REVIEW

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Current concepts in preoperative anemia management in obstetrics

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Purpose of review
The purpose of this article is to provide an overview of currently recommended treatment approaches for anemia during pregnancy, with a special focus on iron deficiency and iron deficiency anemia (IDA).

Recent findings
As consistent patient blood management (PBM) guidelines in obstetrics are still lacking, recommendations regarding the timing of anemia screening and the treatment recommendations for iron deficiency and IDA during pregnancy are still controversial. Based on increasing evidence, early screening for anemia and iron deficiency should be recommended at the beginning of each pregnancy. To reduce maternal and fetal burden, any iron deficiency, even without anemia, should be treated as early as possible during pregnancy. While oral iron supplements administered every other day are the standard treatment in the first trimester, the use of intravenous iron supplements is increasingly suggested from the second trimester onwards.

Summary
The treatment of anemia, and more specifically iron deficiency anemia during pregnancy, holds many possibilities for improvement. The fact that the period of risk is known well in advance and thus there is a long optimization phase is per se an ideal prerequisite for the best possible therapy of treatable causes of anemia. Standardization of recommendations and guidelines for screening and treatment of IDA in obstetrics is required for the future. In any case, a multidisciplinary consent is the precondition for a successfully implementation of anemia management in obstetrics to establish an approved algorithm easily enabling detection and treatment of IDA during pregnancy.

Keywords
iron deficiency anemia, obstetrics, patient blood management, peripartum hemorrhage, pregnancy

INTRODUCTION

Nearly all modern concepts in preoperative anemia management in obstetrics based on patient blood management (PBM) strategies, aim to maintain hemoglobin concentration, optimize hemostasis, minimize blood loss, and limit blood transfusions during delivery to improve maternal and fetal outcomes. PBM is primarily described as a patient-focused, evidence-based, and multidisciplinary approach to optimize safety and care of patients who are at risk to require blood transfusion during surgical interventions and has recently been implemented in several medical areas according to the World Health Organization (WHO) recommendation in 2010 [1]. Recent studies demonstrated that adhering to a PBM algorithm significantly minimizes perioperative bleeding, reduces the requirement of blood transfusion, decreases perioperative morbidity, mortality, as well as length of stay, and costs [2]. However, implementation of PBM strategies in obstetrics is challenging and thus is still underrepresented in many hospitals, even though the high prevalence of iron deficiency and iron deficiency anemia (IDA) during pregnancy as

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KEY POINTS

- As consistent patient blood management (PBM) guidelines in obstetrics are still lacking, standardization of recommendations for screening and treatment of iron deficiency anemia (IDA) in obstetrics is required.
- Early screening for anemia and iron deficiency at the beginning of each pregnancy is strongly recommended so that any iron deficiency, even without anemia, can be treated as early as possible during pregnancy.
- As oral iron doses $\geq$ 60 mg/day trigger a rise in hepcidin levels that subsides after 48 h, associated with lowered fractional iron absorption on the following day, oral iron doses $\geq$ 60 mg should be given every other day.
- Administration of intravenous iron in IDA during pregnancy is considered superior to oral supplementation in terms of efficacy and duration of therapy and should therefore be used preferentially from the second trimester onwards.
- A multidisciplinary consent is the precondition for a successfully implementation of PBM in obstetrics to establish an approved algorithm to easily enable detection and treatment of IDA during pregnancy.

well as the risk of peripartum hemorrhage (PPH) for every woman indicate that implementation of PBM in obstetrics is promising. Especially the long period of time between a possible detection of iron deficiency or IDA during pregnancy care and a potential blood loss at delivery represents an almost perfect prerequisite for the implementation of the first pillar of PBM in obstetrics, the detection and correction of antenatal anemia [3].

According to PBM strategies in surgical procedures with an estimated blood loss of >500 ml, PBM should be realized for any intervention where there is a probability of excessive bleeding, including vaginal delivery or nonelective caesarean section [4▪]. A multidisciplinary consensus is the precondition for a successfully implementation of PBM in obstetrics, involving midwives, resident gynecologists, obstetricians, anesthetists, and hematologists to establish an approved algorithm to easily enable detection and treatment of iron deficiency and IDA during pregnancy.

During the past years, several national and international guidelines for PPH management and PBM programs in obstetrics have been published [5,6]. However, comparing these guidelines, substantive inconsistencies could be observed [6]. Therefore, many obstetrical departments are still in need of reliable PBM recommendations for their daily practice that fit to their individual patient flow and current process of care [3].

PERIPARTUM HEMORRHAGE

Although mortality rates from PPH have significantly declined in the developed countries over the last years [7], PPH remains one of the leading causes of maternal mortality worldwide, with an incidence of more than 15% [8] and contributes to maternal mortality ranging from 16% in developed regions to more than 30% in some African areas [9]. Usually, PPH is defined as a blood loss of >500 ml within 24 h during vaginal delivery or of >1000 ml during caesarean section [8,10,11]. However, the definition of PPH has recently been updated by the Committee on Practice Bulletins-Obstetrics defining PPH as a blood loss leading to signs of hypovolemia regardless of the method of delivery [12]. Apart from the measured or estimated blood loss, other signs (indicating shock) should also be considered in making the diagnosis [11].

Irrespective of which definition is used, severe PPH increases the risk of the need for red blood cell transfusions associated with potential complications for the mother [5,8,13▪]. This risk is increased in patients suffering from preexisting anemia.

Considering merely risk factors for PPH with an odds ratio >2, the Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis (NATA) recently published the following list to be considered when assessing patients [5]:

- multiple pregnancies (odds ratio [OR] 2.3-4.7);
- a history of PPH (OR 3.3);
- pregnancy-induced hypertension (OR 1.9-2.5);
- chorioamnionitis (OR 2.5);
- episiotomy (OR 1.4–2.2);
- prelabor caesarean section (OR 1.3-2.3);
- caesarean section during labor (OR 1.7–3.6);
- macrosomia (OR 1.7–3.5);
- operative vaginal delivery (OR 2.3).

In addition to the above, uterine atony, placental anomalies, preeclampsia, coagulopathies, and a preexisting anemia have been described as the most common obstetrical risk factors for PPH [3,8,10,13▪,14]. It is of utmost importance, however, to take into consideration that PPH can occur during every pregnancy and the majority of women developing a PPH have none of the described risk factors [3,8]. Even using a scoring system to identify women at risk often fails in daily practice due to their lack of reliability, thus there is need for further improvement [10,13▪]. In recent years, artificial intelligences and machine learning has been applied to perform an unbiased approach to hemorrhage risk prediction, which eventually may be superior to human risk assessment and represents an area for future research [15▪]. These facts emphasize the importance of a PBM algorithm in obstetrics, since a

preexisting anemia, one of the commonest risk factors for PPH associated with maternal and fetal morbidities, can easily be assessed and corrected during pregnancy care.

IRON DEFICIENCY AND IRON DEFICIENCY ANEMIA DURING PREGNANCY

According to the WHO, the prevalence of anemia in the general population is about 25% worldwide, whereas significantly less people are affected in industrialized countries. In pregnant women, the prevalence of anemia is estimated to be about 42% worldwide and still around 25% in Europe [16]. In contrast to an Hb-threshold of 12 g/dl in nonpregnant women, anemia in pregnant women has been defined by the WHO as Hb-values <11 g/dl irrespective of the gestational age. In contrast to this definition, the Centers for Disease Control and Prevention (CDC) define anemia of pregnancy as Hb <11 g/dl during the first and third trimesters, and Hb <10.5 g/dl in the second trimester [17–19]. This definition relates to the recognition that the Hb-value is reduced by 0.5 g/dl between the third and sixth months of pregnancy [3]. However, these limits are based only on population-based distributions of Hb values and do not indicate whether it would not be more appropriate to treat anemia before it occurs in the presence of iron deficiency. After all, anemia is only a consequence of iron deficiency that usually develops late.

Globally, iron deficiency is the most common micronutrient deficiency and accordingly anemia during pregnancy is most commonly caused by iron deficiency [20▪▪]. Although the prevalence of isolated iron deficiency is unknown and still being researched, the results of recently published studies indicate that 42% of women in the first trimester had isolated iron deficiency [21] and even 75% of women had iron deficiency or IDA by the third trimester [22]. In general, iron deficiency, not only during pregnancy, remains underdiagnosed, understudied, and undertreated, in spite of its high prevalence and the associated negative effects on both mother and fetus [23]. Iron deficiency and IDA during pregnancy are known to increase maternal morbidity and mortality (Table 1). Maternal IDA is associated with preterm labor, placental abruption, preeclampsia, increased risk of infection, additional cardiovascular stress, fatigue, reduced physical and mental performance, headache, dizziness, prolonged hospitalization, reduced milk production, increased transfusion rates in PPH, increased risk of postpartum depression and even maternal death [20▪▪,24]. Fetal complications include a higher rate of premature birth, low birth weight, fetal distress, intrauterine growth retardation, unfavorable impact on placental development, memory disorders, intellectual disability, autism and reduced fetal iron stores [24,25]. According to Georgieff, newborns with iron deficiency have compromised recognition memory, slower speed of processing and poorer bonding that persists despite postnatal iron repletion [25]. Reduced concentration, cognition, and motor function are still detectable 25 years after delivery in children born with iron deficiency, compared to those born with sufficient iron stores [26]. Although there is growing evidence that fetal iron deficiency can affect the growth and function of multiple major organ systems, particularly the heart, muscles, gastrointestinal tract and the brain [20▪▪], only the SGGG (Swiss Society of Gynaecologist and Obstetrics) guideline recommends routine screening for iron deficiency for nonanemic first trimester women during antenatal care [27▪▪]. To reduce maternal complications caused by iron deficiency and IDA and to ensure the safety of fetal development, especially neurodevelopment during late gestation, early screening for anemia and iron deficiency at the beginning of each pregnancy should be strongly recommended.

Table 1. Maternal and fetal risks associated with iron deficiency and IDA [20▪▪,24,25]

Maternal risks	Neonatal risks
• Preterm labor • Placental abruption • Preeclampsia • Increased risk of infection • Additional cardiovascular stress • Fatigue, headache, dizziness • Reduced mental performance • Prolonged hospitalization • Reduced milk production, • Increased transfusion rates in PPH • Increased risk of postpartum depression • Maternal death	• Higher rate of premature birth • Low birth weight • Fetal distress • Intrauterine growth retardation • Unfavorable impact on placental development • Reduced fetal iron stores • Memory disorders • Autism • Intellectual disability

IRON METABOLISM DURING PREGNANCY

The so-called *physiological anemia of pregnancy* is hypothesized to be an adaptive process serving the purpose to increase placental blood flow by a reduced maternal blood viscosity and to facilitate the oxygen and nutrient supplies to the fetus by increasing the erythrocyte mass. From the sixth week of pregnancy, the plasma volume increases disproportionately compared to the erythrocyte

mass reaching a maximum around the 24th week of pregnancy. At this time, the plasma volume of the pregnant woman is about 40–50% higher than at the beginning of pregnancy, whereas the erythrocyte mass only increases by 15–25%, which explains the drop in Hb-values due to the dilutional effect [28].

Increased erythropoiesis is the main reason for increased iron requirements and is estimated at 500 mg during pregnancy. Approximately 350 mg of iron is required for fetal and placental development and 250 mg are associated with blood loss at delivery, which results in an extra maternal iron requirement of approximately 1 g over the entire course of pregnancy [20▪▪,28]. The iron requirement of pregnant women depends on the gestational age and increases from 0.8 mg/day in early pregnancy to 7.5 mg/day in late pregnancy, so that an average iron requirement of 4.4 mg/day is assumed during pregnancy [28]. In industrialized countries, a balanced diet contains about 12–18 mg of iron per day. However, to meet the increased iron requirement, the recommended daily intake of iron during pregnancy is about 27 mg, considering, that the proportion of iron absorbed is only 10–15% of elemental iron [20▪▪]. Preexisting iron deficiency often leads to IDA during pregnancy, even in developed countries, suggesting that physiological adaptations are often inadequate to meet increased demands and iron intake is often below nutritional requirements. IDA in pregnancy, if undiagnosed and untreated, can have significant effects on maternal and fetal health.

SCREENING RECOMMENDATIONS

To reduce the possible negative effects of iron deficiency and IDA, several international guidelines suggest adjusted screening in pregnant women. Considering that the incidence of anemia and iron deficiency is associated with geographic and ethnic factors, different screening methods are recommended in different guidelines worldwide. This applies not only to the selection of the laboratory parameters to be determined, but also to their thresholds and the timing of screening [29▪]. The recommendations of some associations on screening and therapy for iron deficiency and IDA during pregnancy are summarized in Table 2. Noticeably, not all countries routinely recommend anemia diagnosis at the beginning of pregnancy, and only professional societies in Switzerland and Australia suggest to screen for iron deficiency.

Serum ferritin, as a marker of reticuloendothelial iron stores, and transferrin saturation (TSAT) being below the normal range in the first trimester was able to detect women who subsequently had anemia predelivery, with ferritin being most discriminatory. Both were superior to hemoglobin concentration [35]. A recent systematic review of serum ferritin thresholds for iron deficiency in pregnancy reported that most studies used ferritin values of 12–15 μg/l but that thresholds ranged as high as 30 μg/l, thus further evaluation and investigations are needed to hopefully be able to standardize recommendations in the future [36]. As lower ferritin thresholds are associated with significantly decreased sensitivity for iron deficiency with a minimal increase in sensitivity, and serum ferritin <30 μg/l indicates that there is a 90% probability that iron stores are depleted [24], a threshold of < 30 μg/l seems to represent a reasonable threshold to detect iron deficiency during pregnancy. Although low serum ferritin always indicates iron

Table 2. Screening and therapy for iron deficiency and IDA during pregnancy according to different international guidelines (according to Helmer [29▪])

Recommendations	WHO [30]	NICE [31] UK	SGGG [27▪▪] Switzerland	DGEM [32] Germany	NBA [33] Australia	Health Canada [34]
1. Trimester	–	CBC	CBC + ferritin	–	CBC + ferritin (women at risk)	–
2. Trimester		CBC (28. WOP)	Hb			
3. Trimester		–	Hb			
Iron replacement						
prophylactic	30–60 mg/day	No	No	No	No	16–20 mg/day
Therapeutic	30–60 mg/day	Yes	Yes	Yes	Yes	Yes
Folate replacement						
Before pregnancy	400 μg/day	400 μg/day	400 μg/day	400 μg/day up to the 12th WOP	–	400 μg/day
During pregnancy	400 μg/day	400 μg/day up to the 12th WOP	400 μg/day up to the 12th WOP	800 μg/day up to the 12th WOP		400 μg/day

CBC, complete blood count; Hb, hemoglobin; WOP, week of pregnancy.

deficiency, serum ferritin is an acute-phase reactant that may be elevated out of proportion to iron stores due to infection or inflammation. Although inflammatory markers such as C-reactive protein can be helpful in this case, if iron deficiency is assumed despite normal or elevated ferritin levels, the diagnosis can be made using additional parameters of iron metabolism.

Both a decreased transferrin saturation (TSAT < 15–20%) and an elevated serum soluble transferrin receptor (sTfR) concentration correlate with other indicators of iron deficiency in pregnancy and may indicate iron deficiency in patients with normal ferritin concentrations who are clinically suspected of having iron deficiency [28]. Although TSAT may be reduced in inflammatory disease, sTfR is not affected by an infection [37].

Additional parameters of iron metabolism are promising but not yet widely available and not in use for routine diagnosis of iron-deficiency anemia. For example, elevated values of zinc protoporphyrin can reliably indicate iron deficiency in more complex patients. Further, reticulocyte parameters including reticulocyte hemoglobin equivalent (Ret-He) and immature reticulocyte fraction (IRF) are newly recognized hematological parameters that are being used for diagnosis and follow-up of anemic patients. Although these parameters can be valuable and helpful in difficult cases, the determination of the Hb value, the percentage of transferrin saturation and the serum ferritin are sufficient to assess the iron status in the majority of otherwise healthy young pregnant women [17].

Another reason for anemia during pregnancy is folate deficiency, however, due to the widespread supplementation for the prophylaxis of neural tube defects, the manifestation of anemia caused by folate deficiency during pregnancy is rare [29▪]. If there is evidence of hyperchromic anemia, a Vit B12 deficiency should be ruled out.

If the proven PBM concept for major elective surgery is applied to anemia screening in pregnant women, anemia diagnostics with iron status should be recommended at the beginning of every pregnancy. As consistent guidelines in obstetrics are still lacking, a simple algorithm that is easy to implement should be developed in consent with the obstetricians to ensure the safe care of mother and fetus in daily practice (Fig. 1). The determination of Hb, serum ferritin and TSAT is inexpensive and should be sufficient to diagnose iron deficiency or IDA in most pregnant women. In addition, it should

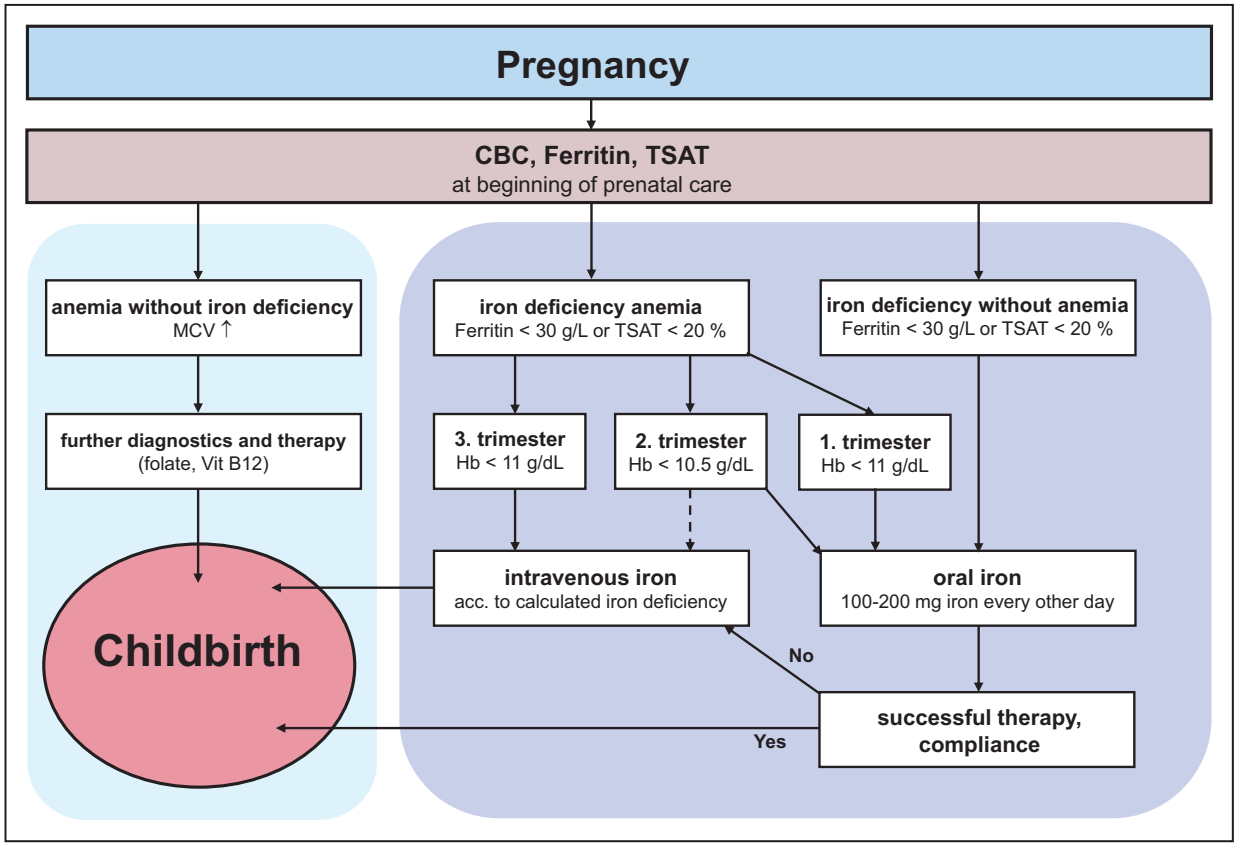

FIGURE 1. Proposed algorithm for diagnosing and treating iron deficiency anemia in pregnancy (modified according to Helmer [29▪]). CBC, complete blood count; TSAT, transferrin saturation; Hb, hemoglobin; MCV, mean corpuscular volume.

be recommended to check these values at the beginning of each trimester and immediately before delivery. For patients at risk, e.g. vegans, patients with a history of abnormal bleeding, women with multiple pregnancies, very young mothers and if the last pregnancy was less than a year ago, Jehovah's Witnesses, or for patients with an anemia of unclear cause, further laboratory parameters should be determined during the screening examination [29▪]. Nevertheless, the limit values and intervention thresholds given can only provide guidance and should be supplemented by individual considerations. If in the third trimester a considerable drop in hemoglobin level is detected even hemoglobin levels >11 g/dl may justify i.v. iron supplementation to avoid a further drop in the subsequent weeks until the period at risk during birth.

TREATMENT OF IRON DEFICIENCY AND IRON DEFICIENCY ANEMIA DURING PREGNANCY

While the guidelines of some national professional societies such as the American College of Obstetricians and Gynecologists (ACOG) and the CDC, but also the WHO, recommend the prophylactic administration of oral iron during every pregnancy [20▪▪], most guidelines recommend against it. The reasons against prophylactic administration during each pregnancy are the relatively high prevalence of hemochromatosis in some industrialized countries [29▪] and the increased risk of infection with iron-dependent microorganisms and parasites, including malaria, in several developing countries. However, iron supplementation is considered to be at low risk and a daily iron supplement of 65 mg of elemental iron is usually sufficient to prevent iron deficiency during pregnancy [28].

Any iron deficiency, even without anemia, should be treated during pregnancy, with oral iron supplementation in the first trimesters as the standard treatment. The recommendations for oral iron supplementation vary from 60 to 200 mg/day of elemental iron, given once to three times daily. Unfortunately, up to 70% of women experience significant gastrointestinal adverse effects such as nausea, constipation, diarrhea, indigestion or metallic taste, which prevent compliance with treatment [38]. Although these complaints do not necessarily seem to be dose-dependent, the results of recently published studies demonstrate that oral iron doses ≥60 mg/day trigger a rise in hepcidin levels that subsides after 48 h, and are associated with lowered fractional iron absorption on the following day. Therefore, to maximize fractional iron absorption, and to reduce side effects to enhance compliance, oral doses ≥60 mg should be given every other day [39,40]. As the SGGG considers iron doses < 100 mg/day ineffective for isolated iron deficiency [24], the recommended two-day iron dose for iron deficiency and IDA should not be <100 mg. This dosing seems to be very low, especially if a severe IDA is present. In this case, twice the daily target iron dose may be given every other day, but it must be taken into account that fractional iron absorption decreases considerably with increasing iron doses and unabsorbed luminal iron likely has adverse effects on the gut. [39]. Currently however, oral iron represents the only approved option for iron supplementation during the first trimester of pregnancy, and the administration of intravenous iron remains restricted to the second and third trimesters due to lack of safety data in early pregnancy.

Recent studies have shown that parenteral iron administration is superior to oral therapy in terms of efficacy and duration of therapy for IDA in pregnancy [41]. There are a number of intravenous iron preparations with different dosing regimens, the latest of which allow the use of high doses in a single administration. Due to the ease of use and associated patient satisfaction, single-dose infusions should be used nowadays, which require only one patient visit and are therefore more cost-effective than older formulations [20▪▪]. Iron dextran preparations are no longer recommended because of the increased risk of anaphylactic reactions compared to the newer intravenous iron preparations [29▪], even though more recent data has shown a similar safety profile of low molecular weight iron dextran to other common products [20▪▪], but still requires a test dose. Both, ferric carboxymaltose and iron isomaltoside are based on carbohydrates with reduced immunogenic properties [17] and should be currently the treatment options of first choice. The higher rate of hypophosphatemia associated with ferric carboxymaltose administration appears to be short-lived in pregnant individuals (usually receiving only a single intravenous infusion) if it occurs [20▪▪,42]. On the other hand, a potential advantage of ferric carboxymaltose can be seen with a lower risk for hypersensitivity reactions compared with iron isomaltoside [43].

So far, intravenous iron has been recommended if oral iron preparations are not tolerated due to gastrointestinal side effects, Hb-values do not rise sufficiently due to intestinal absorption disorders or poor compliance, severe anemia (Hb < 9 g/dL) is present, or if rapid anemia treatment is required due to advanced gestational age [3]. With the advent of new intravenous iron formulations that allow complete replacement dosing in just 15–60 min associated with more favorable safety profiles, recent

recommendations place a higher priority for the use of intravenous iron as a treatment for iron deficiency during pregnancy [17,20▪▪,26]. These recommendations include treating iron deficiency and IDA with intravenous iron as early as possible in pregnancy. Accordingly, all pregnant women with an iron deficiency in the second trimester who have Hb-values <10.5 g/dl, and all women in the third trimester could be treated with intravenous iron. Administration of 1000 mg ferric carboxymaltose in the second or third trimester of pregnancy maintains iron stores more consistently and reduces the need for repeat infusion or subsequent monitoring [44▪].

CONCLUSION

PBM strategies in obstetrics are still underrepresented, although the high prevalence of iron deficiency and IDA during pregnancy as well as the risk of PPH for every woman indicate that implementation of PBM in obstetrics might be promising. As most of the available PBM-guidelines in obstetrics are inconsistent, the timing of anemia screening and the thresholds for anemia and iron diagnostics during pregnancy should be standardized and performed on a regular basis. To reduce maternal complications caused by iron deficiency and IDA and to ensure the safety of fetal development, early screening for iron deficiency at the beginning of each pregnancy should be strongly recommended. Any iron deficiency, even without anemia, should be treated during pregnancy, with oral iron supplements given every other day being the standard treatment in the first trimester. With the advent of new intravenous iron formulations associated with more favorable safety profiles, it has recently been recommended that iron deficiency and IDA should be treated with intravenous iron as early as possible in pregnancy. A multidisciplinary consent – at least on a departmental level – is the precondition for a successfully implementation of PBM in obstetrics to establish an approved algorithm to easily enable detection and treatment of iron deficiency and IDA during pregnancy.

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A single 1000 mg dose of intravenous iron represents an efficient and effective method to manage iron deficiency and IDA clinically in pregnancy.