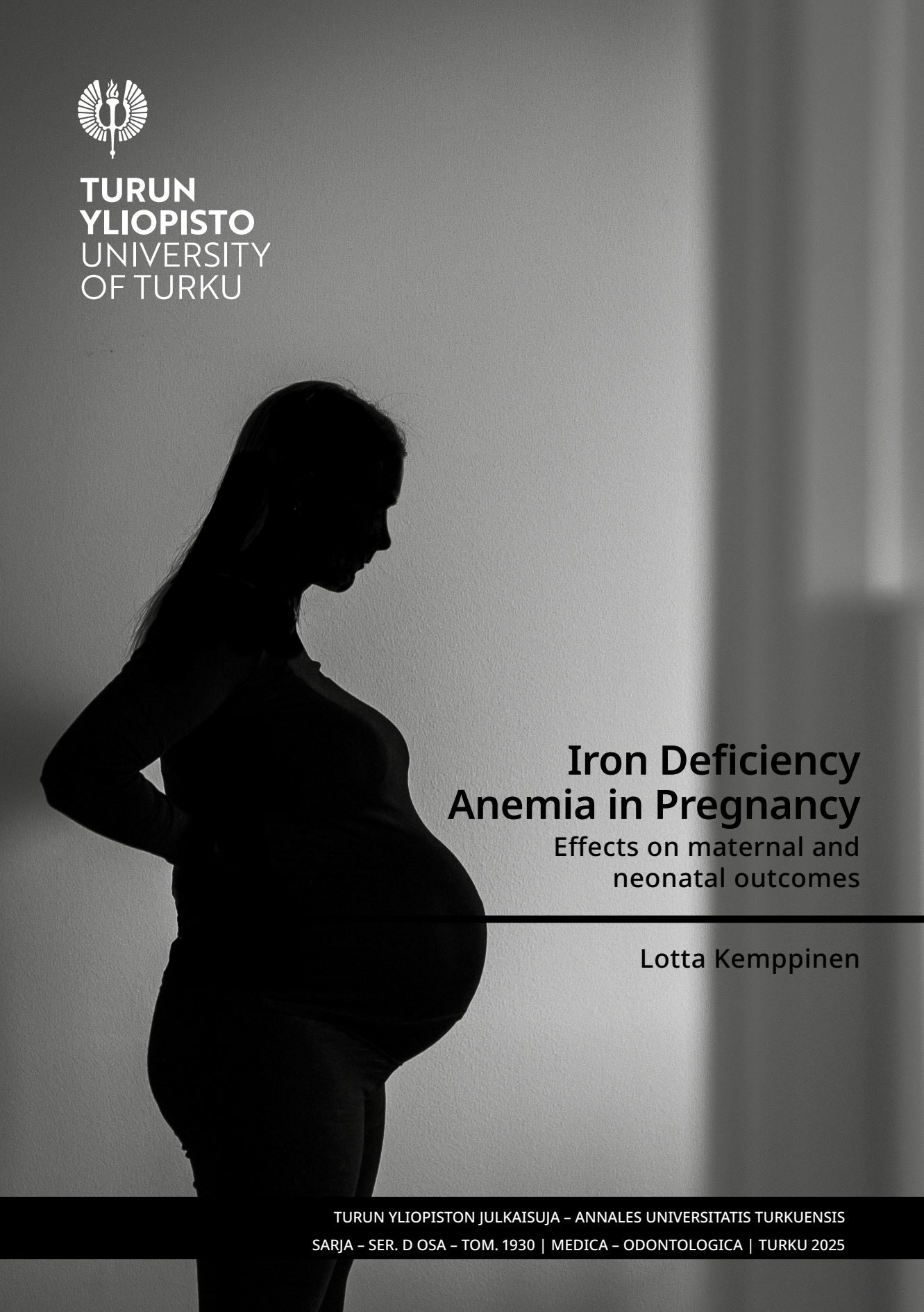

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Effects on maternal and neonatal outcomes

Lotta Kemppinen

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To my grandparents

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LOTTA KEMPPINEN: Iron deficiency anemia in pregnancy – effects on maternal and neonatal outcomes
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ABSTRACT

According to the World Health Organization (WHO), approximately 40% of pregnant women suffer from gestational anemia, most commonly caused by iron deficiency (ID). Gestational iron deficiency anemia (IDA) has been associated with pregnancy and delivery complications, as well as adverse neonatal outcomes. Our goal was to assess how gestational IDA affects maternal and neonatal outcomes in Finland. Comparison of intravenous iron substitution to orally administered iron was also one target of our study. In addition, we aimed to assess whether gestational anemia increases the risk of maternal psychological distress and shortens the duration of breastfeeding.

In a Clinical Birth Cohort with 11 669 pregnancies delivered at Turku University Hospital, Turku, Finland, between 2016 and 2018, 215 pregnant women had anemia with hemoglobin (Hb) levels <100 g/l. Moderate or severe gestational anemia was associated with prematurity, fetal growth restriction, maternal postpartum infections, and longer postpartum hospital stay. While intravenous iron corrected Hb values more effectively, no differences in maternal and neonatal outcomes were detected.

The associations between anemia and maternal psychological distress as well as breastfeeding were explored using a prospectively collected FinnBrain Birth Cohort with 1 273 pregnant women, who delivered during 2011–2015. Maternal Hb <110 g/l did not increase the risk of maternal psychological distress during pregnancy or postpartum. However, Hb <100 g/l was associated with anxiety symptoms in late pregnancy. Additionally, anemia in the third trimester did not shorten the duration of breastfeeding, and women with gestational anemia achieved the nationally recommended goal of exclusive breastfeeding as often as non-anemic women.

Even in a high-standard maternity care setting, gestational anemia is associated with an increased risk of clinically significant adverse maternal and neonatal outcomes. However, maternal antenatal anemia does not increase the risk of psychological distress or shorten breastfeeding duration. Adequate treatment should be available to pregnant women to prevent adverse maternal and neonatal outcomes.

KEYWORDS: Gestational anemia, iron deficiency anemia in pregnancy, preterm birth, small-for-gestational-age fetal growth restriction, oral iron supplementation, intravenous iron substitution, maternal depression, maternal mental distress, maternal psychological distress, maternal anxiety, pregnancy, breastfeeding

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
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TIIVISTELMÄ

Maailman terveysjärjestön (WHO) mukaan n. 40 % raskaana olevista naisista kärsii raskausajan anemiasta, jonka yleisin syy on raudanpuute. Raskausajan raudanpuuteanemia on yhdistetty raskaus- ja synnytyskomplikaatioihin sekä vastasyntyneen ennusteen huonontumiseen. Tavoitteemme oli arvioida, miten raskausajan raudanpuuteanemia vaikuttaa äidin ja vastasyntyneen ennusteeseen Suomessa. Suonensisäisen ja suun kautta annosteltavan rautalisän vertailu oli myös yksi tutkimustavoitteistamme. Lisäksi halusimme arvioida, lisääkö raskausajan anemia äidin riskiä psyykkisille oireille ja lyhentääkö se imetyksen kestoa.

Turun yliopistollisesta sairaalasta vuosina 2016–2018 kerätyssä 11 669 synnyttäjän kohortissa hemoglobiini (Hb) <100 g/l todettiin 215 raskaana olevalla naisella. Keskivaikea tai vaikea anemia yhdistyi ennenaikaisuuteen, sikiön kasvuhidastumaan, äidin synnytyksen jälkeisiin infektioihin ja pidempään synnytyksen jälkeiseen sairaalassaoloaikaan. Suonensisäinen rautalisä korjasi Hb-arvon tehokkaammin kuin suun kautta annosteltu rauta, mutta eroja äidin ja vastasyntyneen ennusteessa ei havaittu.

Yhteyttä anemian ja äidin psykologisten oireiden sekä imetyksen välillä tutkittiin prospektiivisesti kerätyllä FinnBrain tutkimuskohortilla, joka koostui 1238 raskaana olevasta naisesta, jotka synnyttivät vuosina 2011–2015. Äidin Hb <110 g/l ei lisännyt riskiä äidin psyykkisille oireille raskausaikana tai synnytyksen jälkeen, mutta Hb <100 g/l yhdistyi äidin lisääntyneeseen ahdistuneisuuteen loppuraskaudessa. Anemia kolmannessa raskauskolmanneksessa ei myöskään lyhentänyt imetyksen kestoa ja raskausanemiasta kärsivät naiset saavuttivat kansallisen imetyssuosituksen, neljä kuukautta täysimetystä, yhtä usein kuin ei-aneemiset naiset.

Raskausajan anemia lisää riskiä äidin ja vastasyntyneen huonoon ennusteeseen. Kuitenkaan äidin psyykkisiin oireisiin raskausajan anemialla ei ole vaikutusta eikä se lyhennä imetyksen kestoa. Asianmukaisesta ja oikea-aikaisesta hoidosta tulee huolehtia äidin ja vastasyntyneen ennusteen optimoimiseksi.

AVAINSANAT: Raskausajan anemia, raskausajan raudanpuuteanemia, ennenaikainen synnytys, pienipainoinen, sikiön kasvuhidastuma, suun kautta annosteltu rauta, suonensisäinen rauta, äidin masennus, äidin psyykkinen oireilu, äidin ahdistuneisuus, raskaus, imetys

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Abbreviations

ACOG	American College of Obstetricians and Gynecologists
BE	Base excess
BMI	Body mass index
CI	Confidence interval
CRP	C-reactive protein
EBF	Exclusive breastfeeding
EPDS	Edinburgh Postnatal Depression Scale
FBC	Full blood count
FGR	Fetal growth restriction
Hb	Hemoglobin
HIV	Human immunodeficiency virus
ID	Iron deficiency
IDA	Iron deficiency anemia
NICU	Neonatal intensive care unit
OR	Odds ratio
PPD	Postpartum depression
PRAQ	Pregnancy-Related Anxiety Questionnaire
RCT	Randomized controlled trial
RR	Risk ratio
SCL	Symptom checklist-90
SD	Standard deviation
SGA	Small-for-gestational-age
TfR	Transferrin receptor
TSAT	Transferrin saturation
WHO	World Health Organization

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Kemppinen L, Mattila M, Ekholm E, Pallasmaa N, Törmä A, Varakas L, Mäkikallio K. Gestational anemia is associated with preterm birth, fetal growth restriction, and postpartum infections. *Journal of Perinatal Medicine*, 2021;49(4): 431-438.

II Kemppinen L, Mattila M, Ekholm E, Pallasmaa N, Huolila L, Pelto J, Karlsson H; Mäkikallio K, Karlsson L. Gestational anemia and maternal antenatal and postpartum psychological distress in a prospective FinnBrain Birth Cohort Study. *BMC Pregnancy and Childbirth*, 2022; 22: 704.

III Kemppinen L, Mattila M, Ekholm E, Pallasmaa N, Laura P, Karlsson H; Mäkikallio K, Karlsson L. Effect of gestational anemia on breastfeeding –a prospective follow-up study. *BMC Pregnancy and Childbirth*, 2025; 25: 653.

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1 Introduction

Gestational iron deficiency anemia (IDA) is a prevalent medical condition that affects patient populations worldwide. Pregnancy predisposes to iron deficiency (ID) due to an increased iron demand, which can lead to IDA. The World Health Organization (WHO) estimates that nearly 40% of pregnant women suffer globally from gestational anemia (WHO, 2025). The most common cause for gestational anemia is ID, which accounts for at least half of the cases (Stevens et al., 2013). In low- and middle-income countries, nutrient deficiencies are more prevalent compared to high-income countries such as Finland (Kebede et al., 2025). However, in Finland, gestational anemia, primarily by ID, remains to affect 10–20% of pregnancies (Tiitinen, 2018).

Symptoms of gestational anemia are often nonspecific, such as fatigue and weakness, and many patients are asymptomatic (Weckmann et al., 2023). Gestational anemia is associated with an increased maternal and neonatal morbidity and mortality: it has been shown to increase risks of cesarean section, significant hemorrhage during delivery, postpartum depression (PPD), and postpartum infections (Chaim et al., 2000; Drukker et al., 2015; Jung et al., 2019). In addition, maternal anemia is associated with adverse neonatal outcomes, such as prematurity and growth restriction (Drukker et al., 2015; Levy et al., 2005; Rahmati et al., 2020; Young et al., 2019). However, the causal relationship remains unclear and most of the studies have been conducted in low- and middle-income setting (Peña-Rosas et al., 2015).

Pregnancy affects maternal psychological well-being in various ways and increases the risk of mental distress (Otchet et al., 1999). Gestational anemia has been recognized as a risk factor for PPD (Azami et al., 2019; S. Y. Kang et al., 2020), which is known to increase the risk of early cessation of breastfeeding (Henderson et al., 2003). In some studies, gestational anemia has been suggested to shorten the duration of breastfeeding (Park et al., 2003; Rioux et al., 2006); however, research evidence on this association remains limited, and no studies have been conducted in Finland.

The treatment of gestational IDA is iron supplementation, and in severe cases, red blood cell transfusions. Iron can be administered both orally and intravenously.

However, the most appropriate form of iron administration remains a topic of debate. Oral iron is economical, widely available, and safe, but the side effects restrict the adherence; therefore, intravenous iron supplementation has been proposed as a solution. Although intravenous iron corrects the hematologic parameters more effectively, no difference in the frequency of adverse maternal and neonatal outcomes has been shown, when compared with oral iron (Govindappagari & Burwick, 2019; Neogi et al., 2019).

In this project, we aimed to assess how gestational IDA affects maternal and neonatal outcomes in a high-income country with a high standard maternity care, and whether treatment with either the oral or intravenous route impacts the rates of adverse maternal and neonatal outcomes as well as hematologic parameters. While anemia has been associated with PPD, we also sought to evaluate the effect of gestational anemia on maternal psychological symptoms during both pregnancy and the postpartum period in a Finnish population. Furthermore, given the lack of research on the relationship between anemia during pregnancy and breastfeeding, we explored whether pregnant women with gestational anemia succeed to breastfeed their infants as well as non-anemic women.

2 Review of the Literature

2.1 Hematologic changes in pregnancy

2.1.1 Hemoglobin and other anemia-related laboratory parameters

In pregnancy, plasma volume increases significantly due to changes in vascular resistance due to hormonal changes (Chandra et al., 2012). The increased plasma volume leads to decreased hemoglobin (Hb) levels due to hemodilution (Aguree & Gernand, 2019; Soma-Pillay et al., 2016). The hemodilution process begins at 6–12 gestational weeks (Bernstein et al., 2001). Plasma volume increases by 30–50%, peaking at 34 weeks (Akinlaja, 2016; Carlin & Alfirevic, 2008). This phenomenon is physiological and prepares the mother for the labor and intrapartum blood loss, as well as ensures adequate blood flow to the uterus by reducing blood viscosity (Gaillard et al., 2014). Inadequate hemodilution and smaller plasma volume has been shown to correlate with higher risk of fetal growth retardation (Rosso, 1992, Redman, 1984, Murphy, 1986), whereas maximal hemodilution correlates with higher fetal weight (Campbell & MacGillivray, 1972; Hytten & Paintin, 1963). The changes in maternal plasma volume return to the non-pregnant levels by six weeks postpartum (Hytten & Paintin, 1963).

During pregnancy, physiological hemodilution causes decreases in Hb, hematocrit, and erythrocyte concentrations. **Figure 1a** illustrates the changes in Hb levels throughout normal pregnancy (Milman et al., 2000; Stevens et al., 2013, Whittaker, et al. 1996). Erythropoiesis accelerates during pregnancy, leading to an increased number of reticulocytes in the bloodstream (Choi & Pai, 2001). This increase can be detected as rise in mean corpuscular volume. The increase in erythropoiesis is proportionally smaller compared to plasma volume expansion, resulting in decreased concentrations of erythrocytes and Hb. Hb reaches its lowest point during the second trimester (Milman et al., 2000).

Other laboratory parameters, such as the iron storage protein ferritin, also decrease during a normal pregnancy due to hemodilution and increased utilization of iron stores, as shown in **Figure 1b** (Fisher & Nemeth, 2017; Mei et al., 2021; Milman et al., 2007). Physiologically, the lowest ferritin levels occur between 35

and 38 weeks, after which ferritin levels rise steadily (Fisher & Nemeth, 2017; Larsson et al., 2008; Milman et al., 2007).

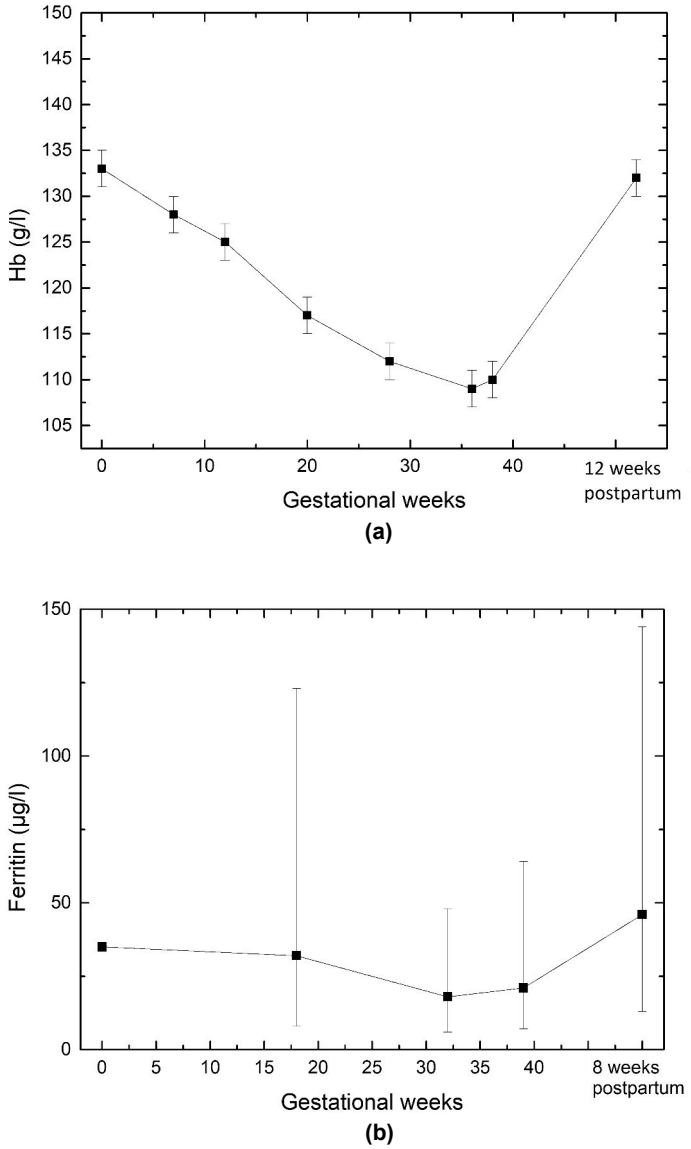

Figure 1. **a.** Mean Hb levels with 95% CI (modified from Milman et al., 2000 and Stevens et al., 2013, Whittaker et al., 1996) and **b.** Mean (range) ferritin levels (modified from Fisher & Nemeth, 2017; Mei et al., 2021; Larsson et al., 2008; Milman et al., 2007) during pregnancy.

When Hb values remain at non-pregnant levels or only decrease slightly, physiological hemodilution is considered to be inadequate (Carlin & Alfirevic, 2008). Inadequate plasma volume expansion can lead to increased blood viscosity and reduced oxygen flow to the placenta (Gaillard et al., 2014). This may predispose the fetus to decreased oxygen intake, potentially resulting in adverse neonatal outcomes (Ronkainen et al., 2019; Stephansson et al., 2000; Yip, 2000). High Hb levels have also been associated with maternal complications (Goshtasebi & Moghaddam Banaem, 2012; Sissala et al., 2022; Young et al., 2019).

Regarding maternal and neonatal complications associated elevated Hb levels, values greater than 130–132 g/l during pregnancy have been linked to increased risks of hypertension and preeclampsia (Goshtasebi & Moghaddam Banaem, 2012; Young et al., 2019) as well as gestational diabetes (Sissala et al., 2022; Young et al., 2019). Moreover, Hb ≥146 g/l increased the risk of stillbirth in a Swedish study (Stephansson et al., 2000), and a Finnish study revealed that Hb >135 g/l was associated with an increased risk of having a small-for-gestational-age (SGA) neonate (Ronkainen et al., 2019). Similar results have been reported in other studies (Yip, 2000; Young et al., 2019). The association between high Hb levels and prematurity has also been investigated; however, a meta-analysis conducted by Young et al. found that high Hb (>130 g/l) value was not associated with prematurity (Young et al., 2019).

2.1.2 Iron requirement and metabolism during pregnancy

Iron is an essential micronutrient, serving as a component of several proteins required in fundamental physiological processes such as oxygen transport, cell signalling, and immunity (Dev, 2017). However, in excessive amounts, iron is known to be toxic and, therefore, its absorption is tightly regulated (Dev, 2017). Most of the body's iron is utilized as a component of Hb in red blood cells and is subsequently recycled and stored as ferritin by macrophages and liver hepatocytes (Ganz, 2013). Dietary absorption in the intestine and iron loss due to epithelial desquamation and hemorrhage constitute only a small part of overall iron metabolism (Pantopoulos, 2012). In the bloodstream, iron is carried bound to transferrin and delivered to the bone marrow for erythropoiesis and other tissues for uptake by transferrin receptor (Pantopoulos, 2012). During pregnancy, iron is transferred from the mother to the fetus through the placenta. The amount of iron transferred increases as pregnancy progresses and is regulated by transferrin receptors on the placental surface (McArdle et al. 2003).

The estimated daily iron requirement for a healthy woman of reproductive age is 2.2 mg (Beard, 2000). During pregnancy, the demand for iron increases progressively. The total amount of extra iron needed during the whole pregnancy is

around 1000–1200 mg (Fisher & Nemeth, 2017). The increased need for iron begins in the second trimester and continues to rise until the end of the pregnancy (Bothwell, 2000). Approximately 0.8 mg, 4–5 mg, and 7.5 mg of iron per day are required during the first, second, and third trimesters, respectively (Bothwell, 2000). In the first trimester, the demand for iron is lower compared to the prepregnant state due to the absence of menstruation and the loss of iron through hemorrhage. During early pregnancy, iron is primarily used for accelerated maternal erythropoiesis. The iron requirements in the second trimester mainly support the infant's erythropoiesis and the growth of the placenta. In the third trimester, iron is also needed for the accelerated neurogenesis of the fetus. ID is known to affect several processes in the developing brain, including myelination, monoamine metabolism, and the development of the hippocampus (Lozoff & Georgieff, 2006; Georgieff, 2008). Alterations in monoamine regulation have been shown to persist into adulthood in rodent studies (Lozoff et al., 2006; Beard et al., 2003). The iron need of the fetus is at its highest after 30 weeks (Allen, 1997).

Dietary iron intake and absorption vary considerably between diets. Iron is absorbed in the intestine in two forms: heme and non-heme iron. Heme iron, which has higher bioavailability, is found in animal products such as meat and fish, whereas non-heme iron is present in fruits and vegetables (Roughead, 2002). Iron absorption from the intestine is physiologically enhanced during pregnancy, particularly in the second and third trimesters, to meet the increased iron demand (Svanberg et al., 1975). The mechanism underlying the increased absorption is thought to be largely due to changes in hepcidin metabolism (Bah et al., 2017; Koenig et al., 2014; Van Santen et al., 2013). In a healthy non-pregnant individual, iron absorption in the intestine is around 2–30% of dietary iron (Piskin et al., 2022), whereas during pregnancy, it increases to 7%, 36%, and 66% during the first, second, and third trimesters, respectively (Barrett et al., 1994). Therefore, the recommended intake of iron from foods and supplements during pregnancy is 27 mg daily to cover the iron needs (Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, 2002). However, in Finland, the estimated iron intake during pregnancy is 10.2–11.4 mg per day; therefore, most pregnant women do not reach the recommended goal (Milman, 2020).

Hepcidin is a peptide hormone responsible for the regulation of iron absorption in the intestine (Koenig et al., 2014). It is produced by the liver and is known to regulate iron homeostasis and availability (Ganz & Nemeth, 2012). Depletion of maternal hepcidin is associated with increased iron stores and vice versa (Ganz & Nemeth, 2012). During pregnancy, hepcidin levels are shown to be lower compared to the prepregnancy state (Koenig et al., 2014). The etiology of this phenomenon is unknown, but it is suggested to be related to decreased maternal iron stores (Van Santen et al., 2013). Sangkhae et al. suggested, that the placenta secretes a hepcidin-

suppressing factor (Sangkhae, 2020), leading to decreased hepcidin levels and increased iron absorption during pregnancy. Furthermore, inflammatory conditions associated with pregnancy, such as preeclampsia, obesity, and malaria infection, have been shown to increase hepcidin levels, resulting in impaired iron absorption and availability (Dao et al., 2013; Toldi et al., 2010).

The requirement for elemental iron during pregnancy is presented in **Figure 2**.

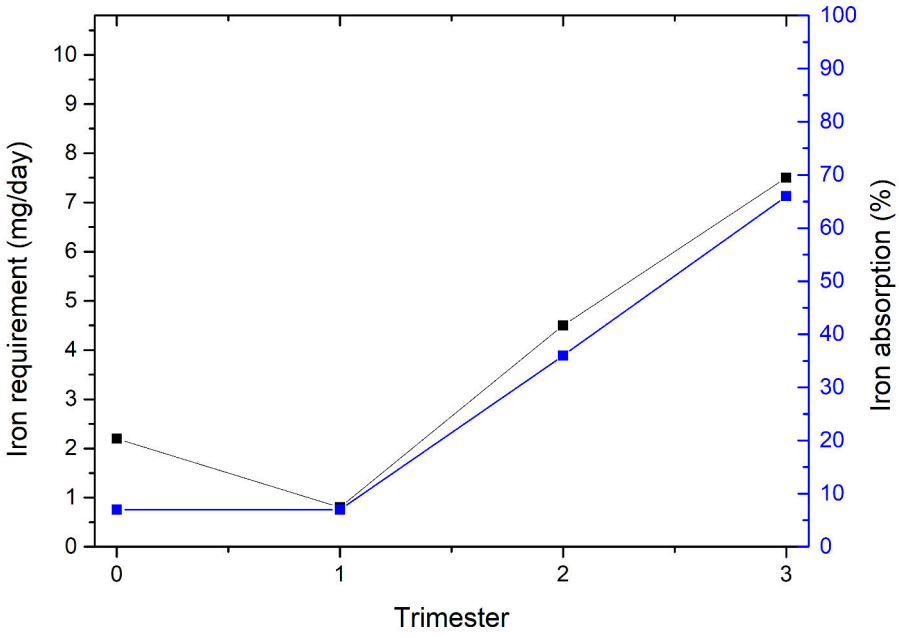

Figure 2. Estimated daily iron requirement during pregnancy (modified from Bothwell, 2000) and iron absorption (modified from Barrett et al. 1994). The estimated iron intake during pregnancy in Finland is 10.2–11.4 mg/day (Milman 2020).

2.2 Gestational anemia

Anemia is defined as a condition characterized by low Hb concentration in the blood. Several cut-off values for Hb exist for different patient populations. According to current WHO guidelines, gestational anemia is defined as an Hb level <110 g/l at any gestational age (WHO, 2012). In some countries, for example, in the United Kingdom, Hb value of 105 g/l is used as a cut-off during the second and third trimesters of pregnancy and 100 g/l postpartum (Pavord et al., 2020). American Centre of Disease Control in the United States and American College of Obstetricians and Gynecologists (ACOG) define gestational anemia as Hb <110 g/l in first and third trimesters and <105 g/l in the second trimester (ACOG, 2021; Yip

R et al., 1998) In Finland, patients with Hb <110 g/l are considered anemic in all three trimesters of pregnancy (Tiitinen, 2018).

According to WHO, gestational anemia is classified as mild (Hb 100–109 g/l), moderate (Hb 70–99 g/l), and severe (Hb <70 g/l) (WHO, 2011) (**Table 1**).

Table 1. Classification of gestational anemia according to WHO (WHO, 2011).

WHO Classification	Hb level (g/l)
Gestational anemia	<110
Mild	100–109
Moderate	70–99
Severe	<70

Globally, the prevalence of gestational anemia is estimated to be around 36% (WHO, 2025). The prevalence of gestational anemia varies widely among low-, middle-, and high-income countries (**Figure 3**). Generally, the prevalence is the highest in low-income countries, where the incidence of maternal and neonatal adverse outcomes caused by anemia is also the greatest due to a high prevalence of comorbidities (Karami et al., 2022; Rahman et al., 2016). In a study conducted in northeastern India, the prevalence of gestational anemia was as high as 89.6% (Bora et al., 2014). Gestational anemia is usually mild (Hb 100–109 g/l), with the highest prevalence occurring in late pregnancy (Karami et al., 2022). WHO estimates that 15% of pregnant women are anemic in Finland (WHO, 2024). There has been an increasing trend in the prevalence of moderate or severe anemia (Hb <100 g/l) in Finland, ranging from 1.4% in 2005 to 5.8% in 2024 (Finnish Institute for Health and Welfare, 2025). WHO has listed a 50% reduction in maternal anemia by 2030 as one of its global goals (WHO, 2025). However, the global prevalence of gestational anemia has not decreased sufficiently to meet this target (WHO, 2025). In the United States, the prevalence of gestational anemia increased from 10.1% to 11.4% between 2008 and 2018 (Kanu et al., 2022).

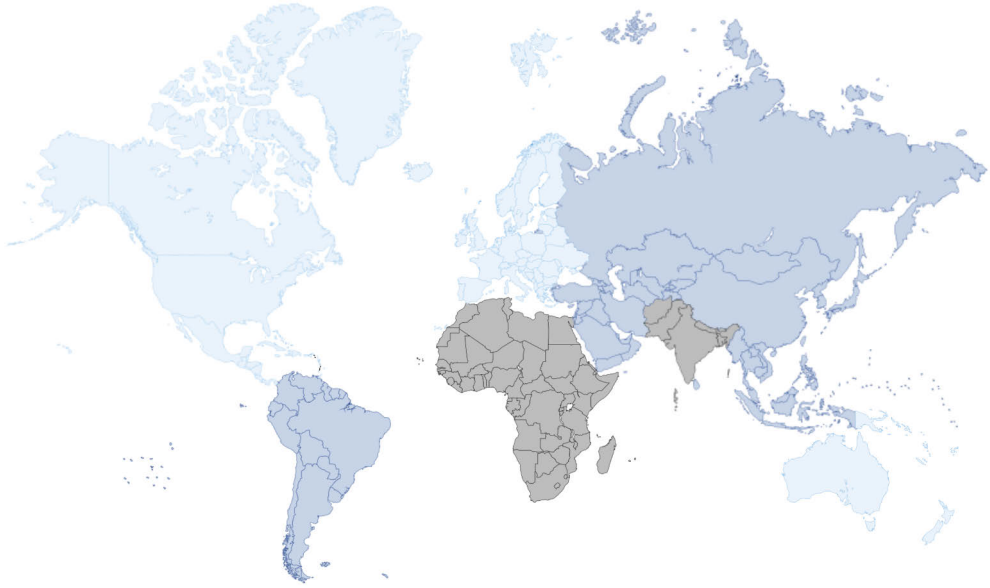

Figure 3. Global prevalence of gestational anemia. Light blue <30%, dark blue 30–40%, and black >40% (modified from WHO, 2025). The prevalence of gestational anemia is highest in Mali (62.1%), Benin (60.2%), and Sierra Leone (53.7%).

2.2.1 Etiologies of gestational anemia

ID is known to cause more than 50% of gestational anemia cases (Stevens et al., 2013), while rarer causes, such as thalassemia, specific medications, and folate deficiency, account for the remainder. Anemia, defined as a decreased amount of Hb circulating in the blood, results from decreased production of red blood cells, increased loss of red blood cells, or destruction of red blood cells.

Decreased production of red blood cells results from reduced activity in the bone marrow. This can be attributed to various factors, including nutrient deficiencies, certain medications, inflammation, or kidney disease, which leads to decreased erythropoietin production (Fischer et al., 2004; Morton et al., 2021). Macrocytic anemia is often caused by folate deficiency, particularly in women adhering to special diets, such as vegetarianism (Sifakis & Pharmakides, 2000; C. Tan et al., 2019). In sub-Saharan Africa, ID is the most common etiology of gestational anemia. However, anemic women are often diagnosed with additional nutritional deficiencies. In a study conducted in Malawi, nearly 40% and 21-34% of anemic women were diagnosed with vitamin A deficiency and folate deficiency, respectively (Van den Broek et al., 2000). Various medications, such as antiepileptics, are known to predispose to folate deficiency, especially during pregnancy, when the need for folate is physiologically increased, thus predisposing to anemia (Wlodarczyk et al.,

2012). Vitamin B12 deficiency is a rare cause of gestational anemia, as it negatively impacts to fertility (Molloy et al., 2008).

Hemoglobinopathies such as alpha and beta thalassemia and sickle cell disease lead to the destruction of red blood cells, resulting in hemolytic anemia. These conditions are most commonly diagnosed in patients with African, Middle Eastern, and Asian descent (Sifakis & Pharmakides, 2000). The prevalence of hemoglobinopathies varies by region. In a study conducted in Thailand, where the prevalence of thalassemia is high, 54.9% of anemic pregnant women were found to be thalassemia carriers, whereas 43.1% had ID (Sukrat et al., 2006). Additionally, chronic malaria can cause hemolytic anemia in malaria-endemic regions, especially when combined with sickle cell disease (Rahimy et al., 2000). An acute cause of hemolytic anemia during pregnancy is Hemolysis, Elevated Liver enzymes, and Low Platelets syndrome (HELLP). It is a rare condition that occurs globally in 0.2–0.8% of pregnancies and is associated with hemolytic anemia (Abildgaard & Heimdal, 2013).

In chronic inflammatory diseases, anemia is caused by inflammation and alterations in hepcidin metabolism (Weiss et al., 2019). Furthermore, in low-and middle-income countries, infections such as human immunodeficiency virus (HIV), and intestinal worm infections increase the risk of anemia (Stoltzfus et al., 1997; N. Van Den Broek, 1998; Kefiyalew et al., 2014; J. Zhang et al., 2022).

2.2.2 Maternal symptoms and complications associated with gestational anemia

2.2.2.1 Maternal symptoms

The symptoms of anemia are nonspecific and depend on its severity and timing, and whether the onset of anemia is acute or chronic (Weckmann et al., 2023). The symptoms range from asymptomatic to life-threatening, influenced by patient characteristics and possible comorbidities. During pregnancy, various physiological changes occur in the cardiovascular system, including increased cardiac output, hemodilution, and lowered blood pressure, complicating the differentiation between normal physiological changes related to pregnancy and symptoms caused by anemia (Soma-Pillay et al., 2016).

The most common symptoms reported by anemic patients include fatigue and weakness. In a study conducted in Bangladesh, 75% of women with anemia with Hb <100 g/l presented with fatigue (Singal et al., 2018). Several other symptoms with anemia have also been reported, such as palpitations (Weber & Kapoor, 1996), dizziness, dyspnea, tachycardia, paleness, hair loss, restless legs syndrome, reduced physical performance, poor concentration skills, and headache (Breymann &

Auerbach, 2017; Camaschella, 2015; Lee & Okam, 2011; Weber & Kapoor, 1996). Severe anemia can even lead to cardiac heart failure. A South African randomized controlled trial (RCT) showed a correlation between iron supplementation in iron deficient pregnant women and improved cognitive functions suggesting that IDA can manifest as cognitive symptoms (Beard et al., 2004). IDA typically develops slowly allowing the body to adjust. Therefore, it is common that the patient is asymptomatic or experiences mild symptoms. In Finland, most anemic pregnant patients have Hb between 100 and 110 g/l and, thus, suffer from mild anemia and are often asymptomatic.

Fast-developing acute anemia, such as that caused by hemorrhage, typically results in significant and potentially life-threatening symptoms that vary based on the severity of the anemia. Most commonly these include hypotension, dizziness, tachycardia, pallor, and even unconsciousness.

2.2.2.2 Maternal complications

Data on adverse maternal outcomes associated with gestational anemia have been reported in systematic reviews and a meta-analysis (Drukker et al., 2015; Haider et al., 2013; Jung et al., 2019; Rahmati et al., 2020; Young et al., 2019, Daru et al., 2018). While the association between anemia and maternal morbidity is well established, the causality has not been clarified. Maternal anemia is the most common pregnancy complication and often exist with other morbidities, raising questions about whether adverse outcomes are solely attributable to anemia itself. The complications of gestational anemia vary based on the timing and severity of the condition. Generally, the risk of adverse maternal outcomes related to gestational anemia is reported to be higher in low- and middle-income countries (Black et al., 2013).

Data regarding the relationship between gestational anemia and preeclampsia are controversial, and the mechanisms linking the two are completely unknown, although factors such as micronutrient deficiency and endothelial dysfunction related to high BMI have been suggested (Ali et al., 2014; Bilano et al., 2014; Yoo et al. 2009). Most studies have associated high Hb values (≥130 g/l) with an increased risk of preeclampsia (Young et al., 2019). However, in some studies, anemia during pregnancy has been linked to an increased risk of preeclampsia (Karaşahin et al., 2007; Patra et al., 2005; Wang et al., 2018). Bilano et al. reported that severely anemic women with Hb <70 g/l have a threefold risk of preeclampsia (Bilano et al., 2014), and in a study conducted in Sudan, severe maternal anemia with Hb <70 g/l increased the risks of both preeclampsia and eclampsia (Ali et al., 2011). Furthermore, non-anemic pregnant women had a 60% lower risk of preeclampsia compared to anemic women with adjusted OR of 0.4 (95% CI 0.2–0.8) in a case-

control study of 337 Ethiopian pregnant women (Aweke et al., 2024). In an Iranian prospective study with 520 participants, pregnant women who were diagnosed with preeclampsia, had a significantly lower Hb level at 6–11 gestational weeks (Khoigani et al., 2012). Interestingly, in this study, the change in hematocrit between the first and the second half of pregnancy was significantly less in those diagnosed with preeclampsia (Khoigani et al., 2012).

Anemia increases the risk of significant hemorrhage by altering the function of the coagulation system. In addition, patients suffering from anemia are less tolerant for blood loss (Evensen et al., 2017; Harrison, 2021; Youssry et al., 2018). Hemorrhage is the most common cause of maternal morbidity among women with anemia, making the prevention of anemia highly important (Haeri & Dildy, 2012). In their meta-analysis including 117 studies, Jung et al. reported that the incidence of significant postpartum hemorrhage was 30% higher in the presence of maternal anemia (Jung et al., 2019). In a retrospective cohort study including 59 282 deliveries, maternal anemia with Hb 95–105 g/l and <95 g/l increased the risk of perinatal red blood cell transfusion ORs up to 3.03 (95% CI 2.43–3.79) and 12.65 (95% CI 10.35–15.46), respectively (Ehrenthal et al., 2012). Soltan et al. reported that moderate anemia with Hb < 90 g/l on admission for delivery was associated with an increased nitric oxide level–which, in turn, predisposes to atonic postpartum hemorrhage (Soltan et al., 2012). Furthermore, some studies have associated maternal anemia with placental abruption and, thus, maternal peripartum hemorrhage (Arnold et al., 2009; Shi et al., 2022).

According to systematic reviews and meta-analyses, gestational anemia increases the incidence of cesarean deliveries (Adam et al., 2023; Jung et al., 2019; Young et al., 2019). In a large retrospective study including over 75 000 parturients, gestational anemia at birth raised the risk of cesarean section (OR 1.30; 95% CI, 1.13–1.49) in otherwise healthy women (Drukker et al., 2015). Adam et al. also reported in their meta-analysis including a total of 336 128 pregnant women that maternal anemia significantly increased the risk of cesarean section (OR 1.63; 95% CI 1.23–2.17) (Adam et al., 2023), and according to a Korean study, cesarean section rate due to fetal distress was reported to be increased among anemic women (Hwang et al., 2010).

ID and IDA predispose to infections by limiting the function of immunological system (Beard, 2001; Kumar & Choudhry, 2010). In addition, decreased blood flow and tissue oxygenation, leading to impaired wound healing, has been suggested to act as mechanisms (Harrison et al., 2021). Indeed, several studies have associated maternal anemia with an increased risk of infections (Rukuni et al., 2016; Smith et al., 2019). In a Canadian retrospective study including 65 906 anemic women, women with mild (Hb 90–109 g/l) or moderate (Hb 70–89 g/l) anemia in the third trimester or at admission to delivery were more likely to have postpartum infections

such as urinary tract infections or endometritis (Smith et al., 2019). In a large American study, diagnosis of maternal anemia increased the risks of wound infections, chorionamnionitis, and endometritis (Harrison et al., 2021).

However, iron is also known to serve as an essential nutrient for pathogens, and therefore, excess iron could increase the risk of infections (Kortman et al., 2012)

Systematic reviews and meta-analyses have linked gestational anemia to increased risks of antenatal depression and PPD (Azami et al., 2019; Kang et al., 2020), although only a few studies regarding anemia's role in antenatal depression have been published (Armony-Sivan et al., 2012; Babu et al., 2018; Kwak et al., 2022). Majority of these studies have used the Edinburgh Postnatal Depression Scale (EPDS) to assess the severity of maternal depressive symptoms, although some have applied scales such as Kessler Psychological Distress Scale (K10), CESD-10 and, in some studies confirmed ICD-10 diagnoses have been used to define depression (Corwin et al., 2003; Lukose et al., 2014; Saptarini & Setyonaluri, 2019; Xu et al., 2018). EPDS is an internationally validated and widely used questionnaire (Cox & Holden, 2003; Cox et al., 1996; Rubertsson et al., 2011), and as a cut-off value indicating depression either EPDS ≥10 or EPDS ≥12 is most commonly used (Cox et al., 1996; Navarro et al., 2007).

In a meta-analysis including 10 studies, postpartum anemia was significantly associated with PPD with an RR of 1.240 (95% CI 1.001–1.536, p = 0.048) (Azami et al., 2019). In an observational case-control study with 352 Saudi women, postpartum anemia with Hb <110g/l increased the risk of PPD defined as EPDS ≥10 with an OR 1.70 (95% CI 1.05–2.74, p=0.03) (Alharbi & Abdulghani, 2014). On the other hand, an RCT conducted with 300 Slovenian women reported no difference in postpartum EPDS scores between anemic (Hb <100g/l) and non-anemic groups (Bombač Tavčar et al., 2023).

Data regarding the association between anemia during pregnancy and PPD are more controversial. In a recently published prospective study with 1 128 pregnant women, no association between antenatal anemia with Hb <105 g/l in the second trimester and Hb <110 g/l in the third trimester and PPD was detected, but postpartum anemia with Hb <100 g/l was significantly associated with PPD (Maeda et al., 2020). However, several studies and a meta-analysis have reported a link between antenatal anemia and PPD (Azami et al., 2019; Goshtasebi et al., 2013; Xu et al., 2018). In an Iranian prospective study, pregnant women with Hb <110 g/l at delivery had an increased risk of PPD with an OR 4.64 (95% CI 1.33–16.08) (Goshtasebi et al., 2013), and in a meta-analysis including over 32 million women, antenatal anemia was significantly associated with both antenatal depression with an OR 1.36 (95% CI 1.07–1.72) and PPD with an OR 1.53 (95% CI 1.32–1.78) (Kang et al., 2020).

Only a few studies have assessed the relationship between anemia during pregnancy and antenatal depression. Yilmaz et al. found a connection between antenatal anemia with Hb <110 g/l and depressive symptoms in the third trimester of pregnancy (Yılmaz et al., 2017). In addition, Woldetensay et al. reported that anemia with Hb <110 g/l between 12 and 32 gestational weeks was associated with antenatal depression (Woldetensay et al., 2018). In a Korean prospective study including 4067 pregnant women, anemia with Hb <110 g/l in the first trimester was not associated with an increased risk of depression, defined as EPDS ≥10, during pregnancy, but the risk was increased postpartum with an adjusted OR of 1.61 (95% Cl 0.93–2.80, p = 0.092) (Kwak et al., 2022).

Several different mechanisms have been suggested to act as mediators in the association between anemia and depression. The most commonly suggested mechanism is ID and its impact on neurotransmitter metabolism (Lozoff, 2011). Iron is required for several reactions in the monoamine synthesis and metabolism of neurotransmitters, such as dopamine, norepinephrine, glutamate, γ-aminobutyric acid, and serotonin (Erikson et al., 2001; J. Kim & Wessling-Resnick, 2014). These neurotransmitters are involved in major emotional and behavioral responses in the brain, potentially explaining the connection between IDA and depression. Chandrasekaran et al. suggested that ID alone, not anemia, could account for the increased risk of PPD (Albacar et al., 2011; Chandrasekaran et al., 2018). In a retrospective Canadian study assessing 142 pregnant women with ferritin levels available after gestational week 20, women with ferritin <12 µg/l were more likely to develop antenatal depression (OR 2.51, 95% CI 1.14–5.52) (Dama et al., 2018). In addition, major hormonal changes in pregnancy are recognized to increase the risk of depressive symptoms in pregnant women, thus making pregnancy and postpartum periods of vulnerable time for mental distress (Asher et al., 1995). Anemia is also known to increase the risk of significant peripartum hemorrhage, which is suggested to predispose to depression (Eckerdal et al., 2016). However, in a study conducted by Eckerdal et al., there was no association between postpartum hemorrhage and PPD (Eckerdal et al., 2016). In addition, fatigue has been linked to an increased risk of depression (Albacar et al., 2011), and since fatigue is commonly caused by anemia, it could explain the association with PPD. Moreover, a negative delivery experience and adverse outcome at birth have been suggested to predispose the mother to depressive symptoms (Eckerdal et al., 2016).

Previous research has focused on the relationship between anemia and maternal depression (Azami et al. 2019; Kang et al., 2020), with only a few studies assessing the role of anemia in maternal anxiety. In some studies, gestational anemia has been identified as a risk factor for maternal anxiety (Kang et al., 2016; Kwak et al., 2022), while an Indian study assessing risk factors for anemia found no association between anemia and anxiety (Vindhya et al., 2019). A postpartum decline in maternal anxiety

has been observed in various studies, suggesting that some anxiety may be related to concerns about the delivery (Heron et al., 2004; A. M. Lee et al., 2007).

2.2.3 Neonatal complications associated with gestational anemia

Gestational anemia increases the risks of prematurity and fetal growth restriction (FGR), also known as intrauterine growth restriction (IUGR) (Jung et al., 2019; Rahmati et al., 2020; Sukrat et al., 2013; Xiong et al., 2000; Young et al., 2019). FGR happens when fetus does not reach their growth potential in the utero, and is diagnosed when the estimated fetal weight is below 10th percentile or -2 SD. Some studies have also suggested that antenatal anemia is associated with neurodevelopmental complications in the offspring (Leonard et al., 2006; Wiegersma et al., 2020). Furthermore, data indicate that maternal anemia is associated with increased risks of admission to the neonatal intensive care unit (NICU) and even stillbirth (Chu et al., 2020; Conde-Agudelo et al., 2000; Geelhoed et al., 2006; Harrison et al., 2021; Tomashek et al., 2006; Watson-Jones et al., 2007). The causality and biological mechanisms linking gestational anemia to adverse neonatal outcomes remain unclear.

Maternal anemia during pregnancy increases the risk of prematurity according to several meta-analyses (Jung et al., 2019; Rahmati et al., 2020; Sukrat et al., 2013; Young et al., 2019). However, data regarding the effect of the timing of the maternal anemia on prematurity are scarce and contradictory.

In a meta-analysis including over four million pregnancies, maternal anemia increased the risk of prematurity (gestational age <37 weeks) twofold (Jung et al., 2019), and another systematic review and meta-analysis from 2019 reported that premature birth was associated with maternal Hb <110 g/l in each trimester (Young et al., 2019). Sukrat et al. also described that maternal anemia Hb <110 g/l in the first and the third trimesters is associated with an increased risk of prematurity with ORs of 1.10 (95% CI 1.02–1.19) and 1.30 (95% CI 1.08–1.58), respectively (Sukrat et al., 2013). In a meta-analysis including 10 observational studies, gestational anemia with Hb <100–110 g/l during the first and second trimesters increased the risk of prematurity, but not in cases with gestational anemia in the third trimester (Xiong et al., 2000). Rahmati et al. concluded in their meta-analysis that maternal anemia with Hb <110g/l was a risk factor for prematurity, but the risk increased statistically significantly only with anemia in the first trimester (Rahmati et al., 2020).

One of the mechanisms proposed to explain the increased risk of prematurity associated with gestational anemia is elevated corticotropin-releasing hormone, which is thought to play a key role in the onset of labor (McLean et al., 1995). Allen et al. suggested that both ID and hypoxia stimulate norepinephrine production–

which, in turn, stimulates corticotropin-releasing hormone production, leading to preterm birth (Allen, 2001).

In addition to prematurity, gestational anemia is associated with FGR (Anwar et al., 2019; Badfar et al., 2019; Jung et al., 2019; Rahmati et al., 2017; Young et al., 2019). The association is well established, but the causality remains unclear. The effect of gestational anemia on FGR seems to differ according to the timing and severity of anemia.

A meta-analysis including 903 pregnant women showed that maternal anemia is associated with FGR, with a pooled OR of 2.01 (95% CI 1.44–2.82, p <0.01) (Yang et al., 2023). Kozuki et al. reported in their meta-analysis that severe and moderate anemia with Hb <80 g/l and Hb <90 g/l increased the risk of having a neonate with SGA by 53%, but no association with mild anemia (Hb 90–109 g/l) was observed (Kozuki et al., 2012). Interestingly, in a large Chinese retrospective study with nearly 19 million pregnant women, mild anemia with Hb 100–109 g/l was associated with a decreased risk of FGR (adjusted OR 0.79, 95% CI 0.76–0.81) (Shi et al., 2022).

The biological mechanisms underlying the effect of gestational anemia on fetal growth are unclear. Maternal anemia is suggested to cause oxidative stress and chronic hypoxia, thus leading to impaired fetal growth (Kozuki et al., 2012). However, more research is needed to establish the plausible mechanism.

Iron stores form in utero (Friel et al., 2018). A full-term neonate with adequate growth, delayed cord clamping at birth, and born to a healthy mother possesses iron stores sufficient to support her/his growth for four to six months (Friel et al., 2018; Lönnerdal, 2017). Delayed umbilical cord clamping is used to maximize iron stores at birth and prevent ID (Andersson et al., 2011; McDonald et al., 2014). Adequate iron stores are essential since iron serves as an essential substrate in fetal and neonatal brain development (Beard & Connor, 2003).

Maternal IDA is known to correlate with decreased cord-blood ferritin levels (Mireku et al., 2016; Shao et al., 2012; Terefe et al., 2015). In several studies maternal IDA has been associated with IDA and ID in infancy at the age of 14 weeks, 6 months, and 12 months (Abioye et al., 2019; Kilbride et al., 1999; Shukla et al., 2019). However, a systematic review and a meta-analysis published in The Lancet in 2020 including 65 studies, concluded that maternal hematologic status has a low positive correlation with newborn's iron status (Sanni et al., 2020).

Various studies have associated maternal IDA with neurodevelopmental complications in the offspring (Leonard et al., 2006; Lozoff, 2011; Wiegersma et al., 2020). These neurological disorders are thought to develop due to ID in the developing brain, where iron is needed for several processes such as neurotransmitter metabolism (Lozoff, 2011). It has been suggested that maternal anemia and ID leads to ID and impaired oxygenation in the developing fetal brain.

Fetal neurodevelopment is thought to be compromised when maternal ferritin levels reach below 13.6 µg/l (Shao et al., 2012). The effects of ID depend on the timing, as different areas of the brain develop during different periods of pregnancy (Rees & Harding, 2004). Neonatal ID is associated with psychopathological conditions, such as schizophrenia and neurocognitive disorders (Insel et al., 2008; Tamura et al., 2002). However, in an Australian RCT, maternal iron supplementation of 20 mg per day for non-anemic women during pregnancy did not influence the neurodevelopment of the offspring in the four-year follow-up (Zhou et al., 2006).

In a large Swedish cohort study, including 532 232 women, maternal anemia before 30 gestational weeks was associated with autism spectrum disorder, attention-deficit/hyperactive disorder, and intellectual disability in the offspring between 6 and 29 years of age (Wiegersma et al., 2020). Leonard et al. also found that anemia during pregnancy was associated with intellectual disability in the offspring (Leonard et al., 2006). In addition, maternal anemia has been linked to lower IQ scores at seven years of age (Camp et al., 1998; Drassinower et al., 2016). In contrast, elevated maternal ferritin levels (+1SD, mean 170.3 µg/l) during early pregnancy have been associated with smaller brain volume and poorer cognitive abilities in the offspring (Sammallahti et al., 2022). Therefore, determining a sufficient maternal iron level for optimal fetal neurocognitive development is crucial in the future.

2.3 Iron deficiency and iron deficiency anemia

2.3.1 Pathophysiology of gestational iron deficiency anemia

Figure 4 illustrates the parameters related to the development of gestational IDA. More than 50% of gestational anemia cases are known to be caused by ID (Stevens et al., 2013). Iron requirements significantly increase during pregnancy, as discussed above, which predisposes individuals to IDA if the iron demand is not adequately met. ID can develop due to a lack of nutritional supply or impaired absorption from the intestine. Patients with inflammatory bowel disease, celiac disease, or those who have undergone bariatric surgery are known to have inadequate intestinal absorption of nutrients, including iron (Gowanlock et al., 2020; Nielsen et al., 2015). Due to the increased demand, the need for iron during pregnancy is greater, and this alone, or in combination with inadequate absorption, can lead to ID, and subsequently, to IDA.

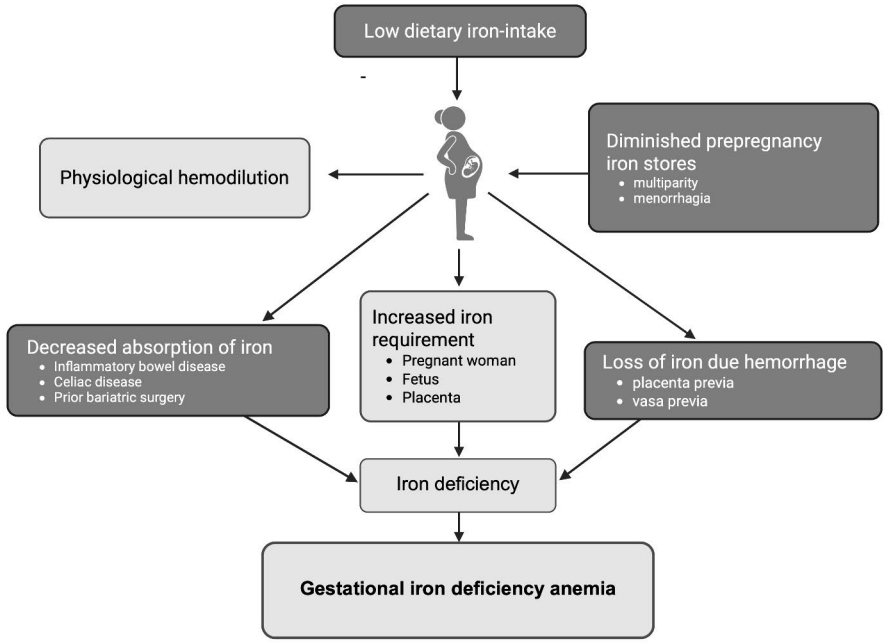

Figure 4. Pathophysiology of gestational iron deficiency (ID) and gestational iron deficiency anemia (IDA).

2.3.2 Iron deficiency without anemia

IDA is the end stage of ID, where iron stores are depleted and cannot sustain erythropoiesis in the bone marrow. Before IDA develops, it is always preceded by ID. ID is the most common nutrient deficiency in both non-pregnant and pregnant populations (Al-Naseem et al., 2021). Like IDA, ID is more prevalent in low-income countries due to comorbidities and lack of adequate alimentation (Rahman et al., 2016). In pregnant women, ID is estimated to be 2–2.5 times more common than IDA (Camaschella, 2019). The prevalence of ID varies on the laboratory parameters and cut-off values used. A review assessing the iron status of reproductive aged women in Europe reported that the prevalence of ID was 10-32% when using a 15 µg/l ferritin cut-off level, and the prevalence increased in pregnant women without iron supplementation to 28–85% (Milman et al., 2017). In the United States, 42% of non-anemic pregnant women were iron deficient, when ferritin <30 µg/l and TSAT 19% were used as cut-off values (Auerbach et al., 2021). In a large retrospective Canadian study including 44 552 pregnant women, about 30% had ferritin value <30 µg/l (Teichman et al., 2021).

Only a few studies have assessed the association between ID without anemia and maternal and neonatal outcomes, and the results are contradictory (Goldenberg et al.,

1996; Kelly et al., 1978; C. Khambalia, et al., 2016; Verhoeff et al., 2001). ID has been associated with lower cord serum ferritin values (Kelly et al., 1978). In a Chinese study including 3702 pregnant women, maternal ferritin levels <13.6 µg/l were associated with a 0.17 SD decrease in cord serum ferritin levels in neonates (p=0.001) (Shao et al., 2012). 76% of pregnant women included in the study cohort had ferritin levels <19 µg/l. Furthermore, low cord serum ferritin levels have been linked to poorer performance on mental and psychomotor tests in infants at five years of age (Tamura et al., 2002). On the other hand, high maternal ferritin values with a mean 170.3 µg/l have also been linked to decreased infant intelligence quotient (Sammallahti et al., 2022).

ID has been associated with fatigue (Patterson et al., 2000), and in a small double-blind prospective study including 136 Swiss pregnant women, oral iron administration to patients improved fatigue symptoms compared to a placebo group (Verdon et al., 2003). The effect was detected in patients with ferritin levels <50 µg/l, suggesting that patients with fatigue and ID or borderline ferritin levels without anemia might benefit from oral iron substitution. Similar results were reported in another RCT, including 198 women with ferritin <50 µg/l and complaints of fatigue (Vaucher et al., 2012). In a double-blinded RCT, including 90 premenopausal non-pregnant women with ferritin level ≤15 µg/l, who received intravenous iron supplementation had a statistically a decrease in fatigue symptoms compared to placebo group (65% vs. 40%, p=0.02). No difference was observed when treating women with ferritin ≥15 µg/l and ≤50 µg/l (Krayenbuehl et al., 2012). At the time of writing, no studies on the effect of intravenous iron treatment for iron repleted pregnant women exist.

2.3.3 Risk factors for iron deficiency anemia

Risk factors for IDA are presented in **Table 2**. Factors influencing nutritional iron intake, intestinal iron absorption, and iron storage, can predispose individuals to ID and subsequently to IDA.

Maternal characteristics identified as risk factors for gestational anemia include young age (Hämäläinen et al., 2003; Idowu et al., 2005; Uche-Nwachi et al., 2010) and low education levels (Bencaiova et al., 2012). Tobacco smoking has been linked to maternal anemia. In a Polish study, hepcidin and Hb levels were shown to be significantly lower in women who smoked during pregnancy (Chełchowska et al., 2016). In an observational study including 100 pregnant women in India, tobacco smoking increased the risk of IDA by 14-fold (OR 14.3, 95% CI 2.6–77.9) independently regardless of the consumption of iron rich foods or household food insecurity (Mistry et al., 2018), while another Indian study linked smoking to IDA in randomly selected hospital patients (Vivek et al., 2023). On the other hand, a prospective study conducted in the Netherlands, found no association between

smoking and maternal anemia (Gaillard et al., 2014). Interestingly, smoking has also been shown to cause an increase in Hb due to exposure to carbon monoxide, potentially masking ID (A. J. Sharma et al., 2019).

Low body mass index (BMI) is associated with an increased risk of IDA (Al-Mehaisen et al., 2011; Charles et al., 2010; Sunuwar et al., 2020; J. Tan et al., 2018), although data regarding the relationship between BMI and anemia remains controversial (Bodnar et al., 2004; Harrison et al., 2021). High pre-pregnancy BMI has also been linked to an increased risk of postpartum anemia. Bodnar et al. reported that compared to women with BMI of 20, women with BMI of 28 and 36 had 1.8-fold and 2.8-fold risk of postpartum anemia, defined as Hb <120 g/l, respectively (RR (risk ratio) 1.8, 95% CI 1.3–2.5 and RR 2.8, 95% CI 1.7–4.7) (Bodnar et al., 2004). Women with higher BMI are in a significant risk for postpartum hemorrhage and tend to breastfeed for a shorter duration, thus decreasing the period of lactational amenorrhea (Blomberg, 2011; Donath et al., 2000). In addition, obesity is known to cause inflammatory reactions–which, in turn, affect hepcidin expression and therefore impair iron absorption (Garcia-Valdes et al., 2015). In studies conducted in non-pregnant patient populations, obesity has been associated with IDA (Nead et al., 2004; Zimmermann et al., 2008).

A diet lacking iron-rich foods, such as vegetarian and vegan diets, predisposes to ID. Dietary iron is absorbed in the intestine as heme and non-heme component (Miret et al., 2003). Conditions affecting iron absorption, such as inflammatory bowel disease, including Crohn's disease and colitis ulcerosa, and celiac disease, are known to increase risk of ID and consequently IDA (Goonewardene et al., 2012; Greco et al., 2004; Guerrero Vinsard et al., 2022; Lopez et al., 2016). In addition, patients who have undergone bariatric surgery have impaired absorption of nutritients, including iron, and are at an increased risk for ID and IDA, particularly with long intervals between surgery and pregnancy (Crusell et al., 2016; Gowanlock et al., 2020; Nomura et al., 2011; Patel et al., 2008).

Multiparity has been recognized as a risk factor for gestational anemia in several studies (Al-Farsi et al., 2011; Çelik Kavak & Kavak, 2017; Hailu Jufar & Zewde, 2014; Harrison et al., 2021; Kagu et al., 2007; Karaoglu et al., 2010; Looker et al., 1997; Uche-Nwachi et al., 2010). During pregnancy, the demand for and consumption of iron significantly increase. Therefore, multiparity, particularly with short intervals between pregnancies, predisposes to IDA as iron stores may not have sufficient time to replenish. Additionally, women with multiple gestation have been reported to have an increased risk of gestational anemia (Ru et al., 2016).

Hypothyroidism, especially if untreated, is known to be associated with iron metabolism and increase the risk of ID by altering the composition of gastric secretion, thereby impairing iron absorption in the intestine (Banday et al., 2018). Thus, severe cases of hypothyroidism may lead to IDA (Hess & Zimmermann, 2004;

Taher & Ghalib, 2023). One meta-analysis identified even treated hypothyroidism as a risk factor for gestational anemia (Y. Yang et al., 2020), and frequent Hb follow-ups for pregnant women with hypothyroidism have been suggested. Pregnant women with pregestational diabetes and hypertension also have an increased risk of IDA (Cao et al., 2024; Thomas et al., 2004)

Table 2. Risk factors for gestational iron deficiency anemia (IDA).

Risk factor	Definition	Result	Publication
Young age	<18 years 18–20 years 26.2 vs. 27.7 15–24 years	1.5-2.6% vs. 0.6%, p=0.02 1.33 (95% CI 1.29–1.37) p<0.001 1.74 (95% CI 1.29–2.34)	Hämäläinen et al., 2003 Wu et al., 2020 Harrison et al., 2021 Sunuwar et al., 2020
Advanced age	>39 years ≥35 years	1.21 (95% CI 1.93–11.1) 1.39 (95% CI 1.10–1.74)	Hailu Jufar et al., 2014 Lin et al., 2018
Dietary factors (veganism, vegetarianism, diet lacking iron-rich food)	Inadequate intake of iron-rich food Eating meat ≤3 times per week	4.3 (95% CI 1.75–10.53) 2.02 (95% CI 1.55–2.50)	Samuel et al., 2020 Zhang et al., 2022
Low level of education	Illiterate Illiterate Illiterate	2.12 (95% CI 2.47–6.8) 1.56 (95% CI 1.03–2.37) 2.23 (95% CI 1.35–3.45)	Hailu Jufar et al., 2014 Gebre et al., 2015 Taner et al., 2015
Smoking during pregnancy	Antenatal tobacco use	14.3 (95% CI 2.6–77.9)	Mistry et al., 2018
Low BMI	<19.8 kg/m^2 <18.5 kg/m^2 <18.5 kg/m^2 <18.5 kg/m^2	2.9 (95% CI 1.02–8.3) 1.35 (95% CI 1.21–1.51) 1.36 (95% CI 1.05–1.77) 1.24 (95% CI 1.02–1.50)	Al-Mehaisen et al., 2011 Tan et al., 2018 Sunuwar et al., 2020 Lin et al., 2018
High BMI	25.9 vs. 25.4 >28 kg/m^2 >36 kg/m^2	p<0.001 1.8 (95% CI 1.3–2.5) 2.8 (95% CI 1.7–4.7)	Harrison et al., 2021 Bodnar et al., 2004 Bodnar et al., 2004
History of bariatric surgery	Roux-en-Y gastric bypass	11.5% vs. 1.1%, p=0.001	Patel et al., 2008
History of menorrhagia before pregnancy	Heavy menstrual bleeding	No data on pregnant population 1.64 (95% CI 1.16–2.30)	Dugan et al., 2024
Hypothyroidism	Overt hypothyroidism	3.74 (95% CI 1.95–7.15)	Yang et al., 2020
Celiac disease	Undiagnosed/Known	35/33% vs. 13.7%, p=0.0045	Greco et al., 2003
Inflammatory bowel disease	Crohn's diseases and colitis ulcerosa	5.26 (95% CI 4.01–6.90)	Vinsard et al., 2021
Multiparity	≥5 pregnancies Multiparous Multiparous	2.92 (95% CI 2.02–4.59) 2.19 (95% CI 2.65–5.12) 3.9 (95% CI 1.57–9.7)	Al-Farsi et al., 2011 Hailu Jufar et al., 2014 Samuel et al., 2020
Short pregnancy interval	<2 years	1.21 (95% CI 2.16–5.19)	Hailu Jufar et al., 2014
Hyperemesis	Admission with an ICD-10 code O21.0 or O21.1	1.28 (95% CI 1.23–1.33)	Fiaschi et al., 2017

CI: Confidence interval; BMI: Body mass index.

2.3.4 Diagnostics of iron deficiency anemia

As hematologic parameters change physiologically throughout the pregnancy, the diagnosis of IDA and the assessment of maternal iron status remain challenging (Pavord et al., 2012). Due to physiological hemodilution, the diagnostic values for gestational anemia are lower than those for the general population (Milman et al., 2000). Hb <110 g/l is used as a cut-off value for the diagnosis of gestational anemia in all trimesters, and ferritin level <30 µg/l is adapted to indicate ID in Finland (ACOG, 2021; Tiitinen, 2018). Currently, in Finland, other iron parameters are not in routinely explored when assessing gestational ID. Laboratory values for assessing ID and IDA during pregnancy are presented in **Table 3**.

Ferritin, an iron storage protein, is considered to be the most reliable marker for estimating iron stores during pregnancy (Byg et al., 2000; Daru, Allotey, et al., 2017; Thompson, 1988; Walsh et al., 2011). Its expression is regulated by intracellular iron concentration, and it decreases when iron stores are depleted. Ferritin is produced by the liver, and it also serves as an acute phase protein (Elin et al., 1977). Consequently, ferritin levels elevate during inflammation, complicating the diagnosis of ID. In addition, conditions such as malignancies, neurodegenerative diseases, and significant liver damage can elevate ferritin values, potentially masking ID (Knovich et al., 2009). Therefore, in Switzerland, it is recommended that C-reactive protein (CRP) be measured simultaneously with ferritin to exclude inflammation (O'Toole et al., 2024).

A low ferritin value is considered diagnostic for ID in otherwise healthy patients, with cut-off values varying among different patient populations (Daru et al., 2017; Knovich et al., 2009). ID is the most common condition that leads to a decreased ferritin value. Other rare conditions that are known to associate with low ferritin levels include hypothyroidism and ascorbate deficiency (Knovich et al., 2009). The accurate cut-off value for ferritin indicating ID in pregnancy remains under discussion as ferritin physiologically decreases during a normal pregnancy as shown in **Figure 1b** (A. Daru et al., 2017; Fisher & Nemeth, 2017). Currently, WHO recommends using a cut-off value <15 µg/l to indicate iron depletion (WHO, 2020). Various studies have reported the cut-off value <15 µg/l as specific but not sensitive for iron depletion (Hallberg et al., 1993; Van Den Broek et al., 1998). After severe iron depletion (<12 µg/l), ferritin does not correlate with the severity of ID (Pfeiffer & Looker, 2017). In a study, including non-pregnant patients with normocytic anemia, ferritin <50 µg/l is shown to be consistent with ID (Koulaouzidis et al., 2009). In a Finnish study, a ferritin level <35 µg/l had a sensitivity of 66% and a specificity of 100% when assessing ID based on histologic bone marrow iron staining in first and third trimesters (Puolakka, 1980). A ferritin value <30 µg/l has been shown to be associated with 98% specificity and 92% sensitivity with the absence of bone marrow hemosiderin (Mast et al., 1998). ACOG recommends a

ferritin cut-off value of <30 µg/l as indicative of ID, and this threshold is used in several countries, including Finland (ACOG, 2021).

Various other hematologic biomarkers have been studied and suggested to describe iron stores during pregnancy. These include soluble transferrin receptors (TfR) and transferrin saturation (TSAT) (Åkesson et al., 1998; Choi et al., 2000). However, these markers are not widely used, as there is no consensus on their physiological changes during pregnancy, leading to a lack of adequate information on cut-off values are lacking (Pavord et al., 2012).

TfR is used alongside ferritin in the diagnostics of IDA in non-pregnant patient populations (Punnonen et al., 1997). TfR is a receptor expressed on the surface of iron incorporating cells, and its level in the plasma is increased in functional ID and accelerated erythropoiesis (Choi et al., 2000). Unlike ferritin, TfR is not an acute phase protein, allowing for the assessment of ID in the presence of inflammation (Mast et al., 1998). However, the role of TfR in diagnosing gestational IDA is contradictory due to its metabolism being affected by accelerated erythropoiesis (Åkesson et al., 1998; Choi et al., 2000). TfR is used in diagnosing IDA when evaluating pregnant women with inflammatory conditions, such as inflammatory bowel disease.

TSAT is considered to be the most reliable iron parameter in the presence of inflammation and is calculated by dividing serum iron by the level of transferrin in the plasma (Auerbach, 2023). The test must be taken after an overnight fast to ensure accuracy. Values below 20% during pregnancy are suggested to indicate ID (Auerbach, 2023). Currently, TSAT is used in Finland in conjunction with ferritin, if the diagnosis of ID is unclear or if the adequate oral treatment does not elevate the Hb levels.

Hepcidin has been explored over the last decade as a potential option for assessing iron stores (Girelli et al., 2016). It has been suggested to accurately indicate ID in pregnancy (Bah et al., 2017); however, it is not yet in clinical use and requires further research.

Table 3. Laboratory values assessing iron deficiency (ID) and iron deficiency anemia (IDA) during pregnancy. *Values currently used in the diagnostics of gestational anemia.

Laboratory parameter	Cut-off value	Physiologic changes during pregnancy	Reference
Hemoglobin (Hb)*	**<110 g/l**	Decreases during pregnancy	WHO, 2011; Tiitinen, 2018
Ferritin (Ferrit)*	**<30 µg/l**	Decreases during pregnancy affected by inflammation	ACOG, 2021; Mast et al., 1998; Daru et al., 2017
Mean corpuscular volume (MCV)	<80 fl	Increases during pregnancy due to accelerated erythropoiesis	Ali, 2025
Transferrin receptor (TfR)	Not agreed	Increases during pregnancy due to accelerated erythropoiesis Not affected by inflammation	Choi et al., 2000
Transferrin saturation (TSAT)	<20% suggested	Test requires fasting Not affected by inflammation	Auerbach, 2023
Hepcidin	Not agreed	Decreases during pregnancy	Bah et al., 2017

2.3.5 Screening recommendations for gestational anemia

Several guidelines exist regarding the screening of gestational anemia. ACOG recommends screening for anemia in the first trimester and again in the end of second trimester between 24 and 28 gestational weeks (ACOG, 2021), whereas in the United Kingdom, women with risk factors for ID are routinely screened by measuring full blood count and ferritin for risk groups at booking and again at 28 and 40 weeks (Pavord et al., 2020). In Australia and Turkey, in addition to full blood count, it is advised to measure ferritin routinely at booking and the third trimester and in the first trimester, respectively (Api et al., 2015; Australian Red Cross, 2020). However, Federation of Gynecology and Obstetrics guideline advises against routine ferritin measurement (Di Renzo et al., 2019; O'Toole et al., 2024). A summary of the screening recommendations from various guidelines is presented in **Table 4** (O'Toole et al., 2024).

In Finland, all pregnant women receive cost-free prenatal primary care, with nearly 100% visiting their primary care givers regularly. They are screened for gestational anemia once during each trimester by measuring the Hb levels using a point-of-care test (Klemetti & Hakulinen-Viitanen, 2013). If the finger stick test indicates an abnormal result, a venous blood sample is drawn for further testing. Hb levels are also measured if there is a clinical indication or the pregnant woman experiences symptoms that could be attributed to gestational anemia. If necessary,

ferritin is measured to confirm the diagnosis of ID, and diagnostics are performed if risk factors for other etiologies are present. ID is advised to be screened in high-risk groups, including women with a history of gestational anemia or significant hemorrhage during delivery, short pregnancy intervals, pregestational diabetes, low or high BMI, and women with inflammatory bowel disease. However, the screening practices currently vary between different wellbeing services counties in Finland.

Table 4. Parameters and time points (if available) for screening of iron deficiency (ID) and iron deficiency anemia (IDA) during pregnancy according to various guidelines. Modified from O'Toole et al., 2024. (ACOG, 2021; Api et al., 2015; Australian Red Cross, 2020; Di Renzo et al., 2019; Directorate of Clinical Strategy and Programs Ireland, 2019; Klemetti & Hakulinen-Viitanen, 2013; Nicholson et al., 2024; Pavord et al., 2020; WHO, 2016; Yip R et al., 1998).

Guideline/recommendation	Screening of gestational IDA
ACOG bulletin no 233	FBC at the first trimester and 24/28 weeks
Auckland Practice Guideline	FBC at booking and 26–28/40 weeks Ferritin at booking and 26–28/40 weeks
Australian Red Cross Lifeblood guideline	FBC at booking and 26–28/40 weeks Ferritin at booking and 26–28/40 weeks
CDC Recommendation	FBC (timing not commented)
FIGO Commitee Report	FBC at booking and 28/40 weeks Ferritin not advised
Finnish primary maternity care guideline (NEUKO)	Hb at every trimester
Ireland Clinical Practice Guideline	FBC (timing not commented) Ferritin
SSGO Guideline	Hb at every trimester CRP, if ferritin is taken
Turkish Working Group Consensus	FBC at every trimester Ferritin at the first trimester
UK Guidelines	Hb at booking and 28/40 weeks Ferritin for risk groups
US Task Force Recommendation	Insufficient evidence for recommendation
WHO Recommendation	Hb (timing not commented)

ACOG: The American College of Obstetricians and Gynecologists; CDC: Center for Disease Control; CRP: C-reactive protein; FCB: full blood count; FIGO: The International Federation of Gynecology Hb: hemoglobin; Hct: hematocrit; SSGO: Swiss Society of Gynecology and Obstetrics. UK: United Kingdom; WHO: World Health Organization.

2.3.6 Treatment and management of iron deficiency anemia in pregnancy

2.3.7 Oral iron supplementation

The treatment for gestational IDA is adequate iron supplementation. Iron can be administered orally or intravenously. In cases of severe anemia with Hb <80 g/l, red blood cell transfusions are considered. When treating IDA during pregnancy, two main goals are present: preventing possible adverse maternal and neonatal outcomes and treating maternal symptoms caused by anemia. The choice of treatment depends on the severity and timing of gestational anemia and maternal characteristics and the severity of maternal symptoms (Klemetti & Hakulinen-Viitanen, 2013). The treatment of gestational IDA is presented in **Figure 5**.

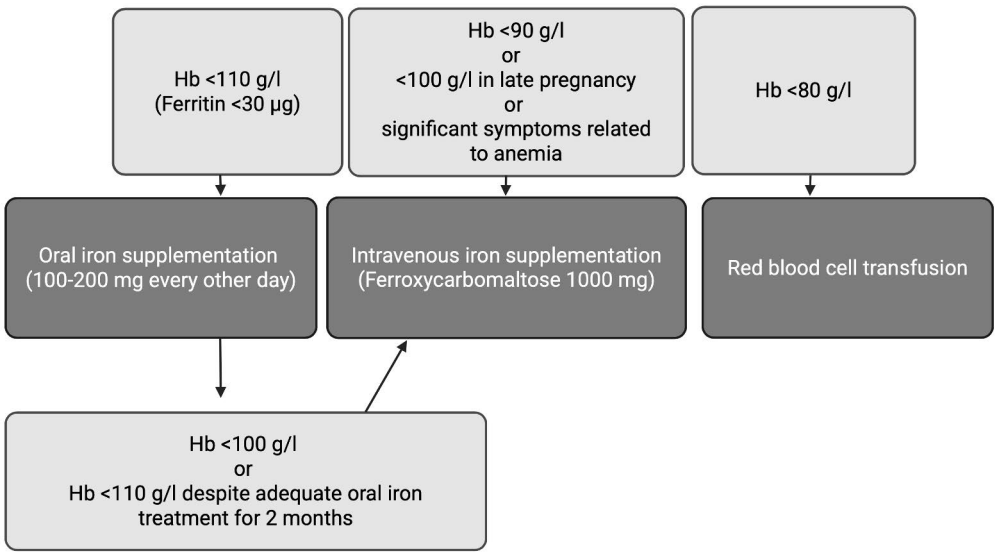

Figure 5. Treatment of gestational iron deficiency anemia (IDA) in Finland during the second and the third trimesters. Intravenous iron is contraindicated in the first trimester (European Medicines Agency, 2013).

Oral iron supplementation is the primary treatment for IDA. It is safe, effective, economical, and readily available. Several formulations are available on the market, including ferrous fumarate, ferrous sulfate, ferrous gluconate, ferrous bisglycinate, and sucrosomial/liposomal iron (Stoffel et al., 2020; Tarantino et al., 2015). These supplements vary in their bioavailability (Stoffel et al., 2020). In addition, a newer iron formulation, sucrosomial/liposomal iron, differs in its method of absorption compared to other iron supplements (Tarantino et al., 2015).

Research has sought to clarify the optimal dose of oral iron supplementation; however, the data remain inconclusive. Traditionally, oral iron has been prescribed at a dose of 100 mg per day, with the recommendations varying from 40 to 200 mg of elemental iron per day (O'Toole et al., 2024; Pavord et al., 2020). Various studies have reported that absorption of oral iron is enhanced with lower doses (Moretti et al., 2015; Stoffel et al., 2017). In the United Kingdom, a daily dose of 40–80 mg is currently recommended (Pavord et al., 2020). However, in a meta-analysis conducted by Haider et al., a higher daily dose of iron up to 66 mg was associated with an increase in birth weight (Haider et al., 2013). In Finland, oral iron at 100–200 mg every other day or sucrosomial iron at 30 mg daily is used as the primary treatment for gestational IDA (Klemetti & Hakulinen-Viitanen, 2013). Oral iron is recommended to be taken on an empty stomach, and vitamin C is known to enhance its absorption.

The optimal dosing of oral iron supplementation has been discussed. Some studies have suggested that the absorption of oral iron is more effective when administered intermittently every other day compared to daily administration (Stoffel et al., 2020). Intermittent dosing is thought to evade the decreased absorption caused by increased hepcidin levels (Stoffel et al., 2020). Oral iron supplementation stimulates hepcidin expression–which, in turn reduces iron absorption in the intestine (Moretti et al., 2015). By using intermittent dosing, for example, every other day, hepcidin levels are not elevated due to its 48-hour circulation time (Moretti et al., 2015). In many countries, including Finland, oral iron is advised to be administered at 100 mg every other day (Fernandez-Gaxiola & De-Regil, 2020; Moretti et al., 2015; Peña-Rosas et al., 2015).

Oral iron supplementation is often poorly tolerated. Up to 70% of patients taking oral iron supplements experience side effects, primarily gastrointestinal symptoms such as nausea, vomiting, diarrhea, and constipation (Tolkien et al., 2015). Adverse symptoms decrease the adherence to treatment, with only 36–50% of pregnant women using the oral iron supplementation as instructed (Breymann & Auerbach, 2017; Habib et al., 2009). Patients suffering from ID and side effects of oral iron supplementation are instructed to use oral iron every other day or even less frequently to minimize the adverse symptoms. In addition to enhanced absorption, intermittent dosing decreased the incidence of side effect, thereby improving adherence to the treatment (Banerjee et al., 2024; Peña-Rosas et al., 2015). Due to sucrosomial absorption in the intestine, the gastrointestinal side effects appear to be less frequent with liposomal iron (Gómez-Ramírez et al., 2023; Parisi et al., 2017).

When tolerated and used accordingly, oral iron supplementation increases Hb levels by approximately 0.2 g/l per day (Pavord et al., 2020). Control Hb and ferritin levels are measured in three to four weeks after starting the treatment. Once the target

Hb level is achieved, iron supplementation should be continued for four to six months to replenish iron stores (Pavord et al., 2020).

2.3.8 Intravenous iron substitution

Intravenous iron substitution is better tolerated and more effective in correcting hematologic parameters than oral iron supplementation (Bhavi & Jaju, 2017; Breymann et al., 2017; Govindappagari & Burwick, 2019; Gupta et al., 2014; Neogi et al., 2019; Wong et al., 2016). However, multiple studies have failed to demonstrate significant clinical advantages for maternal and neonatal outcomes (Neogi et al., 2019; Qassim et al., 2018). Recently, a large prospective Indian study including 2018 women with Hb 50–80 g/l at 20–28 gestational weeks and 50–90 g/l at 29–32 gestational weeks showed that intravenous iron significantly improved maternal Hb levels, but no significant differences in clinical outcomes were observed between the intravenous and oral treatment groups (Neogi et al., 2019).

Commonly used intravenous iron formulations include low-molecular-weight iron dextran, ferric carboxymaltose (FCM), ferumoxytol, ferric derisomaltose, ferric gluconate, iron polymaltose, and iron sucrose. All of these formulations have been shown to be effective and safe during the second and third trimesters of pregnancy (Qassim et al., 2018, Gupta et al., 2014; Bayoumeu et al., 2005; Krafft & Breymann, 2011; Wali et al., 2002; Auerbach et al. 2017; Khalafallah et al., 2012).

The most common side effects reported in the literature associated with new include local skin reactions, rashes, pruritus, headache, nausea, and hypophosphatemia (Avni et al., 2015; Blazevic et al., 2014; Froessler et al., 2014). In the non-pregnant general population, the administration of intravenous iron has not increased the incidence of severe adverse outcomes (Avni et al., 2015; Wong et al., 2016). In a prospective trial with 73 iron intolerant gravidas receiving 1000 mg of low-molecular-weight iron dextran, six subjects experienced minor side effects, such as facial flushing and myalgia, and no serious side effects were observed (Auerbach et al., 2017). Similarly, a prospective trial on 863 parturients assessing the effectiveness and safety of FCM observed no serious adverse effects, with minor side effects like local skin irritation, headache, and nausea reported in 11% of patients (Froessler et al., 2018). A meta-analysis by Bellos et al. noted that the incidence of hypophosphatemia, defined as serum phosphate <2 mg/dl (<0.65 mmol/l) was higher with FCM compared to other intravenous iron treatments (Bellos et al., 2020); however, this effect seems to be transient and have little clinical significance (Pasricha et al., 2023). The most feared adverse outcome of intravenous iron substitution is an anaphylactic reaction, which can be fatal. With the new formulations, such as iron sucrose, FCM, and low-molecular-weight iron dextran, anaphylaxis remains a rare complication, and no death or severe anaphylaxis with

the newer formulations was reported in a large meta-analysis including over 10 000 non-pregnant patients (Avni et al., 2015). Detailed biological effects of intravenous iron infusion on the fetus are unknown.

Older intravenous iron formulations, such as iron dextran, are no longer in clinical use due to their significant risk of anaphylactic reactions and various side effects (Auerbach & Ballard, 2010; Chertow et al., 2006). New formulations have a carbohydrate core, which slows the release of labile free iron by binding it more tightly (Breymann & Auerbach, 2017).

In a prospective study including 863 pregnant women who received FCM, Hb and ferritin levels were significantly improved across all groups with anemia, with mean Hb increasing by 9.8–21.5 g/l, depending on the severity of anemia (Froessler et al., 2018). Similar results were reported in other RCTs (Shim et al., 2018; Qunibi et al., 2011; Van Wyck et al., 2007). Notably, FCM does not cross the placenta (Malek, 2010), and in a retrospective study with 206 pregnant patients, FCM resulted in fewer mild adverse events (7.8% vs. 10.7%) compared to iron sucrose, likely due to its tighter binding to the carbohydrate core, which leads to slower release of labile free iron in the blood (Christoph et al., 2012). FCM is predominantly used in Finland.

When assessing the need for intravenous iron administration, factors such as gestational age, maternal symptoms, and severity of anemia define the chosen treatment. In Finland, clinicians may consider intravenous iron during the second and third trimesters, if anemia is primarily with Hb <90 g/l or Hb persists <110 g/l despite of adequate oral iron substitution or if oral iron is poorly tolerated. Intravenous iron is also often considered if Hb is <100 g/l after 36 gestational weeks in order to ensure adequate maternal iron storage prior entering the delivery (Breymann et al., 2017). Intravenous iron, usually FCM, is given 1000 mg primarily, and depending on the starting Hb level, an additional dose of 500 mg can be given after one week, if necessary. After intravenous iron infusion, oral iron treatment is paused for five days due to impaired absorption in the intestine and is continued after that, if there are no contraindications. Hb and ferritin values can be controlled after four weeks of infusion to ensure adequate response to treatment. The maximum dosage of FCM is 2000 mg.

Contraindications for intravenous iron administration include a history of anaphylactic reactions to intravenous iron supplementation and first trimester due to a lack of safety data (European Medicines Agency, 2013). Acute infection is a relative contraindication for intravenous iron administration, as iron is known to be a growth factor for pathogens and may potentially worsen the infection (Camaschella, 2019; Litton et al., 2013). The benefits and disadvantages of oral versus intravenous iron supplementation are summarized in **Table 5**.

Table 5. The benefits and disadvantages of oral and intravenous iron supplementation in the treatment of gestational iron deficiency anemia (IDA).

	Oral iron	Intravenous iron
Availability	Over-the-counter medication, easily accessible	Requires referral to a secondary/tertiary unit, obstetrician consultation, and infusion given in hospital environment
Economics	Inexpensive	Expensive
Dosing	100-200 mg every other day for up to 6 months after delivery	1000 mg infusion once, if needed can be repeated
Timing	Can be used during all trimesters and postpartum	Contraindicated in the first trimester due to a lack of safety data
Effectiveness on hematologic parameters	Corrects the Hb and ferritin levels, but slower than intravenous iron	Corrects the Hb and ferritin levels faster that oral iron
Effectiveness on clinical outcomes	Decreases the risks of adverse maternal and neonatal outcome	Decreases the risks of adverse maternal and neonatal outcomes
Safety	Safe	Safe; severe adverse outcome extremely rare
Side effects	Up to 70% of patients experience gastrointestinal symptoms	Minor side effects experienced by 11% of patients

The number of blood product transfusions administered during pregnancy and postpartum is increasing, despite the efforts to limit unnecessary transfusions, highlighting the need of recognizing patients at risk in advance to initiate appropriate treatment in time to avoid transfusions (ACOG, 2021).

2.3.9 Red blood cell transfusion

In Finland, red blood cell transfusions are considered for pregnant women with severe anemia (Hb <80g/l). As red blood cell transfusions have significant risks, the need for administration should always be well evaluated. By diagnosing and treating IDA adequately before it presents as severe, transfusion can be avoided. One unit of red blood cells elevates the Hb level by approximately 10 g/l (Sharma et al., 2011).

Red blood cell transfusions carry both infectious and non-infectious risks, and they are associated with increased morbidity and mortality (Thomson et al., 2009). The transmission of diseases such as HIV, hepatitis B and C, syphilis, and other bloodborne infectious diseases may occur during transfusions (Dellinger & Anaya,

2004). However, in Finland and other high-income countries, the screening protocols for blood products are efficient, resulting in minimal risk of infections, whereas low- and middle-income countries still lack adequate protocols (Bloch, 2022). Side effects and complications from blood transfusions range from mild allergic reactions, such as itching, to severe anaphylactic reactions (Hirayama, 2013). If transfusions are administered rapidly, the resulting increase in plasma volume can lead to volume overload, and in worst cases, to pulmonary edema and heart failure (Semple et al., 2019).

2.3.10 Prophylactic iron supplementation

The research and data regarding prophylactic iron substitution during pregnancy are inconclusive, and therefore, Cantor et al. stated in 2015, that no conclusive recommendation can be given (Cantor et al., 2015). This perspective has been adopted in several countries, including Finland (O'Toole et al., 2024).

In an RCT conducted in 2003, a prophylactic dose of 30 mg iron administered from 28 gestational week onwards for iron-depleted but non-anemic women did not significantly reduce the incidence of gestational anemia or premature birth (Cogswell et al., 2003). Interestingly, however, the incidence of low-birth-weight infants decreased although no effect on maternal iron stores was detected, which could indicate that fetal iron needs are prioritized in cases of maternal ID (Cogswell et al., 2003). In the United States, ACOG recommends a daily oral iron supplement of 30 mg for all pregnant woman in the second and third trimesters (ACOG, 2021). Peña-Rosas et al. concluded in their Cochrane review that women receiving prophylactic iron during pregnancy had lower rates of IDA and higher Hb levels and the risks for prematurity and low birth weight were reduced (Peña-Rosas et al., 2015). Milman et al. studied the relationship between ferritin levels and prophylactic iron and suggested that pregnant women with ferritin ≤70 μg/l should be instructed to take 40 mg of iron daily to prevent IDA (Milman et al., 2006). As regards to the effectiveness of intravenous iron prophylaxis compared to oral iron, no clinically significant benefits have been observed with the parenteral route (Bencaiova et al., 2009).

Concerns remain regarding routine iron supplementation for iron-replete pregnant women. In some studies, routine iron supplementation has been associated with an increased risk of gestational diabetes, hypertensive disorder, and the likelihood of having an SGA neonate (Zhang et al., 2021; Ziaei et al., 2007). Further research is needed to establish the role of prophylactic iron supplementation during pregnancy.

Excessive iron can deposit in tissues and cause oxidative stress (Brissot et al., 2019) Like other nutrients, iron provides no additional health benefits when

consumed in excess amounts once sufficient levels have been reached. The risk curve associated with maternal Hb is shown to be U-shaped, and the excess iron may be attributable to increased risks of adverse outcomes when considering high Hb values (Dewey & Oaks, 2017). Therefore, especially when treating pregnant women, reaching the optimal level of iron is important, and overtreating should be avoided. Iron overload has been linked to several pregnancy complications, including preeclampsia and gestational diabetes, and can in severe cases, be life-threatening for the pregnant woman (Fernández-Cao et al., 2017; A. Khambalia, et al., 2016). In a prospective study including 3776 women, higher serum ferritin level (32.8 vs. 24.8 μg/l, p = 0.001) was associated with an increased risk of gestational diabetes with an OR of 1.41 (95% CI 1.11–1.78) (A. Khambalia, et al., 2016), and in a meta-analysis, high Hb or ferritin levels increased the risk of gestational diabetes by 50% (Fernández-Cao et al., 2017). Most of these studies have adjusted the analysis by CRP, indicating that inflammation does not explain the increased risk. Instead, the effect is likely due to high iron levels impacting glucose metabolism. Iron accumulates in pancreatic cells and could therefore damage β-cells by oxidative stress, thereby impairing insulin secretion (Lenzen et al., 2008). In an RCT including 727 patients, oral iron supplementation in non-anemic pregnant women has been detected to increase the risks of hypertension and having an SGA neonate (Ziaei et al., 2007b). Impaired iron metabolism and high ferritin levels have been suggested to be linked to the pathophysiology of preeclampsia. High iron levels can cause oxidative stress, leading to endothelial dysfunction, which is believed to contribute to the pathophysiology of preeclampsia. In addition, elevated iron concentration is suggested to increase blood viscosity, potentially impairing placental perfusion (Palma et al., 2008). Especially pregnant women with risk factors should not be treated with iron without clear indications of ID (Maitra et al., 2019; Rayman et al., 2002), although iron overload remains a rare complication in pregnancy.

In addition to maternal complications, excess iron has been associated with adverse neonatal outcomes. In a Norwegian prospective study, maternal iron supplementation during pregnancy increased the risk of celiac disease in children, with an adjusted OR of 1.33 (95% CI 1.05–1.68, p = 0.019), while maternal anemia in the early pregnancy did not have the same effect (Størdal et al., 2014).

2.4 Breastfeeding

The WHO recommends exclusive breastfeeding (EBF) until six months of age (Kramer & Kakuma, 2004; WHO, 2001). However, currently, only 39% of children in low-and middle-income countries are exclusively breastfed for the recommended six months (Cai et al., 2012) and only 18% achieve this in high-income countries (Vaz et al., 2021). By increasing the prevalence and duration of breastfeeding, it is

estimated that mortality among children and women could be significantly decreased (Victora et al., 2016). While the trend in breastfeeding prevalence is slightly increasing, it remains well below the set goal (Global Nutrition, 2015). In Finland, EBF is recommended until four months of age, when the tasting of solid foods is typically started. An estimated 50 % of Finnish women reach this goal (Ikonen et al., 2020).

Breastfeeding is known to benefit both the mother and the newborn. Maternal benefits include lactational amenorrhea, a decreased risk of breast and ovarian cancer, and a decreased risk of type II diabetes (Babic et al., 2020; Chowdhury et al., 2015a; Horta & de Lima, 2019; Islami et al., 2015; Zhou et al., 2015).

The health benefits of breastfeeding for the infants are widely acknowledged. Breastfed newborns have decreased mortality, particularly in low- and middle-income countries, due to a reduced risk of infections such as diarrhea and respiratory infections (Arifeen et al., 2001; Lamberti et al., 2011; Pandolfi et al., 2019). A large study from Bangladesh reported a 2.40- and 3.94-fold risk of dying before 12 months of age from acute respiratory infection and diarrhea, respectively, among partial or no breastfed infants compared to exclusively breastfed infants in the first months of life (Arifeen et al., 2001). In a meta-analysis including studies from low- and middle-income countries, infants who were not breastfed at all had a 3.5–4.1 times higher mortality compared to those who received any breast milk (Victora et al., 2016). In addition, in a meta-analysis with an OR of 0.40 (95% CI 0.35–0.44), the risk of sudden infant death syndrome significantly decreased among the neonates who were breastfed compared to those who were never breastfed (Hauck et al., 2011). Breastfed infants are shown to have lower arousal thresholds than formula-fed infants, which could function as a protective mechanism (Horne et al., 2004).

Other benefits of breastfeeding for the infants, especially in high-income settings, include a decreased risk of obesity (Yan et al., 2014), type 1 and 2 diabetes (Pereira et al., 2014), allergic rhinitis (Hoang et al., 2022) and asthma (Dogaru et al., 2014). Strong evidence associates breastfeeding with higher IQ scores (Der et al., 2006; Horta et al., 2015; McGowan & Bland, 2023); it also enhances the mother–newborn bonding (Peñacoba & Catala, 2019).

The disadvantages of breastfeeding are minimal, and the benefits strongly overweigh the potential risks. Children who are breastfed for more than 12 months have been shown to have an increased risk of dental caries, likely due to insufficient dental hygiene (Branger et al., 2019). Some infectious diseases, such as HIV, can be transmitted through breast milk (Nduati et al., 2000), and guidelines regarding breastfeeding and HIV vary between countries (Keane et al., 2024). Longer duration of EBF has been consistently associated with ID in children (Chantry et al., 2007; Marques et al., 2014). Macguire et al. conducted a cross-sectional study assessing

1647 children: ID was more common in infants breastfed for over 12 months, with an OR of 1.71 (95% CI 1.05–2.79) (Maguire et al., 2013).

2.4.1 Effects of maternal anemia on duration and quality of breastfeeding

Few studies have assessed the relationship between maternal anemia and breastfeeding. Rioux et al. found an association between maternal postpartum anemia and early discontinuation of breastfeeding; women with Hb <95 g/l were more likely to stop breastfeeding before four months compared to non-anemic women (Rioux et al., 2006). In addition, two studies suggested that maternal anemia is associated with later initiation of breastfeeding (Örün et al., 2010; Park et al., 2003).

Iron concentration in breast milk is low, but its bioavailability is high (Friel et al., 2018). According to Kumar et al., the iron status of breast milk is affected by severe maternal anemia with Hb ≤60 g/l (Kumar et al., 2021). Iron stores of the newborn develop in utero during pregnancy, and they are suggested to be sufficient to keep iron levels adequate until six months of age (Friel et al., 2018). Delayed cord clamping is shown to improve iron stores; therefore, it is now a clinical practice (Andersson et al., 2011; McDonald et al., 2014). Meinzen-Derr et al. found that gestational anemia and EBF >6 months may predispose infants to IDA by nine months of age (Meinzen-Derr et al., 2006). Similar results were detected in a Brazilian study (Teixeira et al., 2010).

3 Aims

The aim of the study was to evaluate the effect of gestational anemia on maternal and neonatal outcomes.

The specific aims were as follows:

1) To assess the effect of gestational IDA on the risks of maternal and newborn short-term adverse outcome in high-income setting, and to evaluate whether intravenous iron substitution result in more effective correction of IDA and associate with improved maternal and neonatal outcome compared to oral iron supplementation. (Study I)

2) To evaluate whether gestational anemia increases the risks of maternal psychological distress during pregnancy and postpartum, defined as incidences of depressive and anxiety symptoms and pregnancy-related anxiety. (Study II)

3) To evaluate whether gestational anemia in third trimester is associated with a shorter duration of breastfeeding. (Study III)

4 Materials and Methods

4.1 Study cohorts and data collection

The material in this thesis consists of two cohorts: The Clinical Birth Cohort from Turku University Hospital in 2016–2018 (Study I) and the FinnBrain Birth Cohort collected from Southwest Finland in 2011–2015 (Studies II–III). The study populations and aims of Studies I–III are presented in **Table 6**.

Table 6. The characteristics of studies assessing gestational anemia and maternal and neonatal outcomes (Study I), maternal psychological distress (Study II), and duration and quality (exclusive/partial) of breastfeeding (Study III).

Study	Study population	Inclusion criteria	Hypothesis	Study design	Methods
I	Clinical Birth Cohort N=11 669 Hb <100 g/l during pregnancy (Anemic 215/Non-anemic 11 545)	Singleton pregnancies Thalassemia, sickle cell disease, folate deficiency were excluded	Gestational iron deficiency anemia (Hb <100 g/l) increases the risk of adverse maternal and neonatal outcomes.	Retrospective	Medical records review
	Subgroup N=215 Hb <100 g/l during pregnancy (Intravenous iron 52/Oral iron 163)		Intravenous iron supplementation corrects hematologic parameters more effectively and improves maternal and neonatal short-term outcomes.	Retrospective	Medical records review
II	FinnBrain Birth Cohort N=1273 Hb <110 g/l during pregnancy (Anemic 301/Non-anemic 972)	Singleton pregnancies Finnish or Swedish spoken	Psychological distress is more common in pregnant women with gestational anemia compared to non-anemic women.	Prospective	Validated questionnaires: EPDS, SCL, PRAQ
	Subgroup N=1221 Hb <100 g/l during pregnancy (Anemic 39/Non-anemic 1182)		Psychological distress is more common in pregnant women with Hb <100 g/l compared to women with Hb ≥100 g/l.	Prospective	Validated questionnaires: EPDS, SCL, PRAQ
III	FinnBrain Birth Cohort Hb <110 g/l in the third trimester of pregnancy N=1238 (Anemic 150/Non-anemic 1088)	Singleton pregnancies Finnish or Swedish spoken	Mothers diagnosed with gestational anemia discontinue breastfeeding earlier compared to non-anemic mothers.	Prospective	Duration of breastfeeding self-reported

Hb: hemoglobin; EPDS: Edinburgh Postnatal Depression Scale, SCL: Symptom Checklist 90; PRAQ: Pregnancy-Related Anxiety Questionnaire.

4.1.1 The Clinical Birth Cohort (Study I)

Study I, assessing the relationship between gestational anemia and maternal and neonatal outcomes, was a retrospective study and based on the digital pregnancy register maintained by Turku University Hospital, Turku, Finland (**Table 6**). The study cohort included all mothers with singleton pregnancies, antenatal Hb <100 g/l, and birth between January 1, 2016, and October 31, 2018, in Turku University Hospital, Turku, Finland (n = 215). Women diagnosed with anemia of other etiology, such as sickle cell anemia or thalassemia were excluded. All pregnancies delivered in Turku University Hospital during the study period (n = 11 545) served as a reference group. The incidences of adverse outcomes were compared between the studied groups to determine the effect of IDA on maternal and neonatal outcomes.

In addition, based on the iron substitution received, the effect of intravenous iron substitution (n = 52) was compared with that of oral iron substitution (n = 163) by dividing the anemic group into subgroups. During the time of Study I in 2016–2018, if the Hb level persisted at <100 g/l or was initially <90 g/l, the pregnant woman was referred to Turku University Hospital for consideration of intravenous iron supplementation. In the subgroup analysis comparing the treatment modalities, maternal and neonatal variables were evaluated to determine the effect of used iron supplementation on adverse outcome.

4.1.2 The FinnBrain Birth Cohort (Studies II and III)

The studies exploring the relationship between gestational anemia and psychological distress assessed as depressive and anxiety symptoms and pregnancy-related anxiety (Study II), and breastfeeding (Study III) were based on the prospectively collected FinnBrain Birth Cohort, which consisted of 3808 pregnant women recruited from maternal prenatal care clinics in the Hospital District of Southwest Finland and Åland Islands, Finland, between December 2011 and April 2015 (**Table 6**). For participation, a verified pregnancy and sufficient knowledge of one of the official languages in Finland, Finnish, or Swedish, were required. Pregnant women who attended maternity welfare clinics in Turku and whose venous blood sample Hb values during pregnancy were available (n = 1 273) were included in the Studies II and III. Prior to the recruitment of the FinnBrain Cohort, approval was obtained from the local ethics committee (57/1801/2011), and a written informed consent was required at study entry.

In Finland, Hb concentration is measured as a point-of-care test from the fingertip in every trimester in the primary maternity care. If the Hb level is abnormal, a venous blood sample is drawn. In Studies II and III, Hb concentrations were obtained from venous blood samples and collected from patient records from all

study subjects at three time points: 20 weeks, 20–30 weeks, and >30 weeks. In Study II, pregnant women with antenatal Hb level <110 g/l at any of the three measurement points were included to the anemic study group (n = 301). In the subgroup analysis, we also assessed also the effect of Hb <100g/l (n = 39) on maternal psychological distress during pregnancy and postpartum. In Study III evaluating the effect of anemia on breastfeeding, women with Hb <110 g/l in the third trimester (>30 weeks) of pregnancy (n = 150), were included in the study group and women with Hb ≥110 g/l (n = 1088) served as a control group.

4.2 Methods

4.2.1 Assessment of maternal and neonatal outcome (Study I)

The lowest and highest Hb values from venous blood samples during pregnancy were recorded for all study subjects. In addition, the following variables for women with Hb <100 g/l were manually collected from the patient records by a single researcher (LK) and are presented in **Table 7**. Ferritin and TfR values were also recorded when available. Postpartum infection was defined as endometritis, wound infection, urinary tract infection, or sepsis. The outcomes regarding the reference group were retrieved from patient register.

Table 7. Variables collected manually from patient records for Study I to evaluate maternal and neonatal outcome.

Study I	
Medical patient records data	
Maternal age	
Parity	0=nulliparous, 1=multiparous
Maternal BMI kg/m2	
Prior cesarean delivery	0=no, 1=yes
Hypertension	0=no, 1=yes
Diabetes type I and II	0=no, 1=yes
Smoking	0=no, 1=yes
Alcohol consumption	0=no, 1=yes
Hb values during pregnancy	
Pre-eclampsia	0=no, 1=yes
Hepatogestosis	0=no, 1=yes
Thromboembolia	0=no, 1=yes
Induction of labor	0=no, 1=yes
Mode of delivery	1=vaginal, 2=cesarean section
Cesarean section	1=elective, 2=emergency, 3=crash
Hemorrhage (ml)	
Infection	0=no, 1=yes
Vaginal tears (3^{rd}-4^{th} degree)	
Red blood cell transfusion	0=no, 1=yes
Hospital stay after delivery (days)	
Gender of the newborn	1=female, 2=male
Birth weight (grams)	
Birth weight <-2SD	0=no, 1=yes
Gestational age (weeks)	
Fetus mortus	0=no, 1=yes
Apgar 1 min	
Apgar 5 min	
Apgar 1 min <7	0=no, 1=yes
Apgar 5 min <7	0=no, 1=yes
Umbilical artery pH	
Umbilical artery BE	
Neonatal intensive care	0=no, 1=yes
Neonatal intensive care (days)	

BMI: body mass index; Hb: hemoglobin; SD: standard deviation; BE: base excess.

4.2.2 Assessment of psychological distress (Study II)

The outcomes presented in **Table 8** were obtained from the Medical Birth Register kept by the National Institute for Health and Welfare (www.thl.fi). Data on Hb values and BMI were collected manually from the patient registers by researchers (LK and MM). The questionnaires used for the assessment of psychological distress are shown in **Table 9**. Maternal psychological distress was assessed using internationally validated, self-reported questionnaires, which pregnant women filled in online or sent via postal mail. Depressive symptoms were assessed using EPDS, which is in a routine clinical use for screening antenatal and postpartum depression in Southwest Finland and it has been validated in several countries (J. Cox & Holden, 2003; J. L. Cox et al., 1996). It has 10 questions on a 4-point Likert scale from 0 to 3. In previous studies, EPDS ≥10 and EPDS ≥12 have been used to indicate depression (J. L. Cox et al., 1996; Navarro et al., 2007).

Symptom Checklist-90 (SCL) was used to evaluate general anxiety. It consists of 10 questions rated from 0 to 5, with a total score ranging between 0–50. SCL has been proven to be reliable for assessing anxiety symptoms in research as well as in clinical settings (Derogatis et al., 1973; Holi et al., 1998).

To evaluate maternal stress and adaptation to pregnancy, we used the Pregnancy-Related Anxiety Questionnaire-Revised (PRAQ-R2), a revised version of the PRAQ, which is suitable both for primiparous and multiparous women. PRAQ-Q2 is referred to as PRAQ in this thesis and Study II. It is used to estimate pregnancy-related anxiety, which is typical for pregnancy (Huizink et al., 2016; Van Den Bergh, 1990). PRAQ-R2 consists of 10 questions scored from 1 to 5; the total score ranging thus between 5–50.

All three questionnaires, EPDS, SCL, and PRAQ, were assessed as continuous variable at three different time points during pregnancy (14, 24, and 34 gestational weeks). EPDS and SCL were also evaluated at 3 and 6 months postpartum. In addition, the incidence of high EPDS scores, indicating depression, was assessed in late pregnancy as well as at 3 and 6 months postpartum, using the cut off value of ≥10.

Table 8. Variables obtained from the national Medical Birth Register kept by the National Institute for Health and Welfare and maternal self-reports for studies assessing the relationship between gestational anemia and psychological distress (Study II) and breastfeeding (Study III).

Studies II and III	
Medical Birth Register data	
Parity	0=nulliparous, 1=multiparous
Maternal BMI kg/m^2	
Gestational age (weeks)	
Threatening prematurity	0=no, 1=yes
Antenatal corticosteroids	0=no, 1=yes
Duration of labor (minutes)	
Induction of labor	0=no, 1=yes
Mode of delivery	1=vaginal, 2=cesarean section
Red blood cell transfusion	0=no, 1=yes
Birth weight (grams)	
Gender of the newborn	1=female, 2=male
Umbilical artery pH	
Umbilical vein pH	
Neonatal intensive care	0=no, 1=yes
Maternal self-reported data	
Hypertension	0=no, 1=yes
Type 1 diabetes	0=no, 1=yes
Type 2 diabetes	0=no, 1=yes
Use of SSRI / SNRI medication	0=no, 1=yes
Alcohol consumption during pregnancy	0=no, 1=any alcohol consumption
Smoking during pregnancy	0=no smoking, 1=any smoking
The level of education	1=secondary school, 2=high school or vocational education, 3=university or polytechnic degree or higher
Exclusive breastfeeding (months)	
Partial breastfeeding (months)	

BMI: body mass index; SSRI: selective serotonin reuptake inhibitor, SNRI: selective norepinephrine reuptake inhibitor.

Table 9. The questionnaires used to evaluate maternal psychological distress.

Questionnaire	Edinburgh Postnatal Depression Scale	Symptom Checklist-90	Pregnancy-Related Anxiety
Abbreviation	EPDS	SCL	PRAQ
Evaluation target	Depressive symptoms	Anxiety symptoms	Adaptability to pregnancy
Scoring range	0–30	0–50	5–50
Number of questions	10	10	10
Cut-off values	≥10, ≥12	No cut-off value	No cut-off value
Reference	Cox et al.,1996 Cox et al., 2003 Navarro et al., 2007	Derogatis et al., 1973 Holi et a., 1998	Huizink et al. 2016

4.2.3 Assessment of breastfeeding (Study III)

Information on the duration and quality (exclusive/partial) of breastfeeding was collected via a self-reported questionnaire (**Table 8**). Breastfeeding was assessed both as a categorical and a continuous variable. When categorical variable was used, the cut-off value was selected according to the Finnish national breastfeeding guidelines: EBF for at least four months (yes/no). The duration of breastfeeding was also evaluated as a continuous variable, distinguishing between the durations of exclusive and partial breastfeeding in months.

4.3 Statistical analysis

Statistical analyses were conducted using SPSS software (IBM SPSS Statistics 25.0). P-values <0.05 were considered statistically significant in all studies. Statistical analyses were performed in collaboration with a statistician from the University of Turku, Turku, Finland (Study I), and with FinnBrain statisticians (Studies II–III).

4.3.1 Study I

Categorical measures between the studied groups were assessed using Chi-square and Fisher's exact tests. The distribution of data was assessed using the Kolmogorov-Smirnov test, the Shapiro-Wilks test, and visual inspection. For continuous data, an independent t-test was used if the data were normally distributed; otherwise, the Mann-Whitney U-test was applied.

4.3.2 Study II

A general linear model univariate analysis was employed to assess the relationship between maternal anemia and maternal psychological distress (measured by EPDS, SCL, PRAQ) at three different time points during pregnancy and six weeks postpartum (Study II). The analyses were adjusted for maternal age, smoking during pregnancy, parity, maternal education, and gestational age, as they are known risk factors for gestational anemia (Drukker et al., 2015; Hailu Jufar & Zewde, 2014; Nordenberg et al., 1990). Logistic regression was used to evaluate differences in the incidence of EPDS score ≥10, incorporating the same confounding factors. Chi-square and Fisher's exact test were used when assessing the differences in categorical measures between the studied groups. To assess continuous data, independent t-test and Mann-Whitney U-test were applied according to data distribution.

4.3.3 Study III

Breastfeeding was analyzed as both a categorical and continuous variable. A stepwise general linear model was applied to assess the association between maternal anemia in the third trimester and breastfeeding as a continuous variable (exclusive/partial). The analysis was adjusted for mode of delivery, parity, and level of education, which are all known to affect the duration of breastfeeding (Hobbs et al., 2016; Pippins et al., 2006; Thulier & Mercer, 2009). To explore the effect of EPDS scores on the duration of breastfeeding, a stepwise model was used. Antenatal and postpartum EPDS scores were used as categorical variables and EPDS ≥12 served as a cut-off value to indicate depression. In the assessment of EBF as a categorical variable, a similar stepwise model was employed using logistic regression. Differences between the groups were analyzed using the Chi-square test or Fisher's exact test for categorical data. For continuous data, either the independent t-test or the Mann-Whitney U test was used, depending on the data distribution.

4.4 Ethical considerations

Ethics Committee Approval 11/2018, T07/017/18, was obtained from the local ethics committee for the evaluation of The Clinical Birth Cohort. Approval was also obtained from the local ethics committee (57/1801/2011) prior to the recruitment for the FinnBrain Cohort, and written informed consents were required prior to the study entry. All studies were conducted in concordance with the Declaration of Helsinki.

5 Results

5.1 Maternal characteristics

5.1.1 The Clinical Birth Cohort (Study I)

During the study period from January 2016 to October 2018, 215 women with singleton deliveries at Turku University Hospital, Turku, Finland, had Hb <100 g/l during pregnancy. All pregnancies from the same period served as controls (n = 11 545). Women in the anemic group were younger (29 years vs. 30 years, $p < 0.001$) and had used alcohol more frequently during pregnancy (2.8% vs. 0.5%, $p = 0.001$) than the control group. Hypertension and pregestational diabetes were more prevalent in the group with anemia, and anemic women were more often multiparous. The lowest mean (range) Hb of 94 g/l (65–99) was observed at 31 gestational weeks. Maternal characteristics are presented in **Table 10**. Ferritin and TfR values in the anemic and control groups were available from 22.8% and 27.4% pregnant women, respectively; therefore, they were not included in the analyses. The median (range) for ferritin and TfR were 8.0 mg/l (3–254) and 7.8 μg/l (2–42), respectively, indicating that gestational anemia was caused by ID in the vast majority of cases.

In the subgroup analysis comparing intravenous and oral iron supplementation, no differences in maternal characteristics were observed between the groups (Study I).

5.1.2 The FinnBrain Birth Cohort (Study II and III)

In the study focusing on psychological distress and anemia (Study II), the FinnBrain Cohort was used: 301 (23.6%) women had Hb <110 g/l at some measurement point during the pregnancy, leaving 972 women with Hb >110 g/l in the control group. The characteristics are presented in **Table 10**. The anemic group had a significantly lower prepregnancy BMI compared to the control group (22.0 vs. 23.5 kg/m^2, $p < 0.001$). In addition, women with anemia smoked more frequently and were more often multiparous, and by definition, Hb values were significantly lower in all measurement points in the anemic group. When exploring the association between

breastfeeding and anemia (Study III), 1238 women in the FinnBrain cohort had Hb measured in the third trimester (>30 weeks) and 150 (12%) of them had Hb <110 g/l, and by definition, Hb values in the third trimester were significantly lower than those among the controls. Within the group with anemia, smoking, a lower level of education, and multiparity were more frequent. In addition, prior cesarean section was more frequent (10.9% vs. 5.5%, $p = 0.011$) in women with Hb <110g/l in the third trimester. No differences among age, BMI, diagnosis of hypertension, or alcohol consumption were observed.

Table 10. Maternal characteristics in Studies I–III evaluating the associations between gestational anemia and pregnancy outcomes (Study I), maternal psychological distress (Study II), and duration and quality (exclusive and partial) of breastfeeding). Values are presented as % (n), mean (SD), and median (range).

	Study I Anemia and maternal and neonatal outcomes			Study II Anemia and psychological distress			Study III Anemia and breastfeeding		
Maternal characteristics	**Hb <100 g/l n=215**	**Hb ≥100 g/l n=11 545**	**p**	**Hb <110 g/l n= 301**	**Hb ≥110 g/l n=972**	**p**	**Hb <110 g/l >30 weeks n=150**	**Hb ≥110 g/l >30 weeks n=1088**	**p**
Age at delivery (years)	29 (5.8)	30 (5.2)	***<0.001***	30 (18–45)	30 (17–44)	*.658*	29 (18–45)	30 (17–44)	*.089*
Primiparous	77 (35.8%)	5252 (43.3%)	*.032*	155 (52.5%)	612 (64.2%)	***<0.001***	54 (36.7%)	692 (64.9%)	***<0.001***
Body mass index (kg/m^2)	24 (17–43)	24 (16-59)	*.458*	22 (16–45)	23.5 (17–46)	***<0.001***	23 (16–45)	23 (17–46)	*.67*
Prior cesarean delivery	25 (11.6%)	1148 (10.6%)	*.634*	21 (7.1%)	55 (5.8%)	*.398*	16 (10.9%)	59 (5.5%)	***.011***
Hypertension	3 (1.4%)	23 (0.2%)	***<0.001***	4 (1.8%)	18 (2.3%)	*.799*	3 (2.8%)	18 (2.0%)	*.492*
Type 1 or 2 diabetes	8 (3.7%)	135 (1.2%)	***<0.001***	0	2 (0.3%)		3 (2.8%)	2 (0.2%)	***.011***
Smoking	25 (11.6%)	1162 (11.2%)	*.848*			***.016***			***.001***
I trimester				31 (10.4%)	99 (10.2%)		18 (12.1%)	110 (10.2%)	
III trimester				30 (10.0%)	55 (5.7%)		17 (11.4%)	60 (5.6%)	
Alcohol consumption	6 (2.8%)	49 (0.5%)	***.001***						
I trimester				46 (20.4%)	192 (24.6%)	*.213*	22 (20.6%)	210 (24.1%)	*.422*
III trimester				22 (11.6%)	75 (10.8%)	*.696*	11 (12.4%)	84 (10.8%)	*.658*
Level of education	NA	NA				*.579*			***.044***
Secondary school				83 (36.2%)	267 (33.4%)		47 (43.1%)	292 (32.7%)	
High school or vocational education				65 (28.4%)	220 (27.5%)		31 (28.4%)	248 (27.8%)	
University/polytechnic degree or higher				81 (35.4%)	312 (39.0%)		31 (28.4%)	353 (39.5%)	

Hb: hemoglobin; NA: not applicable. P-values <0.05 were considered statistically significant.

5.2 Anemia and maternal and neonatal complications

5.2.1 Maternal obstetric complications (Study I)

In Study I, postpartum infections, including endometritis, urinary tract infection, sepsis and wound infection, (9.3% vs. 3.5.%, $p < 0.001$), and red blood cell transfusions (5.6% vs. 2.6%, $p = 0.002$) were more common in the group with anemia than among the controls (**Table 11**). In addition, hospital stay was significantly longer in women with Hb <100 g/l than the controls (3.0 vs. 2.0, $p < 0.001$). No significant differences among rates of labor inductions, cesarean sections, operative deliveries, hemorrhages during delivery, and vaginal 3rd-or 4th -degree tears were observed.

In the subgroup analysis of the Clinical Birth cohort regarding iron medication and outcome parameters, hematologic parameters were corrected more efficiently evaluated as Hb increase in the group that received intravenous iron (18.0 g/l (0–48.0) vs. 10.0 (0–55.0), $p < 0.001$). However, no significant difference in the Hb values after oral and intravenous iron supplementation was observed (109 g/l vs. 107 g/l, $p = 0.338$). Labors of women who received intravenous iron were more likely to be induced (44.2% vs. 27%, $p = 0.019$) than women with oral iron medication, but no other differences in maternal characteristics were detected.

Table 11. Maternal outcomes in Studies I–III evaluating the associations between gestational anemia and pregnancy outcomes (Study I), maternal psychological distress (Study II), and duration and quality (exclusive and partial) of breastfeeding). Values are presented as % (n), mean (SD), and median (range).

	Study I Anemia and maternal and neonatal outcomes			Study II Anemia and psychological distress			Study III Anemia and breastfeeding		
Maternal outcome	**Hb <100g/l n=215**	**Hb ≥100 g/l n=11 545**	**p**	**Hb <110 g/l n=301**	**Hb ≥110 g/l n=972**	**p**	**Hb <110 g/l >30 weeks n=150**	**Hb ≥110 g/l >30 weeks n=1088**	**p**
Duration of labor (min)	NA	NA		430 (38–2066)	464 (39–2204)	*.196*	369 (59–1814)	472 (39–2204)	***.002***
Induction of labor	67 (31.2%)	3453 (29.9%)	*.691*	70 (23.7%)	233 (24.5%)	*.794*	36 (24.5%)	259 (24.3%)	*.959*
Mode of delivery			*.992*						
Vaginal delivery	159 (74.0%)	7995 (73.9%)		242 (82.0%)	778 (81.6%)	*.877*	120 (81.6%)	870 (81.5%)	*.978*
Operative vaginal delivery	20 (9.3%)	1030 (9.5%)							
Cesarean section	36 (16.7%)	1788 (16.5%)	*.922*	53 (18.0%)	175 (18.4%)	*.931*	27 (18.4%)	197 (18.5%)	
Elective	12 (33.3%)	666 (37.2%)		20 (6.8%)	62 (6.5%)		12 (44.4%)	70 (35.5%)	*.611*
Emergency	22 (61.1%)	1024 (57.3%)		30 (10.2 %)	101 (10.6%)		12 (51.9%)	114 (57.9%)	
Crash emergency	2 (5.6%)	98 (5.5%)		3 (1.0%)	12 (1.3%)		1 (3.7%)	13 (6.6%)	
Significant hemorrhage at delivery	NA	NA		NA	NA		19 (12.9%)	126 (11.8%)	*.696*
>500ml	61 (28.4%)	2763 (25.6%)	*.331*	NA	NA		NA	NA	
>1000ml	12 (5.6%)	709 (6.6%)	*.576*	NA	NA		NA	NA	
Hemorrhage (ml)	400 (100–3300)	400 (50–10830)	*.507*	NA	NA		NA	NA	
Postpartum infection	20 (9.3%)	374 (3.5%)	***<0.001***	NA	NA		NA	NA	
3rd–4th degree vaginal tear	4 (1.9%)	174 (1.5%)	*.570*	NA	NA		NA	NA	
Red blood cell transfusion	12 (5.6%)	269 (2.6%)	***.002***	14 (4.7%)	25 (2.6%)	*.083*	10 (6.8%)	29 (2.7%)	***.020***
Hospital stay after delivery (days)	3.0 (0–15)	2.0 (0–35)	***<0.001***						

Hb: hemoglobin; NA: not applicable. P-values <0.05 were considered statistically significant.

5.2.2 Neonatal complications (Study I)

Neonatal outcomes in pregnancies complicated by maternal anemia and the controls are presented in **Table 12**. In our retrospective Clinical Birth Cohort (Study I), maternal anemia (Hb <100 g/l) was associated with prematurity: 10.2% of anemic women and 6.1% of non-anemic women delivered prior to 37 weeks ($p = 0.009$) and the respective percentages at 32–34 weeks were 4.7% and 1.4% ($p = 0.001$). In addition, FGR, defined as birth weight <-2 SD, was detected in 1.9% of pregnancies with maternal anemia and in 0.3% of control pregnancies ($p = 0.006$).

As regards to the neonatal state at birth, Apgar scores at the age of 1-minute (8.5 vs. 8.7) and 5-minute (9.0 vs. 9.1) were lower in the group with maternal anemia compared to the controls (Study I). No differences among birth weight (g), gender, umbilical artery or vein pH values, and the incidence of NICU admission were detected.

In the subgroup analysis, comparing oral iron supplementation and intravenous iron substitution, no differences in neonatal outcome between the studied groups were detected.

Table 12. Neonatal outcomes in Studies I–III evaluating the associations between gestational anemia and pregnancy outcomes (Study I), maternal psychological distress (Study II), and duration and quality (exclusive and partial) of breastfeeding. Values are presented as % (n), mean (SD), and median (range).

	Study I Anemia and maternal and neonatal outcomes			Study II Anemia and psychological distress			Study III Anemia and breastfeeding		
Neonatal outcome	**Hb <100g/l n=215**	**Hb ≥100 g/l n=11 545**	**p**	**Hb <110 g/l n=301**	**Hb ≥110 g/l n=972**	**p**	**Hb <110 g/l >30 weeks n=150**	**Hb ≥110 g/l >30 weeks n=1088**	**p**
Male	96 (44.7%)	5495 (50.9%)	*.069*	147 (49.2%)	500 (51.8%)	*.423*	75 (50.7%)	553 (51.2%)	*.913*
Birth weight (g)	3505 (760–5040)	3640 (268–5445)	*.382*	3634 (1560–4950)	3550 (820–5200)	*.512*	3650 (1560–4950)	3554 (820–5200)	***.041***
Birth weight <-2SD	4 (1.9%)	37 (0.3%)	***.006***						
GA at delivery (weeks)	NA	NA		39.9 (33.2–42.2)	40.1 (29.2–42.4)	*.073*	40 (34.8–42.1)	40 (29.3–42.4)	*.230*
GA at delivery <37 weeks	22 (10.2%)	41 (6.1%)	***.009***	NA	NA		NA	NA	
GA at delivery 32-34 weeks	10 (4.7%)	151 (1.4%)	***.001***	NA	NA		NA	NA	
GA at delivery <32 weeks	5 (2.3%)	127 (1.2%)	*.190*	NA	NA		NA	NA	
Fetus mortus	1 (0.5%)	31 (0.3%)	*.446*	NA	NA		NA	NA	
Apgar 1min	8.5 (1.3)	8.7 (1.2)	*.002*						
Apgar 5min	9.0 (0.8)	9.1 (0.8)		NA	NA		9 (5–10)	9 (3–10)	*.635*
Apgar 1min <7	19 (8.9%)	627 (5.4%)	*.031*						
Apgar 5min <7	4 (1.9%)	182 (1.6%)	*.587*	NA	NA		2 (1.4%)	16 (1.5%)	*1.000*
Umbilical artery pH	7.28 (6.98–7.53)	7.27 (6.59–7.54)	*.263*	7.28 (6.99–7.48)	7.27 (6.80–7.54)	*.373*	7.28 (7.05–7.45)	7.27 (6.80–7.54)	*.256*
Umbilical artery BE	-3.6 (3.5)	-3.7 (3.3)	*.870*						
Umbilical vein pH	NA	NA		7.36 (7.11–7.52)	7.35 (6.94–7.52)	*.387*	7.37 (7.13–7.52)	7.35 (6.94–7.52)	*.296*
NICU	21 (9.8%)	755 (7.0%)	*.114*	53 (18.0%)	128 (13.4%)	*.053*	27 (18.4%)	146 (13.7%)	*.132*

Hb: hemoglobin; GA: gestational age; NA: not applicable; BE: base excess; NICU: admission to neonatal intensive care unit. P-values <0.05 were considered statistically significant.

5.2.3 Anemia and maternal psychological symptoms (Study II)

Gestational anemia was not associated with maternal depressive and anxiety symptoms in our prospectively collected cohort of 301 anemic women with Hb <110 g/l when adjusting the analysis by maternal age, parity, smoking during pregnancy, maternal education, and gestational age (**Table 13**). In early pregnancy, the median (range) EPDS scores were 5.0 (0–26) and 5.0 (0–27) in pregnant women with Hb <110 g/l and in the controls, respectively (p = 0.446). About 15% of the anemic pregnant women had EPDS score ≥10 in late pregnancy, indicating depression, while the corresponding proportion was 14% among the controls (p = 0.882).

In early pregnancy, the median (range) SCL score, assessed to detect general anxiety, was 3.0 (0–30) and 2.0 (0–28) for the anemic and non-anemic groups, respectively (p = 0.043). However, no differences between the groups were observed at the mid- and late-pregnancy measurement points. Neither did we detect differences in SCL scores of the anemic and non-anemic women three and six months postpartum.

In the subgroup analysis in Study II, assessing whether lower Hb values in moderate maternal anemia (Hb <100 g/l) increase the risk for maternal psychological distress, no differences in EPDS scores between women with Hb <100 g/l and the controls were detected. A higher number of anemic women compared to the controls had EPDS score ≥10 in late pregnancy, but the difference was not statistically significant (27.8% vs. 13.2%, p = 0.336). Pregnant women with Hb <100 g/l had significantly higher median (range) SCL score in late pregnancy, indicating anxiety symptoms, than the control group (5.5 (0–14) vs. 2.0 (0–27) p = 0.028), but the SCL scores at other measurement points during pregnancy and postpartum did not differ. Furthermore, in the assessment of pregnancy-related anxiety symptoms, no differences between PRAQ scores in women with Hb <100 g/l and the controls were detected.

When exploring the psychological distress and anemia among pregnant women in the FinnBrain cohort, maternal clinical outcomes were recorded as well, and no differences in the labor induction rates, duration of labor, mode of delivery, and red blood cell transfusions were detected between anemic (Hb <110 g/l) and non-anemic groups (**Table 11**).

Table 13. Evaluation of maternal depression (EPDS), anxiety (SCL), and pregnancy-related anxiety (PRAQ) in women with anemia and the controls (Study II).

	Study II Anemia and psychological distress		
Depressive symptoms	**Hb <110 g/l n=301**	**Hb ≥110 g/l n=972**	**p**
EPDS I trimester	5.0 (0–26)	5.0 (0–27)	*.349*
EPDS II trimester	4.0 (0–22)	4.0 (0–25)	*.960*
EPDS III trimester	4.0 (0–19)	4.0 (0–19)	*.654*
EPDS 3 months postpartum	4.0 (0–17)	3.0 (0–21)	*.440*
EPDS ≥10 3 months postpartum	16 (9.6%)	60 (9.9%)	*.790*
EPDS 6 months postpartum	3.0 (0–24)	3.0 (0–22)	*.677*
EPDS ≥10 6 months postpartum	20 (14.4%)	55 (10.7%)	*.259*
Anxiety symptoms			
SCL I trimester	3.0 (0–30)	2.0 (0–28)	*.051*
SCL II trimester	3.0 (0–21)	3.0 (0–29)	*.462*
SCL III trimester	2.0 (0–25)	2.0 (0–27)	*.647*
SCL 3 months postpartum	1.0 (0–17)	1.0 (0–24)	*.432*
SCL 6 months postpartum	1.0 (0–20)	1.0 (0–29)	*.612*
PRAQ I trimester	21.0 (12–40)	22.0 (11–45)	*.964*
PRAQ II trimester	22.0 (10–43)	23.0 (10–46)	*.146*
PRAQ III trimester	24.0 (10–50)	23.0 (10–49)	*.776*

Hb: hemoglobin; EPDS: Edinburgh Postnatal Depression Scale; SCL: Symptom Checklist-90; PRAQ: Pregnancy-Related Anxiety Questionnaire. P-values <0.05 were considered statistically significant.

5.3 Anemia and breastfeeding (Study III)

Approximately 60% of women with antenatal anemia and 66% of non-anemic women reached the recommended goal of four months of EBF (p = 0.277, Study III). When breastfeeding was analyzed as a continuous variable, the median (range) durations of EBF varied between 4 (0–6) months and 4 (0–10) months in women with antenatal anemia and the controls (p = 0.461). Furthermore, no significant difference between the studied groups in partial breastfeeding was observed (7 months vs. 8 months, p = 0.080).

The duration of EBF was not associated (p = 0.107) with gestational anemia in late pregnancy after adjustments by mode of delivery, parity, level of education, antenatal EPDS score ≥12, and postnatal EPDS score ≥12. However, the goal of EBF at least four months was more rarely reached among pregnant women with EPDS score ≥12 three months postpartum (p = 0.006).

Although no significant association was seen in the linear regression analysis, in the adjusted analysis (mode of delivery, parity, and level of education), the duration of partial breastfeeding was shorter among anemic women (p = 0.034). However, if the EPDS score ≥12 in late-pregnancy and postpartum was added to the model, the difference was no longer significant. The detailed results regarding the duration of breastfeeding are presented in **Table 15**.

In our study focusing on breastfeeding and anemia, pregnant women with gestational anemia in the third trimester were more likely to receive red blood cell transfusions (6.8% vs. 2.7%, p = 0.020) than non-anemic women. However, no difference in the incidence of significant hemorrhage was detected between the groups (12.9% vs. 11.8%, p = 0.696). Neither did the mode of the delivery differ between the groups, but the total duration of labor (min) was statistically shorter in the group with anemia than in the controls (369 minutes vs. 472 minutes, p = 0.002). The results regarding maternal outcome are presented in **Table 11**.

No differences in neonatal outcome were detected despite a slight difference in birth weight – where in the anemic group, birth weight was greater than that in the non-anemic group (3650 grams vs. 3554 grams, p = 0.041). Detailed neonatal outcomes in Studies I–III are presented in **Table 12**.

Table 14. Evaluation of the duration and quality (exclusive/partial) of breastfeeding between the anemic and non-anemic groups. Analysis was adjusted by mode of delivery, parity, level of education, antenatal EPDS score ≥12, and postnatal EPDS score ≥12.

	Study III Anemia and breastfeeding					
Breastfeeding variable	**Hb <110 g/l >30 weeks n=150**	**Hb ≥110 g/l >30 weeks n=1088**	**Unadjusted p**	**B/OR**	**95% CI**	**Adjusted p**
EBF (months)	4.0 (0–6)	4.0 (0–10)	*.461*	−0.42	−0.94–0.09	*.107*
Partial breastfeeding (months)	7.0 (0–22)	8.0 (0–25)	*.080*	−1.05	−2.36–0.25	*.114*
EBF			*.277*			
≥4 months	47 (59.5%)	451 (65.6%)		1.56	0.88–2.79	*.131*
<4 months	32 (40.5%)	236 (34.4%)				

CI: Confidence interval; Hb: hemoglobin; EBF: exclusive breastfeeding; OR: odds ratio. P-values <0.05 were considered to be statistically significant.

6 Discussion

6.1 Iron deficiency anemia among pregnant population in Southwest Finland (Studies I–III)

WHO defines Hb 100–110 g/l as mild, Hb 79–99 g/l as moderate, and <70 g/l as severe gestational anemia (WHO, 2011). In Finland, the prevalence of gestational anemia has been estimated to be approximately 15% in 2024 (WHO, 2025), and the prevalence of moderate and severe gestational anemia defined as Hb <100 g/l is around 5.8%, having increased from 1.4% in 2005. (Finnish Institute for Health and Welfare, 2025).

In our studies, we assessed the prevalence of gestational anemia in two different cohorts: the Clinical Birth Cohort (n = 11 669) and the FinnBrain Birth Cohort (n = 1273). In the Clinical Birth Cohort assessing the effect of maternal anemia on maternal and neonatal outcomes, 1.8% of women had antenatal Hb <100 g/l, indicating moderate or severe gestational anemia at some point during the pregnancy. The prevalence of moderate or severe anemia (Hb <100 g/l) was also assessed in the subgroup analysis in the study evaluating anemia and psychological distress (Study II): 3.2% of pregnant women had moderate or severe anemia during pregnancy in the FinnBrain Cohort. These prevalences are in line with previously published data based on the Finnish Medical Birth Register during 2006–2010 (Räisänen, Kancherla, et al., 2014).

In Finland, the majority of anemic pregnant women suffer from mild gestational anemia, defined as Hb 100–110 g/l by WHO (WHO, 2011). Our studies assessing the effect of gestational IDA on maternal psychological symptoms (Study II) and the duration of breastfeeding (Study III) were based on the prospectively collected data from the FinnBrain Cohort (Karlsson et al., 2018). In Study II, focusing on psychological distress, 23.6% of participants had gestational anemia at some point during the pregnancy, and in Study III, which assessed the relationship between anemia and breastfeeding, the prevalence of gestational anemia in the third trimester was 12.1%. Thus, gestational anemia was more common in our cohort (23.6%) than the estimated 15 % prevalence of anemia during pregnancy in Finland (WHO, 2025). The FinnBrain Cohort data were collected between 2011 and 2015, while the estimation by WHO is from 2023, indicating a decrease in the prevalence of anemia.

The increase in awareness, widespread public debate, and easier access to sucrosomial and intravenous iron supplementation may have contributed to the decrease. However, even in a high-income country with adequate nutrition and information available, gestational anemia continues to affect a significant proportion of pregnancies, warranting more attention to adequate treatment. The growing popularity of vegetarianism in high-income settings, especially among young women, might contribute to the fact that the prevalence of gestational IDA is not decreasing as fast as hoped, even though the information about the need for vitamin and iron supplements is available. In addition, the increased migration influences the prevalence, as IDA is more common in low- and middle-income countries. The global goal of WHO is to half the number of gestational anemia cases by 2030 (WHO, 2025). If we use the 23.6% prevalence of gestational anemia detected in Study II, and the annual delivery rate of 46 000 as a starting points and aim for a prevalence of 12% by 2030 in Finland, we can estimate that about 5 500 pregnant women in Finland need a proper IDA prevention annually in order to achieve the goal set by WHO. Thus, knowledge on risk factors is essential.

Iron parameters, ferritin or TfR, were available only for 27.4% or 22.8% of pregnant women in the Clinical Birth Cohort and were not available at all in the FinnBrain Cohort, since these measures were not advised to be routinely checked in Finland at the time of these studies; and nor are they used in a routine fashion today. IDA in pregnancy is currently screened by measuring only the Hb level, as ID, is by far, the most common etiology for gestational anemia, particularly in a high-income setting. In our Studies I–III, we used the official diagnostic criteria for gestational IDA, which is hemoglobin measurement.

6.2 Risk factors and comorbidities of gestational anemia (Studies I–III)

6.2.1 Maternal risk factors for gestational anemia

In the study evaluating the effect of maternal anemia on maternal and neonatal outcomes, women with Hb <100 g/l were younger than those in the control group (29 years vs. 30 years, $p < 0.001$), but in studies focusing on psychological distress and breastfeeding, there were no statistically significant differences in the ages of the anemic and non-anemic women. Earlier research has recognized young age (<18 years, <19 years) as a risk factor for maternal anemia, and although many of the studies have been conducted in low- and middle-income countries (Idowu et al., 2005; Uche-Nwachi et al., 2010), where the mean maternal age is lower, similar results have been detected in Finland (Hämäläinen et al., 2003; Räisänen et al., 2014). Young age predisposes to menstruation disorders, such as menorrhagia, and

could therefore be one of the factors leading to increased loss of iron and ID prior pregnancy. Therefore, treating menorrhagia in reproductive aged women is the first step to prevent gestational IDA.

WHO defines underweight as BMI <18.5 kg/m2, normal weight as BMI 18.5–24.9 kg/m^2, overweight as 25.0–29.9 kg/m^2, and obesity as BMI >30 kg/m^2 (Weir & Jan, 2025). In our study assessing maternal psychological distress, anemic women were more likely to have lower BMI (22 vs. 23.5, $p < 0.001$). Research has associated underweight and overweight/obesity with an increased risk of anemia when compared to pregnant women with normal weight (Al-Mehaisen et al., 2011; Bodnar et al., 2004; Charles et al., 2010; Tan et al., 2018). Both, low and high BMI are associated with nutritionally poor diet, thus predisposing to nutrient, for example, iron, deficiencies (Tan et al., 2018; Wawer et al., 2021). Furthermore, obesity is known to cause low-grade inflammation, which increases hepcidin expression and, therefore, decreases the absorption of iron in the intestine (Christian & Porter, 2014; Garcia-Valdes et al., 2015). However, in Studies I and III, no differences in prepregnancy BMIs were detected between the anemic and non-anemic groups. In Finland, the prevalence of obesity in pregnant women is 20.8% (Finnish Institute of Health and Welfare, 2025), while in the United States, where the prevalence is the highest, one-third of pregnant women are estimated to be obese (Chen et al., 2018). The prevalence of obesity among pregnant women is increasing in every high- and middle-income country, and this important risk factor should be taken into account when treating women with gestational anemia as well as in the prevention of IDA (Chen et al., 2018).

In our study focusing on breastfeeding (Study III), a low level of education was associated with an increased risk of anemia. This finding is in line with earlier research conducted in Switzerland (Bencaiova et al., 2012). Low level of education is known to associate with smoking during pregnancy (Härkönen et al., 2018; Ventura et al., 2003). In Study II, evaluating psychological distress in the FinnBrain Cohort, smoking during pregnancy was more prevalent in the third trimester among anemic women. No decline between the first and the third trimesters was observed (10.4% vs. 10.0%), indicating that almost all of the anemic women continued smoking throughout pregnancy, whereas in the non-anemic group almost half quit smoking (10.2% vs. 5.7%). Smoking has well known risks for the pregnant woman and the fetus, and according to earlier reports about 53% of women stop smoking after the first trimester (Lange et al., 2018). As regards to gestational anemia, smoking has been recognized as a risk factor in several studies (Chełchowska et al., 2016; Mistry et al., 2018; Räisänen et al., 2014), thus adding the morbidity burden. Attention should be paid to pregnant women, who continue to smoke throughout pregnancy, as they are at increased risk of developing anemia and other maternal and fetal comorbidities as well. However, some studies have reported that smoking

increases the Hb values due to the effect of carbon monoxide (Sharma et al., 2019), and this can misleadingly cover ID. In the Clinical Birth Cohort (Study I), no significant association between tobacco smoking during pregnancy and gestational anemia was observed. The prevalence of smoking during pregnancy in Study I was 11.6% among the women with Hb <100 g/l, which is higher than the reported prevalence in the whole European region (8.1%) (Lange et al., 2018), but slightly less as reported in earlier Finnish study from year 2014 (15%) (Ekblad et al., 2014).

Alcohol consumption in Study I was shown to be more common within the pregnant women with moderate or severe anemia (Hb <100 g/l) compared to non-anemic women (2.8% vs 0.5%, p = 0.001). Although alcohol consumption has been shown to reduce the risk of IDA (Ioannou et al., 2004), heavy alcohol consumption during pregnancy has been associated with an increased risk of neonatal ID, indicating that consuming alcohol during pregnancy could affect iron metabolism (Carter et al., 2007). Pregnant women, who continue to use alcohol throughout pregnancy, might have poorer adherence to treatment and are less likely to use iron supplements as advised. In the FinnBrain Cohort (Studies II–III), however, no difference in alcohol consumption during the pregnancy was detected between anemic and non-anemic women, but the overall prevalence (20.4–24.6%) was high compared to earlier research published from Finnish pregnant population, which has been estimated it to be approximately 4.5% (Voutilainen et al., 2022). The questionnaires in the FinnBrain Cohort surveyed whether any alcohol during the pregnancy was used, with an “yes”/“no” -answer. Therefore, in these self-reports pregnant women might have answered affirmative due to alcohol usage in the first trimester, before they knew of being pregnant. The prevalence of alcohol consumption halved during pregnancy in the anemic and non-anemic groups in the FinnBrain Cohort. In Europe, approximately 16% of pregnant women consume alcohol during pregnancy (Mårdby et al., 2017), which is significantly higher than among pregnant women in the studies included in this thesis or reported earlier from Finland (Voutilainen et al., 2022).

6.2.2 Obstetric risk factors and comorbidities of gestational anemia

As discussed earlier, pregnancy increases iron requirement, and multiparity, especially with short pregnancy intervals, is known to deplete iron stores and, thus, predispose women to ID and anemia. This was detected in all our studies included in this thesis, aligning with previous research (Al-Farsi et al., 2011; Çelik Kavak & Kavak, 2017; Hailu Jufar & Zewde, 2014; Harrison et al., 2021; Kagu et al., 2007). Multiparous women, particularly those with pregnancy intervals of <2 years, are at increased risk for gestational IDA. Therefore, they are screened routinely by

measuring ferritin in addition to Hb in the United Kingdom (Pavord et al., 2012), a practice that could be adopted in Finland as well, where approximately 57% of the pregnant women are multiparous (Finnish Institute of Health and Welfare, 2025).

In all studies included in this thesis, pregnant women with anemia were more frequently diagnosed with pregestational diabetes. Anemia is a common comorbidity in diabetic patients (Thomas et al., 2004) due to decreased kidney function, and anemia can be the first sign of renal disease. In addition, ID and altered hepcidin metabolism increase the risk of anemia in diabetic pregnant women (Gangopadhyay et al., 2011). Attention should be paid to the management of gestational IDA among pregnant women with pregestational diabetes should be paid. Interestingly, also excess iron, as well as elevated Hb and ferritin values, has been shown to affect glucose metabolism and increase the risk of gestational diabetes (Fernández-Cao et al., 2017; A. Khambalia, et al., 2016). High Hb levels could reflect impaired glucose metabolism and subclinical prepregnancy insulin resistance (H. Y. Kim et al., 2021). On the other hand, excess iron can lead to increased oxidative stress, which interferes with glucose metabolism and is associated with hyperglycemia (Puntarulo, 2005).

In the Clinical Birth Cohort, pregestational hypertension was more common among the women with anemia (Hb <100 g/l) compared to the non-anemic group (1.4% vs. 0.2%, $p < 0.001$). In Studies II and III, using the FinnBrain Cohort, no difference in the incidence of prepregnancy hypertension was detected between the anemic and non-anemic groups. In non-pregnant patients, hypertension has been shown to be associated with IDA, and even a genetic link between the two has been suggested (Cao et al., 2024). Our findings show that anemia often exists as a comorbidity with pregestational chronic diseases, and may, thus, further increase maternal and fetal risks. This underlies the importance of screening and early management of ID and IDA.

6.3 Maternal obstetric complications associated with iron deficiency anemia (Studies I–III

Gestational IDA has been associated with an increased maternal morbidity and mortality in several studies and meta-analyses (Drukker et al., 2015; Haider et al., 2013; Jung et al., 2019b; Rahmati et al., 2020b). However, high Hb values have also been linked to adverse outcomes, and the relationship between Hb and maternal outcomes seems to be U-shaped (Dewey & Oaks, 2017).

In our study focusing on the effect of anemia on maternal and neonatal outcomes, gestational IDA increased the risk of maternal postpartum infections (endometritis, urinary tract infection, sepsis, and wound infection) three-fold. This is in line with some of the studies published earlier (Chaim et al., 2000; Harrison et al., 2021; Rukuni et al., 2016; Smith et al., 2019). Anemia and ID are known to limit the

function of the immunological system and, therefore, increase the risk of infections (Beard, 2001; V. Kumar & Choudhry, 2010). Harrison et al. also suggested that impaired tissue oxygenation and decreased blood flow could lead to increased susceptibility to infection (Harrison, 2021b). While cesarean section is associated with an increased risk of infections (Hofmeyr & Smaill, 2010), the cesarean delivery rate did not differ among anemic and non-anemic women in our study, and, therefore, does not explain the increase in infection rates. In addition, no differences in operative deliveries (vacuum/forceps) were observed between the groups. As regards other possible explanatory factors predisposing to adverse outcome/infections in our study, anemic women had more often pregestational diabetes and hypertension, although the number of diabetic patients in the anemic group was small (n = 8). According to our adjusted analyses, gestational anemia itself seems to predispose women to maternal postpartum infections, and since the infections often occur within the first weeks after delivery, IDA should be treated adequately during pregnancy to prevent maternal infections. In addition, the importance of treating gestational anemia effectively in diabetic patients should be underlined to avoid cumulative risks; adequate follow-up and consideration of intravenous iron infusions, if needed, should be organized.

In our Clinical Birth Cohort (Study I), the length of hospital stay was significantly longer for women with Hb <100g/l during the pregnancy (3 days vs. 2 days, $p < 0.001$). The most common symptoms of maternal anemia are fatigue and weakness, which may increase morbidity and contribute to longer duration of hospital stay. Furthermore, in Studies I and III, red blood cell transfusions were more often given to anemic women increasing the likelihood of a longer hospital stay.

No differences in cesarean section rates were detected between the anemic and non-anemic groups in any of the studies included in this thesis, although prior research has linked anemia to an increased cesarean section rate (Drukker et al., 2015). Compared to other high-income countries, the cesarean section rate in Finland was low at the time of the studies, being 16.5% in 2016; and, therefore, it is possible that the effect of gestational IDA on cesarean section rate does not show in our studies.

6.4 Neonatal complications associated with iron deficiency anemia (Studies I–III)

Prematurity has been associated with gestational anemia in several meta-analyses (Jung et al., 2019; Rahmati et al., 2020; Sukrat et al., 2013; Young et al., 2019). In our Clinical Birth Cohort (Study I), anemic women were more likely to deliver prematurely (gestational age <37 weeks) compared to women with Hb ≥100 g/l. When comparing the incidence of very premature neonates born at 32–34 weeks, the

difference was three-fold between the anemic and non-anemic groups. However, no differences in extremely premature neonates born before 32 weeks were observed between the groups. Allen et al. suggested that chronic hypoxia due to anemia leads to an increased secretion of corticotropin-releasing hormone–which, in turn, is known to regulate the onset of labor and could lead to prematurity (Allen, 2001). However, no difference between anemic (Hb <110 g/l) and non-anemic groups in prematurity was detected in studies assessing psychological distress or duration of breastfeeding. This could indicate that moderate and severe anemia (Hb <100 g/l), but not mild anemia, increases the risk of prematurity. In the studies included in this thesis, the etiology of prematurity (iatrogenic/spontaneous) was not specifically assessed. However, no differences in common maternal indications for induction of labor prior to <37 weeks (preeclampsia, gestational diabetes, and hepatogestosis) were detected, indicating that the increase was indeed due to fetal reasons, spontaneous prematurity, and FGR.

In the Clinical Birth Cohort (Study I), women with Hb <100 g/l were six times more likely to deliver a growth-restricted neonate, with a birth weight <-2 SD. Elevated corticotropin-releasing hormone levels have been shown to associate with increased cortisol levels–which, in turn, are associated with FGR (Diego et al., 2006). Alternatively, ID is suggested to cause oxidative damage to the fetoplacental unit affecting fetal growth (Allen, 2001). In Studies II–III conducted with the FinnBrain Cohort, no clinically significant differences in birth weights were detected, although in the study evaluating breastfeeding (Study III), the mean birth weight was 96 grams higher in the anemic group ($p = 0.041$). It should be noted that the assessment of fetal growth solely by birth weight does not take into account gestational weeks. Therefore, research reporting only the actual birth weight with no reference to the corresponding gestational age should therefore be interpreted with caution. Some studies have associated moderate and severe anemia with FGR, but no association with mild anemia was detected (Kozuki et al., 2012; Shi et al., 2022), which could indicate that the effect of anemia on fetal growth is altered by severity. In our Studies II–III, the prevalence of moderate and severe anemia was low, making reliable evaluation of severity of anemia on FGR challenging, although the increased risk of FGR was observed in Study I with Hb <100 g/l, and no differences in fetal growth in Studies II–III with Hb <110 g/l were detected.

In the Clinical Birth Cohort (Study I), 1-minute and 5-minute Apgar scores were lower in the group with maternal Hb <100 g/l compared to those with maternal Hb ≥100 g/l (8.5 vs. 8.7, $p = 0.002$ and 9.0 vs. 9.1, $p = 0.007$). These numbers indicate a significant statistical difference, but the clinical difference may be small. Several studies have linked maternal anemia and anemia in the third trimester, to lower Apgar scores (Drukker et al., 2015; Smith et al., 2019; Sun et al., 2021). In our study assessing the effect of gestational anemia in the third trimester on breastfeeding, no

differences in the 5-minute Apgar scores were detected between the groups, and neither was any difference detected in the Apgar scores in the study evaluating psychological distress. The effect of gestational anemia on Apgar scores could depend on the severity of anemia, and our findings might reflect the fact that the number of severely anemic women in our studies was small.

In addition to elevated risks of prematurity and FGR, gestational IDA has been linked to adverse neurocognitive outcomes in the offspring at age 6–29 years (Leonard et al., 2006; Wiegersma et al., 2020). Maternal IDA has been shown to reduce hippocampal volume (Basu et al., 2018). As the iron storage of the newborn forms mainly during pregnancy and breast milk contains low amounts of iron, the adequate iron transfer from the mother to the fetus is essential (Friel et al., 2018). Thus, gestational IDA increases the risk of ID and IDA in the newborn (Zhao et al., 2024), subsequently affecting the neurocognitive development of the infant. Screening of IDA from infants born to anemic mothers could allow earlier detection of iron depletion in neonates and decrease the risks of adverse neurocognitive outcomes (Macqueen et al., 2017). Furthermore, an association between maternal anemia and childhood asthma has also been detected warranting further research on the long-term consequences of gestational anemia (Harju et al., 2018; Triche et al., 2011).

6.5 Effect of iron deficiency anemia on maternal psychological symptoms (Study II)

6.5.1 Maternal antenatal and postpartum depression

In the prospectively collected FinnBrain Cohort, maternal antenatal anemia with Hb <110 g/l or Hb <100 g/l did not significantly increase antenatal and postpartum EPDS scores (Study II). The finding was surprising, since gestational anemia has been recognized as a risk factor for depression in earlier reports (Azami et al., 2019; S. Y. Kang et al., 2020; Maeda et al., 2020; Räisänen et al., 2014; Vindhya et al., 2019). However, most of the studies have assessed the relationship between postpartum anemia and PPD (Albacar et al., 2011; Alharbi & Abdulghani, 2014; Babu et al., 2018; Corwin et al., 2003; Surkan et al., 2017), and no association between antenatal anemia and PPD has been reported (Armony-Sivan et al., 2012; Kwak et al., 2022; Maeda et al., 2020; Paterson et al., 1994). This may indicate that the changes caused by anemia, which potentially increase the risk of depressive symptoms, occur after delivery. For example, increased hemorrhage during delivery leading to postpartum anemia and a negative delivery experience could predispose women to PPD. However, no association between the hemorrhage and PPD was

found in a Swedish study (Eckerdal et al., 2016). Further research is needed to assess the effect of postpartum anemia on maternal depression in the Finnish population.

Our study revealed that mild or moderate/severe gestational anemia did not increase the risk of maternal antenatal depressive symptoms. Two meta-analyses have previously shown that anemia during pregnancy increases the risk of antenatal depressive symptoms (Azami et al., 2019; S. Y. Kang et al., 2020). A Finnish population-based analysis, using data gathered from health registers, found that anemia with Hb ≤100 g/l increased the risk of major depression during pregnancy (Räisänen et al., 2014), although the prevalence of major depression, defined as an ICD-10 diagnosis, was only 0.8%. The subgroup analysis conducted with our prospective study cohort with Hb <100 g/l did not show association between moderate/severe anemia and an increased risk of depression defined as EPDS ≥10. The prevalence of EPDS score ≥10, indicating depression, was 27.8% and 13.2% among women with Hb <100 g/l and the controls, respectively. Although the difference in prevalence is clinically substantial, no statistically significant difference in the analysis was observed.

An Ethiopian prospective study including 4 680 pregnant women found that gestational anemia with Hb <110 g/l increased the risk of antenatal depressive symptoms with an OR of 1.30 (95% CI 1.31–2.32). However, the study was performed in a rural low-income setting, where the access to health care providers differs greatly compared to a high-income country setting (Woldetensay et al., 2018). In Finland, almost 100% of pregnant women visit primary maternal care, where their mental wellbeing is screened regularly by the primary care givers. The identified women receive psychologic support, and if needed, they are referred for further treatment.

Globally, approximately 15% of pregnant women suffer from antenatal depression and 17% from postpartum depression. In the prospectively collected FinnBrain Cohort the corresponding percentages were 14.8% and 13.6% in the anemic and 14.4% and 10.7% in the non-anemic groups, respectively. The prevalence in Southwest Finland is slightly less than the global average. A slightly lower incidence of maternal depression in the FinnBrain Cohort could reflect well-functioning primary maternity care with easy access to psychological support. On the other hand, it could be that mothers with depressive symptoms were less likely to participate in the prospective research protocol. However, depression continues to affect a significant portion of pregnancies, and, thus, should be treated properly.

In everyday clinical practice during the recent years, obstetricians have often faced demands for intravenous iron treatment due to maternal fatigue and mental exhaustion. Therefore, the results of this first prospective study regarding maternal anemia and psychological distress, assessing both depressive and anxiety symptoms in the Finnish population, are reassuring. Gestational anemia and maternal

depression should be treated properly, but pregnant women can be counselled about the non-significant association between gestational anemia and psychological distress.

6.5.2 Maternal antenatal and postpartum anxiety

No major differences in SCL scores, were detected between anemic women with Hb <110g/l and non-anemic group, although a weak connection in one subgroup analysis was shown: pregnant women with Hb <100 g/l had higher SCL points in the third trimester, reflecting maternal anxiety, than the control group (5.5 vs. 2.0, p = 0.028). In late pregnancy, women with Hb <100g/l are referred to a tertiary care unit for a consultation and possible intravenous iron infusion, which could be a factor increasing maternal anxiety and explain our finding. No other differences during pregnancy and postpartum between the groups with Hb <100 g/l and Hb ≥100 g/l were detected. Our SCL finding in the third trimester and the factors affecting anxiety in the third trimester should be explored more thoroughly. Earlier studies have found an association between anemia in the first trimester and postpartum anxiety symptoms (Kwak et al., 2022). According to our longitudinal evaluation, the SCL scores in both anemic and non-anemic women increased progressively with advancing gestation and decreased postpartum. This has been speculated to reflect maternal anxiety of delivery (Heron et al., 2004) or beneficial hormonal changes postpartum (Kammerer et al., 2002).

6.5.3 Pregnancy-related anxiety

PRAQ is specifically used to measure pregnancy-related anxiety, and it is a normally distributed variable without a clinical cut-off value. It reflects maternal adaptability to pregnancy. In our study focusing on psychological distress, PRAQ was also assessed, and no differences between the anemic and non-anemic groups were detected. No previous research has assessed the relationship between gestational anemia and PRAQ. Our findings are reassuring and indicate that maternal adaptability to pregnancy is not affected by antenatal anemia.

6.6 Maternal anemia and breastfeeding (Study III)

To the best of our knowledge, the study exploring the association between maternal anemia and the duration and quality of breastfeeding (Study III) is the first publication exploring the subject. According to our analyses, the women with late-pregnancy anemia with Hb <110 g/l reached the recommended breastfeeding goal of EBF of four months as often as non-anemic women (59.5% vs. 65.6%, p = 0.277).

In Finland, the recommendation of EBF for four months differs from the WHO guideline, which is six months globally. The EBF recommendation of for four months may be adapted due to cultural reasons: Nearly all Finnish women work outside the home, return to work relatively soon after the delivery, and there is a long history of starting of tasting solid foods at the age of four months. The Finnish guideline emphasizes the role of EBF, especially during the first months of life. Despite the shorter goal of EBF in Finland, only two-thirds of women reach this recommendation. Much more work is needed to reach the breastfeeding goals in the high-income countries, although the situation is improving (Vaz et al., 2021). Factors such as insufficient milk, nipple pain, and lack of support are believed to impact breastfeeding (Stordal, 2023), and attention should be paid to improve breastfeeding while simultaneously cumulating evidence of major health benefits even in high-income settings (Klemetti & Hakulinen-Viitanen, 2013; Victora et al., 2016).

In the FinnBrain Cohort, no differences in the duration of partial and exclusive breastfeeding between the anemic and non-anemic groups were detected when breastfeeding was assessed as a continuous variable. However, when high EPDS scores three months postpartum were added into the analysis, the difference was significant, reflecting the well-known fact that women with depression breastfeed for a shorter duration (Ystrom, 2012). In Southwest Finland, depression is routinely screened in the primary maternity care using the validated EPDS questionnaires. Attention should be paid to support the breastfeeding practices with pregnant women with high EPDS scores, since depression is known to increase the risk of early cessation and a shorter duration of breastfeeding (Gagliardi et al., 2012).

Iron stores of the newborn are known to develop during the pregnancy and suggested to meet the needs of a neonate born to a healthy mother for six months after delivery. Breast milk contains relatively low concentration of iron, which is, however, high in bioavailability (Friel et al., 2018), but does not meet the iron requirements of the infant after few months. Prolonged duration of EBF has been repeatedly associated with ID in infants (Clark et al., 2017; Maguire et al., 2013), emphasizing the need for iron-rich food and/or iron supplements in infancy, and in some countries iron supplements are routinely recommended for breastfed infants after four months of age. To ensure the development of adequate fetal iron stores during pregnancy, maternal IDA and ID should be treated efficiently.

Breastfeeding has several widely acknowledged health benefits, both for the mother and the newborn, and, yet many women does not reach the recommended goals, although in high-income countries, the information and supportive measures are available for those who need them. Thus, it is important to recognize factors affecting the duration and quality of breastfeeding (Rollins et al., 2016; Victora et al., 2016). From a general point of view, our findings of no association between anemia and breastfeeding are reassuring, while maternal anemia remains extremely

common across low-, middle-, and high-income countries. However, it should be noted that in our Finnish cohort, women in the study group suffered from relatively mild anemia. Future research may address the association between the severity of anemia and breastfeeding.

6.7 Treatment of iron deficiency anemia in pregnancy (Study I)

In our study with the Clinical Birth Cohort (Study I), we conducted a subgroup analysis to assess whether intravenous iron substitution is more effective compared to oral iron substitution. In the study cohort, 24% (n = 52) of women with Hb <100 g/l received intravenous iron, and the rest were advised to use oral iron substitution. As in previous reports (Bencaiova et al., 2009; Neogi et al., 2019; Qassim et al., 2019; Reveiz et al., 2007), hematologic parameters were corrected more efficiently in the group that received intravenous iron, but no significant differences in maternal or neonatal clinical outcomes, such as hemorrhage during delivery, need of red blood cell transfusion, prematurity, and FGR, were detected. In a very recently published Indian RCT, single-dose intravenous FCM decreased the risk of FGR compared to oral iron substitution when treating pregnant women with moderate anemia, defined as Hb <100 g/l (Derman et al., 2025). In our study, women, who received intravenous iron had more severe anemia (89 g/l vs. 95 g/l, $p < 0.001$), which may indicate that IDA was more effectively corrected, and therefore, no difference in clinical outcome was observed. In addition, since oral iron is over-the-counter medication in Finland, no data on the usage were available in the medical records of the study subjects, although the last Hb prior delivery was higher than the lowest Hb recorded during pregnancy in both groups, letting us assume that oral iron was used mostly as instructed. In addition, no significant difference in the Hb values after oral and intravenous iron supplementation was observed (109 g/l vs. 107 g/l, $p = 0.338$). The values in both groups after treatment were <110 g/l, indicating that gestational IDA was not optimally treated, and the target Hb level was not reached in either group. In our study we did not differentiate between primarily healthy anemic women and anemic women with risk factors for ID, who could possibly need more extensive treatment to correct the Hb level.

Since oral iron is often poorly tolerated and the adherence to treatment is low, intravenous iron substitution is an effective and safe choice of treatment for selected patient groups with moderate and severe anemia. Pregnant women with a history of bariatric surgery, inflammatory bowel disease, or other significant risk factors, such as multiparity, for IDA might benefit from intravenous iron. In addition, intravenous iron supplementation should be considered for pregnant women with IDA and poor tolerance for oral iron to avoid adverse maternal and neonatal outcome.

Excess maternal iron has been linked to an increased risk of gestational diabetes, and high maternal ferritin levels with a lower child intelligence quotient (Fernández-Cao et al., 2017; Khambalia et al., 2016; Sammallahti et al., 2022). Therefore, intravenous iron should be given only in the presence of diagnosed ID and when the first-line therapy, oral iron supplementation, has been proven to be ineffective. Recently, intravenous iron supplementation has been widely discussed among pregnant women in Finland, and in public discussions, health effects of intravenous iron infusion are believed to be significant. In patient counselling, the benefits and risks related to excess iron should be carefully weighted in order to achieve optimal outcomes.

Among the anemic group receiving intravenous iron, the incidence of induction of labor was more frequent compared to the group with anemia and oral iron (44.2% vs. 27%, $p = 0.019$). No data on the indications of labor inductions were available, but the finding could reflect the fact that this patient population had more severe anemia and were controlled more frequently, resulting more likely in labor induction. In addition, prior studies have shown that pregnant women with symptoms such as fatigue and exhaustion are more likely to be induced (Jung et al., 2019; Levy et al., 2005; Malhotra et al., 2002).

In Studies I and III, assessing maternal and neonatal outcomes and breastfeeding, women with anemia were more likely to receive red blood cell transfusions more likely than the non-anemic women. In Study II, exploring the psychological distress, 4.7% of women with anemia received red blood cell transfusions, while 2.6% of non-anemic women needed this treatment, although the difference was statistically non-significant ($p = 0.083$). Anemic patients are at an increased risk of transfusions, since anemia affects the coagulation system and increases the risk of hemorrhages. Red blood cell transfusion itself has significant health risks, such as infections and allergic reactions, which can be even fatal (Thomson et al., 2009). Therefore, treating gestational anemia adequately beforehand by providing sufficient iron supplementation is crucial to avoid blood transfusions and their adverse effects.

6.8 Strengths and limitations

The studies included in this thesis have several strengths. Most research on the effects of gestational anemia has been conducted in low- or middle-income settings, and reliable data from high-income countries with high standard maternity setting, such as Finland, are needed. In Study I, assessing maternal and neonatal outcomes, data regarding maternal characteristics and maternal and neonatal outcomes as well as Hb values, during pregnancy were collected from the medical records of one institution by a single investigator. Studies II and III were based on a prospectively collected cohort (Karlsson et al., 2018). A large sample size was one of the main

strengths in the studies included in this thesis, particularly considering that both the antenatal and postnatal psychological symptoms were addressed in Study II. Furthermore, the cohorts in this thesis reflect well the general pregnant population in Southwest Finland, while many previous studies have relied on registries.

In Study II, assessing the maternal anemia and psychological distress, a longitudinal prospective approach was used; measurements were performed at three time points during pregnancy (<20 weeks, 20–30 weeks, and >30 weeks) and two time points postpartum (three and six months), while previous research has mainly focused on postpartum data (Azami et al., 2019; Goshtasebi et al., 2013; Maeda et al., 2020). Furthermore, maternal distress was widely assessed using several validated questionnaires simultaneously: EPDS and SCL to evaluate depressive and anxiety symptoms and PRAQ to assess pregnancy-related anxiety (J. L. Cox et al., 1996; Derogatis et al., 1973; Holi et al., 1998; Huizink et al., 2016; Navarro et al., 2007), and EPDS scores were analyzed as both continuous and categorical variables.

To the best of our knowledge, Study III is the first published report regarding the relationship between maternal antenatal anemia and breastfeeding duration. The large, prospectively collected clinical data allowed us to explore the effects of both anemia and maternal psychological distress on breastfeeding.

Several limitations are also acknowledged in the studies included in this thesis. In Study I, assessing maternal and neonatal outcomes in the presence of maternal anemia, Hb measurements were taken at various time points, making it impossible to explicitly evaluate the effect of the timing and duration of gestational anemia on maternal and neonatal outcomes. While iron parameters, ferritin and TfR, were not available for the study population, the definition of IDA is based on the fact that ID is the most common cause for gestational anemia in Finland, and other etiologies such as thalassemia, are extremely rare among the Finnish pregnant population. Nevertheless, the results of this study reflect the real-life situation in Finland, where maternal anemia is screened in the primary care using the fingertip point-of-care tests, with venous blood samples performed only in the presence of detected anemia from the fingertip test or anemia-related symptoms.

In Studies II and III, focusing on psychological distress and breastfeeding, data from the regular health care visits and research surveys were combined, complicating the interpretation of causality. Furthermore, self-reported questionnaires may always under- or overestimate maternal symptoms; however, psychological symptoms are inherently subjective, and psychological distress is clinically evaluated by using interviews.

Unfortunately, no postpartum Hb values were available in the studies assessing gestational anemia and psychological distress and breastfeeding, and thus, evaluation of the impact of postpartum anemia was not possible.

6.9 Clinical implications

Gestational anemia, most often caused by ID, has previously shown to impact maternal and neonatal outcomes. The studies included in this thesis showed that this is also the case in a high standard maternity care setting in Finland. In our Clinical Birth Cohort, gestational IDA with Hb <100 g/l increased the risks of adverse maternal and neonatal outcomes, underlining the importance of effective treatment of gestational anemia. On the other hand, the results showing that maternal anemia during pregnancy has no significant effect on maternal psychological distress and duration and quality of breastfeeding are comforting.

To improve maternal and neonatal outcomes, screening and prevention should be effectively targeted. In Finland, maternal anemia is currently screened by measuring only the Hb level in each trimester using the fingertip as a point-of-care test, even in the high-risk groups for gestational anemia. Consequently, ID prior to the development to IDA might go undiagnosed. Ferritin, an economical and readily available laboratory test, is not routinely used for screening in Finland, unlike in some other high-income countries. With accumulating research evidence, the use of ferritin as a screening test could be considered also in Finland as well. While ferritin is an acute phase protein, some countries recommend simultaneous CRP measurement. However, since ID is the only condition known to cause low ferritin levels, routine evaluation of CRP is not necessary and could be considered only in women with inflammatory diseases. Special attention should be paid already in early pregnancy to risk groups for gestational IDA, such as multiparas, pregnant women with chronic illness, such as inflammatory bowel disease, diabetes, and hypertension, and women who have undergone bariatric surgery. By screening Hb, ferritin, and if necessary, CRP levels routinely during the first trimester, iron supplementation could be started in time to optimize the outcomes, and the risk of excess iron supply would be minimized.

The adequate treatment of gestational IDA has been widely discussed. Poor tolerance and adherence to oral iron, which is the primary treatment due to its safety and efficacy, combined with accumulating data on the safety of intravenous iron and its effectiveness in correcting the hematologic parameters, has increased the use of parenteral treatment, even though no differences in clinical outcomes between oral and intravenous treatments have been detected (Neogi et al., 2019, Qassim et al., 2019). Sucrosomial iron has recently entered the market and represents a potential treatment option, as it is better tolerated than other oral iron supplements. However, it is a costly over-the-counter medicine without reimbursement, negatively affecting adherence. However, it seems to have improved the oral treatment of gestational IDA.

Currently, intravenous iron is administered in secondary and tertiary care units, and commonly obstetric consultation including ultrasound assessment is provided.

While maternal anemia is associated with FGR and other complications, assessment of fetal growth and well-being is justified. On the other hand, allergic and anaphylactic reactions during intravenous iron infusion are extremely rare, and thus treatment in primary care units would be safe and might even increase the accessibility and decrease the cost simultaneously. However, evidence-based data regarding this are needed prior to any changes in clinical practice, and at least pregnant women with comorbidities as well as a history or risk factors of severe allergic reactions should be still referred to secondary/tertiary units. Despite its safety profile and efficacy, effects of intravenous iron on the fetus remain unclear, although animal studies have shown that it does not cross the placenta (Malek, 2010). As regards effective treatment, proper screening of women with conditions affecting iron absorption in the intestine and the treatment of their anemia with intravenous iron infusion as a first-line approach should be considered, as it is well known that oral iron does not absorb from the intestine in these patients.

6.10 Future aspects

Future research should focus on decreasing the prevalence of ID and IDA in reproductive aged women prior to their first pregnancy. Several options for additional iron supplementation could be explored, such as adding iron to food or combining it to medication, which is commonly used by women in fertile age, for example contraceptives.

To avoid the adverse consequences of excess iron and to reach women with ID, access to screening for ID and IDA could be improved. Since ID is by far the most common etiology of low ferritin values (Knovich et al., 2009), women could be offered ferritin tests, for example, in the pharmacies, and guidelines and recommendations for additional iron supplements targeting reproductive aged and pregnant women could be provided. However, since research regarding high ferritin values is inconclusive, the test should only assess ID in a yes/no format, to avoid unnecessary anxiety related to high and borderline ferritin levels. In the future, other ID markers, such as hepcidin, could be used to evaluate iron stores.

The development of better tolerated oral iron supplements remains crucial, as it is significantly more accessible than intravenous iron, particularly in low- and middle-income countries, where the prevalence of gestational IDA is the highest. Oral sucrosomial iron has already shown promising results in improved tolerance and adherence, although it remains expensive. The safety and increasing accessibility of intravenous iron supplementation enables more effective correction of laboratory values across a broader patient population. However, further research is needed to establish the clinical effects of rapid correction of ID on maternal and neonatal outcomes to avoid unnecessary invasive and costly treatments.

Since maternal IDA is associated with an increased risk of impaired neurocognitive development in the offspring (Wiegersma et al., 2020), and several studies have detected a link between gestational IDA and newborn's ID (Abioye et al., 2019; Kilbride et al., 1999; Shukla et al., 2019), screening for ID and IDA in the offspring, at least of the neonates born to women with ID and IDA, should be investigated to allow earlier recognition, treatment, and prevention of poor long-term neurocognitive outcomes in these infants.

7 Conclusions

The main findings are as follows:

1) Gestational anemia increases the risks of prematurity, FGR, and maternal postpartum infections. Women with moderate anemia are more likely to deliver before to 37 weeks, and the risk of having a very premature neonate is three-fold. Among women with anemia, the risk of FGR is six times higher than that in non-anemic women, and the risk of postpartum maternal infections, such as urinary tract infections, endometritis, sepsis, and wound infections, increases three-fold. Intravenous iron supplementation corrects Hb more effectively than oral iron supplementation, but there is no difference in maternal or neonatal clinical outcomes. (Study I)

2) Mild gestational anemia does not increase the risk for maternal psychological distress during pregnancy and postpartum. Maternal depressive and anxiety symptoms, as well as pregnancy-related anxiety, are similar between the anemic (Hb <110 g/l) and non-anemic groups. However, in late pregnancy moderate or severe anemia (Hb <100 g/l) may be associated with slightly more anxiety symptoms. (Study II)

3) Gestational anemia in the third trimester does not affect the duration and quality (partial/exclusive) of breastfeeding. Women with anemia achieve the recommended four-month goal of exclusive breastfeeding in Finland as often as non-anemic women. (Study III)

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