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Patient blood management in obstetrics: management of anaemia and haematinic deficiencies in pregnancy and in the post-partum period: NATA consensus statement

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INTRODUCTION

Patient blood management (PBM) is the timely application of evidence-informed medical and surgical concepts designed to maintain haemoglobin concentration, optimise haemostasis and minimise blood loss in an effort to improve patient outcomes. The aim of this consensus statement is to provide recommendations on the management of anaemia and haematinic deficiencies in pregnancy and in the post-partum period as part of PBM in obstetrics. A multidisciplinary panel of physicians with expertise in obstetrics, anaesthesia, haematology, policymaking and epidemiology was convened by the Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis (NATA) in collaboration with the International Federation of Gynaecology and Obstetrics (FIGO) and the European Board and College of Obstetrics and Gynaecology (EBCOG). Members of the task force assessed the quantity, quality and consistency of the published evidence and formulated recommendations using the system developed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group. The recommendations in this consensus statement are intended for use by clinical practitioners managing the perinatal care of women in all settings and by policymakers in charge of decision making for the update of clinical practice in health-care establishments. They need to be tailored for application in individual patients or any population after consideration of the values and preferences of both health-care providers and patients, as well as equity issues; explicit assessment of harms and benefits of each recommendation; feasibility including resources, capacity and equipment; and implementability.

A multidisciplinary consensus statement developed by the Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis (NATA) in collaboration with the International Federation of Gynaecology and Obstetrics (FIGO) and the European Board and College of Obstetrics and Gynaecology (EBCOG).

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SUMMARY OF RECOMMENDATIONS

Anaemia in pregnancy

Detection and classification

1. We recommend that a full blood count (FBC) be obtained to screen for anaemia at booking and at 28 weeks, as well as at any time during pregnancy if symptoms of anaemia are present (1A).
2. In a woman with microcytic or normocytic anaemia, iron deficiency (ID) should be confirmed by a trial of oral iron (unless she is known to have a haemoglobinopathy) or a serum ferritin measurement (1B).

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3. In the absence of an haemoglobin (Hb) increment in response to a trial of oral iron conducted correctly, we recommend the further evaluation of iron status by checking serum ferritin and considering whether additional laboratory testing is needed (1C).
4. In anaemic women of Mediterranean, Middle and Far East and African origin, we recommend confirming the presence or absence of a haemoglobinopathy either by selective (based on a family of origin questionnaire) or universal screening for haemoglobinopathies depending on regional demographics (1C).
5. Anaemic women with a known haemoglobinopathy should have their serum ferritin checked and should only be offered oral iron therapy if their serum ferritin level is $<30\ ng\ mL^{-1}$ (1B).

Prevention

6. In areas with a high prevalence of anaemia in pregnancy, we recommend daily oral iron (30–60 mg) and folic acid (400 μg) supplementation as part of routine antenatal care to reduce the risk of maternal anaemia and ID and infant low birthweight (1B).
7. In areas with a low prevalence of anaemia in pregnancy, non-anaemic women identified to be at an increased risk of ID should have their serum ferritin checked early in pregnancy and be offered oral supplements (30–60 mg/day) if serum ferritin is $<30\ ng\ mL^{-1}$ (1C).

Treatment: oral iron

8. We recommend treating mild to moderate iron-deficiency anaemia (IDA) (Hb $\geq 80\ g\ L^{-1}$) in early pregnancy (first and second trimesters) with oral ferrous iron (80–100 mg/day elemental iron) and folic acid (400 μg/day) (1B).
9. Once the Hb concentration is in the normal range, we recommend that iron supplementation be continued for at least 3 months to replenish iron stores (1A).

Treatment: IV iron

10. We recommend that the administration of intravenous (IV) iron be considered in women with severe IDA (Hb $<80\ g\ L^{-1}$) or newly diagnosed IDA beyond 34 weeks of gestation (1B).
11. We recommend that the administration of IV iron be considered in women with confirmed IDA who fail to respond to the correct administration of oral iron (Hb concentration increase <10 or $20\ g\ L^{-1}$ in 2 or 4 weeks, respectively) or are intolerant to oral iron treatment, if the gestational age is >14 weeks (1B).

Treatment: ESA

12. We suggest that administration of an erythropoiesis-stimulating agents (ESA) be considered in women with moderate to severe anaemia not responding to IV iron due to inappropriate synthesis of, and/or response to, endogenous erythropoietin levels, in consultation with a haematologist (2C)

Treatment: RBC transfusion

13. We recommend that referral to a secondary care clinic be considered if there are significant symptoms of anaemia and/or severe anaemia (Hb $<70\ g\ L^{-1}$) or late gestation (>34 weeks) (1C).
14. We recommend that obstetric units have guidelines for red blood cell (RBC) transfusion in women with antenatal and post-natal anaemia who are not actively bleeding (1C).
15. In the absence of bleeding, should transfusion be deemed necessary, we recommend a single-unit transfusion followed by clinical reassessment and/or Hb measurement to determine the need for further transfusion (1C).

Post-partum anaemia

Detection and classification

16. We recommend that pregnant women, especially those with antenatal anaemia, have an Hb determination prior to delivery (1C).
17. We recommend that the Hb concentration be determined in all women after significant peri-partum bleeding (1C).

Prevention

18. We recommend that every effort be made to correct anaemia prior to delivery (1A).
19. We recommend that women with moderate to severe anaemia or at high risk of haemorrhage be advised to deliver in a hospital setting (1C).
20. We recommend active management of the third stage of labour to minimise blood losses (1A).
21. We recommend cell salvage for women undergoing Caesarean section in whom excessive blood losses are anticipated (1C).
22. We recommend that a clear multidisciplinary, multimodal protocol for management of major obstetric haemorrhage be in place. This protocol should be activated as soon as major obstetric haemorrhage is identified (1C).

Treatment: oral iron

23. Oral iron supplementation, either alone or in combination with folic acid, is recommended for 6–12 weeks following delivery to reduce the risk of anaemia in settings where gestational anaemia is a public health concern (1B).
24. We recommend that 80–100 mg elemental iron daily for 3 months be given to women with mild to moderate post-partum anaemia (PPA) (Hb $90–110\ g\ L^{-1}$) who are haemodynamically stable and asymptomatic or mildly symptomatic (1B).

Treatment: IV iron

25. We recommend that women who fail to respond to the correct administration of oral iron (Hb increase <10 or 20 g L^{-1} in 2 or 4 weeks, respectively) or are intolerant to oral iron be switched to IV iron (1B).
26. We recommend the administration of IV iron to cover individually calculated total ID in women with moderate to severe PPA (Hb <90 g L^{-1}) (1B).

Treatment: ESA

27. In severely anaemic patients with blunted erythropoiesis due to infection and/or inflammation who do not respond adequately to IV iron treatment, as well as in severely anaemic patients who refuse blood transfusions, we suggest considering treatment with an ESA after consultation with the haematologist (2B).

Treatment: RBC transfusion

28. We recommend that all pregnant women should by typed for blood groups (ABO and D) and screened for the presence of red cell antibodies early in pregnancy (at booking) and at 28 weeks gestation. In D-negative women, the 28-week sample should be taken before the administration of routine antenatal anti-D Ig prophylaxis (1B) (White *et al.*, 2016).
29. We recommend that RBC transfusion not be dictated by Hb levels alone (1C).
30. We recommend that transfusion be considered in non-bleeding patients with an Hb <60 g L^{-1}, taking clinical signs and symptoms (risk of bleeding, cardiac compromise or symptoms requiring immediate attention) into consideration (1A).
31. In the absence of bleeding, should transfusion be deemed necessary, we recommend a single-unit transfusion followed by clinical reassessment and/or Hb measurement to determine the need for further transfusion (1C).

PATIENT BLOOD MANAGEMENT

PBM has become the *buzzword* in transfusion medicine. A few years ago, clinicians who spoke about PBM at meetings were considered abstruse visionaries. With time, their vision has evolved and come into focus. This has allowed the health-care community to better understand the concept and, most importantly, to apply it in everyday clinical practice.

Definition of PBM

PBM or, more precisely, patient-centred blood management "is the timely application of evidence-informed medical and surgical concepts designed to maintain haemoglobin concentration, optimise haemostasis and minimise blood loss in an effort to improve patient outcomes" (Shander *et al.*, 2016). By definition, the approach is multidisciplinary and focuses on the treatment of each individual patient in whom significant blood losses are likely to occur and where transfusion of blood products is part of the established treatment (Gombotz, 2012). PBM involves – but is not restricted to – the appropriate use of blood products, defined by the World Health Organisation (WHO) as "the transfusion of safe blood products to treat a condition leading to significant morbidity or mortality that cannot be prevented or managed effectively by other means." (WHO, 2001a).

Although PBM is known best in the management of elective surgical procedures, it can (and should) also be applied to any procedure likely to result in excessive bleeding, post-procedural anaemia and the use of blood products. The "three pillars" of PBM require that (i) perioperative erythropoiesis be optimised, (ii) blood losses be minimised and (iii) tolerance to anaemia be harnessed appropriately (Isbister, 2013). PBM is a continuous process, initiated early in the preoperative period and continued intra- and post-operatively. The whole concept of PBM has been elegantly summarised by Hofmann *et al.* (Hofmann *et al.*, 2007) (Figure S1, Supporting Information).

Importance of PBM

At present, preoperative anaemia is often ignored, surgery proceeds as planned, and RBCs are transfused when deemed necessary (Muñoz *et al.*, 2015; Meier *et al.*, 2016) Yet, cohort studies (in cardiac, non-cardiac and vascular surgery) have shown that preoperative anaemia is associated with an increased incidence of post-operative adverse events, including mortality (Wu *et al.*, 2007; Ranucci *et al.*, 2012; Gupta *et al.*, 2013) In addition, preoperative anaemia and low intraoperative haemoglobin (Hb) concentration are important predictors of perioperative allogeneic RBC transfusions (Muñoz *et al.*, 2015).

Blood transfusions entail a number of known risks (e.g. transmission of infectious agents, transfusion reactions, ABO mismatch, transfusion-related acute lung injury, transfusion-associated circulatory overload, *etc.*) and other less well-known ones. The latter are related, in essence, to emergent pathogens and to immunomodulation (increased incidence of infections and cancer recurrence) (Goodnough & Shander, 2012). At present, it remains difficult to determine whether the observed adverse events and mortality are related to preoperative anaemia *per se* or to the increase in allogeneic transfusions secondary to anaemia (Figure S2). Notwithstanding, the overall outcome is negative, so preoperative anaemia must be managed in a timely fashion (Muñoz *et al.*, 2015). PBM implementation remains inadequate, even in centres where audits are conducted on a regular basis (Gombotz *et al.*, 2014; Van der Linden & Hardy, 2016). That being said, it has not been unequivocally demonstrated that correction of preoperative anaemia is associated with improved outcomes (Muñoz *et al.*, 2015). High-quality evidence in that direction would definitely improve adherence to PBM principles.

CONSENSUS ORGANISATION

Scope and purpose

This consensus statement reflects the position of the NATA, the FIGO and the EBCOG. It includes recommendations on the management of anaemia and haematinic deficiencies in pregnancy and in the post-partum period as part of PBM in obstetrics. The prevention and treatment of post-partum haemorrhage (PPH) will be addressed in a separate consensus statement.

Target audience

The recommendations in this consensus statement are intended for use by clinical practitioners managing perinatal care of women in all settings and by policymakers in charge of decision making for the update of clinical practice in health-care establishments. It is important to note that these recommendations need to be tailored for application in individual patients or any population after consideration of the values and preferences of both health-care providers and patients, as well as equity issues; explicit assessment of harms and benefits of each recommendation; feasibility including resources, capacity and equipment; and implementability. Further involvement of relevant stakeholders at the local level is advised.

Development process

A multidisciplinary panel of physicians with expertise in obstetrics, anaesthesia, haematology, policymaking and epidemiology was convened in Paris, France on 28 February 2015 by NATA in collaboration with FIGO and EBCOG with the aim of developing a consensus statement on the detection, evaluation and management of anaemia and haematinic deficiencies in pregnancy and in the post-partum period. The experts were asked to:

1. Determine the scope of the problem;
2. Identify the optimal methods to detect the problem and establish a differential diagnosis;
3. Assess the evidence and its quality for the detection, evaluation and management of anaemia and haematinic deficiencies in pregnancy and in the post-partum period;
4. Agree on recommended methods to minimise peri-partum blood losses;
5. Define the role of RBC transfusions in pregnancy and in the post-partum period and
6. Issue recommendations on the use of oral iron, IV iron and ESA to treat anaemia during pregnancy and in the post-partum period.

Members of the task force assessed the quantity, quality and consistency of the published evidence and formulated recommendations using the system developed by the GRADE working group (Guyatt *et al.*, 2008) (Figure S3). A preliminary version of the consensus statement was drafted by M. M. and circulated among the members of the panel for additional input and editing. The document was further reviewed by two experts in the field (F. G. and N. M.) who were not previously involved in the process. The document was then submitted for publication and underwent the journal's regular peer-review process. The recommendations in this statement are expected to remain valid for an estimated standard period of 10 years.

Plans for dissemination, adaptation and evaluation

This statement will be disseminated to all members of NATA, FIGO and EBCOG, and open access will be provided. Additionally, the recommendations will be presented at international forums and specialised events targeting clinicians in charge of the management of anaemia and haematinic deficiencies in pregnant and post-partum women.

ANAEMIA IN PREGNANCY

Anaemia occurs frequently during pregnancy. Anaemia can be aggravated by childbirth and is associated with adverse events. In most cases, it is possible to identify and correct the situation prior to childbirth, thereby improving patient outcomes.

Definitions

During pregnancy, there is a considerable increase (40–45%) in plasma volume (Sanghavi & Rutherford, 2014). The maternal plasma erythropoietin level also increases during pregnancy, with a peak in the third trimester, to accelerate erythropoiesis and help compensate for the dilution effect. These changes, resulting in an increase in total blood volume, are important to meet the increased demands of blood flow for the uterus and foetus, and may protect pregnant woman against the adverse effects of blood loss during labour. However, the disproportion in volume expansion between the plasma and RBC volumes results in haemodilution, and therefore, cut-off values for the definition of anaemia during pregnancy should be lower than those for non-pregnant women (Milman, 2008).

The definition of a normal Hb concentration in pregnancy is controversial and lacks consistency across studies. Ideally, the cut-off values for pre-partum anaemia should be derived from studies of healthy iron-replete (as well as folate- and vitamin B_{12}-replete) women who had a normal singleton pregnancy and delivery (Milman *et al.*, 2000; Milman *et al.*, 2007). The WHO has defined anaemia in pregnancy as an Hb $<110\,g\,L^{-1}$ and classified anaemia as mild (Hb $100–109\,g\,L^{-1}$), moderate (Hb $70–99\,g\,L^{-1}$) or severe (Hb $<70\,g\,L^{-1}$) (WHO, 2011). There are no WHO recommendations on the use of different Hb cut-off points by trimester, but it is recognised that during the second trimester of pregnancy, Hb concentration decreases by approximately $5\,g\,L^{-1}$. Additionally, the WHO states that 'mild' anaemia is a misnomer as iron deficiency is already advanced by the time anaemia is detected. Iron deficiency has consequences even when no anaemia is clinically apparent. The American

College of Obstetricians and Gynaecologists (ACOG) and British Committee for Standards in Haematology (BCSH) guidelines define anaemia in pregnancy as an Hb $<110\ g\ L^{-1}$ in the first trimester and $<105\ g\ L^{-1}$ in the second and third trimesters (ACOG, 2008; Pavord *et al.,* 2012).

Prevalence

It is estimated that in 2011, 38% of pregnant women worldwide were anaemic, with wide variations between regions (Stevens *et al.*, 2013). The prevalence of anaemia among pregnant women was 48.7% in the Southeast Asian region, compared with 46.3% in the African region and 25.8% in the European region.

Causes

ID accounts for most cases of anaemia in pregnant women (Stevens *et al.*, 2013) as iron stores are often insufficient to meet the increasing demands of pregnancy due to the increase in RBC mass (450 mg), foetal growth (225 mg), placental development (80 mg) and blood losses during normal vaginal delivery (250 mg). A total of approximately 1000 mg of extra iron is required during a normal pregnancy, equivalent to $6.3\ mg\ day^{-1}$. In addition, lactation will require an additional supply of $1\ mg\ day^{-1}$ (Bothwell, 2000). Without supplementation, 80% of women at term will have no detectable iron stores according to bone marrow samples, and it will take 2 years of normal dietary iron to replace the iron lost with each pregnancy (De Leeuw *et al.*, 1966).

Although most of the burden of anaemia is assumed to be due to ID, other contributors should be considered. Nutritional deficiencies of folate and vitamin B_{12}, infectious diseases, parasitic infections and haemoglobinopathies are additional and often neglected causes of anaemia (WHO, 2001c; Kassebaum *et al.*, 2014).

Consequences

Iron depletion reduces iron availability for erythropoiesis and results in decreased Hb and oxygen delivery to tissues, resulting in clinical signs and symptoms. These include reduced exercise tolerance, tiredness and fatigue, impaired cognitive performance tests, decreased mental concentration ability, irritability, tendency of depression, palpitations, headaches, pallor, glossitis, angular cheilitis, nail ridging, koilonychias, reduced immunity, increased frequency of infections and pica. Anaemia is the most common indirect cause of adverse maternal outcomes, including maternal mortality (Filippi *et al.*, 2016). Low Hb concentrations indicative of moderate or severe anaemia during pregnancy have been associated with an increased risk of premature delivery and child mortality and infectious diseases (Filippi *et al.*, 2016). An Hb $<70\ g\ L^{-1}$ is an associated cause in up to half of the maternal mortalities worldwide. Moreover, IDA may affect growth and development both of the foetus *in utero* and of the newborn child in the long term (Lumbiganon *et al.*, 2014; Vogel *et al.*, 2014; New & Wirth, 2015) (Table S1).

There are significant concerns about the suboptimal management of maternal anaemia even in high-resource areas, likely due in part to a lack of consistent good-quality evidence mandating therapeutic interventions (Parker *et al.*, 2012). The development of more standardised approaches to reporting outcomes of maternal anaemia, together with the impact of therapy, is a research priority (Allard, 2015).

Detection and classification

The National Institute for Health and Care Excellence (NICE) in the UK recommends that screening for haematological conditions in pregnancy should be offered at booking and at 28 weeks, thus allowing adequate time for treatment should anaemia be detected (NICE, 2008). Hb concentrations below the normal range for pregnancy should be investigated and iron supplementation considered if indicated. It has been proposed that the first antenatal haematological screening should also include serum ferritin, thus allowing the early assessment of body iron status and an immediate decision whether or not there is an indication for oral iron supplementation in early pregnancy (Milman, 2006). However, there is currently no consensus on this issue. The 2015 U.S. Preventive Services Task Force recommendation concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for IDA in pregnant women to prevent adverse maternal health and birth outcomes (Siu, 2015). The authors indicate, however, that this recommendation does not apply to pregnant women who are malnourished, have symptoms of IDA or have special haematological conditions or nutritional needs that increase iron requirements. In the UK, unselected screening with routine use of serum ferritin is generally not recommended, although guidelines note that it may be helpful in individual centres with a particularly high prevalence of women at risk of ID (Pavord *et al.*, 2012).

A FBC screening test to detect anaemia in pregnancy may reveal an Hb below the defined threshold. Following detection of anaemia, a standard haematological approach is generally applied to determine if the anaemia is secondary to increased blood loss or decreased production of red cells. Red cell indices, other FBC parameters and a blood film are usually reviewed. Blood film reviews may identify variation in size and shape of cells, uniformity, fragments, inclusion bodies or sickle cells. However, they are time consuming and are hardly ever performed at diagnosis. The mean red cell volume (MCV) may suggest a microcytic (ID, haemoglobinopathy), macrocytic (vitamin B_{12} or folate deficiency, thyroid disease, reticulocytosis, increased alcohol intake or liver dysfunction) or normocytic (anaemia of chronic disease, marrow suppression or dual haematinic deficiency) cause for anaemia. Additional blood tests may be considered, including haematinics (iron, vitamin B_{12}, folate), and in certain cases, reticulocytes, haemoglobin electrophoresis, lactate dehydrogenase, haptoglobin, bilirubin and a direct antiglobulin test (to exclude haemolysis) would be

needed for a definite classification of anaemia (Hallberg *et al.*, 1993; van den Broek *et al.*, 1998; Muñoz *et al.*, 2011).

In the presence of IDA during pregnancy, the MCV, the mean red cell haemoglobin (MCH) and the mean red cell haemoglobin concentration (MCHC) may be low, and the blood film may confirm microcytic, hypochromic red cells and elliptocytes. However, the increased erythropoietic drive in pregnancy leads to a higher proportion of young, large, red cells and may mask the effect of ID on MCV. A normal MCV does not exclude ID, whereas microcytic, hypochromic indices may occur in haemoglobinopathies. The red cell distribution width, i.e. the variation in the volumes of red cells, can help differentiate ID from other microcytic anaemias, for instance, thalassaemia. Therefore, it is important to confirm whether a haemoglobinopathy is present. Plasma or serum ferritin is a measure of iron stores. It declines early in the development of ID and is not affected by ingestion of iron. Because serum ferritin is an acute-phase protein, it is recommended to determine the C-reactive protein level at the same time if inflammation is present or suspected. In pregnancy, a serum ferritin concentration $<30\ ng\ mL^{-1}$ indicates insufficient body iron reserves and hence a high risk for developing IDA; a serum ferritin concentration $<12\ ng\ mL^{-1}$ indicates established ID at all stages of pregnancy (Hallberg *et al.*, 1993; van den Broek *et al.*, 1998; Muñoz *et al.*, 2011).

A trial of oral ferrous iron therapy (100 mg elemental iron/day) has also been considered a first-line diagnostic test for IDA (ACOG, 2008; Pavord *et al.*, 2012). In women of Mediterranean, Middle and Far East and Africa descent who may have haemoglobinopathies, an oral iron trial could be offered whilst waiting for their haemoglobinopathy status to be determined. The chances of iron overload would be minimal, and the benefits would outweigh the risks. An Hb increment in 2–4 weeks (positive response) is supportive of a diagnosis of IDA. In case of negative response, further investigation including serum vitamin B_{12} and folate should be considered (Annex S1).

Recommendations

- ***Recommendation 1:*** We recommend that an FBC be obtained to screen for anaemia at booking and at 28 weeks as well as at any time during pregnancy if symptoms of anaemia are present (1A).
- ***Recommendation 2:*** In a woman with microcytic or normocytic anaemia, ID should be confirmed by a trial of oral iron (unless she is known to have a haemoglobinopathy) or a serum ferritin measurement (1B).
- ***Recommendation 3:*** In the absence of an Hb increment in response to a trial of oral iron conducted correctly, we recommend the further evaluation of iron status by checking serum ferritin and considering whether additional laboratory testing is needed (1C).
- ***Recommendation 4:*** In anaemic women of Mediterranean, Middle and Far East and African origin, we recommend confirming the presence or absence of a haemoglobinopathy either by selective (based on a family of origin questionnaire) or universal screening for haemoglobinopathies depending on regional demographics (1C).
- ***Recommendation 5:*** Anaemic women with a known haemoglobinopathy should have their serum ferritin checked and should only be offered oral iron therapy if their serum ferritin level is $<30\ ng\ mL^{-1}$ (1B).

Good practice points

- Aside from the oral iron trial, the serum ferritin level is the most useful and easily available laboratory parameter for assessing ID during pregnancy.
- Serum ferritin levels $<12\ ng\ mL^{-1}$ indicate established ID. A serum ferritin level $< 30\ ng\ mL^{-1}$, with or without anaemia, indicates insufficient body iron reserves and should prompt treatment. However, as ferritin is an acute-phase reactant, a serum ferritin level within the normal range may not rule out ID in the presence of inflammation.

Prevention

Interventions aimed at preventing ID and IDA in pregnancy include iron- and folic acid-containing supplements, fortification of staple foods with iron and other vitamins and minerals, health and nutrition education, control of parasitic infections and improvement in sanitation (INACG, 1977). A supplemental daily dose of 30–60 mg of elemental ferrous iron is recommended by the WHO for all pregnant women in all settings (WHO, 2012). In most countries, a prenatal supplement containing 30 mg iron is offered, although iron content may vary (e.g. 45 mg in the USA and 60 mg in the UNICEF product). A study of Danish women showed that a supplement of 40 mg ferrous iron/day for 18 weeks of gestation appears adequate to prevent ID in 90% of the women and IDA in at least 95% of the women during pregnancy and the post-partum period (Milman *et al.*, 2005). Prophylactic iron supplementation should be started as soon as pregnancy is confirmed and maintained throughout its entire duration. In settings where anaemia in pregnant women is a severe public health problem (prevalence of 40% or higher), a daily dose of 60 mg of elemental ferrous iron is preferred over a lower dose (WHO, 2012).

Two recent meta-analyses concluded that daily prenatal use of iron substantially reduces the risk of maternal anaemia and ID in pregnancy but that the positive effect on other maternal and infant outcomes is less clear (Haider *et al.*, 2013; Peña-Rosas *et al.*, 2015a). Implementation of iron supplementation recommendations improves birthweight, probably leading to a reduction in the risk of low birthweight, but it produces heterogeneous results depending on the population's background risk for low birthweight and anaemia, as well as the level of adherence to the intervention (Peña-Rosas *et al.*, 2015a).

A Cochrane systematic review suggests that intermittent iron and folic acid supplementation regimens produce similar

maternal and infant outcomes at birth as daily supplementation and are associated with fewer gastrointestinal side effects and increased compliance (Peña-Rosas *et al.*, 2015b). The risk of reaching high Hb in mid and late pregnancy was reduced, whereas the risk of having mild anaemia near term increased. Thus, intermittent oral ferrous iron may be a feasible alternative to daily iron supplementation among those pregnant women who are not anaemic and have adequate antenatal care.

The 2015 U.S. Preventive Services Task Force recommendation states that the current evidence is insufficient to assess the balance of benefits and harms of routine iron supplementation for pregnant women in order to prevent adverse maternal health and birth outcomes (Siu, 2015). Similarly, routine iron supplementation for all pregnant women has not been recommended in the UK (Pavord *et al.,* 2012).

As for folic acid, a prophylactic dose of 400 μg (0.4 mg) per day, peri-conceptionally and throughout pregnancy, is recommended for the prevention of neural tube defects. If supplementation is started after the first trimester of pregnancy, it will not help prevent congenital anomalies. Therefore, folic acid supplementation should begin as early as possible (ideally prior to conception).

Daily oral iron and folic acid supplementation during pregnancy is a strong WHO recommendation, with overwhelming implications for patients, clinicians, policymakers, quality monitors and funding agencies (WHO, 2012). There are currently no specific recommendations for prophylactic vitamin B_{12} supplementation in pregnancy.

Recommendations

- ***Recommendation 6:*** In areas with a high prevalence of anaemia in pregnancy, we recommend daily oral iron (30 – 60 mg) and folic acid (400 μg) supplementation as part of routine antenatal care to reduce the risks of maternal anaemia and ID and infant low birthweight (1B).
- ***Recommendation 7:*** In areas with a low prevalence of anaemia in pregnancy, non-anaemic women identified to be at increased risk of ID should have their serum ferritin checked early in pregnancy and be offered oral supplements (30 – 60 mg day^{-1}) if serum ferritin is <30 ng mL^{-1} (1C).

Good practice points

- According to the United Nations International Multiple Micronutrient Preparation, in high-risk areas, supplements may be formulated to include, in addition to iron and folic acid, other vitamins and minerals to overcome other possible maternal micronutrient deficiencies.
- In malaria-endemic areas, provision of iron and folic acid supplements should be implemented in conjunction with measures to prevent, diagnose and treat malaria (WHO, 2012). In cases where a combined folic acid – iron tablet is not available, a daily dose of 400 μg folic acid can be used separately (RBMP, 2015).
- Non-anaemic women at risk of ID include those with previous anaemia, multiparity, consecutive pregnancy <1 year following delivery and vegetarians. Special attention should also be given to pregnant teenagers, women at high risk of bleeding or with a recent history of bleeding, and Jehovah's Witnesses (Pavord *et al.,* 2012). When logistically difficult, these women should receive daily oral iron (30 – 60 mg) without checking serum ferritin.
- All pregnant women should be counselled and receive plain-language written information regarding diet and iron-rich food sources, factors that may inhibit or promote iron absorption and the importance of maintaining adequate iron stores during pregnancy (Pavord *et al.,* 2012).

Treatment: Oral iron

The primary treatment for mild to moderate cases of IDA (Hb 70 – 105 g L^{-1}) during the first and second trimesters is daily oral iron therapy, and doses ranging from 40 to 200 mg day^{-1} of elemental ferrous iron, ideally on an empty stomach, have been recommended. The same also applies to depleted iron stores without anaemia (serum ferritin <30 ng mL^{-1}) at the beginning of pregnancy (60 mg day^{-1} elemental iron) because of the additional requirement for iron during the course of the pregnancy (ACOG, 2008; Breymann *et al.*, 2011; Pavord *et al.,* 2012; WHO, 2012).

However, lower-dosage iron supplements can be effective for the treatment of IDA and are associated with less gastrointestinal side effects. In non-anaemic young women with plasma ferritin levels <20 ng mL^{-1}, providing lower dosages (40 – 60 mg iron) and avoiding twice-daily dosing was found to maximise fractional absorption due to the effect of absorbed iron on hepcidin release (Moretti *et al.,* 2015). Whether these data also apply to anaemic women is not known. As anaemia-induced hypoxia and erythropoietin production down-regulate the expression of hepcidin, this may counterbalance the stimulatory effect of iron, allowing the use of higher oral iron doses (Muñoz *et al.,* 2011).

Recommendations

- ***Recommendation 8:*** We recommend treating mild to moderate IDA (Hb ≥80 g L^{-1}) in early pregnancy (first and second trimesters) with oral ferrous iron (80 – 100 mg day^{-1} elemental iron) and folic acid (400 μg day^{-1}) (1B).
- ***Recommendation 9:*** Once the Hb concentration is in the normal range, we recommend that iron supplementation be continued for at least 3 months to replenish iron stores (1A).

Good practice points

- Women should be advised on the appropriate intake of oral iron to optimise absorption (empty stomach, preferably 1 h before breakfast, with a vitamin C-containing drink).
- Systems must be in place for rapid review and follow up of blood results.

- Clinical staff should be familiar with the iron content of over-the-counter supplements that women take during pregnancy as many contain insufficient elemental iron to be therapeutic.

Treatment: Intravenous iron

A switch to an IV iron preparation can be advantageous in certain cases, including: (i) a lack of response to oral iron (Hb levels rising by less than 10 or 20 g L^{-1} within 14 or 28 days, respectively) due to impaired intestinal absorption; (ii) lack of compliance or intolerance of oral iron preparations (gastrointestinal side effects); (iii) severe, advanced or progressive anaemia (Hb <80 g L^{-1}); and (iv) desire for rapid anaemia treatment (e.g. advanced gestational age, Jehovah's Witness faith) (Breymann *et al.,* 2011; WHO, 2011; WHO, 2012) (*for a summary of the characteristics of available IV iron formulations*, Table S2).

We identified 12 randomised controlled trials (RCT) comparing oral and IV iron in a total of 1519 pregnant women (14–37 weeks of gestation) with anaemia (Hb 69–109 g L^{-1}) (al-Momen *et al.,* 1996; Singh *et al.,* 1998; Bayoumeu *et al.,* 2002; Al *et al.,* 2005; Khalafallah *et al.,* 2010; Neeru *et al.,* 2012; Shafi *et al.,* 2012; Froessler *et al.,* 2013; Kochhar *et al.,* 2013; Abhilashini *et al.*, 2014; Gupta *et al.,* 2014; Breymann *et al.,* 2017) (Table S3). Compared with oral iron, antenatal IV iron administration hastened recovery from anaemia, led to a higher rate of anaemia correction and resulted in better replenishment of iron stores and lower rates of adverse drug events or poor treatment compliance. No study showed superiority of oral iron over IV iron.

One study assessed the long-term effect of iron therapy during pregnancy on well-being and health-related quality of life (HRQoL) during a 3-year follow-up period (Khalafallah *et al.,* 2012). Patients receiving IV iron had significantly higher Hb and serum ferritin levels ($P < 0.001$). There were strong associations between iron status and a number of HRQoL items, including improved general health, improved physical energy, less psychological downheartedness, less clinical depression and overall improved mental health. The duration of breastfeeding was longer in women who had received IV iron. In a more recent trial, in which a significantly larger proportion of women treated with IV iron vs oral iron achieved correction of anaemia (Hb ≥110 g L^{-1}; 83.5 vs 70.2%; $P < 0.05$) and did so within a shorter time frame (3.4 vs 4.3 weeks; $P < 0.05$), changes in all SF-36 components favoured IV iron, with significant improvements in vitality and social functioning (Breymann *et al.,* 2017).

The available evidence suggests benefits of IV iron administration, especially for patients with moderate to severe anaemia. Intramuscular iron administration is less effective (Wali *et al.,* 2002; Singh & Singh, 2013) and no longer recommended in the majority of clinical situations; however, it may be an option in certain clinics in case of high throughput or community administration. Two observational studies found no differences between different IV iron formulations (Christoph *et al.,* 2012; Myers *et al.,* 2012). IV iron formulations allowing the administration of large doses in a single session may facilitate treatment and be more convenient both for the patient (fewer venepunctures, less time out from work) and for the health system (shorter administration time, fewer visits to day hospital and fewer ambulance transfers) (Table S2).

Neither serious life-threatening adverse events attributable to IV iron nor significant differences in maternal or foetal outcomes were reported in the studies reviewed above. Nonetheless, these studies commonly used Hb and iron indices as endpoints and were usually underpowered to evaluate the impact of IV iron therapy on more clinically relevant outcomes.

On 27 June 2013, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) completed a review of IV iron-containing medicines and concluded that all IV iron preparations carry a small risk of adverse reactions that can be life-threatening if not treated promptly. "During pregnancy, the CHMP noted, allergic reactions are of particular concern as they can put both the mother and unborn child at risk. IV iron medicines should therefore not be used during pregnancy unless clearly necessary. Treatment should be confined to the second or third trimester, provided the benefits of treatment clearly outweigh the risks to the unborn baby (such as anoxia and fetal distress)" (EMA, 2013). A number of iron experts disagree with this statement because overemphasising the avoidance of IV iron may not only be counterproductive but also potentially harmful (Auerbach *et al.,* 2015). Guidance for risk minimisation and management of hypersensitivity reactions to IV iron has been published (Rampton *et al.,* 2014). If minor infusion reactions occur with one IV iron formulation, switching to another is appropriate and safe (Auerbach *et al.,* 2015). Nevertheless, we should be aware of the small risk of reactions, and as such, it is not appropriate to go straight for IV iron in all cases. First-line treatment is oral iron based on safety and cost, and the benefits of IV iron outweigh its risks when the oral route is insufficient or poorly tolerated, provided measures are taken to minimise the risk of hypersensitivity reactions (EMA, 2013). Women should be informed of potential side effects of IV iron, and written information should be provided.

Recommendations

- ***Recommendation 10:*** We recommend that the administration of IV iron be considered in women with severe IDA (Hb <80 g L^{-1}) or newly diagnosed IDA beyond 34 weeks of gestation (1B).
- ***Recommendation 11:*** We recommend that the administration of IV iron be considered in women with confirmed IDA who fail to respond to correct administration of oral iron (Hb concentration increase <10 or 20 g L^{-1} in 2 or 4 weeks, respectively) or are intolerant to oral iron treatment if the gestational age is >14 weeks (1B).

Good practice points

- IV iron should not be given together with oral iron or in the presence of an active infection.
- Health-care staff should be trained to detect, evaluate and manage hypersensitivity reactions in accordance with published guidelines.

Treatment: Erythropoiesis-stimulating agents

There is only one each of an RCT, observational study and case series including a total of 135 women with confirmed IDA (Hb 83–95 g L^{-1}; >16 weeks of pregnancy) treated with iron sucrose or iron sucrose plus an ESA (Breymann *et al.,* 1995; Breymann *et al.,* 2001; Krafft *et al.,* 2009) (Table S2). Compared with IV iron alone, addition of an ESA, namely recombinant human erythropoietin (rHuEPO), resulted in higher Hb increments and higher rates of anaemia correction, especially if endogenous erythropoietin levels were low at baseline. Thus, patients not adequately responding to IV iron treatment might benefit from the additional administration of ESAs, although the level of evidence is low.

Neither serious life-threatening adverse events attributable to ESAs nor significant differences in maternal or foetal outcomes were reported in the studies reviewed above. However, it must be remembered that ESAs are not approved for treating anaemia in pregnant women without chronic kidney disease (off-label use). Women should be informed of potential side effects, and written information should be provided.

Recommendation

- ***Recommendation 12:*** We suggest that administration of an ESA be considered in women with moderate to severe anaemia not responding to IV iron due to inappropriate synthesis of and/or response to endogenous erythropoietin levels, in consultation with a haematologist (2C).

Treatment: Red blood cell transfusion

Our literature search identified only one small multicentre RCT ($n = 72$) examining the effect of prophylactic vs indication-driven (restrictive) transfusion in pregnant women, and this study was restricted to women with sickle cell anaemia (Koshy *et al.,* 1988). No other studies have been identified that report on the effect of RBC transfusion on maternal or neonatal mortality, functional or performance status or measures of foetal outcome in a general maternity population. Therefore, any recommendations are based on expert consensus regarding maternal or foetal indications for blood transfusion.

In the context of severe bleeding, there is no question that blood transfusion can save lives; however, it is less certain whether blood transfusion is of benefit to maternity patients not actively bleeding. Furthermore, many inherent risks are involved with blood transfusion, and certain women may refuse blood transfusions due to religious beliefs. Therefore, blood transfusion should be reserved for those at risk of further bleeding, imminent cardiac compromise or symptoms requiring immediate attention (maternal indications).

Severe anaemia with a maternal Hb <60 g L^{-1} has been associated with abnormal foetal oxygenation, resulting in non-reassuring foetal heart rate patterns, reduced amniotic fluid volume, foetal cerebral vasodilatation and foetal mortality (Sifakis & Pharmakides, 2000; Carles *et al.,* 2003). In such a case, maternal transfusion should be considered for foetal indications (ACOG, 2008; NICE, 2008). Transfusion indications should be backed up by local guidelines and effective patient information (Pavord *et al.,* 2012).

Recommendations

- ***Recommendation 13:*** We recommend that referral to a secondary care clinic be considered if there are significant symptoms of anaemia and/or severe anaemia (Hb <70 g L^{-1}) or late gestation (>34 weeks) (1C).
- ***Recommendation 14:*** We recommend that obstetric units have guidelines for RBC transfusion in women with antenatal and post-natal anaemia who are not actively bleeding (1C).
- ***Recommendation 15:*** In the absence of bleeding, should transfusion be deemed necessary, we recommend a single-unit transfusion followed by clinical reassessment and/or Hb measurement to determine the need for further transfusion (1C).

Good practice points

- Women receiving an RBC transfusion should be given full information regarding the indication for transfusion and alternatives available, according to national policy procedures (WHO, 2001b).
- Informed consent should be given by the patient and documented in the clinical notes.
- One red cell concentrate contains approximately 240 mg of iron, which is insufficient to replace total ID and replenish iron reserves. Therefore, concomitant IV iron to replete the iron reserves in order to minimise the number of transfusions may be considered. Concomitant ESA may also be considered to maximise erythropoiesis and minimise transfusions.

POST-PARTUM ANAEMIA

Anaemia as well as ID without anaemia are common in the post-partum period and represent significant health problems in women of reproductive age. Predisposing factors should be identified and modified when possible, and routine screening should be considered in order to provide early and appropriate treatment.

Definition

Ideally, the cut-off value for PPA should be derived from the studies of healthy iron-replete women who had a normal

singleton pregnancy and delivery without excessive blood losses (<500 mL). However, PPA is usually defined by an Hb <100 g L^{-1} within 24–48 h after delivery, although a recommendation has been made to define PPA as an Hb <110 g L^{-1} at 1 week post-partum and Hb <120 g L^{-1} at 8 weeks, the latter corresponding to the definition of anaemia in non-pregnant women of reproductive age proposed by the WHO (Milman, 2011; WHO, 2011; Milman, 2012).

Prevalence

PPA is common. In a consecutive series of German women ($n = 43\,807$) who delivered in 1993–2008, the prevalence of PPA (Hb < 100 g L^{-1}) 24–48 h after delivery was 22% (up to 50% if PPA was defined as Hb <110 g L^{-1}) (Bergmann *et al.,* 2010). In Danish healthy women, the prevalence of PPA 1 week after normal delivery was 14% with iron supplementation and 24% without iron supplementation (Milman *et al.,* 1991). In developing countries, the prevalence of PPA is in the range of 50–80% and represents a major cause of maternal morbidity and mortality. It has been estimated that peri-partum haemorrhage and anaemia are responsible for approximately 100 000 delivery-associated maternal mortalities yearly on a global scale.

Causes

In some countries, pre-partum IDA and/or acute bleeding during delivery are the main causes of PPA (Patel *et al.,* 2006; Bergmann *et al.,* 2010; Allary *et al.,* 2013). Normal peri-partum blood losses range from 200 to 300 mL, whereas PPH is defined as blood losses ≥500 mL and severe PPH as blood losses ≥1000 mL (RCOG, 2009; Rajan & Wing, 2010). In a fraction of women, factors such as ethnicity, multiple birth, folate and vitamin B_{12} deficiencies, inflammatory response (especially after Caesarean section), infectious disorders and haemoglobinopathies may contribute to PPA (Krafft *et al.,* 2003; Milman, 2008; Murray-Kolb & Beard, 2009; Bergmann *et al.,* 2010).

Consequences

In the post-partum period, anaemia as well as ID without anaemia are associated with decreased physical performance (tiredness, breathlessness, palpitations), increased risk of infection (urinary tract), impaired lactation, reduced cognitive abilities, emotional instability and depression and thus represent significant health problems in women of reproductive age (Bergmann *et al.,* 2010). They also interfere with mother–child interactions as women experience difficulties in caring for their newborn, which compromises the emotional bonds between the mother and baby (Perez *et al.,* 2005). Maternal iron supplementation protects against these negative effects (Murray-Kolb & Beard, 2009). PPA may also increase health-care resource utilisation and costs (Duarte *et al.,* 2014). Therefore, factors predisposing to PPA should be identified and modified when possible.

Detection and classification

Routine screening for PPA should be considered in order to provide early and appropriate treatment. According to UK guidelines, every woman should have an Hb determination after significant peri-partum bleeding (Pavord *et al.,* 2012). Due to the combination of peri-partum haemorrhage and haemodynamic changes, the post-partum Hb concentration should be allowed to stabilise after delivery for at least 48 h before a reliable diagnosis of PPA can be made. Hb concentration at 1 week post-partum allows a more reliable detection of PPA (Milman, 2012). In case of excessive blood loss (>1000 mL), a protocol should be in place to manage the haemorrhage (including sequential Hb measurements) (Pavord *et al.,* 2012).

As is the case with antenatal anaemia, an algorithm for the diagnosis of PPA should be implemented. Some guidelines state that no treatment is required if the Hb concentration is >110 g L^{-1}.

Recommendations

- ***Recommendation 16:*** We recommend that pregnant women, especially those with antenatal anaemia, have an Hb determination prior to delivery (1C).
- ***Recommendation 17:*** We recommend that the Hb concentration be determined in all women after significant peri-partum bleeding (1C).

Good practice point

- A complete blood count plus a serum ferritin level at 4–8 weeks post-partum are adequate to assess anaemia and iron status and diagnose ID/IDA in the majority of women with antenatal anaemia or significant peri-partum bleeding (Milman, 2008).

Prevention

As pre-partum ID and IDA are closely associated with the occurrence of PPA, securing an adequate iron status during pregnancy is the first step in the prevention of PPA; anaemic women are more at risk of bleeding and more vulnerable to even moderate amounts of blood loss. All placebo-controlled studies have shown that pregnant women taking oral iron supplements have an improved iron status and a lower rate of anaemia both during pregnancy and in the post-partum period compared with women taking placebo (Haider *et al.,* 2013; Peña-Rosas *et al.,* 2015a; Peña-Rosas *et al.,* 2015b).

Many medical and gynaecological/obstetrical disorders predispose to peri-partum bleeding, PPH and PPA. Uterine atony is the most common aetiology for post-partum bleeding. Risk factors for uterine atony include prolonged second stage of labour, operative vaginal delivery, over-distention of the uterus (e.g. foetal macrosomia, multiple gestation, polyhydramnios), medications (e.g. nifedipine, magnesium sulphate, halogenated anaesthetic agents), abnormal placentation and retained conception

products. Traumatic lacerations of the uterus or vagina and congenital or acquired coagulation disorders, including anticoagulant therapy, can also cause excessive blood loss at delivery (Myers, Myers *et al.,* 2012). Therefore, careful obstetric evaluation and treatment prior to and during delivery is essential to reduce the frequency of both expected and unexpected complications and bleeding (Milman, 2012).

Different approaches may be used to prevent PPH, depending on the setting and availability of skilled birth attendants and resources, and international guidelines on PPH vary in their recommendations (Bohlmann & Rath, 2014). Active management of the third stage of labour and post-partum care immediately following placenta removal, regardless of third-stage management (active vs expectant), reduces blood losses and transfusion requirements. The usual components of active management of the third stage of labour include: administration of oxytocin (alternatively, ergometrine or misoprostol) within 1 min after birth of the infant, cord clamping and controlled cord traction and uterine massage after delivery of the placenta (Prendiville *et al.,* 2000; Lalonde and International Federation of Gynecology and Obstetrics, 2012). Cell salvage is recommended for women undergoing caesarean section in whom blood loss >500 mL is anticipated, provided that health-care teams have the necessary expertise and experience and the patient's informed consent is obtained (RCOG, 2009). Recent publications suggest that adhering to local guidelines significantly reduces the prevalence of severe PPH (Bohlmann & Rath, 2014).

Even with major advances in the prevention of PPH, some women will still require treatment for excessive bleeding. Timely interventions and appropriate access or referral and transfer to basic or comprehensive emergency obstetric care facilities for treatment are essential to save the woman's life (Lalonde and International Federation of Gynecology and Obstetrics, 2012). Therefore, a protocol for PPH management should be in place (RCOG, 2009; Rajan & Wing, 2010; Lalonde and International Federation of Gynecology and Obstetrics, 2012; Pavord *et al.,* 2012). It is beyond the scope of this document to go into details regarding the prevention and management of PPH, which will be the topic of a separate consensus statement.

Recommendations

- ***Recommendation 18:*** We recommend that every effort be made to correct moderate to severe anaemia prior to delivery (1A).
- ***Recommendation 19:*** We recommend that women with anaemia or at high risk of haemorrhage be advised to deliver in a hospital setting (1C).
- ***Recommendation 20:*** We recommend active management of the third stage of labour to minimise blood losses (1A).
- ***Recommendation 21:*** We recommend cell salvage for women undergoing caesarean section in whom excessive blood losses are anticipated (1C).
- ***Recommendation 22:*** We recommend that a clear multidisciplinary, multimodal protocol for management of major obstetric haemorrhage be in place. This protocol should be activated as soon as major obstetric haemorrhage is identified (1C).

Treatment: Oral iron

In women with mild to moderate anaemia who are haemodynamically stable, asymptomatic or mildly symptomatic, treatment should be initiated with oral ferrous iron (80–100 mg elemental iron daily for at least 3 months) (WHO, 2016). The interaction between food intake and absorption of iron supplements should be taken into account and clearly explained to the patient in order to increase the efficacy and reduce the side effects of the treatment (Pavord *et al.,* 2012).

In the three studies comparing oral iron with placebos, anaemia symptoms were not reported, and it remains unknown whether benefits of oral iron outweigh documented gastrointestinal harms (Markova *et al.,* 2015). In addition, implementation of oral iron therapy is inconsistent. In 2008, a multicentre study across 11 maternity units in the UK ($n = 2013$) found that 30% of women who had post-natal Hb levels checked were anaemic, and depending on the centre, 16–86% of these women received iron therapy (Barroso *et al.,* 2011). These data suggest that ensuring more effective iron replenishment during the hospital stay could alleviate the burden of anaemia in the post-partum period.

Recommendations

- ***Recommendation 23:*** Oral iron supplementation, either alone or in combination with folic acid, is recommended for 6–12 weeks following delivery to reduce the risk of anaemia in settings where gestational anaemia is a public health concern (1B).
- ***Recommendation 24:*** We recommend that 80–100 mg elemental iron daily for 3 months be administered to women with mild to moderate PPA (Hb 90–110 g L^{-1}) who are haemodynamically stable, asymptomatic or mildly symptomatic (1B).

Good practice points

- Whenever possible, Hb concentration in women receiving oral iron for PPA should be determined after approximately 2–4 weeks in order to evaluate the efficacy of the treatment.
- The interaction between food intake and absorption of ferrous and ferric iron supplements should be taken into account and clearly explained to the patient.

Treatment: Intravenous iron

Women with confirmed IDA and lack of response (Hb increment <10 or 20 g L^{-1} in 2 or 4 weeks, respectively) or intolerance to oral iron may benefit from IV iron. We identified 14 RCTs comparing oral and IV iron in a total of 2363 women with PPA who were followed up for 2–12 weeks (Breymann *et al.,*

2000; Bhandal & Russell, 2006; Van Wyck *et al.,* 2007; Breymann *et al.,* 2008; Seid *et al.,* 2008; Westad *et al.,* 2008; Giannoulis *et al.,* 2009; Daniilidis *et al.,* 2011; Verma *et al.,* 2011; Froessler *et al.,* 2013; Jain *et al.,* 2013; Perelló *et al.,* 2014; (Holm *et al.,* 2017); Rathod *et al.,* 2015) (Table S4). Compared with oral iron (standard therapy), IV iron resulted in faster Hb increments during treatment, higher final Hb increments, higher rates of anaemia correction, higher ferritin increments and lower rates of drug-related adverse events. There were no significant differences in treatment compliance or transfusion rates, and no RCT showed superiority of oral iron over IV iron.

Regarding quality of life, in one RCT, the total fatigue score was significantly improved in the IV iron group at weeks 4, 8 and 12 compared with the oral iron group, whereas SF-36 scores did not differ (Van Wyck *et al.,* 2007). In another study, a 1200-mg single-dose infusion of IV iron was associated with a statistically significant aggregated change of approximately 1 point on the 16-point Multidimensional Fatigue Inventory, suggesting less fatigue within 12 weeks after PPH (Holm *et al.,* 2017). In contrast, an RCT found that patients assigned to IV iron or oral iron experienced similar increases in SF-36 scores and decreases in Fatigue Linear Analog Scale Assessment scores, and between-group differences were not significant at any study interval (Bhandal & Russell, 2006).

There were one RCT and one observational study comparing iron sucrose with ferric carboxymaltose in women with PPA (Pfenniger *et al.,* 2012; Rathod *et al.,* 2015). Mean post-partum Hb ranged between 77 and 82 g L^{-1}. The RCT showed that, compared with iron sucrose, ferric carboxymaltose administration produced greater and more rapid increases of Hb and serum ferritin as well as a higher rate of anaemia correction at the end of follow up (the same was true for both IV iron preparations compared with oral iron) (Rathod *et al.,* 2015). In the observational study, no difference in efficacy was observed between iron sucrose and ferric carboxymaltose (Pfenniger *et al.,* 2012). Overall, there were no differences in transfusion exposure or drug-related adverse events in these studies. As stated above, IV iron formulations allowing the administration of single high doses are more convenient both for the patient and for the health system.

No serious, life-threatening adverse events or increases in post-partum infection rates attributable to IV iron were reported in the studies reviewed above. IV iron was superior to oral iron regarding gastrointestinal harms; however, anaphylaxis occurred in three women and cardiac events occurred in two women (more data are needed to establish whether this was caused by IV iron) (Markova *et al.,* 2015). This is in agreement with the European Medicines Agency's CHMP report concluding that the benefits of IV iron exceed its risks provided adequate measures are taken to minimise the risk of allergic reactions (EMA, 2013). All staff involved in IV iron administration should be aware of recommendations on the prevention and management of rare hypersensitivity reactions (Rampton *et al.,* 2014).

Transient decreases in serum phosphate are frequent among patients receiving IV ferric carboxymaltose but also among those receiving oral iron (Bhandal & Russell, 2006; Van Wyck *et al.,* 2007; Breymann *et al.,* 2008). Hypophosphataemia was asymptomatic and was not associated with reports of mortalities, adverse events or treatment discontinuation in this setting.

Breymann *et al.* did not observe a transfer of iron sucrose into maternal milk in women receiving a 100-mg dose during an observation period of 4 days (Breymann *et al.,* 2007). However, mean iron values in breast milk increased transitorily after ferric carboxymaltose administration (mean dose, 1350 mg) (Breymann *et al.,* 2008) or iron isomaltoside 1000 (1200 mg) (Holm *et al.,* 2017) when compared to control, although no differences in breastfed infant outcomes were observed.

Currently available information suggests IV iron administration is beneficial, especially for patients with moderate to severe anaemia. However, a recent Cochrane review suggests that RCTs with clinical endpoints are needed (Markova *et al.,* 2015). Women should be informed about the potential side effects of IV iron therapy, and written information should be provided.

Recommendations

- ***Recommendation 25:*** We recommend that women with confirmed ID who fail to respond to the correct administration of oral iron (Hb increase <10 or 20 g L^{-1} in 2 or 4 weeks, respectively) or are intolerant to oral iron be switched to IV iron (1B).
- ***Recommendation 26:*** We recommend the administration of IV iron to cover individually calculated total ID in women with moderate to severe PPA (Hb <90 g L^{-1}) (1B).

Good practice points

- IV iron should not be given together with oral iron or in the presence of an active infection.
- Staff should be trained to detect, evaluate and manage hypersensitivity reactions in accordance with published guidelines.

Treatment: Erythropoiesis-stimulating agents

Women with a higher post-partum inflammatory response (e.g. after caesarean section) may show a poor response to iron therapy, an inadequate erythropoietin secretion for the level of anaemia and/or blunted response to endogenous erythropoietin, as seen in anaemia of chronic diseases (Weiss & Goodnough, 2005). These women, as well as those severely anaemic refusing blood transfusion, may benefit from adjuvant therapy with an ESA, but the quality of the evidence is moderate to low.

There are two RCTs including a total 114 women with moderate to severe PPA who received oral iron sulphate (80 – 200 mg day^{-1}) or oral iron sulphate plus ESA (rHuEPO 40 000 – 180 000 IU) and were followed up for 6 weeks (Huch *et al.,* 1992; Makrydimas *et al.,* 1998). Compared with oral iron alone, rHuEPO plus oral iron resulted in faster Hb increments during treatment, higher Hb increments at 6 weeks, similar rates

of drug-related adverse events and no significant differences in transfusion rates, which were very low (Table S4).

There are five RCTs including a total of 272 women with moderate to severe PPA who received iron sucrose (300–1600 mg) or iron sucrose plus ESA (rHuEPO 20 000–40 000 IU) and were followed up for between 2 and 6 weeks (Lebrecht *et al.,* 1995; Breymann *et al.,* 1996; Breymann *et al.,* 2000; Wågström *et al.,* 2007; Krafft & Breymann, 2011). Most women also received oral iron (80–160 mg day^{-1}) after discharge. Compared to IV iron alone, rHuEPO plus IV iron resulted in a trend to faster Hb increment during treatment, similar Hb and ferritin increments at the end of the study period, similar rates of drug-related adverse events and no significant differences in transfusion rates, which were very low. The benefit seemed to be greatest in the blunted erythropoiesis subgroup with elevated C-reactive protein levels after caesarean section (Breymann *et al.,* 1996; Krafft & Breymann, 2011) (Table S3).

No serious, life-threatening adverse events attributable to ESA therapy were reported in the studies reviewed above. However, it must be remembered that in pregnant women without chronic kidney disease, administration of ESAs is off label. Women should be informed of potential side effects, and written information should be provided.

Recommendation

- ***Recommendation 27:*** In severely anaemic patients with blunted erythropoiesis due to infection and/or inflammation and not responding adequately to IV iron treatment, as well as in severely anaemic patients who refuse blood transfusion, we suggest considering treatment with an ESA after consultation with the haematologist (2B).

Treatment: Red blood cell transfusion

The 2009–2012 MBRRACCE-UK Perinatal Mortality Surveillance Report identified 17 direct mortalities due to obstetric haemorrhage (Knight *et al.,* 2014). Three of these women were anaemic antenatally. The report included a review of how care could have been improved and suggested actions including follow up of abnormal blood results and treatment of antenatal anaemia. The decision to prescribe RBC transfusion is mainly based on post-partum Hb concentration: RBC transfusion may be recommended when the Hb concentration is $<60\ g\ L^{-1}$, whereas it is rarely appropriate in women with an Hb concentration $>90\ g\ L^{-1}$.

In a series of 1954 Finnish women with moderate PPA (Hb $70–100\ g\ L^{-1}$), 13.3% received 1–2 RBC units (Palo *et al.,* 2007). RBC transfusions resulted in higher Hb levels on discharge but had no impact on length of hospital stay. Thus, in the absence of risk of bleeding, cardiac compromise or symptoms requiring immediate attention, transfusion is unlikely to be appropriate when the Hb is $70–90\ g\ L^{-1}$.

In a recent non-inferiority trial, 521 women with acute anaemia (estimated blood loss >1000 mL, Hb $48–79\ g\ L^{-1}$, 12–24 h post-partum) who did not have severe symptoms of anaemia or severe comorbidities were randomised to non-intervention (iron and folic acid supplementation; RBC transfusion permitted in case of severe symptoms of anaemia) or RBC transfusion (target Hb $\geq 89\ g\ L^{-1}$) (Prick *et al.,* 2014a, 2014b). Overall, 517 RBC units were transfused in the intervention arm vs 88 in the non-intervention arm. Adverse events and Hb concentration at 6 weeks were comparable. Although non-inferiority could not be demonstrated, there was only a small difference in physical fatigue at 3 and 7 days post-partum and no differences in secondary outcomes. Additionally, a cost-effectiveness analysis showed that RBC transfusion was, on average, €249 more expensive than non-intervention (Prick *et al.,* 2014a, 2014b).

Although the implementation of a restrictive approach seems clinically justified, RBC transfusions were needed in 33 (12.6%) women in the non-intervention group (Prick *et al.,* 2014a, 2014b). Using data from 262 randomised and 362 non-randomised women, the authors derived a model where clinical variables (primiparity, multiple pregnancy, total blood loss during delivery >1500 mL and Hb concentration 12–24 h post-partum) and HRQoL were independent predictors for the need of RBC transfusion (Prick *et al.,* 2015). This model may be an important tool for patient counselling and decision making in clinical practice.

In summary, RBC transfusion should be restricted to severely anaemic women who develop circulatory instability due to PPH, should be given in the minimal amount required to stabilise the patient and should be followed by pharmacological treatment of anaemia.

Recommendations

- ***Recommendation 28:*** We recommend that all pregnant women should be ABO and D typed and screened for the presence of red cell antibodies early in pregnancy (at booking) and at 28 weeks gestation. In D-negative women, the 28-week sample should be taken before the administration of routine antenatal anti-D Ig prophylaxis (1B) (White *et al.,* 2016).
- ***Recommendation 29:*** We recommend that RBC transfusion not be dictated by Hb levels alone (1C).
- ***Recommendation 30:*** We recommend that transfusion be considered in non-bleeding patients with an Hb $<60\ g\ L^{-1}$, taking clinical signs and symptoms (risk of bleeding, cardiac compromise or symptoms requiring immediate attention) into consideration (1A).
- ***Recommendation 31:*** In the absence of bleeding, should transfusion be deemed necessary, we recommend a single-unit transfusion followed by clinical reassessment and/or Hb measurement to determine the need for further transfusion (1C).

Good practice points

- In post-partum women who refuse RBC transfusions and are not actively bleeding, there is the option of using a

plasma expander, IV iron and ESA for the treatment of anaemia.

- Women receiving RBC transfusion should be given full information regarding the indication(s) for transfusion and alternatives available. Consent should be given by the patient and documented in the clinical notes.

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DISCLAIMER

The authors are responsible for the views expressed in this article, which do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated. They have aimed high and provided what they consider at the present to be 'optimal' guidelines. However, they also acknowledge that the evidence is not clear-cut for all circumstances. Feasibility, costs, values and preferences and balance of harms–benefits need to be considered in the adoption and adaptation of these recommendations. Budget, equipment and capacity also need consideration. Therefore, these recommendations have to be adapted to the specific situations, the resources and the strategies of the individual countries and regions.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. The three pillars of patient blood management.
Figure S2. The relationship between anaemia, transfusion and adverse events.
Figure S3. The grading system used to evaluate the quality of the evidence and grade recommendations.
Table S1. Complications/adverse effects of anaemia during pregnancy.
Table S2. Some characteristics of the different intravenous iron formulations.
Table S3. Clinical studies of intravenous iron intravenous iron and/or erythropoiesis-stimulating agents for the treatment of iron-deficiency anaemia in pregnancy.
Table S4. Clinical studies of intravenous iron and/or erythropoiesis-stimulating agents for the treatment of iron-deficiency anaemia in the postpartum period.
Annex S1. Diagnosis of vitamin B_{12} and folic acid deficiency.