Maternal Anaemia and How It Associates with Perinatal Outcomes - a Registry-Based Study of Singleton Births in Finland 2006-2020

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Abstract

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The aim in this thesis was to emphasize the importance of appropriate iron level during pregnancy to prevent maternal anaemia and to find out how maternal anaemia associates with perinatal outcomes. The objective was to compare perinatal outcomes between anaemic and non-anaemic women, who gave singleton birth in Finland between 2006 and 2020. Also, the objective was to assess how gestational anaemia has evolved in Finland during the past 15 years and identify both the risk and protective factors for maternal anaemia.

Anaemia is a major public health problem globally. It has remained one of the main health concerns especially during pregnancy and it has been associated with several adverse perinatal outcomes both in low-, middle- and high-income countries. Iron deficiency is the main reason for anaemia, and one cause for it is the increased demand of iron for example during pregnancy. Iron supplement use is globally the cost-effective preventable method for anaemia in addition to other micronutrients and it is primarily used when treating anaemia.

Data was extracted from Finnish Medical Birth Register which is maintained by Finnish Institute of Health and Welfare, n= 813555. Anaemia has been recorded in Finland if the haemoglobin value during pregnancy is <100 g/l. The association between maternal anaemia and adverse perinatal outcomes was assessed by statistical analysis.

The total prevalence of anaemia has risen slowly over the years being 3,6 % in whole study period. When comparing non-anaemic and anaemic groups, there was significantly increased prevalence in the anaemic group for caesarean section, gestational diabetes, placenta praevia, prior fertility treatments, induced labour, blood transfusion, abruption of placenta, admission to neonatal intensive care unit and preterm birth (<37 weeks). When calculating the adjusted odd ratios, highest odd ratios were in placenta praevia and blood transfusion. Eclampsia and small for gestational age, SGA, had lowest adjusted odd ratios, SGA being not significant. The risk factors for maternal anaemia were the age <19years, BMI <18,5, no-cohabiting, and nulliparous or previous births more than two. The prior fertility treatment was seen a risk factor too. Protective factors were controversially the age of 20 or more and at least normal weight (BMI at least 18,6).

The high standards of maternal health care in Finland can compensate many adverse perinatal outcomes. The systematic screening of haemoglobin values during antenatal care gives opportunity to adequate iron supplementation and anaemic situation can be diagnosed and even fixed before birth. However, there is a greater risk for negative impacts, especially among young mothers and for those who have more than two previous births. These aspects should be carefully monitored in antenatal care as a part of preventative health education.

Keywords: anaemia, iron deficiency, maternal anaemia, perinatal outcome

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Raskausajan anemia ja sen vaikutukset perinataaliaikaan - rekisteritutkimus yksisikiöisillä synnyttäjillä Suomessa vuosina 2006–2020

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Opinnäytetyön tarkoituksena oli korostaa optimaalisen rauta-arvojen tärkeyttä estämään raskaudenaikaista anemiaa ja selvittää, miten äidin raskauden aikainen anemia vaikuttaa raskauteen, synnytykseen ja syntyvään lapseen. Tavoitteena oli verrata perinataaliajan tuloksia niiden aneemisten ja ei-aneemisten odottajien kesken, jotka synnyttivät Suomessa 2006–2020 välisenä aikana ja joilla oli yksisikiöinen raskaus. Toisena tavoitteena oli arvioida, miten raskauden aikainen anemia on kehittynyt Suomessa tutkittavan 15 vuoden ajanjakson aikana sekä identifioida aineiston pohjalta niin riskitekijöitä kuin anemialta suojaavia tekijöitä.

Anemia on yksi suurimmista terveysongelmista maailmassa. Se on pysynyt vuodesta toiseen yhtenä suurimmista raskausajan terveysongelmista ja se on yhdistetty useisiin haitallisiin perinataaliajan tuloksiin niin matalan, keski-, kuin korkean tulotason maissa. Raudanpuute on anemian pääsyy, ja yksi syy sille on lisääntynyt raudantarve raskausaikana. Rautalisän käyttö on maailmanlaajuisesti kustannustehokas ennaltaehkäisevä keino anemiaa vastaan yhdessä muiden ravinteiden kanssa ja sitä käytetään myös anemian hoidossa ensisijaisesti.

Aineisto opinnäytetyölle on johdettu Terveyden ja Hyvinvoinnin laitoksen ylläpitämästä Suomen syntymärekisteristä, n= 813555. Raskauden aikainen anemia on tilastoitu, jos hemoglobiinitaso on raskausaikana <100 g/l. Raskauden aikaisen anemian vaikutus perinataaliajan tuloksiin analysoitiin tilastollisen analyysin avulla. Kokonaisesiintyvyys raskausajan anemialle on noussut vuosien saatossa, ollen tässä aineistossa 3,6 %. Tutkittaessa ei-aneemisten ja aneemisten synnyttäjien välisiä eroja, tilastollisesti merkittävästi enemmän havaittiin keisarileikkauksia, raskausdiabetesta, etistä istukkaa, edeltäviä hedelmöityshoitoja, synnytyksen käynnistyksiä, verensiirtoja, istukan ennenaikaista irtoamista, vastasyntyneen valvontaosastohoitojaksoja sekä ennenaikaisia synnytyksiä (<37 raskausviikkoa) anemia diagnoosin saaneiden ryhmässä. Taustamuuttujien huomioinnin jälkeen suurin todennäköisyyskerroin (odd ratio) saatiin etiselle istukalle ja verensiirrolle, kun taas raskausajan komplikaatioista kouristus sekä pienipainoisuus raskausviikkoihin nähden (small for gestational age, SGA) saivat pienimmät kertoimet ilman tilastollista merkitsevyyttä. Riskitekijöiksi raskausajan anemialle voidaan tulosten perustella luokitella ikä <19 v, alipainoisuus (BMI <18,5), yksin asuminen sekä ensisynnyttäjyys tai vähintään kaksi lasta edeltävästi synnyttäneisyyttä. Raskautta edeltänyt hedelmöityshoito nähtiin myös riskitekijänä. Suojaavina tekijöinä voidaan pitää ikää yli 20 v sekä vähintään normaalipainoisuutta (BMI vähintään 18,6).

Korkealuokkainen suomalainen äitiyshuolto kompensoi useita haitallisia perinataaliajan ongelmia. Systemaattinen hemoglobiinin mittaus neuvolassa lisää mahdollisuuksia kohdentaa rautalisän käyttöä, sillä anemia pystytään diagnosoimaan ajoissa ja tilanne korjaamaan ennen synnytystä. Kuitenkin on syytä huomioida, että erityisesti nuorten ja alipainoisten odottavien äitien keskuudessa, sekä niiden odottajien kohdalla, joilla aikaisempia synnytyksiä on enemmän kuin kaksi, todellinen riski haitallisiin vaikutuksiin on selvästi kohonnut. Nämä ryhmät tulisi erityisesti huomioida äitiysneuvolassa osana ennaltaehkäisevää terveyskasvatusta.

Asiasanat: anemia, raudanpuute, raskaudenaikainen anemia, perinataaliajan tulos

Contents

1 Introduction

Anaemia is a serious health challenge for women globally. Especially among reproductive aged women, World Health Organization (WHO 2020) estimates that every third woman and nearly 42 % of all pregnant women suffers from anaemia worldwide. However, the prevalence of maternal anaemia varies around the globe from 2-5 % in Europe, Canada, and USA (Jouanne, Oddoux, Noël & Voisin-Chiret 2021) up to 48 % in South-East Asia (WHO 2021). This thesis has focus on reproductive health among women.

Maternal anaemia is the situation where haemoglobin (Hb) level in the body has decreased and during pregnancy the haemoglobin concentration is lower than 110 g/l. Measuring iron levels during pregnancy is included as a routine in ante-natal care and low iron levels could be treated with oral iron substitution. Iron deficiency is the most common reason for anaemia in non-malarial areas and the reasons for iron deficiency are either related to increased demand of iron (e.g., during pregnancy), decreased supply of iron (poor nutrition) or blood loss (heavy menstruation). There is a variation in recommendations, but a shared consensus among nutritional specialists summarises that reacting early to mild anaemia is essential to detect severe anaemia. (Sinisalo & Collin 2016; Di Renzo et al. 2015; Rodger, Sheppard, Gándara & Tinmouth 2015; Pavord et al. 2019.) Iron deficiency is the leading cause for women YLD (years lived with disability) burden according to Global Burden of Disease Study 2016 (GBD 2017).

Several researchers have shown from an obstetrical viewpoint, that when anaemia has been diagnosed during pregnancy, different adverse perinatal outcomes such as low birthweight, prematurity, and intrauterine growth restriction, occur more often compared to non-anaemic women (Jung et al. 2019; Vural, Özcan, Töz, Biler & Sanci 2016; Haider et al. 2013). In Finland there are similar results (Kemppinen et al. 2020; Räisänen, Kancherla, Gissler, Kramer & Heinonen 2014). In low-income settings, severe maternal anaemia is one of the reasons for perinatal and neonatal mortality (Rahman et al. 2016) and for maternal mortality (WHO 2016, 14).

The absorption of iron is a complex mechanism of many nutrients, which highlights the importance of dietary advice given during pregnancy but also shows how (easily) preventable the maternal anaemia can be on many occasions with correct nutrition with additional iron substitution. This thesis uses term “maternal anaemia”, and it means iron deficiency anaemia, which has been diagnosed with a laboratory test any time during pregnancy, the prenatal period. This thesis report excludes all other forms of anaemia, such as different chronical disorders behind anaemia, sickle cells anaemia, haemolytic anaemias, and pernicious anaemia.

This thesis aims to emphasize the importance of appropriate iron level during pregnancy to prevent maternal anaemia and to find out how maternal anaemia associates with perinatal outcomes. The first objective for this thesis is to introduce how the situation of maternal anaemia in Finland has evolved during last 15-year period between 2006 and 2020 and secondly, to compare adverse perinatal, both maternal and infant, outcomes between anaemic and non-anaemic groups. The third thesis objective is to identify both risk and protective factors for anaemia. The results of this study could be considered in antenatal care health promotion to prevent maternal anaemia and its consequences. This could be done by precise dietary advice to risk groups shown in this study. The core component of the antenatal care is to ensure healthy pregnancy and anaemia prevention is part of that health education.

The study includes data from all singleton births in Finland between 2006 and 2020, n=813 555. The data is conducted from Finnish Medical Birth Register (MBR), where perinatal data has been collected systematically since 1987 and register is maintained by Finnish Institute for Health and Welfare. Anaemia has been recorded since 2006 from all Finnish hospital districts with a cut-off value of 100 g/l.

This thesis is a registry-based quantitative study. The study design is retrospective, observational, and cross-sectional. The data-analysis has both descriptive and analytical calculations.

2 Physiological aetiology of maternal anaemia

In every pregnancy, it is a physiological fact that maternal blood volume increases due to foetal demand. The increase is estimated to be 40-50 %. The red blood cell mass increase does not perform at same rate as plasma volume increase, and therefore the relative portion of red blood cells decreases temporarily and causes the dilution of blood and a drop in haemoglobin value. Usually this happens during pregnancy weeks 20-32. This is called haemodilution and it is a normal phenomenon in pregnancy. (Vääräsmäki & Kaaja 2019, 485; Rodger et al. 2015.)

Normal development of foetus and placenta increase the demand of iron. During the first trimester, starting from pregnancy week 6, the demand increases and depending on the source, the highest peak in haemodilution is reached during pregnancy weeks 20-28 (Soma-Pillay, Nelson-Piercy, Tolppanen & Mebazaa 2016) or week 30 according to Rodger et al. (2015). The overall demand of iron is an additional 1g during singleton pregnancy (Georgieff

2020) which is approximately two- to three-fold increase compared to normal iron requisite for non-pregnant women (Soma-Pillay et al. 2016).

Oxygen demand increases during normal pregnancy causing maternal hyperventilation (Soma-Pillay et al. 2016) and as haemoglobin is the protein in red blood cells which carries oxygen in the human body, Hb tells indirectly the level of red blood cells. It is crucial for both mother and foetus, that the level of oxygen stays high. The foetus acquires iron for progress of normal growth and oxygen for its metabolic, especially brain system, development. The placenta plays the key role between mother and foetus and can storage some iron as a "buffer", to guarantee an iron supply to the foetus even if the mother has low maternal iron level (Georgieff 2020). The absorption capacity of iron is increased towards the end of pregnancy to guarantee for the foetus an iron storage, which is essential for the first six months of its postnatal life (Georgieff 2020; Jouanne et al. 2021).

In a normal situation, when the level of iron is adequate even before pregnancy starts, the female body copes with the physiological changes without any problems. Cardiovascular adaptation follows to compensate the increased plasma volume. The female body prepares itself not only for the pregnancy, but for the childbirth and blood loss in it, and for the lactation after childbirth. Sufficient nutrition should be enough to cover all changes and needs, but as it is known, this is not always the optimal situation. (Jouanne at al. 2021.)

2.1 Diagnosing anaemia during pregnancy

Anaemia can be simply defined as "low haemoglobin concentration". Haemoglobin can be easily and cost-effectively measured from capillary blood sample from the fingertip in primary healthcare and the method is reliable and usable also in countries with limited facilities. For non-pregnant women the normal range of haemoglobin is between 117 – 155 g/l (Synlab 2019). During pregnancy, when haemoglobin value is below 110 g/l, the situation is diagnosed as anaemia. According to WHO (2017), maternal anaemia can be classified as moderate, mild, or severe as follows:

- mild anaemia: Hb 100 – 109 g/l
- moderate anaemia: Hb 70 – 99 g/l
- severe anaemia: Hb < 70 g/l

These values are established already in 1968 and they are adjusted for people living no more than 1000 meters above sea level, as altitude can affect to haemoglobin values. (WHO 2017, 17.)

Centers for Disease Control and Prevention (CDC 1998,12) has recommended a classification according to pregnancy trimesters. The cut-off values for anaemia are <110 g/l in the first and third trimester and <105 g/l in the second trimester. These threshold values are generally used in literature and are based on European women data. Like WHO´s values for anaemia classification, these values are adjusted for under 1000 metres above sea level. It is suggested by WHO (2017, 7-8) to adjust ethnicity as additional criteria for diagnosing anaemia in different settings.

In Finnish portal, Terveyskylä, the cut-off values are <110 g/l in first and third trimester and <100 g/l in second trimester. The haemoglobin value less than 80 g/l is considered harmful for both the mother and the foetus. (Terveyskylä 2019.) Terveyskylä is a joint portal of all hospital districts of Finland.

WHO (2016, 110) recommends measuring haemoglobin minimum three times during the pregnancy. The first measurement should take place during the first ante-natal consultation as part of the maternal assessment procedure. Measuring is recommended to be repeated during pregnancy week 26-28 and week 36. This procedure is used globally, for example in Australia (NHMCR 2014), UK (Pavord et al. 2019) and Finland (Klemetti & Hakulinen 2013), and more frequent testing is advisable whenever there is need to check iron levels. However, WHO recommends full blood count to be performed whenever possible to confirm the diagnosis (WHO 2016, 40-41).

2.2 Maternal anaemia as a global problem

The WHO sources show the anaemia prevalence in pregnant women in Europe 24%, in Americas 19% and in Western Pacific 21% while the highest prevalence of anaemia in South-East Asia 48%, in Africa 46% and in the Eastern Mediterranean area 37%. Only a minor declination has occurred during past years when looking at the statistics. (WHO 2021.)

Due to population growth, the number of anaemic non-pregnant women has increased from 464 million to 578 million between year 2000 and 2016 and anaemia can be considered as a moderate to severe public health problem (WHO 2018, 2). In industrialized countries iron deficiency anaemia is diagnosed in 2-5% pregnant woman during first trimester and 10-20% in third trimester (Jouanne et al. 2021). The gap between industrialized and developing countries is large (Camaschella 2019), which can be seen from the adverse perinatal outcomes studied globally by Jung et al. (2021), Haider et al. (2013) and the WHO review (2020a).

The global burden of anaemia between 1990 and 2016 performed by Global Burden of Disease Study shows that iron deficiency anaemia has remained one of the leading causes for women globally for years of life lived with disability (YLD) and has stayed there over the years. (Kassebaum et al. 2014; GBD 2017.)

2.3 Clinical signs of anaemia

Clinical signs of anaemia have a wide variety. The most characteristic symptom of anaemia is fatigue. An anaemic person can also have symptoms such as pallor, headache, weakness, hair loss and restless legs. Some anaemic pregnant women have severe problems to survive at work and through normal household work due to altered brain function and lack of physical capability to normal performance. Both work productivity and physical activity do have an impact on women´s daily life. Shortness of breath can also be considered as one clinical sign of anaemia as well as changes in behaviour. (Rämet, Parkkila & Harila-Saari 2015; Di Renzo et al. 2015; Hanson et al. 2015; Rodger et al. 2015). All signs are caused by a lowered capacity for oxygen flow in the body which is an effect of lowered red blood cell count and lowered haemoglobin level.

In Finnish medicinal literature (Vääräsmäki & Kaaja 2019, 486) tachycardia and tiredness are general symptoms caused by anaemia, especially when haemoglobin value is lower than 90 g/l. It is important that during antenatal visits these symptoms are discussed when trying to assess risk for anaemia, but whenever possible, proper measurements should be performed. Rämet et al. (2015) remind, that sometimes symptoms can be so mild, that patient does not notice anything special until the iron balance has been fixed. This is the reason why laboratory tests are always needed when diagnosing anaemia.

2.4 Iron deficiency and iron deficiency anaemia diagnosis

Iron deficiency is the most common reason for anaemia globally (Camaschella 2019; Sinisalo & Collin 2016; Kassebaum et al. 2014). Iron deficiency is the situation, where iron demand is higher than iron supply (negative balance). According to Georgieff (2020), iron deficiency anaemia means the situation where iron level in the body is so low, that haemoglobin synthesis, the production of haemoglobin, has been limited. Georgieff (2020) defines anaemia as “the end-stage result of negative iron balance”.

Main reasons behind iron deficiency among reproductive aged women are related to heavy blood loss during menstruation, pregnancy, and childbirth. Pregnancy and childbirth affect especially repeatedly, when body has no time to recover from previous pregnancy and fill up iron storages. Pregnancy and breastfeeding both increase the demand of iron. During childbirth woman can lose a lot of blood in short time and iron storages are depleted. (Rämet et al. 2015; Sinisalo & Collin 2016.)

Factors related to iron absorption are for example other micronutrients. In a situation where nutrition is poor, the deficiency of several micronutrients is evident. Soma-Pillay et al. (2016) estimates, that folic acid demand during pregnancy is ten times higher compared to non-pregnancy and vitamin B12 need is two-folded. Both folic acid and vitamin B12 are needed to build red blood cells, which explains the connection between these micronutrients to iron (Salonen 2020).

Diseases such as malaria, schistosomiasis, genetically inherited hemoglobinopathies, such as thalassemia, or HIV infection effect negatively on iron status of an individual (Di Renzo et al. 2015). In malaria, the infected blood cells are destroyed and eventually by that mechanism it lowers the amount of red blood cells. In malaria endemic areas, the prevention of malaria-related infections could decrease the risk for severe maternal anaemia by 38% among women with their first or second pregnancy (Desai et al. 2007). According to WHO (2016, 14), half of the iron deficiency anaemia in pregnant women could be managed with iron substitution use, but in malaria-endemic areas it is much more challenging.

However, it should be noted, that haemoglobin value alone does not mark iron deficiency (WHO 2017, 8). Ferritin is an iron-specific biomarker, and the ferritin level can be measured for identification of iron deficiency. Serum or plasma ferritin values are the measurements for the body´s iron storage capacity. Ferritin measurements require more advanced laboratory for analysing and it is therefore mostly used in developed countries. Ferritin should be measured together with infection markers since possible inflammation can have an influence on the ferritin level. (Georgieff 2020; Rämet et al. 2015.)

The best definition for the situation is reached when measuring both values, haemoglobin, and serum ferritin, in conjunction (Georgieff 2020). Diagnostic values for iron deficiency anaemia are:

- Hb level <110 g/l in the first and third trimester OR
- Hb level <105 g/l in the second trimester AND
- ferritin level <30 µg/l OR <15 µg/l

Ferritin level less than 30 µg/l is the limit for insufficient iron reserve (Jouanne et al. 2021; Pavord et al. 2019; Ebeling et al. 2019) which is double as high as what WHO recommends as cut-off value for pregnant women, 15 µ/l, in their latest technical brief (2020b). Debate around sufficient serum ferritin level is on-going between researchers and yet there is no final consensus reached. Ebeling et al. (2019) states it is evident that iron supplementation is needed when iron deficiency anaemia has been diagnosed, but situation is unclear, if haemoglobin is between normal values but ferritin value is low.

French study of Harvey, Zkik, Auges and Clavel (2016) shows that 31% of pregnant women in France had ferritin < 15 µg/l. This is one example of iron deficiency not being only the problem of low-income countries.

There are other possible measurements for diagnosing iron deficiency and its further medical evaluations, such as haematocrit, mean cell volume, transferrin saturation or red blood cell distribution width. Ekholm (2019, 355) states, that more precise than ferritin, is to measure transferrin receptor values as it is not related to infections. Georgieff (2020) prefers transferrin saturation measures together with serum ferritin to confirm the diagnosis. Milman, Paszkowski, Cetin and Castelo-Branco (2015) suggest measurement of all these three: serum ferritin, soluble transferrin receptor and transferrin saturation and according to results, individual iron supplementation. As haemoglobin and ferritin are the most common measures, this thesis concentrates mostly on those. Sinisalo and Collin (2016) claim total blood count to be the most important examination.

In low-income settings the detailed analyses are not always possible. World Health Organization (2020b) statement rationalizes that ferritin concentration is an adequate marker for otherwise healthy persons to diagnose iron deficiency. Overall, iron metabolism in the human body is a very complicated system. During pregnancy it is even more complex, because of changes in women’s metabolism which enable healthy development for foetus and placenta.

3 Antenatal care and anaemia preventative measures

In Finland, public antenatal care is universal privilege for all pregnant women. Antenatal care is systematic, and it is recommended that primiparous women visit a public health nurse or midwife 8-9 times during their pregnancy. The first antenatal visit is required to be performed before pregnancy week 18 to obtain governmental maternal benefits, a maternal grant. According to Finnish Institute of Health and Welfare (2021a), only 0,2-0,3% of Finnish pregnant women don´t visit antenatal care during pregnancy. There are also services in Finland for undocumented women during pregnancy if they are not entitled to public antenatal care, but for this special group the prenatal care is often inadequate (Tasa, Holmberg, Sainio, Kankkunen & Vehviläinen-Julkunen 2021).

A minimum of eight routine antenatal care visits is recommended by WHO. Improvement in women´s health is a major improvement in public health and in low-income countries the antenatal care reduces perinatal mortality. Antenatal care in general is a combination of risk identification and health education and promotion in addition to prevention of diseases, either pregnancy-related or other. (WHO 2016, xvi.)

Anaemia screening is a worldwide recommendation during women´s first antenatal visit (WHO 2016, 40-41). Most commonly, during pregnancy the haemoglobin value is measured from the fingertip, and it is a low-cost and cost-effective method for assessing anaemia. In Finland, typically the first visit occurs during pregnancy weeks 8-10.

The early access to antenatal care has been seen important for the dietary advice and nutrition counselling point of view from Hanson et al. (2015, 215). Milman et al. (2016) conclude, that when assessing optional nutritional guidance for pregnant woman, a possible use of dietary history questionnaires, menstrual history assessment and BMI assessment should be an integral part of first antenatal counselling. Milman´s group suggests, that for iron deficiency, the ferritin value should be measured, as it is the most important biomarker of iron deficiency and correct iron supplementation should be advised after result.

3.1 Iron supplement use

According to Vääräsmäki and Kaaja (2019, 485) Finnish women gain 10-20mg iron daily from food, but only 10% of it is absorbed. The daily need for iron in the second and third trimester is 5-9mg which defends the iron substitution use after 20 gestational weeks (Vääräsmäki & Kaaja 2019, 485). In UK, according to Pavord et al. (2019), it is estimated that the daily intake of iron is 10mg of which only 10-15% is absorbed. In comparison to Finland, Pavord et al. (2019) estimates that physiological iron requirement is 1-6mg per day. Finnish authorities state (Eating together – food recommendations for families with children, 2019, 46), that 500mg iron storage is required to ensure maintenance of iron balance even during haemodilution. Both countries, UK, and Finland, emphasize the dietary advice given during antenatal visits. Dietary intake of iron varies between countries, even between high-income countries. High-income countries like UK, Canada, and Australia, which don´t have a current recommendation for iron substitution use before anaemia has been diagnosed, do have counted how much the dietary iron intake should grow to meet the needs of pregnancy and developing foetus.

There is discrepancy between recommendations nationally and globally when the iron substitution should be started, but the clear consensus is, that to prevent severe anaemia, iron substitution is needed. In a table 1 below different recommendations from different countries and WHO are listed.

County / Health Authority	Iron substitution recommendation for non-anaemic women during pregnancy	Iron substitution recommendation when anaemia is diagnosed during pregnancy
Finland (Vääräsmäki & Kaaja 2019, 485) (Eating together… 2019, 54)	50-100mg daily, start after pregnancy week 28	200mg daily (oral) Individual assessment; 50mg after week 12 if Hb <110g/l or <100g/l later
(Klemetti & Hakulinen 2013, 115-116)	not recommended	100mg daily
UK (Pavord et al. 2019)	no routine, only if symptomatic	40-80mg elemental iron daily or alternate days
Germany (Koletzko et al. 2016)	not recommended	considered individually based on medical assessment
Australia (NHMCR 2014)	not recommended	low dose, e.g., 20mg
USA (CDC 1998; ACOG 2008)	30mg daily (CDC) no routine (ACOG)	60-120mg elemental iron daily
WHO	60mg daily in high anaemic settings	60mg daily in high anaemic settings

Table 1: Guidelines for iron substitution in different countries

It is notable, that the US recommendation of CDC is over 20 years old but still a valid recommendation in the country. However, in US there is a debate about iron substitution use, as the American College of Gynaecology, ACOG (2008), recommends routine iron supplementation only when iron deficiency anaemia has been diagnosed.

Also, the Finnish recommendations vary depending on the source. The latest version of "Guidelines for antenatal care" (Klemetti & Hakulinen 2013) dates nearly ten years back and is still the official guideline in public antenatal care, although there are newer recommendations available (Vääräsmäki & Kaaja 2019; Eating together -food recommendations for families with children 2019). The Terveyskylä -portal combines recommendations to be between 100-200mg daily in iron deficiency anaemia specifically (Terveyskylä 2019).

Milman et al. (2016) summarise in their study different national recommendations and prefer a tailored doses of iron supplementation. The group also strongly defends the ideology, that any high-iron diet could not prevent iron deficiency anaemia or could not be under any circumstance sufficient treatment for it.

Australian Government´s office of health, National Health and Medical Research Council NHMRC (2014), prefers a holistic approach to anaemia and not solely highlights the use of iron substitution. It recommends iron-rich food and relies its recommendation on systematic review of Reveiz, Gyte, Cuervo and Casasbuenas (2011), where they observed no difference in haemoglobin when using low or high dose of iron substitute, but there were fewer side effects present when using low-dose supplementation.

According to Demuth, Martin and Weissenborn (2018) study of iron supplementation use, only six percent of anaemia-diagnosed pregnant women in Germany do not use iron substitution. There were no significancy between socioeconomic status and iron supplementation use. However, it does show the variety of how guidelines are followed - nearly 20 % of pregnant women did use the iron supplementation without anyone guiding them to do so even they were not diagnosed with maternal anaemia. The tendency to use iron supplementation was higher among those pregnant women, who used other micronutrients as well. (Demuth et al. 2018.) In Finland, it is more emphasized the routine use of vitamin D and folic acid during pregnancy rather than iron (Eating together… 2019) and the same can be seen in German recommendations, where several other supplements are mentioned prior to iron (Koletzko et al. 2016).

Canadian study of Morisset et al. (2006) shows the maternal characteristics for low iron intake. Such groups are age <30 years, BMI either <25 or >25 before pregnancy and being born outside Canada. Lower degree in education influenced another nutrient intake. (Morisset et al. 2016.)

Studies of Dewey and Oaks (2017) and Jung et al. (2019) show also how the U-shaped curve of the haemoglobin level has an association to adverse perinatal outcomes. This means, that both low and high haemoglobin values can have negative associations to perinatal outcomes and this needs to be acknowledged in iron supplementation as well. One example of this is the Finnish study of gestational diabetes by Helin et al. (2012). It showed that high intake of iron during pregnancy increased the risk of gestational diabetes especially for those not being anaemic. Ebeling et al. (2019) declare there is no risk for overdosing iron orally unless there are haematologic chronic diseases on the background and the same warning can be found from WHO (2017, 7) publication, where iron-repleted individuals are mentioned as risk group, too.

In addition to iron substitution use, the absorbance of iron could be improved by correct advice of use. Iron substitution should be taken on an empty stomach, at least two hours prior or two hours after dairy products. The debate about daily versus intermitted intake of iron substitution has risen during recent years. There is not yet clear consensus about this. (Pavord et al. 2019.) Vitamin C is known to improve the absorption of iron (Pavord et al. 2019; Ebeling et al. 2019, 152).

One problematic issue when using oral iron substitution are the gastric problems. It is very common that gastric irritation, nausea, diarrhoea or heavy constipation or some other negative side-effects totally prevent the oral iron supplement use. In UK it is discussed to have iron substitution intermitted, to avoid negative impact of iron substitute and have possibly better absorption. (Pavord et al. 2019; Peña-Rosas, De-Regil, Gomez Malave, Flores-Urrutia & Dowswell 2015).

Peña-Rosas et al. (2015) studied the oral iron substitution advantages taken daily versus intermitted, two to three times per week. The results show no difference for the prevalence of anaemia, but (it) proved the advantage of intermitted substitution for those women, who have difficulties with daily iron intake. Stoffel, Zeder, Brittenham, Moretti and Zimmermann (2020) study show a significantly higher fractional iron absorption of alternative day iron substitute dosing versus consecutive iron dosing.

In severe iron deficiency, and in a case when oral iron supplement use is impossible due to side-effects, iron supplement could be given intravenously. It is a more effective method to raise the iron status than oral supplementation (Kemppinen et al. 2020; NHMCR 2014). Ebeling et al. (2019) see the benefit of intravenous iron substitution especially for those patients, whose ferritin value was between 15 – 30 µg/l. However, in any treatment, the response to treatment should be measured. Pavord et al. (2019) suggests re-assessment after 2-3 weeks starting of the iron supplement use, but Klemetti and Hakulinen (2013) recommends the re-measurement of haemoglobin value every 4 weeks to assess the effectiveness of the supplement use.

3.2 Dietary advice in antenatal care

During antenatal visits dietary advice is highlighted through the pregnancy. The health-care personnel are trained to share important knowledge about nutrition and there is plenty of information available on the internet, too. The role of dietary advice is essential from the beginning of the pregnancy. Diet can have an influence on weight control and glucose balance as well as anaemia.

Hanson et al. (2015) with a multi-professional group highlight prioritizing dietary advice to prevent nutritional problems and optimize the health of adolescent girls and stabilize the micronutrient status before pregnancy. Any deficiencies should be screened, and a recommendation of fortified foods usage is in some cases appropriate. The group reminds, that even in high-income countries the low iron storages can be a real problem for adolescents due to heavy menstrual blood loss and / or poor diet. Same result has reached by Peuranpää, Heliövaara-Peippo, Fraser, Paavonen and Hurskainen (2015) in their Finnish study. According to them, it takes several years to replace the iron deficiency only by diet, so the iron substitution is highly recommended yet still not widely used, even in Finland.

The promotion of healthy eating habits in general does influence on public health. Finnish Food Authority together with THL have published a guide “Eating together – food recommendations for families with children” (2019) where it is recommended that health-promoting eating habits should take place in everyday life, not only during pregnancy, to ensure a healthy starting point for the pregnancy. Cultural diversity and different dietary habits are considered in the edited version of the guide as there are separate chapters for vegan diets, as well as other special diets such as celiac and lactose-intolerance. Good iron sources are whole grain products and vegetable sources such as soy, beans, lentils, peas, and dark green vegetables. To improve the iron absorption the vitamin-C rich berries and fruits should be consumed together. The guide states “pregnant women whose diet is low in energy or who follow a poorly balanced vegetarian diet form the largest risk group for iron deficiency”. Conversely, Piccoli et al. (2015) have reviewed vegan-vegetarian diet women and did not report significant difference in compared to mixed-diet women pregnancy outcomes, but vegan-vegetarian diet women to be at risk of vitamin B12 and iron deficiency.

The different types of iron, hemi iron in meat and fish, and non-hemi iron obtained from plants, are discussed in detailed in the Finnish guide mentioned earlier. This is particularly important once the decreased haemoglobin value has been assessed. During dietary advice, the information how to improve the natural iron absorption should be emphasized. Phytates (obtained from grains and legumes), tea, coffee, cocoa, and dairy products inhibit the absorption of iron. Finnish guide advice mothers with vegan diet to have consultation with a nutritional therapist. (Eating together 2019, 46-51.)

Rämet et al. (2015) say about strict vegan diet, that even it includes less hemi iron, the rich supply of vitamin C compensates it by intensifying iron absorption and therefore iron deficiency is not common with people with vegan diet. In some cases, a vegan diet without dairy products could be even better than mixed diet from the iron absorption perspective. (Rämet et al. 2015.)

Pavord et al. (2019) underline the awareness of the health care personnel about the iron deficiency and that correct information should be given especially for the targeted group of women with high risk, even before waiting for results of serum ferritin measures. Special group includes women with previous anaemia, multiparity of three or more, multiple pregnancy, women with poor dietary habits and those women with vegetarian or vegan diet, teenagers with pregnancy and women with recent history of significant bleeding. The targeted information includes information about hemi-iron absorption, the role of vitamin-C in the process and the knowledge about iron absorption inhibiting factors such as tea and coffee.

Best results in industrialized country for replacing iron deficiency are gained by combining dietary advice and interventions, the use of iron fortified food and the use of iron supplementation. Interventions such as meat consumption, ascorbic acid (vitamin C) increase, and combinations of dietary measures (like decreased intake of iron absorption inhibitors) showed best results in longer term studies of Beck, Conlon, Kruger, and Coad (2014).

3.3 WHO´s actions against anaemia

The importance of the anaemia can be seen in United Nations agenda for Sustainable Development Goals. Goal 2.2 is “*to end all forms of malnutrition*” and “*address the nutritional needs of adolescent girls, pregnant and lactating women*” and one indicator to achieve this target is to lower 50% the prevalence of anaemia among women aged 15-49. (UN 2021.)

According to WHO, iron substitution should be started as soon as positive pregnancy test has been performed to avoid anaemia and it´s negative impacts to pregnancy outcome. But where there is high prevalence of maternal anaemia, the latest recommendation is to use multiple micronutrients instead of iron substitution (WHO 2017, 43; WHO 2020a, 7). The updated WHO recommendation (2020a) highlights the importance of nutritional advice during pregnancy, as of the WHO 2016 guideline nearly every third of all tasks are related to nutrition. WHO has based its latest recommendation into multiple micronutrient supplements instead of iron on data mostly derived from low- and middle-income countries. The aim is to target the micronutrient supply according to population´s situation according to anaemia to achieve healthy pregnancy which can lead to a birth of a healthy baby and this way to improve public health.

WHO advices pregnant women in high anaemic settings to use multiple micronutrients containing 60mg of elemental iron instead of 30mg, which used to be the recommendation until year 2020. The limit for high anaemic setting is the prevalence of 40% or more. Areas of such are South-East Asia, Africa and Eastern Mediterranean area, and the implementation of this guideline to industrialized counties is not clear nor straightforward. Notable is, that the transition into multiple micronutrient supplement did not have any difference to the prevalence of anaemia or other maternal outcomes, but the neonatal mortality decreased.

The use of multiple micronutrient supplement instead of iron (or iron and folic acid combination) substitution was considered moderately cost-effective. (WHO 2020a.)

For even more comprehensive prevention of maternal anaemia, WHO has suggested that adolescent girls under poor-nutritional conditions could benefit from the iron substitution as menstrual blood loss together with poor nutrition remain high risks for anaemia. WHO´s anaemia-prevention strategy for non-pregnant women and adolescent girls suggests 60mg of elemental iron once per week and intermitted in three months periods. The target group includes all menstruating women in areas where anaemia prevalence is at least 20% among non-pregnant women. (WHO 2018, 8.) This means globally all other areas except Western Europe, Northern America and countries Chile, Argentina, Mongolia, Australia, and New Zealand. Implementation of the programme is still in progress in many countries.

In addition to multiple micronutrient use, WHO advocates the serum ferritin concentration measurement as the assessment of iron status in individuals and populations. Ferritin is adequate marker of iron stores and WHO has published cut-off values for different populations. For pregnant women the value is <15 µg/l. (WHO 2020b).

3.4 Maternal anaemia´s associations with perinatal outcome

Perinatal period is a period, which starts after 22 weeks of gestation and continues through pregnancy, covering the time of childbirth and postnatal period up to seven completed days after childbirth. Any outcomes from that period that are related to pregnancy (prenatal outcomes, e.g., which complications there is before time of childbirth) and childbirth (what happens during childbirths, e.g., mode of delivery) are together called maternal outcomes. The infant outcomes can be divided into foetal (e.g., intra-uterine foetal growth restriction) and neonatal (those which can be observed after birth (e.g., congenital abnormalities)). All outcomes from perinatal period are called perinatal outcome. (WHO 1977.)

WHO´s antenatal care panel have listed the outcomes of interest from the nutritional intervention viewpoint. The maternal outcomes of interest are infections, anaemia, pre-eclampsia, gestational diabetes, mode of delivery, excessive weight gain, side effects, maternal mortality, and maternal satisfaction. Foetal and neonate outcomes include neonatal infections, small-for-gestational-age (SGA), low birth weight, pre-term birth, congenital abnormalities, macrosomia (large-for-gestational-age, LGA) and foetal/neonatal mortality. (WHO 2020a, 2.)

Maternal anaemia´s, low haemoglobin value´s and iron deficiency´s association to different perinatal outcomes has been studied by many. The results are slightly different depending on the cut-off values of anaemia at the studies. Studies of Jung et al. (2019), Räisänen et al. (2014), Kemppinen et al. (2020), Vural et al. (2016), Rahman et al. (2016), Haider et al.

(2013), Zhang et al. (2009) and Kozuki, Lee & Katz (2012) are listed in the research table, see appendix 1. A previous Finnish study of Räisänen et al. (2014) compared perinatal outcomes according to parity. In Finland there were no significancy among primiparas, but multiparous had higher probabilities for preterm delivery and SGA and nearly significant risk towards major congenital abnormalities. Jung et al. (2019) have gathered global data in a large systemic review and meta-analysis. In general, the results showed that maternal anaemia increases the risk of low birth weight, preterm birth, perinatal mortality, stillbirth, and maternal mortality. All results were pooled according to study design, sample size, confounding factors, Hb measure time, country income category and geographic region. The strength of Jung et al. (2019) study is also dose-response analysis, which show adverse impact of high iron status likewise to anaemia.

Another Finnish study, Kemppinen et al. (2020), assessed perinatal outcomes of iron deficiency mothers related to oral or intravenous supplementation. There was no significant difference between groups, but the risk for both preterm birth and foetal growth restriction was higher in iron deficiency group compared to normal iron status women.

Like Jung et al. (2019), Haider et al. (2013) studied the effects of anaemia to perinatal outcomes globally. Key finding in the study was that anaemia especially in the second and third trimester increase the risk of preterm birth. Overall, prenatal anaemia increased the risk of low birth weight. Iron supplement use had positive improvement to decrease the iron deficiency anaemia. There was linear connection between the Hb level in third trimester and an increase in birth weight. In subgroup analysis according to country income category there were no significant differences. For comparison between malaria endemic and non-endemic areas the number of studies was too small. (Haider et al. 2013.)

Rahman et al. (2016) had also global viewpoint to maternal anaemia. Her group concentrated on low- and middle-income countries only. First, the prevalence was high in these countries – highest in South Asia with percentage of over 48%. Maternal anaemia was proved as a significant risk factor to low birth weight, preterm births, perinatal mortality, and neonatal mortality. The study group concluded, that no or very little improvement has happened during past 15 years to prevent maternal anaemia and its consequences.

A Turkish study of Vural et al. (2016) studied iron supplementation correlation to anaemia and perinatal outcomes. Turkey had the maternal anaemia prevalence of 25,1% between 2011 and 2014. The group categorized data according to the severity of anaemia. Their study showed that if the Hb was <100 g/l in first and second trimester, the low-birth-weight rate increased significantly in comparison to preterm birth rate when <100 g/l Hb value was measured in second or third trimester. The values >100 g/l showed no significancy.

A Chinese prospective cohort study of Zhang et al. (2009) studied the timing of anaemia diagnosis. When diagnosed in first trimester, anaemia was associated with increased risk for preterm birth but not if diagnosis was made in late pregnancy. Kozuki et al. (2012) studied associations between maternal anaemia and SGA. Their findings showed that only with a haemoglobin cut-off value of 90 g/l or even 80 g/l the significancy towards SGA was associated. With values of this low level, there were no differences in SGA between developed and developing countries.

Say et al. (2019) has estimated that severe anaemia is a reason for maternal mortality globally in 13% of cases together with obstructed labour. Maternal anaemia´s connection to maternal mortality is challenging to demonstrate as facilities in high maternal mortality areas are often poor and the reason for maternal death is more often postpartum haemorrhage or sepsis due to lack of proper management, explains Daru et al. (2018).

As a summary, anaemia causes adverse perinatal outcomes worldwide, but the consequences in developing countries are more fatal than in developed countries. Mortality and morbidity rates are significantly higher in the low-income countries than in the high-income countries (Jung et al. 2019; Rahman et al. 2016; WHO 2017, 5). The situation has been recognized by WHO, which is actively trying to advocate the importance of this topic. Also, the studies use different cut-off values for haemoglobin to diagnose anaemia, which makes the comparison of the results challenging.

Maternal anaemia´s associations to child health later in life is yet another issue. The meta-analysis of Quesada-Pinedo et al. (2021) took into consideration both low and high maternal iron statuses. Low iron status, in most cases identified by ferritin rather than haemoglobin, had connections e.g., to neurodevelopmental outcomes, but the study calls also for clinically meaningful iron deficiency and iron overload determinations. (Quesada-Pinedo et al. 2021.) This is essential to be fully able to compare studies, as each of them has different cut-off values.

4 Methods

4.1 Pico model

In PICO-model P refers to (target) population, I as intervention or treatment, C comparison group without intervention and O outcome (Jensen 2021). In this study, research questions 2 and 3 are based on comparison of two groups, and they represent the P and C in PICO-model. Outcome (O) would be the results of quantitative research. Intervention in this study is more the exposure of study group – exposure to anaemia (diagnosis). The PICO-model used in this study is presented in table 2 below.

P	women who gave singleton birth in Finland between 2006 and 2020
I	women diagnosed anaemia in any time during pregnancy
C	women with no anaemia diagnosis
O	perinatal outcome (comparison of these two groups)

Table 2: The PICO-model used in this study

4.2 Data collection and MBR

This thesis uses data obtained from the Finnish Medical Birth Register, MBR. Finnish Institute of Health and Welfare has maintained Finnish Birth Register since year 1987 and is a statutory controller of the register. Hospitals gather information systematically about all live and stillbirth children who weight minimum 500g and pregnancy weeks is minimum 22 in addition to information about mothers giving birth and they report the data annually. Anaemia is recorded when haemoglobin value is below 100 g/l during any time of pregnancy, and it has been registered since 2006 from all hospital districts. (THL 2021.) The register has undergone several reforms, latest on 2017 (THL 2021b).

According to MBR (THL 2021), “the purpose is to collect data in order to develop and organise maternity care, obstetrical services and neonatal care”. Findata admits permissions for institutions and researchers to use the data according to data permit application, see later chapter 4.2 Data management.

It is notable, that MBR collects data from all births performed in Finland including home births, but the number of Finnish children born differs from Digital and Population Data Services Agency´s information, where also Finnish children born abroad are registered. Ward personnel at hospital send the data electronically to THL when discharging the patient from the hospital after postnatal period. Home deliveries are added to the register by hand, but in Finland the amount is limited (2019 38 deliveries, THL 2020) which does not create any limitations to data credibility. Health register maintenance is based on Finnish legislation and information collection is a routine and does not need an informed consent.

MBR data has been qualified as high quality, according to Lamminpää, Gissler and Vehviläinen-Julkunen (2017). MBR enables maternal health-related outcomes assessment, and it is useful for nurse researchers as it “offers population-based data that can be utilized in research purposes and interpreted with implications for clinical practice to improve the health of mothers and new-borns both nationally and internationally” (Lamminpää et al. 2017). MBR is a reliable register in Finland and its data has been used in many scientific publications, for example between 2012 and 2017 there were 51 studies which were using MBR (Lamminpää et al. 2017).

Gárdenas (2019, 27) recommends the use of national institutions data when research is focused on a specific country, and it has advantages such as having access to more data in less time and the data allows comparisons in time and between cases. However, it is possible that registry-based data does not appropriately give information regarded to research questions (Lamminpää et al. 2017).

4.3 Data management

Findata is the Health and Social Data Permit Authority, that operates in between the Finnish Institute for Health and Welfare, which is the register owner of the Finnish MBR, and the researcher. Actions of Findata are based on the Act on the Secondary Use of Health and Social Data (552/2019) and it is relatively new authority, operations started no earlier than 2020. Findata secures the health and social data management, and issues permits for secondary use of the data. Findata enables secure combination of different registries data. The data permit application is confidential and data permit is granted for a fixed time. The period of use may be extended by author by applying for an extension. The decisions and permits granted by an authority are primarily public and are published on Findata web page. Date of the permit, project name, purpose of the data use and intended use for the data are all public information. If the applicant is an organization, the name is published but as an individual applicant the name is not available on web page. (Findata 2021.)

The data used in this thesis project is a new data, generated from MBR, and the registry owner for this data is the author. The author is responsible to handle the data strictly according to the Data Protection Act. Supervisors were both guiding the author with the data analysis process, but the author performed analyses alone and is the only writer of the thesis report.

Data was pseudonymised by Findata and processed later only in secured remote environment. Any personal information was not available. However, it might be possible to recognize individual despite the pseudonymization by secondary information, but author is not under any circumstances allowed to use that kind of information for her own purposes. Signing in to secured remote access environment requires strong identification with personal account and it is additionally locked with single-use password each time when signing in. All accesses are monitored, and no data can be stored or removed to authors own computer during analysis process. All data-processing events are registered in the log data. All these activities protect data from external threats, including viruses and other attacks which might endanger data protection. (Findata 2021.)

Pseudonymization means the operation, where personal data has been either encoded or processed in such manner that personal identification is not possible. If the personal recognition is possible, the data is considered personal data and it must be handled under the data protection regulations. The decoding is possible with the special code key, and Findata is the owner of that key in this data management. (Tietosuoja 2021.)

The author is the registry owner (data controller) for this pseudonymized new data. The registry owner is aware of the data protection principles and Data Protection Act according to EU General Data Protection Regulation (GDPR). Additionally, the processing of personal data such as health-related data as in this thesis, always requires a basis for the processing. Article 6 of the GDPR enables the use of personal data to scientific research and statistics, which is the situation in this thesis.

The remote access environment includes IBM SPSS Statistics -program, version 27, which was used for data analysis. Findata will delete the data after 1.8.2022 if no extension has been applied. The data can be reproduced if needed, the pseudonymization key and other generating programs are retained, with the diary number of the original data permit which is only known by the applicant. As a registry owner, the author is fully committed to Findata data management procedure (storage, use and deleting the data) in a secured remote environment explained above.

Registry-based research has both advantages and disadvantages. Both characteristics have been collected to the table 3 below, according to Räisänen, Heinonen, Sund and Gissler (2013, 3079).

	Advantages	**Disadvantages**
Data	population-based	missing data
Data collection	data already exists	long waiting period after data permit application pre-processing and inspecting the data possibly takes time
Research perspective	Individual, communal-organizational municipality or national level	
Expenditure	no expenses when collecting data	data permit and the use of remote access environment can be expensive
Data credibility and coverage	Standardized data collection methods (in future automatic)	data can have missing information
Variables	Independent variable can be chosen	Number of variables is limited, especially life-style factors. Changes in data collection over years can change variables.
Study design	Several possibilities; observational cohort-studies, case-control studies Longitudinal- and cross-sectional studies possible.	Data has been collected originally for statistic and administrative purposes, which can set limitations for study design.
Research purpose	Prevalence, incidence, risk factors, correlations, predictions, and effectiveness of care can be determined.	
Time factors	Either retrospective or prospective.	Not necessarily possible to show causality.

Table 3: Advantages and disadvantages of registry-based studies based on Räisänen et al. (2013, 3079)

4.4 Study questions

This thesis aims to emphasize the importance of appropriate iron level during pregnancy to prevent maternal anaemia and to find out how maternal anaemia associates with perinatal outcomes. The objective is to find answers to the following research questions:

1) How maternal anaemia has evolved in Finland during past 15 years (2006-2020)?
2) Do perinatal outcomes differ between anaemic and non-anaemic groups?
3) Which characteristics increase and decrease risk for anaemia? (What are the risk and protective factors for anaemia?)

The following perinatal outcomes will be assessed:

- preterm birth (<37 pregnancy week)
- gestational age
- birth weight
- perinatal mortality (<7 days after birth)
- small for gestational age (SGA)
- gestational diabetes
- eclampsia
- placenta praevia
- abruption of placenta
- delivery mode (caesarean section)
- induced labour
- admission to neonatal ICU
- blood transfusion after birth
- mean hospital stay after birth

The selected perinatal outcome variables are chosen based on literature. In difference to WHO´s interest of perinatal outcomes (WHO 2020a, 2), eclampsia was studied not pre-eclampsia.

The hypothesis to be tested: Maternal anaemia has negative effects on perinatal outcomes.

4.5 Study design

This thesis is an observational study. The researcher is only the observer, without trying to influence the study. As a cross-sectional study, there is no follow-up of study population nor intervention. Analysis is conducted only once. The study is also retrospective since the data is based on previously collected data. Quantitative analysis searches relations between phenomena and focuses on the outcomes according to Gárdenas (2019, 5).

This thesis uses secondary data analysis. According to Bhattacherjee (2012, 48), the secondary data analysis uses data, which has already been collected by other sources and it is not directly involved in the present research (Gárdenas 2019, 25). It is a feasible method, if the data is available at the level that can answer the research questions. There might be limitations if the data is not collected in a systematic or scientific manner which then makes it unsuitable for scientific use.

This thesis consists of univariate descriptive analysis, bivariate and multivariate analysis. Results are presented on tables. As the data is secondary and it is conducted as numbers, the research is called quantitative. According to Gárdenas (2019, 5), “the data to answer the research questions are numbers” in comparison to qualitative research, where the data is most often words.

Finnish Medical Birth Register has over 240 characteristics. Variables requested from Findata are 22 items and they were selected based on literature, including WHO´s outcomes of interested. Description of the requested data and chosen variables can be seen in attachment, Appendix 2. Those variables are listed on Figure 1 below, divided into three categories:

Demographic

- statistical year
- municipality of residence of the mother
- marital status of the mother
- cohabiting
- previous pregnancies (inc. previous miscarriages, induced abortions, ectopic pregnancies
- previous births (inc. stillborn)
- pre-pregnancy weight and length of the mother
- maternal smoking
- risk factors associated with gestation (inc. assisted reproductive treatments in-vitro fertilization, intrauterine insemination, ovulation induction, glucose tolerance test (tested and pathological), anaemia (Hb < 100 g/l)
- maternal diagnosis during pregnancy
- mother age at the time of the delivery, years

Maternal Outcomes

- gestational age during delivery (WW+D, best estimate)
- mode of delivery
- other procedures during delivery (induced labour and blood transfusion during birth/postnatal)
- gestation and delivery diagnoses (placenta praevia, ablatio placentae and eclampsia)
- diagnosis at delivery
- length of hospital stay after birth

Infant Outcomes

- the infant born live/stillborn
- number of foetuses (study includes only singletons)
- birth weight
- procedures concerning the infant (ICU or observation ward)
- perinatal status of the new-born at age of 7 days

Figure 1: Variables requested from Findata divided into three categories

The socio-economic status variable was decided to exclude from the requested data. Also, new-born diagnoses were excluded. In many studies the congenital malformations were also analysed, but as this requires in Finland the use of another registry, congenital malformations are not included in this study.

4.6 Data analysis and operationalization of the variables

This thesis has both descriptive and inferential (analytical) statistical analysis. Descriptive statistics shows numeral characteristic of the study population. Inferential statistics enable comparisons between different groups, and it can present relations between groups and variables (Kellar & Kelvin 2013, 5, 25).

This thesis used univariate descriptive analysis to analyse anaemia in general. Bivariate analysis was used to test rational hypothesis and to find relationships between two variables (Gárdenas 2019, 40), in this thesis between anaemia and other variables. Multivariate analysis has the same purpose, it includes in analysis more than two variables.

The anaemic group was defined by using the anaemia variable and to find sub-groups, each variable was used individually. Several variables were recoded into different variable. Age, smoking habit, parity, and status of the new-born were categorized. Birth method was first categorized according to birth method and further dichotomized into caesarean section vs. no caesarean section variable. Height was recoded into meters so that BMI was possible to calculate. BMI categorization was created according to under-weight (BMI <18,5), normal weight (BMI 18,6-25), overweight (BMI 25,1-34,9) and obese (BMI >35). Pregnancy weeks were recoded into 160 different values according to days for analysis. Cohabiting was recoded and dichotomized, so that cohabiting variable includes all forms of cohabiting (marriage and not married).

The descriptive statistics were calculated using frequencies and percentages. After noticing the extremely low prevalence of anaemia in Helsinki year 2020, the Turku and Tampere prevalence were also calculated. This calculation was not pre-planned but was needed in comparison to Helsinki results.

The significance (p-value) was calculated with independent sample T-test for mean maternal age, mean BMI, cohabiting, caesarean section, gestational diabetes, placenta praevia, ovulation induction, intra-uterine insemination, in vitro fertilization (embryo transfer), mean gestational age, induced labour, blood transfusion, abruption of placenta, admission to neonatal ICU, mean hospital stay, preterm birth, mean birthweight and mortality. In smoking habit variable, the number of missing values were exceptionally large, and they are included in table 3 but excluded from the analysis as explained in chapter 4.8. Independent sample T-test is a parametric test, and it can be used when grouping variable is dichotomous, variables are independent from each other, and the variable is normally distributed and continuous (Kelvin & Kellar 2013, 95). It is particularly used when sample size is large.

Chi square test for p-value was used when calculated significance (p-value) in age group, smoking status, number of prior births and birthweight categories. Chi square test can be used when variable is categorized, sample size is adequate, and measures are independent of each other (Kelvin & Kellar 2013, 295). This large dataset did not have any problems with sample sizes at any point. P-value is considered nearly significant, if the value is <0.05, significant if it is <0.01 and very significant if it is < 0.001.

The small for gestational age (SGA) -variable was counted according to Sankilampi, Hannila, Saari, Gissler and Dunkel (2013) population-based birth size reference model. Model defines SGA when birth weight is <10% from the frequency of birthweight according to pregnancy weeks. Since the data did not include new-born diagnoses, the ICD-10 diagnostic system to select cases by diagnosis was unable to use for SGA analysis. Analysis of significancy for SGA was performed by independent sample T-test after recoding the variable dichotomous.

Kelvin and Kellar (2013, 334) says "*the odd ratio is the ratio of one probability over to the other*". From the logistic regression model, it is possible to gain the statistical significances for the overall model and for each of the adjusted odd ratios as well as the adjusted odd ratios and the confidence intervals around them (Kelvin & Kellar 2013, 328). Recoding the variables into dichotomous variables plays an important role to perform logistic regression models successfully. In logistic regression the confidence interval 95% was used, which means, that the result will fall within the 95% probability between certain values.

The binary logistic regression is used when the determinant variable is binary. In this thesis the anaemia-variable is modelled into 0=no anaemia and 1=yes anaemia. Multivariate logistic regression model includes more than one predictor value (Kelvin & Kellar 2013, 321) and this is used in this analysis. By calculating odd ratios, the incidence odds are calculated as the perinatal outcomes are the one to be assessed. Analyses of both crude odd ratios without confounding factors and adjusted odd ratios are performed. It is known from the literature, that there are several confounding factors affecting to perinatal outcomes, such factors are maternal age, cohabiting, number of previous births, smoking status, and BMI, and therefore no correlation is analysed. In this study, the prior embryo transfer was included in model as confounding factor, as it showed significancy in T-test. The adjusted odd ratios in this study were adjusted by maternal age, cohabiting, parity, smoking status, BMI, and embryo transfer. In logistic regression the confidence interval 95% was used, which means, that the result will fall within the 95% probability between certain values.

Total model included age categories, cohabiting, smoking, BMI, embryo transfer, previous births, gestational diabetes, blood transfusion needed, placenta praevia, eclampsia, admission to neonatal ICU, preterm birth, and caesarean section. From total model the risk and protective factors can be identified and evaluated.

4.7 Ethical aspects of the study

4.7.1 Ethical principles in research

Finnish National Board on Research Integrity TENK (TENK 2019) has created guidelines for ethical principles for research with human participants which all disciplines should follow. The purpose is to respect dignity and autonomy of participants and research should be conducted in a manner that research does not, under any circumstances, cause “significant risk, damage or harm to research participants, communities or other subjects or research”. Participants legal rights are listed in guideline.

Personal data processing must be protected, and any decisions made must be justified and documented. Privacy should be ensured for participants. There are five steps which to follow during data processing (TENK 2019, 56):

1) legal basis for processing data
2) research plan according to personal data process must be defined and each person who participate in data processing, their responsibilities should be individually defined
3) accurate plan for which personal data is used and for what purpose
4) personal data removal from research data when it is no longer necessary, or data should be stored securely. Access to data should be permitted only for those who have the legitimate basis.
5) research participants information of their rights

In this research, ethical review statement from a human sciences ethics committee is not needed, because this research is based solely on registry and documentary data (TENK 2019, 62).

This thesis meets the general criteria for scientific research. It has appropriate research plan and responsible person. Results are published and are public and the research produces new information.

4.7.2 Ethicality of thesis projects at university of applied sciences

The Master´s thesis at the university of applied sciences aims to create and produce new information for the workplaces. It has both developmental and research-oriented perspective and it is characterised as “research-based development project” and according to Laurea University of Applied Sciences (2021) it has, at best, innovative approach. The evaluation criteria for the Master´s thesis is equal in all university of applied sciences, agreed by the National Qualifications Framework and the European Qualifications Framework. Each student must accomplish the research and ethicality -course before graduating. (Laurea 2021.)

The Rectors´ Conference of Finnish Universities of Applied Sciences, ARENE, includes all 24 rectors of Finland´s universities of applied sciences and the universities of applied sciences themselves. It has created ethical guidelines for final thesis reports for all students at university of applied sciences and those recommendations are based on Finnish law and scientific communities international and national principles and recommendations. ARENE recommendations are fully committed to TENK ethical guidelines presented earlier.

The thesis is a public, official document, and it is an integrated part of the university of applied sciences degree. Publicity ensures objective and fair evaluation process. The Theseus database is the place where all thesis documents derived from Laurea UAS are published electronically. The author must ensure that no kind of personal data or information is included in thesis prior to final submission to Theseus. The thesis seminar, where final presentation will be hold, is a public event. (Laurea UAS 2021).

All documents undergo a plagiarism check program and ethical management report is required before thesis plan. The personal data handling during thesis process should be performed with care and in safe environment. The research ethics principles must be familiarized by the author with the help of the supervisor(s). These actions are all required by ARENE ethical guidance. (ARENE 2019, 7, 18).

Author understands that she is fully responsible of the ethicality of the thesis report according to ARENE ethical guidelines (2019). She is the key actor in thesis process and will own the copyrights for the work in future (according to the Copyright Act). Supervisor(s) role is to support, encourage and to provide expert help and instructions on quality management. None of the supervisors nor the author have any conflict of interest. This thesis has no commission from working life.

4.8 Reliability assessment

The large number of data adds reliability of this research. There was some missing information in variables, but in this large it did not influence on reliability of the results. Missing information was excluded from the analysis, analyses were performed with only valid data. As the Sund (2008, 41) states, the completeness of registration being very good increases validity of the data. The process of how data will be transferred into MBR will be automatic in future which will eliminate the human-made mistakes when entering data.

As based on registry that already exists, there were no separate data collection. Data has several variables and those should be well adapted to this study according to previous studies from this field. Registry-based study has limitations to existing data. From the data handling process anonymity viewpoint, it is notable, that no personal ID´s were included in the data, nor the mother or the new-born. Findata requires and controls that any frequencies <5 or min

/ max values should not be reported to avoid identification. The registry-based study and reliability of data collection is more detailed explained in chapter 4.3.

In Finland, all health care equipment undergoes regular inspections which is one aspect of making haemoglobin measurements reliable. Widely, venous measurements are also taken and always when suspecting the fingertip measurement reliability or when fingertip measurement shows low value. This means the actual measurement of haemoglobin is reliable, and, all pregnant mothers are routinely tested, not only those who are symptomatic.

The data is available in MBR, and this research can be repeated.

4.9 Limitations

Even before data analysis, it is known, that the timing of anaemia diagnosis is not available through Finnish Medical Birth Register. It might be more informative to study how the different trimester anaemia effects on perinatal outcomes, as did Zhang et al (2009) and Vural et al. (2016). Räisänen et al. (2014) had this same limitation, as it used the MBR as well.

The impact of possible interventions like iron substitution use was not possible to study on registry-based study like this, as the data does not show if the anaemia has been treated or not. Also, the background characteristics behind anaemia are limited only to those, which are registered. Additional info about e.g., diet or chronic diseases is not available. This is a common disadvantage in registry-based studies (Räisänen et al. 2013).

It is notable too, that MBR includes anaemia when the haemoglobin value has measured lower than 100 µg/l. It is seen from literature, that when assessing iron deficiency anaemia, the biomarker ferritin is widely used nowadays as Quesada-Pinedo et al. (2021) shows. The cut-off value for haemoglobin varies between international studies, so the actual comparison of results is not accurate.

When analysing women with previous births, it is unknown what is the time between pregnancies and births. In registry-based data this information could mean longitudinal study. Time between pregnancies influences blood levels, if the pregnancies occur so often, that the body has no time to recover from the previous one.

For the reliability viewpoint, the researcher´s limited experience from quantitative studies previously can also be one limitation. In this work the author has received guidance from both the thesis supervisor from Laurea and working life representative mentor, research professor from THL to diminish this factor.

5 Results

The total number of cases in data was 813 555 singleton births. The group size for anaemic women was 29292. The prevalence of anaemia in Finland 2006-2020 in total data was 3,6 %.

5.1 Evolvement of anaemia in Finland between 2006 and 2020

During the study period there were differences between years. The growing prevalence of maternal anaemia was seen throughout the study period the year 2020 being an exception. The total frequency of anaemia in Finland 2006 – 2020, in Helsinki and in the group of underweight pregnant women can be seen in a figure 1 below. Helsinki was taken as an example city of whole country and underweight anaemic group was taken as an example of high prevalence sub-group for maternal anaemia based on previous studies.

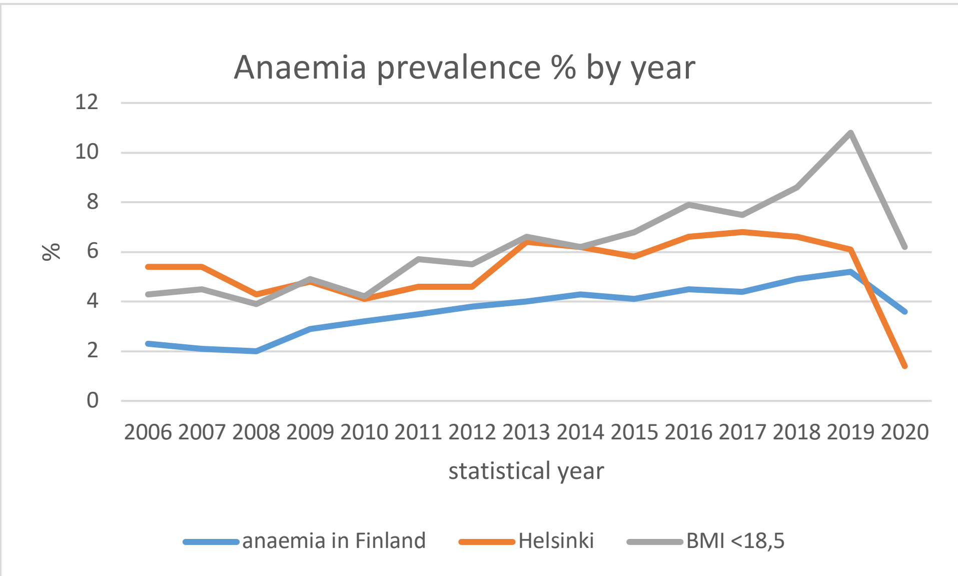

Figure 2: Anaemia prevalence % in this data according to year. Total prevalence in Finland (n=29292), in Helsinki (n=5511) and in the group of underweight women (n=1551) 2006-2020

The total prevalence of anaemia varied between 2 % at year 1008 up to 5,2 % at year 2019. Helsinki was chosen as an example city to see how the maternal anaemia prevalence corresponds with the total prevalence. Helsinki has it highest prevalence 6,8 % in 2017 and lowest prevalence 1,4 % in 2020. The under-weight women had the prevalence of anaemia at highest 10,8% during year 2019.

The figure 3 below shows prevalence in three cities, Helsinki, Turku, and Tampere between 2006 and 2020.

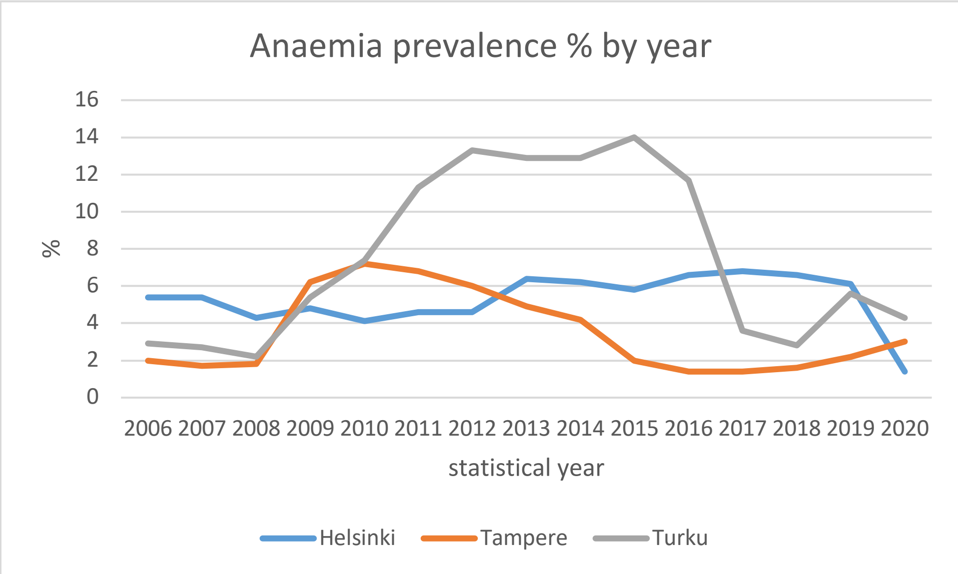

Figure 3: Anaemia prevalence % in Helsinki (n=5511), Tampere (n=1248), and Turku (n=2065) by year, between 2006 – 2020

It is seen from the figure, that cities Tampere and Turku had different prevalence than Helsinki. Tampere had lowest anaemia prevalence 1,4 % years 2016 and 2017 and highest 7,2 % at year 2010. Turku had lowest prevalence 2,2 % year 2008 and then high numbers between 2011 - 2016, 13,3 % being the highest prevalence at year 2012.

5.2 Descriptive analysis of the data

In the following table, Table 4, is the descriptive analysis of the data, divided by non-anaemic and anaemic groups. In the table the prevalence percentages for all variables in both groups and significances between groups (p-values) are listed.

	No anaemia n=784 263	Anaemia n= 29 292	p-value
Mean maternal age, years, SD	29.95 (5.331)	29.60 (5.788)	<0.001
Maternal age, years, %			<0.001
≤19	1.9	3.4	
20-29	45	46.1	
30-39	49.2	46.0	
≥40	3.9	4.5	
Cohabiting, %	89	85.9	<0.001
Mean BMI, SD	24.59 (4.98)	24.23 (4.99)	<0.001
BMI, %			<0.001
<18,5	3.3	5.3	
18,6 - 25	58.9	59.9	
25,1 - 34,9	29.6	28.0	
>35	4.4	3.9	
missing	3.9	2.8	
Smoking status, %			<0.001
non-smoking	82.7	82.6	
stopped during 1st trimester	5.6	6.1	
smoking daily	8.0	8.6	
smoking occasionally	0.3	0.3	
no data available	3.4	2.5	
Number of prior births, %			<0.001
0	41.6	42.6	
1	34	30.4	
2-4	21.6	23.3	
5 or more	2.8	3.6	
Mode of delivery, %			
vaginal (incl. breech)	75.2	68.4	
vacuum extract	8.8	11.0	
caesarean section	15.9	20.6	<0.001
Mean birthweight, g, SD	3521.25 (539)	3541.99 (587)	<0.001
Birthweight, g, %			<0.001
<3000	3.2	3.9	
3000-3499	10.2	9.3	
3500-3999	69.4	67.0	
4000 or more	17.1	19.8	
Mean gestational age, week + days, SD in days	39+5 (13.7)	39+5 (14.9)	0.009
Gestational diabetes (glucose tolerance test pathological), %	13.8	15.1	<0.001
Eclampsia, %	0.1	0.0	0.222
Placenta praevia, %	0.3	1.0	<0.001
Ovulation induction, %	1.2	1.6	<0.001
Intra-uterine insemination, %	0.8	1.0	0.009
In vitro fertilization (embryo transfer), %	2.5	3.5	<0.001
Induced labour, %	22.2	27.2	<0.001
Blood transfusion, %	2.0	10.6	<0.001
Abruption of placenta, %	0.2	0.6	<0.001
Admission to neonatal ICU, %	10.4	13.2	<0.001
Mean hospital stay, days, SD	3.53 (SD 2.5)	3.91 (SD 3.0)	<0.001
SGA (small for gestational age) %	10.0	9.4	<0.001
Preterm birth, <37 weeks %	4.7	5.6	<0.001
mortality, %			0.079
born dead or dead before age of 6 days	0.4	0.5	
alive after 7 days	99.6	99.5	

Table 4: Descriptive statistics of non-anaemic and anaemic groups and perinatal characteristics of the data

In the anaemic group (n=29292) there were more often younger and mature aged women, the mean age being 29,95 years in non-anaemic group and 29,60 in anaemic group, p-value being <0.001, which means significant difference between two groups. The age group was found significant difference (p<0.001) between non-anaemic and anaemic group. Anaemic women were more often either nulliparous or had at least two previous births, number of previous births being significant factor (p<0.001) between two groups. Also, they were more often not-cohabiting (p<0.001). Women in anaemic group had higher prevalence in caesarean section than non-anaemic women and more often operational vaginal birth (either vacuum extract or forceps) than women in the control group. The forceps as an assisted vaginal delivery method had very small frequencies in both groups, the percentage in this data 0,0%. The caesarean section was significantly greater (p<0.001) in anaemic group.

In the anaemic group, the underweight women prevalence was nearly two-folded. The difference in BMI between anaemic and non-anaemic groups was statistically significant, p < 0.001.

It was found that mean birthweight had significant difference (p<0.001). Same was seeing in the mean gestational age (p =0.009), although when value was rounded into full days, it had similar value in both groups. Also, the smoking habits were quite similar, only there was higher prevalence in daily smokers in anaemic group compared to non-anaemic group. The missing data in smoking habits was quite large, that group being 2,8 % in anaemic group and 3,9 % in control group. Smoking status had the significancy of p<0.001.

All modes of fertility treatment, ovulation induction (OI), intra-uterine insemination (IUI) and in-vitro fertilization (IVF) had significantly higher prevalence in anaemic group versus control group. P-value was <0.001 in OI- and IVF-treatments and 0.009 in IUI-treatments.

The anaemic group had higher prevalence in gestational diabetes (glucose test pathological), placenta praevia, induced birth, abruption of placenta and admission to neonatal ICU. All these variables were statistically significant, p-value <0.001. The length of hospital stay was significantly higher in anaemic group, p<0.001. Blood transfusion prevalence was five times higher between anaemic group versus control group and abruption of placenta prevalence was three times higher in anaemic group, both had p <0.001. Eclampsia prevalence was small in both groups, been smaller (close to zero) in non-anaemic group but not significantly, p =0.222.

Preterm birth (<37 pregnancy weeks) had higher prevalence among anaemic group and the difference was statistically significant p<0.001. Small for gestational age (SGA) prevalence was smaller between anaemic women, p<0.001. Mortality rates were small in both groups, the difference being not significant according to p-value.

5.3 Risk and protective factors for anaemia

The highest increased ORs were found in blood transfusion needed and placenta praevia subgroups. The adjusted OR in blood transfusion was 6.503 meaning the risk more than six times higher in anaemic group than in non-anaemic group. The placenta praevia OR was 3.456 which means over three-folded risk for anaemic women compared to non-anaemic women. The adjusted odd ratio interpretation shows 17% increased odd for gestational diabetes, 28% increased odd for induced labour, 39% increased odds for the neonatal intensive care unit admission and preterm birth and 55% increased odd for caesarean section.The results show both high odd ratios and adjusted odd ratios in all perinatal outcomes except eclampsia and small for gestational age (SGA), the eclampsia being the only outcome not significant in both groups, SGA was not significant only in adjusted odd ratios.

For the odd ratios and adjusted odd ratios see the Table 5 below. In the Table 5 the valid numbers for each perinatal outcome variable included in each analysis can also be seen.

Perinatal outcome	**women with no anaemia** **n/data available %**	**women with anaemia** **n/data available %**	**Odd ratio** **CI 95%**	**Adjusted Odd ratio** (adjusted by maternal age, cohabiting, parity, smoking status, BMI, and embryo transfer) **CI 95%**
gestational diabetes	108416 / 784263 13.8%	442/29292 15.1%	1.108 [1.039-1.145]	1.175 [1.123-1.230]
induced labour	174170/784263 22.2%	7956/29292 27.2%	1.306 [1.272-1.341]	1.276 [1.230-1.324]
pl. praevia	2597/784263 0.3%	307/29292 1.0%	3.188 [2.831-3.590]	3.456 [2.978-4.011]
eclampsia	395/784263 0.1%	10/29292 <0.0%	0.678 [0.362-1.270]	0.550 [0.135-2.2233]
blood transfusion needed	15510/784263 2.0%	3097/29292 10.6%	5.860 [5.627-6.102]	6.503 [6.099-6.933]
admission to neonatal ICU	81484/784263 10.4%	3852/29292 13.2%	1.306 [1.261-1.352]	1.387 [1.320-1.458]
preterm birth	36942/784263 4.7%	1643/29292 5.6%	1.202 [1.143-1.265]	1.385 [1.293-1.484]
caesarean section	124984/783871 15.9%	6030/29292 20.6%	1.367 [1.328-1.407]	1.548 [1.485-1.614]
SGA	78294/784263 10.0%	2745/29292 9.4%	0.932 [0.896-0.970]	0.998 [0.939-1.061]

Table 5: Unadjusted and adjusted odd ratios of perinatal outcomes associated with maternal anaemia

In the total model, it was seen that both young mothers (age <19years), underweight (BMI <18,5), not-cohabiting, no prior births, or previous births more than two and prior embryo transfer were factors that increased the odds for anaemia. These characteristics can be labelled as risk factors. Controversially, age over 20 years and at least normal weight (BMI >18,6) can be determined as protective factors. The number of prior births was calculated both separately and in total model to confirm the founding.

6 Discussion

Maternal anaemia has effects on perinatal health both in industrialized countries as well as in low-income countries, although the high-level antenatal care in high-income countries compensates some of the adverse outcomes. However, the total prevalence of maternal anaemia in Finland seeing in this study shows grown numbers over the years, compared to Räisänen et al. (2014) results. Larger population suffering from maternal anaemia means certain perinatal problems occurring more often as seen in this study and this should be noted, with biggest odds in blood transfusion needed and eclampsia, which both require resources and special care in perinatal care. From the patient’s viewpoint all operational births and even longer hospital stay decrease the normality of childbirth and increase the expenses of maternal health care. In big picture this has influence on economic situation, as prolonged hospitalization requires more taxes.

In the antenatal care the more detailed screening for risk groups is advisable. Careful interview during the first visit about dietary habits combined with the first measurement of haemoglobin is an opportunity to highlight the nutritional importance when preventing maternal anaemia. By doing this, it might be possible, that the normal haemodilution during pregnancy would stay between normal limits and not turn into anaemia later in pregnancy. If low haemoglobin value is measured already during the first trimester, the treatment of anaemia with iron substitutes is in a key position. The Finnish antenatal care system guarantees equal access to care for all pregnant women, and since the measurements of screening anaemia are systematic, not based on symptoms, all maternal anaemia cases should be identified.

When measuring only haemoglobin, there is a risk that not all those women, who have low iron storage will be identified. It can be only guessed how large this group might be. Are these women only tip-of-an-iceberg and the prevalence of iron deficiency anaemia could be a lot bigger if also measuring ferritin routinely? That is already routine in Finland, in Oulu area, where ferritin is measured in antenatal care routinely from those pregnant women who are at risk group for iron deficiency anaemia. Finnish Broadcasting Company YLE announced the beginning of the study, and the aim of the research is to detect early those pregnant women who would benefit from iron substitution from the very beginning of the pregnancy (YLE 2021). In Oulu University hospital district area, there is known to live large number of multiparous women. Ferritin measurement might replace haemoglobin measurements in future, and already now some international studies are more based on ferritin measurements rather than haemoglobin values (e.g., Quesada-Pinedo et al. 2021). Globally, in low-income countries, the haemoglobin measurement still maintains the most important diagnostic measurement due to easy access of measurements even in simple health facilities without proper laboratory management.

It is surprisingly wide variety between countries when it comes to iron substitution recommendations. WHO has been criticized about their recommendation about all fertile age women should use iron substitution (preferable combination of other micronutrients) if the country prevalence on anaemia is higher than 40 %. In high-income countries such as Finland, Germany, Australia, UK, and US all have different recommendations.

In Finland there is a new, updated version of the guide to antenatal care arriving later this year replacing Klemetti and Hakulinen (2013) guide. When this thesis will be published hopefully new guide is already in use as obviously Finland is missing congruent guidelines. In present situation the guidance is different depending on source. University hospital districts should have equal guidance, which is available at Terveyskylä for everyone. Opinions about daily versus intermitted iron substitution use differ too. Latest researcher e.g., Stoffel et al. (2021) seem to advocate the intermitted use based on better absorption and less negative side effects for the user.

The reverse studies (Pavord et al. 2019; Rämet et al. 2015; Piccoli et al. 2015) about vegan diet´s impact on maternal nutrition gives different information weather is it an increased risk or not to develop maternal anaemia. For the antenatal care personnel this is not an easy task to solve out. In the future, this might be one of the interests to study further among Finnish pregnant mothers.

The anaemia prevalence in the year 2020 is interesting as the numbers were dropped dramatically. Upcoming years will show weather the prevalence has permanently decreased. In Helsinki and Uusimaa district area a new patient information system was put into service year 2020. That could make one explanation for the decreased numbers, as the data reporting system was new for nurses who import the data into the register. The same kind of decrease was not seen nor in Turku or Tampere. These cities were checked to compare Helsinki to other bigger cities in Finland.

It is nearly impossible to be able to really compare results of different studies and countries because each study has their own cut-off values for anaemia. The problem is the same for other researchers as say also Bencaiova and Breymann (2014). The swiss study of Bencaiova and Breymann (2014) highlight two points when assessing maternal anaemia to adverse outcomes between different studies. Those two points are the timing of anaemia diagnosis (gestational age) and the degree of anaemia diagnosed. Their study showed no significances between anaemic and non-anaemic group when iron supplementation was used after diagnosing anaemia. This is interesting and shows how effective treatment can be.

In this study the cut-off value 100 g/l was used, while WHO (WHO 2017) has cut of value of 110 g/l for maternal anaemia as explained in chapter 2.1. Vural et al. (2016) had the same cut-off value than this study, and the result that maternal anaemia associates with pre-term birth was similar. Jung et al. (2019) and Haider et al. (2013) both had this same association with pre-term birth. The author critically relates to studies of low birthweight and maternal anaemia, as it is also nation-related what is the median of the birth weight in each country. It is the same with perinatal mortality – even if the percentage of stillbirth children was higher in this study among anaemic women than the control group, the difference was not significant. This study did not conclude that maternal anaemia increases the risk of stillbirth in Finland, but it does in low-income countries according to Say et al. (2019) and Daru et al. (2018).

When not considering maternal anaemia as such, it is delightful to notice that smoking among pregnant women has decreased during last 15 years. Räisänen et al. (2014) found more than 11% nulliparous pregnant women to smoke and about every tenth of multiparous. This study showed only less than 9% in both anaemic and non-anaemic groups to smoke daily or occasionally.

7 Conclusions

In this thesis one of the objectives was to assess how maternal anaemia associates with perinatal outcomes. Results showed significant differences in nearly all outcomes assessed between anaemic and non-anaemic group, which proves the hypothesis correct: maternal anaemia does effect on perinatal outcomes and effects are mostly negative. This leads to conclusion, that the prevention of anaemia is important and should be emphasized in antenatal care. The acknowledgment of risk groups and early identification helps the preventative health education in antenatal care, but it also requires constant and updated education of the health personnel.

It should be noted that maternal anaemia has such variety of impacts during pregnancy, but also, the high quality of antenatal care and high standards in hospitalization can compensate the outcomes, like the SGA (small for gestational age) shows. International studies show significances among anaemic group and SGA, but in this study, there were no significant difference between groups. Kozuki et al. (2012) found significancy in SGA only if the anaemia was severe, haemoglobin value being less than 90 g/l.

The prevalence of maternal anaemia shows growing numbers during the study period and the evolvement in total population of pregnant women should be noted. However, in different sub-groups, like different cities Turku and Tampere, there were not seen the same development.

8 Recommendations

For the author´s own interest, the prior embryo transfer was included in adjusted logistic regression analysis as a confounding variable in difference to any other previous studies. In descriptive analysis it was seen, that in anaemic group the prevalence for all fertility-related treatments, ovulation induction, intrauterine insemination and IVF-treatment was significantly higher. This is something that needs further studies: the association between prior-conceiving anaemia and infertility problems and further maternal anaemia, and what could be done by health care professionals to avoid such problems. Fertility awareness among reproductive age women is a challenge, and health care personnel in all fields should support fertility. Anaemia might be one of the issues, but this needs further studies as said.

Beck et al. (2016) found in Canada the groups of women that were less likely to use iron supplementation despite being diagnosed maternal anaemia. Key founding was women who were born outside country. This could be interesting to study also in Finland and to find out how well in our system the immigrant women can obtain the health education given. This could be related to patient´s dietary habits too. And like Morisset et al. (2016) found out, one special group is those who have lower degree in education. All women should have equal information about maternal anaemia and special interest should be shown towards these groups of women.

Maternal anaemia has effects on offspring also in longer term than just perinatal period. This thesis focused only perinatal outcomes, but maternal anaemia´s correlation to further life of children is also widely searched in many countries (e.g., Quesada-Pinedo et al. 2021.) This is one of the suggestions for further studies as prevalence of maternal anaemia has been rising in Finland from 2,4 % (Räisänen et al. 2014) to 3,6 % shown in this study.

Overall, it can be stated, that in antenatal care special attention should be shown towards risk groups to prevent maternal anaemia, and the iron supplementation use should be recommended early to have time to replace the low iron values. Even in Finland the maternal anaemia is a risk for adverse perinatal outcomes and all of them require special care and cause for the family extra burden during childbirth. For further studies the special groups could be studied and the antenatal care personnel´s knowledges and resources could be examined. The theoretical background is strong, and the study of how evidence-based knowledge is finally implemented into practise is missing.

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Figures

Tables

Appendices

Appendix 1: Research table for epidemiological studies of anaemia and pregnancy and adverse perinatal outcomes

1

Reference	Country year	Purpose and aim of the study	Study design	Data and methods	Results
Räisänen et al.	Finland 2014	To study if an association between anaemia and adverse perinatal outcomes differed between nulli- and multiparous women	Retrospective population-based cohort study, singleton births registered to Finnish Medical Birth Register 2006-2010 (n=290662).	Logistic regression analysis separately for nulliparous and multiparous women. Descriptive analysis of background variables which were selected based on literature and bivariable analysis (P < 0,1) Both unadjusted (OR) and adjusted odds ratios (aOR) with 95% confidence intervals were calculated. Pooled analysis to avoid bias.	Prevalence of moderate or severe anaemia was 2,5% in nulliparous and 2,3% in multiparous women. Occurrence of moderate or severe anaemia different by parity which was new founding. In nulliparous women there were no association to adverse perinatal outcomes, but in multiparous the preterm delivery (aOR 1.32 (CI 95% 1.14-1.53)), SGA (aOR 1.27 (1.04-1.55)) and new-born admission to neonatal intensive care (aOR 1.23 (1.10-1.38)) was associated. Also, increase towards major congenital anomalies was shown in multiparous (almost significant).
Jung et al.	Japan 2019	Summarise the evidence for the association between maternal haemoglobin concentrations and maternal or infant outcomes	Systematic literature review and meta-analysis, 117 studies (n=4127430 pregnancies) included using PROSPERO and PRISMA protocols.	Fixed- and random-effects meta-analysis. Variable weighted least squares regression method to assess the pooled dose-response relationship of maternal Hb connection to risk of adverse infant outcomes and maternal outcomes. Stratified analysis (subgroup) according to study designs. Dose-response meta-analysis.	In general: maternal anaemia increased the risk of low birth weight (OR 1.65 (CI 95% 1.45-1.87)), preterm birth (OR 2.11 (1.76-2.53)), perinatal mortality (OR 3.01 (1.92-4.73)), stillbirth (OR 1.95 (1.15-3.31)) and maternal mortality (OR 3.20 (1.16-8.85). Results are pooled by different adverse outcomes by study design, sample size, confounding factors, Hb measure time, country income category and geographic region. Risk for adverse perinatal outcomes increases when Hb level is either lower or higher than recommended.

2

Kemppinen et al.	Finland 2020	Gestational iron deficiency´s effects on pregnancy outcomes and comparison of oral vs. intravenous iron substitution	n= 11545 deliveries compared to n=215 anaemic pregnancies	Tertiary hospital´s deliveries 2016-2018.	Intravenous iron substitute was more effective than oral substitute to increase Hb level but had no significant difference on pregnancy outcomes. Risk for preterm birth was 10,2% in anaemic group comparison to 6,1% in non-anaemic) (p=0.009). Foetal growth restriction risk 1,9% anaemic and 0,3% non-anaemic (p=0,006).
Haider et al.	USA 2013	Summarise the evidence on the associations of maternal anaemia and prenatal iron use with maternal haematological and adverse pregnancy outcomes, in addition to evaluate iron use with pregnancy outcomes in exposure-response relations.	Systematic review and meta-analysis 48 randomised trials and 44 cohort studies, (total n=1869475 women) Effect of intervention on maternal anaemia was assessed in 21 trials.	Data from years 1966-2012. methods used: fixed and random effects models to calculate summary estimates. Subgroup analysis and assessments of publication bias. Mixed effects meta-regression model. Sensitivity analysis. Separate meta-analysis for cohort studies. Statistical methods to evaluate exposure-response relations. Egger and Begg tests.	Studies categorized by high income and low + middle income. Iron dose-response with risk of maternal anaemia, low birth weight and preterm birth. The overall effect of iron in trials: iron use cause 19% reduction in risk of low birth weight, with iron dose up to 66mg/day. Cohort studies: prenatal anaemia significantly increased the preterm birth (OD 1,28 (89% CI 1,12 - 1,47), especially anaemia in first and second trimester. Higher mean Hb concentration in pregnancy linearly increased birth weight in a dose response relation, every 10g/l -> +143g (95% CI 68 – 218g) in birth weight.

3

Vural et al.	Turkey 2016	Investigate the effect of anaemia on perinatal outcomes (preterm delivery and low birth weight) and determinate the correlation between anaemia and perinatal outcomes to iron supplementation during pregnancy.	Retrospective study, n=39587 women. Perinatal outcomes were compared between anaemic and non-anaemic groups.	Data collection 2011-2014, Turkish women deliveries. Perinatal outcomes compared with severity of anaemia, categorized into three; Hb <100g/l, 100-110g/l and >110g/l.	In Turkey the maternal anaemia prevalence was 25,1%. Low birth rate in group where Hb <100 g/l in first and second trimester significantly higher (respectively 13,5%). Preterm birth ratio increased when Hb<100g/l measured in second or third trimester. Average low birth weight and caesarean section rates significantly higher when Hb<100g/l at any time in pregnancy.
Rahman et al.	Japan 2016	To estimate the association between maternal anaemia and pregnancy outcomes in low- and middle-income countries	systematic review (29 studies) and meta-analysis (26 studies)	Risk ratio calculations. Calculation of summary estimates. Publication bias and other biases assessed with Egger-test in addition to trim-and-fill procedures. Calculation of population-attributable fraction (PAF). Pooled and sensitivity analysis. Stratified analyses for each selected adverse pregnancy outcome characteristic estimated by study design, confounding factors, country-income category and geographic region.	Prevalence of maternal anaemia 42,7% (CI 95%, 37% - 48,4%), in South Asia the highest. Significantly higher risk of low birth weight with risk ratio 1,31 (CI 95% 1,13-1,51)), preterm birth RR 1,63 (1,33 – 2,01), perinatal mortality RR 1,51 (1,30 – 1,76) and neonatal mortality RR2,72 (1,19 – 6,25). Overall, 12% of low birth weight, 19% of preterm births and 18% of perinatal mortality attributable to maternal anaemia. Highest anaemia attributable proportion of preterm birth in Pakistan (54%). Mixed results for anaemia and pre-eclampsia.

4

Zhang et al.	China 2009	Maternal anaemia´s connection to preterm birth in different trimesters	Prospective cohort study, singleton live births, n=160700.	Secondary analysis of the data. Risk of preterm birth. multivariable Cox proportional hazards regression models.	Anaemia in first trimester was associated with increased risk for preterm premature rupture of membranes (Hazard ratio 3,3 (95% CI 1,4-7,7)). In comparison to late pregnancy, where anaemia associated with reduced risk for preterm birth.
Kozuki, N., Lee, A.C., & Katz, J.	2012	To study associations between maternal anaemia and SGA outcomes.	Systematic literature review and meta-analysis. Total sample size n= 341823	Categorization the OR value according to the haemoglobin cut-off value. Pooled estimations. A Random effect model used due to the heterogeneity of studies. Three meta-analysis;	Only haemoglobin with cut-off value <90g/l or <80g/l had significancy higher risk associated with SGA and no differences between developed and developing countries.

References:

Electronic

Jung, J., Rahman, M.M., Rahman, M.S., Swe, K.T., Islam, M.R., Rahman, M.O. and Akter, S. (2019), Effects of hemoglobin levels during pregnancy on adverse maternal and infant outcomes: a systematic review and meta-analysis. Annals of the New York Academy of Sciences. 1450: 69-82. Accessed 1.6.2021. https://doi.org/10.1111/nyas.14112

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Appendix 2: The Findata data permit application form

FINDATA

1(1)

REKISTERIN NIMI	Syntymärekisteri
RAJAUKSET	**Kohdejoukko: 2006 – 2020 synnyttäneet (yksisikiöinen raskaus)** Tapaukset ovat ne, joilla on syntymärekisterissä merkintä anemiasta, ja verrokkeja ovat ne, joilla tietoa ei ole.
	Aikaväli, jolta tiedot poimitaan: 1.1.2006 – 31.12.2020
	Muut rajaukset: Poimitaan tiedot kaikista erikoissairaanhoidon käynneistä ja hoitojaksoista sekä tehdyistä toimenpiteistä rajaamatta käyntisyitä tai tehtyä toimenpidettä.
POIMITTAVAT MUUTTUJAT	4: äidin asuinkunta (ASUINKUNTA) 6: äidin siviilisääty (SIVIILISÄÄTY) 7: asuu parisuhteessa (AVOLIITTO) 8: äidin aiemmat raskaudet (AIEMMATRASKAUDET) 8: joista keskenmenoja (spontaaneja) (KESKENMENOJA) 8: joista raskauden keskeytyksiä (KESKEYTYKSIÄ) 8: joista kohdunulkoisia raskauksia (ULKOPUOLISIA) 9: Äidin aiemmat synnytykset yhteensä (AIEMMATSYNNYTYKSET) 12: Äidin paino ja pituus ennen raskautta: 12: paino, kg (APAINO) 12: pituus, cm (APITUUS) 13: Äidin tupakointi raskauden aikana (TUPAKOINTITUNNUS) 14: Raskauteen liittyviä riskitekijöitä ja toimenpiteitä: 14-2: hedelmöityshoito, jossa alkion siirto (ALKIONSIIRTO) 14-3: inseminaatio (INSEMINAATIO) 14-4: munarakkulan kypsytyshoito (KYPSYTYSHOITO) 14-12: sokerirasitus tehty (SOKERI_TEHTY) 14-13: sokerirasitus patologinen (SOKERI_PATOL) 14-14: insuliinihoito aloitettu rask. aikana (INSULIINI_ALOITETTU) 14-15: anemia (Hb <100g/l) (ANEMIA) 15: äidin raskaudenaikaiset sairaudet: (RDIAG1, RDIAG2, RDIAG3, RDIAG4, RDIAG5, RDIAG6, RDIAG7, RDIAG8, RDIAG9, RDIAG10) 19: Paras arvio raskauden kestosta (KESTOVKPV) 22: synnytystapa (SYNNYTYSTAPATUNNUS) 24: muita synnytykseen liittyviä toimenpiteitä: 24-1: käynnistys (KÄYNNISTYS) 24-12: verensiirto äidille synnytyksen yhteydessä (VERENSIIRTO) 25: Raskaus- ja synnytysdiagnooseja: 25-1: etinen istukka (ETINEN) 25-2: istukan ennenaikainen irtoaminen (ISIRTO) 25-3: raskauskouristus (RKOURIS) 26: äidin synnytyksen aikaisia diagnooseja (SDIAG1, SDIAG2, SDIAG3, SDIAG4, SDIAG5, SDIAG6, SDIAG7, SDIAG8, SDIAG9, SDIAG10) 27: lapsen syntymäpäivä (LAPSI_HETUNNUS) –**syntymävuosi riittää!** 29: lapsi syntynyt (SYNTYMATILATUNNUS) 30: sikiöiden lukumäärä (SIKIÖITA) tutkimuksessa vain yksisikiöiset 32: syntymäpaino, g (SYNTYMAPAINO) 37: lapsen hoitotoimenpiteitä 7vrk:n ikään mennessä 37-1: hoito teho- tai valvontaosastolla (VALVONTA) 40: äidin hoitoaika sairaalassa 40-1: äidin sairaalaan tulopäivämäärä (AITI_TUKLOPVM) 40-2: äidin sairaalasta lähtöpäivämäärä (AITI_LAHTOPVM) 41: äidin ikä synnytyshetkellä (AITI_IKA) (numeroimaton) lapsi elossa 7vrk:n iässä (KUOLLEISUUS) (numeroimaton) (TILASTOVUOSI)