Thieme

Diagnosis and Therapy of Iron Deficiency Anemia During Pregnancy: Recommendation of the Austrian Society for Gynecology and Obstetrics (OEGGG)

Diagnostik und Therapie der Eisenmangelanämie in der Schwangerschaft: Empfehlung der Österreichischen Gesellschaft für Gynäkologie und Geburtshilfe (OEGGG)

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ABSTRACT

This overview analyzes the data on the controversial therapy of iron substitution during pregnancy, the diagnosis of iron deficiency anemia and the indication-related therapy, and is the first recommendation issued by the OEGGG on the appropriate therapy. The effects of anemia during pregnancy on postnatal outcomes have been intensively investigated with heterogeneous results. A final scientific conclusion with regards to the "optimal" maternal hemoglobin level is limited by the heterogeneous results of various studies, many of which were conducted in emerging nations (with different

dietary habits and structural differences in the respective healthcare systems). The current literature even suggests that there may be a connection between both decreased and increased maternal serum hemoglobin concentrations and unfavorable short-term and long-term neonatal outcomes. In Austria, 67 percent of pregnant women take pharmacological supplements or use a variety of dietary supplements. Clinically, the prevalence of maternal anemia is often overestimated, leading to overtreatment of pregnant women (iron substitution without a medical indication). To obtain a differential diagnosis, a workup of the indications for treatment should be carried out prior to initiating any form of iron substitution during pregnancy. If treatment is medically indicated, oral iron substitution is usually sufficient. Because of the restricted approval and potential side effects, medical indications for intravenous iron substitution should be limited. Intravenous iron substitution without a prior detailed diagnostic workup is an off-label use and should only be used in very limited cases, and women should be advised accordingly.

ZUSAMMENFASSUNG

Die vorliegende Übersicht und erstmalige Empfehlung soll die Datenlage zur kontrovers diskutierten Therapie der Eisensubstitution während der Schwangerschaft, deren Diagnose und indikationsbezogenen Therapie bewerten. Die Auswirkungen einer Anämie während einer Schwangerschaft auf das postnatale Outcome sind Gegenstand intensiver Forschung mit noch immer widersprüchlichen Erkenntnissen. Eine abschließende wissenschaftliche Bewertung eines „optimalen" maternalen Hämoglobin-Wertes ist durch die unterschiedlichen Studienergebnisse, die überwiegend aus sogenannten Schwellenländern mit spezifischen Ernährungsgewohnheiten und strukturellen Unterschieden in den jeweiligen Gesundheitssystemen stammen, nur eingeschränkt möglich. Der Trend der Datenlage lässt einen Zusammenhang sowohl von erniedrigten als auch erhöhten maternalen Serum-Hämoglobin-Konzentrationen mit einem ungünstigen kurz- und langfristigen neonatalen Outcome als wahrscheinlich erscheinen. In Österreich supplementieren 67 % der Schwangeren pharmakologisch oder nutritiv Eisenprodukte. Die Prävalenz der maternalen Anämie wird dabei klinisch häufig überschätzt und führt konsekutiv zu einer Überbehandlung von Schwangeren (Eisensubstitution ohne Indikation). Vor jeder Eisensubstitution während einer Schwangerschaft sollte daher die Indikationsstellung auch in Hinblick auf die Differenzialdiagnosen abgewogen werden, bei richtiger Indikationsstellung reicht eine orale Eisensubstitution meist aus. Aufgrund der Zulassung und des potenziellen Nebenwirkungsprofils sind die Anforderungen an eine intravenöse Eisensubstitution streng zu stellen. Eine intravenöse Eisensubstitution ohne vorausgegangene vollständige Anämiediagnostik ist als eine Therapie im Off-Label-Use restriktiv zu indizieren und auch als solche aufzuklären.

Introduction

Iron substitution to treat pregnancy-related anemia is one of the most common pharmacological interventions in pregnancy. But the question whether iron substitution during pregnancy is always indicated from a medical standpoint is still unresolved. In Austria alone, 28.1 % of women who take iron supplements start iron therapy before their pregnancy has been clinically confirmed and 46.5 % start iron substitution even before their hemoglobin level has been determined at their prenatal screening [1]. According to the WHO, the prevalence of pregnancy-related anemia in Austria relative to the general population is estimated to be around 15.5 % [2] while the estimated rate for Switzerland is 7 % [3]. The prevalence of anemia varies greatly across the world and depends on ethnic, regional and socioeconomic factors [4 – 6]. Despite widespread iron substitution by pregnant women, the potential therapeutic and preventive benefit of this therapy is still a matter of scientific debate. This overview presents data on the controversially discussed therapy of iron substitution during pregnancy, the diagnosis of iron deficiency anemia and the indication-related therapies. Currently no gynecological professional societies have issued independent recommendations on iron substitution in pregnancy.

Method

The widespread, inconsistent use of iron substitution during pregnancy prompted the authors and the Board of the Austrian Society for Gynecology and Obstetrics to review the evidence on pregnancy-related iron deficiency anemia and the clinical importance of iron substitution and develop a recommendation for the diagnosis and therapy of iron deficiency anemia in pregnancy.

A literature search on clinical neonatal impacts of iron deficiency anemia was carried out in PubMed (key words: pregnancy, anemia, fetal outcome; body of literature reviewed: from 1972 to 07/2021) to find answers to a number of questions on the clinical importance of pregnancy-related iron deficiency anemia and the necessity of iron substitution, and the relevant literature was analyzed.

The recommendation was developed by the lead authors (TF, HH, PK, CF, GB, KMH, CW, HJB) and released for publication by the Board of the Austrian Society for Gynecology and Obstetrics (OEGGG) following a structured process.

Physiological requirement

Physiological changes in blood volume are the leading cause of anemia in pregnancy, followed by iron deficiency anemia as a result of the increased physiological need for iron. Over the course of pregnancy, maternal blood volume increases by up to 30 %, meaning that anemia is initially caused by physiological hemodilution [7 – 9]. The greatest amount of placental and fetal iron is re-

quired in the final trimester of pregnancy; the fetus utilizes maternal iron, reducing maternal erythropoiesis and depleting maternal iron stores [8].

The WHO and the American College of Obstetricians and Gynecologists (ACOG) use time-dependent hemoglobin levels to define anemia in pregnancy [10, 11]:

- 1st trimester: Hb < 11 g/dL
- 2nd trimester: Hb < 10.5 g/dL
- 3rd trimester: Hb < 11 g/dL

Clinical presentation

Depending on the severity and the speed at which iron deficiency develops, typical symptoms of iron deficiency include tiredness, pallor, dizziness, concentration difficulties, increased brittleness of hair and nails, angular cheilitis and decreased hemoglobin (Hb) production. As iron deficiency can affect all cells, some cases may present with exhaustion (e.g., fatigue syndrome), restless legs syndrome, and/or depressive moods [12, 13].

In infants and young children, chronic severe iron deficiency can cause neurological deficits and growth disorders [14, 15]. The availability of iron in maternal blood ensures that iron is delivered through the placenta via transferrin receptors and iron supplies to the fetus are maintained. An initial severe maternal iron deficiency condition can lead to fetal iron deficiency although, to date, studies have not shown clear results. Anemia in the second and third trimester of pregnancy may be caused physiologically by hemodilution, which is why it is important to differentiate this type of anemia from pathological anemia [16]. Severe iron deficiency anemia, which is determined by measuring various iron metabolism parameters, is associated with higher rates of miscarriage, preterm birth and low birthweight [17, 18].

Maternal hemoglobin level and birthweight: "concentration–effect relationship"

Numerous studies have investigated the effects of maternal anemia on the fetus and neonate [19]. The study data are inconsistent and the chosen study methods are often insufficient to make long-term statements. This is because the majority of studies consist of retrospective analyses which did not take numerous contributing factors into account.

One meta-analysis established a direct "concentration–effect relationship" between low maternal Hb levels and low birthweight (< 2500 g, low birthweight [LBW]) [20]. The majority of the studies were from emerging nations and suffered from methodological limitations. Usually, no precise data on birthweight percentiles had been collected. The association between low maternal HB levels and LBW was as follows: Hb ≤ 11 g/dL OR: 1.42; Hb ≤ 10 g/dL OR: 1.49; Hb ≤ 9 g/dL OR: 2.48; Hb ≤ 8 g/dL OR: 2.77; Hb ≤ 7 g/dL OR: 2.97. When Hb levels increased to more than 12 g/dL, the differences were not statistically significant [20]. In principle, higher LBW rates and maternal anemia were present at all prenatal timepoints; however, they were not statistically significant in the second trimester of pregnancy; the highest statistical effect was reported for women presenting with anemia already prior to conception. Higher Hb levels prior to conception and elevated Hb levels in the first trimester of pregnancy were not associated with higher LBW rates.

A "concentration–effect relationship" between maternal Hb levels and preterm births (defined as birth < 37+0 week of gestation) was also found (Hb ≤ 11 g/dL OR: 1.36; Hb ≤ 10 g/dL OR: 1.47; Hb ≤ 9 g/dL OR: 1.73; Hb ≤ 8 g/dL OR: 2.89; Hb ≤ 7 g/dL OR: 3.72). Elevated maternal Hb concentrations of between ≥ 12 g/dL and ≤ 16 g/dL did not have a statistically significant impact on the rate of preterm births [20].

The significance of any statements based on this extensive meta-analysis [20] is limited by the fact that very few studies differentiated between iron deficiency anemia and anemia of other etiologies. Only two studies in the meta-analysis investigated the relationship between iron deficiency anemia and low birthweight (OR: 1.17, CI: 0.95–1.42) and only three studies investigated the association with anemia from other etiologies (OR: 1.43, CI: 0.82–2.50). Two studies reported that the prevalence of SGA (small-for-gestational-age) infants born to pregnant women with iron deficiency anemia was lower (OR: 0.77, CI: 0.68–0.87) compared to infants born to mothers with non-iron deficiency anemia. Four studies reported an increased risk of SGA infants for pregnant women with anemia of other etiology (OR: 1.20, CI: 0.85–1.70). The authors of the meta-analysis were of the opinion that it was not possible to reach a clear conclusion about the impact of iron deficiency anemia on preterm birth rates, as four studies had investigated only patient cohorts with non-iron deficiency anemia (OR: 1.07, CI: 0.68–1.70). There were no studies which distinguished between the etiology of anemia for either intrauterine fetal death or perinatal or neonatal mortality [20].

Cochrane analysis

A Cochrane analysis [21] on daily oral iron substitution during pregnancy came to the conclusion that both high and low Hb levels were associated with negative prenatal and perinatal outcomes. Hb levels of ≤ 10.5 g/dL were especially associated with low birthweight and increased rates of preterm birth. However, the incidence of unfavorable pregnancy outcomes (preterm birth and low birthweight) also increased when maternal Hb levels were > 13 g/dL. A Mexican study was able to show that higher maternal Hb concentrations due to daily oral iron substitution were subsequently associated with an increased risk of low birthweight and higher rates of preterm birth [22].

Effect of maternal hemoglobin level on fetal and neonatal outcomes

Most of the findings on the association between maternal hemoglobin levels and fetal or neonatal outcomes were obtained from retrospective studies, some of which had very large case numbers. A study published in 2000 which investigated a cohort of more than 173 000 pregnant women in 10 American federal states [23] showed that the risk of preterm birth was higher if pregnant women suffered from anemia in the first and second trimester of pregnancy (< 2–3 standard deviations). The odds ratio (OR) for preterm birth (< 37 + 0 week of gestation [GW]) was significantly higher (OR: 1.68) for a standard deviation of < 3. In contrast, the rate of SGA infants (< 10th percentile) born to anemic women was not higher. A high Hb level (> 3 SD) in the first two trimesters was correlated with a higher SGA rate (12th GW: Hb > 14.9 g/dL OR: 1.27; 18th GW: > 14.4 g/dL OR: 1.79) [23]. A Chi-

nese study [24] which investigated 10 430 pregnant women came to different conclusions. The cohort study showed that maternal Hb levels had no impact on the incidence of preterm birth with the following exceptions. The Chinese authors reported that a Hb level < 13.0 g/dL in the first trimester of pregnancy (8.8 ± 2.2 GW) followed by an elevated Hb level (Hb > 13.0 g/dL) in the second trimester (25.8 + < 1.4 GW) correlated with an increase in the preterm birth rate (OR 2.26). Another large Chinese cohort study [25] which analyzed more than 2.7 million pregnant women showed a slight U-shaped association between the distribution of preterm births and cases with either severe anemia (Hb < 7 g/dL OR: 1.19) or significantly elevated Hb levels (Hb ≥ 17 g/dL OR: 1.19). In cases with anemia and Hb levels of 7.0–9.9 g/dL or 10.0–10.9 g/dL, the association with the preterm birth rate was marginal, with an OR of 0.96 and 1.04, respectively. The rate of very early preterm births (< 32 + 0 GW) also showed a slight U-shaped correlation with maternal Hb levels (Hb < 11.0 g/dL and > 15.0 g/dL OR: 1.07 and 1.06, respectively) compared to pregnant women with Hb levels of between 11.0 g/dL and 14.9 g/dL) [25]. In contrast, the data from an extensively randomized, placebo-controlled, Indian study (n = 366; [5]) showed that maternal anemia (Hb < 11.0 g/dL) was correlated with significant rates of preterm birth (RR: 2.67) and low birthweight (< 2500 g, RR: 2.15), which was 166.8 g lower compared to that of infants born to non-anemic mothers.

A Palestinian case-control study [26] investigated the impact of anemia, which was measured using serum Hb concentrations and iron stores (serum ferritin concentrations). The study attempted to exclude biological and socioeconomic factors (age, BMI, parity, number of previous miscarriages, level of education and monthly income) by matching pairs of women. Overall, the duration of pregnancy was slightly shorter for pregnant women with iron deficiency anemia (Hb < 11 g/dL 37.8 ± 1.5 GW; Hb 11.0–12.0 g/dL 38.6 ± 1.4 GW; Hb > 12 g/dL 38.8 ± 1.6 GW; p = 0.012), while the incidence of preterm birth (< 37 + 0 GW) and low birthweight (< 2500 g) did not differ significantly between the three Hb patient cohorts [26]. A recent retrospective, statistically very detailed Chinese cohort study of 11 581 pregnant women came to heterogeneous conclusions [27]). The study found a direct association between maternal anemia and the birthweight of neonates, who were more likely to present with macrosomia or as large-for-gestational-age; there was a reciprocal relationship between preterm birthrates and low birthweight or small-for-gestational-age situations. The study also looked at the weight-dependent relationship between preeclampsia and gestational diabetes and maternal Hb levels in pregnancy [28]. According to the study, the risk of gestational diabetes increased with high serum Hb levels (Hb 13.0–14.9 g/dL OR: 1.27; Hb ≤ 15 g/dL OR: 1.84) in pregnant women with a BMI < 24. The risk of preterm birth increased for maternal anemia of < 11 g/dL (OR: 1.41), while the risk for pregnant women with Hb levels of 13.0–14.9 g/dL or > 15 g/dL decreased (OR: 0.77 and OR: 0.23, respectively). The risk of obese pregnant women with a BMI of ≥ 24 developing gestational diabetes was only demonstrated for Hb levels of 15 g/dL and above (OR: 2.33) [28].

Another prospective Chinese cohort study (163 313 pregnant women; number of intrauterine fetal deaths [IUFD]: 1081; [29]) came to a clinically surprising conclusion. According to their results, maternal anemia of between 9.0–10 g/dL in the third trimester of pregnancy had a protective effect (– 20 %, hazard ratio [HR] 0.89) on the risk of IUFD. A Hb level of more than 12 g/dL was associated with a slightly increased IUFD risk (HR: 1.1). No association was found between maternal anemia and neonatal morbidity. But this was not confirmed by the above-mentioned recent comprehensive meta-analysis [20]. According to the meta-analysis (which included 19 publications), there is a direct association between the IUFD rate and the severity of maternal anemia, with an almost fourfold higher risk when maternal Hb levels are < 7 mg/dL. But because of the quality of the data, it was not possible to draw any conclusions about the etiology of the anemia.

Iron Supplementation

Iron requirements in pregnancy

The physiological need for iron increases during pregnancy as follows [30]:

- fetus 270 mg iron
- placenta 90 mg iron
- erythropoiesis 450 mg iron
- blood loss during birth 150 mg iron
- physiological loss of iron 230 mg

Iron requirements change over the course of pregnancy: the daily requirement in the second trimester of pregnancy is around 5 mg and rises to about 7 mg/day in the third trimester [13]. About 2 months before parturition, iron needs may increase to a maximum of 20–30 mg/day, requiring a constant increase in iron intake which can be met through diet and from reserves [11, 31]. Precise reference values are needed to evaluate iron needs during pregnancy, as levels under 9 g/dL may be associated with higher fetal LBW and higher preterm birth rates and/or maternal cardiovascular disease [17]. If ferritin levels continually decrease in the 2nd trimester and fall under 30 µg/L, oral substitution with 50 mg/day is sufficient to compensate for iron deficiency and iron deficiency anemia [32]. As 5–10 % of pregnant women may not tolerate oral substitution or may be refractory to therapy, intravenous iron administration may be considered, although not in the first trimester. Cases presenting with iron deficiency anemia and a significantly decreased Hb level < 6 g/dL should be given a transfusion of red blood cell concentrates because of its rapid action and higher efficacy [13].

Oral substitution

Based on the above data, the importance of pregnant women avoiding both elevated and decreased Hb levels is clear. For pregnant women, the daily iron requirement of 1 mg increases to a maximum of 20–30 mg/day. For humans, it is easier to meet iron requirements by eating foodstuffs of animal origin rather than plant-based foods. But vegetarians can also meet their iron needs by dietary means if their food is carefully selected and prepared [32]. Many pregnant women additionally increase their iron intake by taking dietary supplements. Dietary supplements are widely used in pregnancy and, with the exception of folic acid and iodine,

are usually unnecessary. For example, each tablet of Femibion, a preparation taken by the majority of pregnant women in Austria during pregnancy, contains 10 or 14 mg iron (Femibion 1 or 2). According to the manufacturer's specifications, this intake already corresponds to 71 or 100 percent of the recommended daily nutrient reference value. Moreover, in Austria 46.5% of pregnant women begin with oral iron "substitution" before the tests for their pregnancy passport have been carried out, and 28.1% start taking supplements even before their pregnancy has been confirmed. There are no data on the diagnostic workup for anemia. In 88.6% of cases, iron substitution is recommended by the treating physician [1]. International recommendations on iron supplementation during pregnancy are very heterogeneous and often influenced by the requirements of different healthcare systems in different countries. Routine iron substitution is not recommended in Great Britain [33]. There are currently no AWMF guidelines which specifically focus on the diagnosis and treatment of anemia during or after pregnancy. A Swiss recommendation [3] advocates carrying out a diagnostic workup for anemia, which includes determining serum Hb and serum ferritin concentrations before initiating iron therapy or substitution. The WHO recommends that all pregnant women should routinely receive iron substitution [34]. But it is important to be aware that this WHO recommendation is aimed at women in developing and emerging countries where diagnostic options are limited (e.g., no Hb screening during pregnancy), women often have nutritional deficits, and the countries' healthcare systems are unable to issue their own adapted recommendations.

Peroral treatment with an iron preparation is indicated if dietary iron intake or iron-containing nutritional supplements (usually the initial form of treatment) are insufficient and the pregnant woman is diagnosed with iron deficiency requiring treatment. Optimally, such a diagnosis would be based on a simultaneous determination of serum Hb and serum ferritin concentrations, transferrin saturation and CRP. Iron substitution based solely on the measurement of Hb levels is not medically indicated as the workup is incomplete and could lead to unnecessary iron substitution in pregnant women with sufficient iron stores. As mentioned above, high serum Hb concentrations in pregnancy have been found to have a negative impact on fetuses and pregnant women, and excessive iron substitution based on incorrect medical indications should therefore be avoided.

It is not clear whether pregnant women with depleted iron stores (decreased serum ferritin concentrations) and *("barely")* normal Hb levels would also benefit from treatment. Some publications have recommended that these women should also receive iron substitution [3].

Peroral administration is the treatment of choice for women requiring iron substitution for mild to moderate anemia. Fewer than 10% of pregnant women in Austria suffer from iron deficiency anemia [1]. Commonly prescribed medications contain iron dosages which are higher than the daily requirements (e.g., Ferretab contains 304.2 mg ferrous fumarate which corresponds to 100 mg bivalent iron; Ferro Sanol Duodenal is ferrous mono-preparation containing 100 mg; Ratiopharm iron tablets 100 mg contain iron [II] sulfate 1 H_2O etc.).

Most preparations are well tolerated by the majority of women, although side effects have been reported for a number of patients and in some cases, these have led to treatment being discontinued.

Intravenous iron substitution

Rare cases with severe anemia which require a fast therapeutic response will need transfusions of red blood cell concentrates, although other alternatives are increasingly preferred. The number of publications and the marketing of intravenously administered iron preparations has increased in recent years. High concentrations of intravenous iron (e.g., Ferinject 1000 mg iron) are effective within 4 weeks of starting treatment [35] and the product characteristics state that treatment is safe for fetuses from the 2nd trimester of pregnancy [36].

Indications for treatment and approval specifications

The conditions of approval state that intravenous treatment must be limited to situations when oral preparations are ineffective or individual cases for whom oral iron substitution is contraindicated. The patient's iron deficiency must be confirmed by laboratory tests (see the summary of product characteristics). Initiating treatment based solely on the patient's serum Hb levels without a more detailed diagnostic workup to investigate existing iron stores (or at least the serum ferritin stores) is forensically problematic but quite common in gynecology. This type of therapy is an off-label use which has higher requirements with regard to counselling patients and documentation. It is important to be aware that approval for intravenous iron administration is restricted as severe side effects can occur in rare cases, and the correct medical indications could be important with regard to legal liability in such cases. The Austrian Federal Office for Safety in Healthcare [37] published a statement in 2014 on the use of intravenously administered iron which emphasized *"that all intravenous iron products can trigger serious and possibly fatal hypersensitivity reactions. Such reactions can even occur if a previous administration was tolerated (including a negative test dose). According to present knowledge, the benefit of using intravenous iron products outweighs the risks if the recommendations* (of the Federal Office for Safety in Healthcare) *are followed"* [37]. The European Medicines Agency has come to similar conclusions [38].

Despite the restricted medical indications and the warnings by the Federal Office for Safety in Healthcare and the European statement, studies carried out in recent years have shown that intravenously administered iron is generally well tolerated. A recent meta-analysis [39] (prepartum therapy: n = 11; postpartum therapy: n = 8) confirmed the good tolerability of intravenously administered iron compared to orally substituted iron, with the latter more commonly associated with side effects, primarily gastrointestinal symptoms such as nausea, vomiting, dyspepsia, diarrhea and constipation. The meta-analysis did not report any serious complications following treatment with intravenous iron [37]. However, extravasates resulting in iron-related hyperpigmentation of the skin which can persist for longer periods are a real risk which patients must be informed about. Intravenous iron substitution to compensate for iron deficiency confirmed by laboratory

tests is more effective than oral substitution [39]. The findings of an American meta-analysis carried out in the same year 2019 were similar, with intravenous iron administration found to be more effective and to have fewer side effects compared to peroral iron substitution [40, 41].

Conclusion

The effects of anemia during pregnancy on the immediate and long-term postnatal health of infants is currently being investigated. The current data is heterogeneous and largely based on retrospective studies carried out in developing and emerging countries, and the quality of the study design of many of these studies is inadequate [42]. In a recent editorial, the Australian Research Fellow Antonia Shand [42] clearly stated that there is still no optimal established management strategy for the prevention, screening and treatment of pregnancy-associated iron deficiency anemia. In Shand's view, it is still not clear, based on the existing data, whether improvements in therapy-associated hematology results [35] actually lead to better clinical outcomes. The recommendation of the U. S. Preventive Services Task Force [43] bears out this critical view by highlighting the contradictory results reported by often poorly designed studies. According to this American recommendation, the evidence that clinically unremarkable pregnant women should be screened for iron deficiency anemia to achieve better maternal and neonatal outcomes is insufficient. These international reports together with the clinically inconsistent approach used in Austria and other German-speaking countries in Europe prompted the OEGGG to publish their own recommendation. Similar to Antonia Shand and the U. S. Preventive Services Task Force, the OEGGG recommends carrying out further studies to evaluate the key issue about the correlation between fetal, neonatal and maternal outcomes and maternal iron deficiency.

Overall, the current data appear to indicate there is probably a connection between maternal anemia or elevated maternal hemoglobin concentrations and unfavorable short-term and long-term neonatal outcomes.

In recent decades, pregnant women have routinely received oral iron substitution in clinical practice, even though the majority of cases did not have a prior diagnosis of anemia or medical indications of anemia. The incidence of pregnancy-related anemia in Austria is often overestimated and is probably less than 10%. The WHO assumes a slightly higher incidence of 15.5%. To investigate for anemia and evaluate whether treatment, for example iron substitution, is medically indicated, a differential diagnostic workup of the cause of anemia based on laboratory tests must be carried out. In individual cases, intravenous iron substitution may be indicated prenatally or postpartum. It should be noted, however, that approval for treatment consisting of intravenously administered iron is limited to iron deficiency conditions *"when oral iron preparations are ineffective or cannot be administered. The diagnosis of iron deficiency anemia must be confirmed by laboratory tests"* [36]. This means that intravenous treatment of anemia which was diagnosed solely based on low hemoglobin levels is not indicated as nothing is known about the patient's in-vivo iron stores. It is possible that in the past, widespread inappropriate iron substitution without a proper diagnostic workup was promoted by aggressive industry-led marketing strategies and publications linked to "conflicts of interest". Nevertheless, there is a high probability that in cases with pregnancy-related iron deficiency anemia, *medically indicated* substitution with iron prepartum has a beneficial impact on short-term and long-term neonatal outcomes. Medically indicated postpartum maternal iron substitution following confirmation of iron deficiency anemia can positively affect convalescence.

- Both maternal anemia and elevated maternal Hb concentrations in pregnancy appear to be associated with unfavorable neonatal outcomes (preterm birth, small-for-gestational-age infants).
- The prevalence of maternal anemia in Central Europe is clinically overestimated and often leads to overtreatment of pregnant women (for whom iron substitution is not medically indicated).
- A differential diagnostic workup to investigate whether anemia is present must be carried out before considering any form of iron substitution during pregnancy and must include the determination of hemoglobin concentrations and ferritin levels.
- Because of the potential side effects and restricted approval, the requirements for intravenous iron substitution are very circumscribed. Intravenous iron substitution without a prior complete diagnostic workup for anemia or in the absence of medical indications is an off-label use and must be recorded as such and the patient must be informed of this.

Conflict of Interest

The authors declare that they have no conflict of interest.

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