 22 % were anemic. Otherwise the mothers did not vary much in the measured variables. They had

their hemoglobin measured and completed a questionnaire on discharge and then got contacted by telephone at 1, 3, 6, 9 and 12 months after giving birth. After this, only those women who were still breastfeeding at 12 months were contacted every 3 months until the breastfeeding was ceased. Anemic mothers reported both more problems with insufficient milk and earlier cessation of breastfeeding. Out of the anemic mothers, 19.7 % reported insufficient milk syndrome, whilst out of the non-anemic mothers only 11.4 % had the same problem (OR=1.7). The mothers with insufficient milk syndrome breastfed exclusively for 3.8 weeks on average. In comparison, mothers without the syndrome were exclusively breastfeeding for 10.5 weeks on average. They could see similar trending on the cessation of breastfeeding: the mothers with insufficient milk syndrome breastfed on average for 12.1 weeks and mothers without the syndrome for 30.7 weeks, leading to a mean difference of 18.6 weeks between the study groups. They could not, however, find a correlation between anemia and the duration of breastfeeding: the anemic mothers were exclusively breastfeeding on average for 9.0 weeks compared to the 9.8 weeks of the non-anemic mothers, and the average age of the infant on cessation of breastfeeding was 26.1 weeks on anemic women and 28.7 weeks on non-anemic. However, the study's results suggest that since anemia affects the production of milk, which in turn leads to decreased duration of breastfeeding, anemia is one of the risk factors of earlier cessation of breastfeeding.[21]

Some studies have shown that red blood cell transfusion is associated with decreased prevalence in initiation of breastfeeding in women who suffered from postpartum hemorrhage and were therefore anemic.[34,35] Drayton et al. (2016) studied retrospectively whether blood transfusion has an effect on breastfeeding from the data on all the mothers giving birth 2007-2012 in New South Wales, Australia. Out of these mothers they selected those who had had mild postpartum hemorrhage (PPH). The number of participants after exclusions were 39 787. Of all the mothers in the study, 88 % were breastfeeding at discharge (82 % exclusively and 6 % partially). Out of mothers who had PPH but did not need red blood cell transfusion, 88 % were breastfeeding at discharge (81 % exclusively and 7 % partially). In the group of mothers who had PPH and received blood transfusion, 82 % were breastfeeding at discharge (70 % exclusively and 12 % partially). The study indicated that the mothers who suffered from PPH and received a blood transfusion were breastfeeding less than the other mothers.[35] This could indicate that there is no correlation between anemia and the initiation of breastfeeding, since the mothers whose anemia was treated with blood transfusion were breastfeeding less than the ones who did not receive the transfusion.

Chessman et al (2018) used the same data as Drayton et al (2016) from 2007-2010. Their study aimed to find out whether red blood cell transfusion had an impact on breastfeeding among women who had suffered PPH, but taking into account postpartum hemoglobin levels. 80 % of the mothers who received a blood transfusion were breastfeeding at discharge, compared to 87 % of the mothers who did not receive a blood transfusion. Altogether 1828 mothers received red blood cell transfusion and out of these mothers, 38 % had hemoglobin level of < 70 g/l pre-transfusion, whilst 43 % had a hemoglobin level of 70-90 g/l, and 19 % had a hemoglobin level of > 90 g/l. In the group of mothers with hemoglobin level of < 70 g/l, 78.6 % were breastfeeding at discharge. The mothers who had a hemoglobin level of 70-90 g/l had an 81.3 % rate of breastfeeding at discharge. Mothers with hemoglobin level of > 90 g/l were breastfeeding at the rate of 80.9 % at discharge. The median hemoglobin level post-transfusion was > 90 g/l in each group. The researchers concluded that since the

correction of severe persisting anemia did not affect positively on the rate of breastfeeding, severe persisting anemia did not have an effect on breastfeeding.[55]

Researchers	**Year**	**Country**	**Anemia decreases the duration of breastfeeding** (yes/no)
Henly et al	1995	USA	yes
Rioux et al	2006	Canada	yes
Drayton et al	2016	Australia	no
Chessman et al	2018	Australia	no

Table 1: The effect of anemia to the duration of breastfeeding according to studies.

3. Anemia and mental well-being

3.1 The effect of anemia during pregnancy on maternal mental well-being

There are a lot of studies from all around the world that assess the association of prenatal anemia with maternal well-being. The results of these studies are not conclusive; there are, though, slightly more studies indicating that anemia during pregnancy does have an effect on maternal mental well-being and especially on the incidence of PPD.

Goshtasebi et al (2013) studied the relationship between anemia during pregnancy and PPD in Iranian population. They recruited 281 non-anemic mothers who had no history of antidepressant-use or chronic illnesses in Sari, Iran. The hemoglobin level was measured at delivery and to evaluate PPD, they used EPDS 4-6 weeks after giving birth. They used EPDS score of 13 to diagnose PPD. The prevalence of postpartum depression was 5.5 % altogether. The results indicated that hemoglobin level of under 110 g/l at delivery increases the risk for PPD (OR=4.64).[56]

In Räisänen et al's (2014) study, all singleton births in Finland between 2002 and 2010 were studied to determine the risk factors behind depression during pregnancy, as well as the outcomes of major depression. They had altogether 511 938 study subjects, out of which 0.8 % had major depression during pregnancy. The data was gathered from national health registers. They divided women into groups depending on the diagnosis codes they had had before and during pregnancy. Anemia was defined as hemoglobin level under 100 g/l, whilst other suspected risk factors were either gathered from diagnosis codes the mothers had or were based on reports from antenatal care. The strongest association was with depression prior to pregnancy. Out of the mothers who had major depression during pregnancy but no history of depression, 3.5 % had anemia, and out of the mothers who had major depression during pregnancy and a history of depression, 2.8 % had anemia, compared to the 1.6 % of mothers with no depression diagnosis and 2.6 % of mothers with prior depression but no depression during pregnancy. Adjusted OR of depression and anemia was 1.49 in their study, which indicates that prepartum anemia is a risk factor of developing a depression during pregnancy.[57]

Alharbi et al (2014) on the other hand wanted to see which obstetric and demographic variables increase the risk of getting PPD in Saudi population. They collected data from 352 mothers who gave birth in King Khalid University Hospital or Riyadh Military Hospital from April 2013 to May 2013 by interviewing the mothers 8 to 12 weeks postpartum and using EPDS to evaluate depressive symptoms. EPDS score of 10 or higher was considered diagnostic for PPD. They measured hemoglobin level both during pregnancy and postpartum, and considered the hemoglobin level anemic if it was under 110 g/l. The prevalence of PPD was 32.2 % altogether. Out of the depressive mothers, 39.8 % had low hemoglobin levels postpartum (OR=1.70), and 40.5 % were anemic during pregnancy (OR=1.44). The findings suggest that both anemia during pregnancy and postpartum play a role in increasing the risk for PPD.[58]

Yilmaz et al (2016) studied the relationship between anemia and depression during pregnancy. They wanted to know whether the severity of anemia in the last trimester had a correlation with depressive symptoms. They did a cross-sectional study where they recruited 450 pregnant women on their routine third trimester antenatal follow-up

from September 2013 to January 2014 in Ankara, Turkey. They evaluated depression by using EPDS and determined a score of 13 points as diagnostic for depression. The subjects were divided into two groups according to their hemoglobin level: anemic group (Hb < 110 g/l) and non-anemic group (Hb ≥ 110 g/l). They discovered that the total EPDS score was significantly higher in the anemic group than it was in the non-anemic group (p=0.000), indicating that there is a relationship between anemia and depression in the last trimester of pregnancy.[59]

Xu et al (2018) studied all mothers who gave birth to their first child in New South Wales, Australia, between 2004 and 2008. After exclusions they had altogether 75 954 study subjects. The study was population based cohort study, and the subjects were traced back for 3 years prepartum and 3 years postpartum. They used hospital admission records to identify the mothers who had both a diagnosis for anemia and a diagnosis for depressive disorder or mental and behavioral disorder associated with puerperium. In their study, the admission to hospital due to depression was higher in women with anemia than those without (OR=1.62). The prevalence of anemia was significantly higher during peripartum period than it was otherwise. The proportion of hospital admissions for depression increased during the first two years postpartum, and was at their lowest on the year before giving birth. This was considered to be due to the fact that in the year before giving birth, the mothers had more hospital admissions altogether. The absolute amount of hospital admissions for depression was, however, higher in the year before giving birth in women with anemia.[60]

One study focused on anxiety during pregnancy instead of depressive symptoms. Kang et al (2016) studied the prevalence of antenatal anxiety and factors associated with it. They conducted a cross-sectional study in Changchun, China between January 2015 and March 2015. They had 467 participants who were all at least 38 weeks pregnant when recruited. To evaluate antenatal anxiety, they used Self-Rating Anxiety Scale (SAS) and the score of 50 or over as a diagnostic value for anxiety. Unfortunately, it is not clear what cutoff point was used to define anemia. The prevalence of antenatal anxiety was 20.6 % altogether. They found multiple variables that had an association with antenatal anxiety, out of which anemia during pregnancy was one (OR=2.387).[61]

There are also studies that found no evidence of the correlation between prepartum anemia and maternal depression. Armony-Sivan et al (2012) evaluated the association between pre- and postpartum maternal iron status with depressive symptoms in two Chinese samples; the pilot sample had 137 study subjects and the confirmatory sample 567. They did an observational study by using data from ongoing longitudinal studies. The pilot sample's data was collected from May 2008 to January 2011 and confirmatory sample's from November 2009 to November 2011. They evaluated iron status by measuring hemoglobin, mean corpuscle volume (MCV), zinc protoporphyrin (ZPP), ferritin, transferrin receptors and transferrin receptors index at mid-pregnancy, late pregnancy and 3 days postpartum. The anemic value for hemoglobin was set at under 110 g/l. EPDS score of 10 or higher was used to determine PPD, and the assessment was conducted at 6 weeks postpartum. In the pilot study, 23.4 % of mothers had PPD, and in the confirmatory sample 20.3 %. They found no difference in EPDS scores in anemic and non-anemic mothers in mid-pregnancy (p=0.16), late pregnancy (p=0.26) or postpartum (p=0.40), nor were there differences in iron statuses.[62]

Maeda et al (2020) made a large study concerning the correlation of anemia in different stages of pregnancy and postpartum with postpartum depression. The study design was a prospective cohort study, and they collected data between May 2010 and November 2013 in Tokyo, Japan. They had altogether 1128 study subjects. They measured hemoglobin on second (24-28 weeks of gestation) and third (35-36 weeks of gestation) trimester and once after childbirth (4-6 days postpartum). To evaluate depression, EPDS was used at 4 weeks postpartum. Hemoglobin level was considered anemic if it was under 105 g/l in the second trimester, under 110 g/l in the third trimester, or under 100 g/l in the postpartum period. EPDS score of 9 or higher was considered diagnostic for PPD. In this study, there was a significant correlation between postpartum anemia and postpartum depression. Similar correlation could not be found between anemia on second or third trimester and postpartum depression.[63]

Researchers	**Year**	**Country**	**Prepartum anemia associated with mental well-being** (yes/no)
Armony-Sivan et al	2012	China	no
Goshtasebi et al	2013	Iran	yes
Räisänen et al	2014	Finland	yes
Alharbi et al	2014	Saudi Arabia	yes
Yilmaz et al	2016	Turkey	yes
Kang et al	2016	China	yes
Xu et al	2018	Australia	yes
Maeda et al	2020	Japan	no

Table 2: The effect of anemia during pregnancy on maternal mental well-being.

Since the findings of the association between anemia and postpartum depression have been controversial in earlier studies, Azami et al (2019) did a of studies that were published of the subject until January 2018. They found a clear association between anemia and postpartum depression and according to their review, anemia during pregnancy increases the risk for PPD significantly.[64]

3.2 The effect of postpartum anemia on maternal mental well-being

The studies concerning the effect of postpartum anemia on maternal mental well-being are leaning more towards the evidence that anemia postpartum does have an effect on mental well-being. There are, however, also two studies that have found no association between the two[62,65].

Xu et al's (2018) study from Australia is described in the previous chapter (3.1 The effect of anemia during pregnancy on mental wellbeing). Their study found a correlation between the hospital admissions for depression and anemia both pre- and postpartum.[60] Alharbi et al (2014) on the other hand found a correlation of both pre- and postpartum anemia with PPD in Saudi population; said study is further described in the previous chapter[58]. Also Maeda et al's (2020) study is described in detail in the previous chapter. They discovered an association between postpartum anemia and PPD (OR=1.63), but no association between prepartum anemia and PPD.[63]

Corwin et al (2003) studied the correlation between hemoglobin levels and postpartum depressive symptoms in Pennsylvania, USA. They recruited 37 healthy mothers from who they measured hemoglobin via finger-prick blood and evaluated depressive symptoms by using The Center for Epidemiological Studies – Depressive Symptomalogy Scale (CES-D). The mother was considered anemic if hemoglobin level was under 120 g/l. In CES-D, 11-15 points indicated mild depression and 16 points or over severe depression. All subjects were visited at their home at 900-1000 hours after discharge and on the 7^{th}, 14^{th} and 28^{th} day postpartum. They found a correlation between anemic hemoglobin level on day 7 and depressive symptoms on day 28. No correlation could be found between hemoglobin levels on day 14 or 28 and depressive symptoms. The results suggest that early postpartum anemia is a risk factor for developing PPD.[66] It is important to take into consideration that finger-prick blood was used instead of venous blood to evaluate hemoglobin, which might cause error in results.

Beard et al (2005) wanted to determine whether iron deficiency anemia has an effect on maternal cognitive and behavioral performance. They conducted a prospective, randomized, controlled intervention trial in Khayelitsha, South Africa, among 3 groups of mothers: non-anemic, anemic with daily iron supplementation (125 mg of $FeSO_4$) and anemic with placebo. The total amount of study subjects was 81. The mothers were assessed at 10 weeks and 9 months postpartum. They defined iron deficiency anemia as follows: hemoglobin level of 90-115 g/l, and at least two of the following iron deficiency parameters: MCV <80 fl, transferrin saturation < 15 %, or serum ferritin < 12 µg/l. They evaluated the mothers' psychological state by using EPDS, the Raven's Colored Progressive Matrices test and 2 Perceived Stress scales. At baseline, there was no difference between the groups in cognitive and behavioral variables. There was, however, a 25 % improvement in depression and stress scales in the group of mothers that were anemic and received iron supplementation at the 9 month evaluation point ($p=0.05$). They concluded that postpartum depression, stress and cognitive impairment may be related to iron deficiency anemia, and that the results suggest that iron therapy might reduce depression and stress in mothers with iron deficiency anemia.[67]

Albacar et al (2011) studied the association of iron status 48 hours after delivery with postpartum depression. The study design was a prospective cohort study. They studied depression-free women after giving birth in several general hospitals in Spain between December 2003 and October 2004. They had 729 study subjects, after excluding mothers with high C-reactive protein (CRP) and other diseases that are known to interfere with iron metabolism. They evaluated depressive symptoms 48 hours, 8 weeks and 32 weeks postpartum by using EPDS. The women with a score of 9 or higher at the 8 or 32 weeks postpartum were identified as probably suffering from depression. To the women with scores lower than 9, a diagnostic interview was conducted to confirm the diagnosis of depression, or the lack of it. From every mother was taken a blood sample 48 hours after delivery in order to measure the ferritin, transferrin, free iron and transferrin saturation, as well as CRP. 19.2 % of mothers got an EPDS score of 9 or higher at 48 hours postpartum, 12.4 % at 8 weeks postpartum, and 13.4 % at 32 weeks postpartum. 9 % of the mothers were diagnosed with major depression during the study. Out of the women who had postpartum depression, 38.5 % had iron depletion (ferritin < 12 µg/l), whereas only 23.3 % of the non-depression group had iron depletion. The

results of the study suggest that there is an association between low ferritin level postpartum and postpartum depression (p=0.001, OR = 2.91).[68]

Eckerdal et al (2016) studied the association between postpartum hemorrhage and postpartum depression, whilst taking into account postpartum anemia, delivery experience and psychiatric history. The study design was a nested cohort study. The study subjects came from two population based longitudinal studies conducted between May 2006 and November 2012 in Uppsala, Sweden. There were altogether 446 study subjects that were divided into two groups: those who had postpartum hemorrhage of over 1000 ml within 24 hours of giving birth (n=196), and those who had postpartum hemorrhage of under 650 ml (n=250). The depressive symptoms of the mother were evaluated at 6 weeks after delivery. They used EPDS score of 12 or higher to identify the study subjects with PPD. In addition to postpartum hemorrhage and postpartum depression, they evaluated multiple other factors, including anemia both during pregnancy and after delivery. They used hemoglobin of 110 g/l or under as a diagnostic level for anemia. They could not find an association between postpartum hemorrhage and postpartum depression. There was, however, a positive association between anemia at discharge and postpartum depression (p=0.014; OR = 2.29). A weaker yet not significant association could also be found between anemia during pregnancy and postpartum depression (p=0.057).[69]

There are, however, also studies that show no association between postpartum anemia and depression. Chandrasekaran et al (2018) aimed to determine whether postpartum anemia is an independent risk factor for PPD in women who had uncomplicated term cesarean section. They recruited 103 women in Canada and measured their hemoglobin and iron status 3-5 days and 6 weeks after delivery. The presence of PPD was evaluated 24 hours after cesarean section, and then at 3 and 6 weeks after delivery. They, too, used EPDS to evaluate PPD and set the diagnostic score for PPD at 10 points or higher. Anemia was defined as hemoglobin level of under 110 g/l. 17 % of participants had a diagnostic score for PPD in EPDS. They found no evidence of the relationship between postpartum anemia and depression; there was no difference in hemoglobin or iron status in women with PPD compared to those without PPD (OR=-0.69). They concluded that anemia or poor iron status are not independent risk factors for PPD in women who have cesarean section.[65] Another study from China found no evidence of association between postpartum depression and pre- or postpartum anemia in two Chinese samples. The study from Armony-Sivan (2012) is described in detail in the previous chapter.[62]

Researchers	**Year**	**Country**	**Postpartum anemia associated with mental well-being** (yes/no)
Corwin et al	2003	USA	yes
Beard et al	2005	South Africa	yes
Albacar et al	2011	Spain	yes
Armony-Sivan et al	2012	China	no
Alharbi et al	2014	Saudi Arabia	yes
Eckerdal et al	2016	Sweden	yes

Xu et al	2018	Australia	yes
Chandrasekaran et al	2018	Canada	no
Maeda et al	2020	Japan	yes

Table 3: The effect of postpartum anemia on maternal mental well-being.

Azami et al's (2019) meta-analysis has been described in detail in the previous chapter. In their study, they also reviewed the association of postpartum anemia with PPD. They evaluated altogether 10 studies considering the association between postpartum anemia and PPD, and in all of them the prevalence of PPD was significantly higher in women with postpartum anemia than in women with no anemia.[64]

4. Conclusions

Anemia is one of the major factors concerning the well-being of a mother postpartum. A consensus whether anemia affects the duration of breastfeeding has not been reached. There are only a few studies of the association between postpartum anemia and duration of breastfeeding, and none of the association between anemia during pregnancy and duration of breastfeeding. Further research on the subject is needed.

On the other hand, the association between anemia and mental well-being has been studied widely. The studies concern mostly the association of anemia and postpartum depression. The evidence suggests that especially postpartum anemia is a major risk factor for postpartum depression. A recent study in which the association of anemia in different trimesters and postpartum with depression was assessed. It seemed that anemia during pregnancy is not a risk factor for postpartum depression but postpartum anemia is.[63]

Since breastfeeding, mother-child bonding and maternal mental well-being are strongly interconnected, we suggest that promotion of maternal health by means of treatment of iron deficiency anemia during pregnancy and postpartum by adequate iron supplementation could be one of the key factors in the prevention of maternal postpartum depression, anemia and cessation of breastfeeding.