

## REVIEW ARTICLE

## Gynecology

# Expert consensus on improving iron deficiency anemia management in obstetrics and gynecology in Asia

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## Abstract

Iron deficiency anemia (IDA) is a major health burden among women in Asia. Key issues in IDA management in Asia are under-diagnosis and under-treatment. The lack of Asia-specific guidelines, and suboptimal utilization of treatment compounds the management of IDA. To address these gaps, a panel of 12 experts in obstetrics, gynecology, and hematology from six regions in Asia convened to review current practices and clinical evidence and provide practical guidance on IDA diagnosis and management in Asian women. The Delphi approach was used to obtain objective opinions and attain consensus on statements pertaining to awareness, diagnosis, and management of IDA. In total, 79 statements attained consensus and are summarized to provide guidance on raising awareness of IDA and approaches for improved diagnosis and treatment of IDA among women in various settings: pregnancy, postpartum, heavy menstrual bleeding, gynecologic cancers, and perioperative care. This clinician-led consensus integrates appropriate recommendations based on clinical evidence and best practices and is intended to guide decision making in the management of iron deficiency/IDA in women. The expert panel raises a call for timely diagnosis and utilization of appropriate treatment, including use of high-dose intravenous iron, stringent blood management, and interdisciplinary collaboration, for optimization of IDA management among women in Asia.

## KEYWORDS

Asia, consensus, gynecology, iron deficiency anemia, obstetrics

## 1 | INTRODUCTION

Anemia is a global public health burden affecting an estimated 2.36 billion individuals.<sup>1</sup> Women of reproductive age are at an increased risk of anemia due to menstrual blood loss and increased demands due to repeated pregnancies and childbirths.<sup>2</sup> The World Health Organization (WHO) estimates a global anemia prevalence of 41.8% in pregnant women and 30.2% in non-pregnant women. The highest burden of anemia is found in Africa and South-East Asia.<sup>3</sup> In a recently published national survey, more than half (52%) of pregnant women, and 47% of non-pregnant women in South and Southeast Asia were anemic, indicating the need for increased awareness and solutions to address the condition in these regions.<sup>2</sup>

Iron deficiency is the most common cause of anemia, accounting for half the cases and is the fourth leading cause of disability worldwide.<sup>2,4</sup> Failure to correct anemia in women impairs quality of life, physical capacity, and productivity, which overall leads to the high global burden of disease from both societal and economic perspectives.<sup>5</sup> Uncorrected iron deficiency anemia (IDA) in pregnancy can lead to serious maternal and neonatal consequences such as increased risk of postpartum hemorrhage, postpartum depression, maternal mortality, low birth weight, preterm birth, and higher risk of perinatal and neonatal mortality.<sup>6</sup> Heavy menstrual bleeding, which is a common cause of IDA, adversely impacts quality of life in women of reproductive age.<sup>7</sup> In patients with gynecologic cancers, anemia has been shown to result in impaired physical performance and quality of life, increased need for transfusions, and poor survival.<sup>8-10</sup> Another area of concern is the prevalence of preoperative anemia, which has a direct correlation with the risks of postoperative morbidity and mortality.<sup>11,12</sup>

While the World Health Assembly aims to halve the anemia incidence in women of reproductive age by 2025, no country in South Asia is prepared to reach this target.<sup>13,14</sup> Low socioeconomic and nutritional status, repeated pregnancies, and parasitic infections are the main reasons for IDA in South Asian women.<sup>2</sup> IDA is often under-diagnosed and under-treated, partly due to non-specific symptoms overlapping with underlying conditions, poor awareness of updated international clinical guidelines, and the utility of treatment options.<sup>15-17</sup>

In the management of iron deficiency/IDA, oral iron is an efficacious first-line treatment option suitable for most obstetrical and gynecologic patients.<sup>18</sup> However, physicians need to be aware that the efficacy of oral iron may be limited by poor tolerance or adherence, underlying inflammation, severe anemia, and situations that need rapid replenishment of iron stores and anemia correction.<sup>18</sup> In these instances, parenteral iron may be useful and should be considered as first-line therapy.<sup>18</sup> Current formulations of parenteral iron consist of both low-dose intravenous iron and high-dose intravenous iron. Factors that are taken into consideration in making this choice are the extent of iron deficit, patients' convenience in single or multiple administrations, and available clinical data.<sup>19</sup> In addition, clinicians should be aware of the differences in potential adverse events with oral and intravenous iron, and their management strategies. Blood transfusion is used to manage the effects of hemorrhage and improve oxygen delivery but could lead to serious infectious

and non-infectious complications and is best reserved for life-saving conditions.<sup>20</sup> Importantly, transfusions only provide temporary respite against anemia, and do not improve iron stores or treat the underlying cause of iron deficiency.<sup>21</sup> As the coronavirus disease 2019 pandemic further exacerbates the blood shortage situations in many countries, improved patient blood management strategies, including anemia correction, are required.<sup>22</sup>

In recent years, important progress has been made in the diagnosis and management of iron deficiency/IDA, blood management strategies, and availability of treatment modalities such as high-dose intravenous iron in Asia. In conjunction with efforts to update guidelines internationally and a current lack of Asia-specific guidelines, this expert panel was convened to review the clinical evidence and current practices, to develop practical guidance on the diagnosis and management of IDA among women in Asia.

## 2 | METHODOLOGY

The study aimed to identify key challenges in the diagnosis of IDA, review current treatment options, and develop guiding statements on the diagnosis and clinical management of IDA among women in Asia. According to WHO, anemia is defined as a hemoglobin level below 12.0g/dL in non-pregnant female adults, and below 11.0g/dL in pregnant women.<sup>21</sup>

A literature search was conducted and articles in English published between January 2000 and October 2020 were extracted. Search terms used were "anemia", "iron deficiency", "iron deficiency anemia", "consensus", "guidelines", "recommendations", "iron therapy", "oral iron", and "intravenous iron". For focused clinical topics, additional specific terms were used: "heavy menstrual bleeding", "pregnancy", "postpartum", and "women in childbearing age", "preoperative anemia", "cancer and oncology", "gynecological surgery", "international", and "Asia".

Publications were prioritized with international society guidelines and expert opinions considered to be of the highest level of evidence, followed by randomized controlled trials in therapeutic areas, meta-analysis of randomized controlled trials, reviews, and clinical case reports/studies.

Following the literature review, statements pertaining to clinical questions on diagnosis and treatment of IDA were generated. The guidelines provided initial statements on diagnosis and treatment, which were subsequently modified and expanded according to expert opinions and clinical studies.

Experts for this Asia working group were convened based on their clinical experience and expertise in managing IDA in women. An expert had to have robust knowledge of current best practices in IDA management and have led their respective institutions or professional medical associations/societies in activities such as the development of IDA management guidelines at national and regional levels. Based on these criteria, a 12-member working group of experts in obstetrics, gynecology, and hematology from across six regions in Asia (Hong Kong, Malaysia, the Philippines, Taiwan, Thailand, and Vietnam) was formed.

Consensus on statements was achieved with an iterative Delphi approach. Sequential surveys, comprising the generated statements, were administered to the panel. The experts were asked to rate each statement based on available evidence and their personal clinical experience, whether the statement was clear ("yes" or "no"), whether the statement should be included (1 = "definitely exclude" to 9 = "definitely include") and whether any comments were required to help in clarifying the meaning of the statement.

All statements were analyzed to determine whether they should be included in the final recommendations, with or without modifications, according to the Delphi technique inclusion criteria (Table 1). Group ratings included median score, percentage of panel rating the statement at least 8, and decision on inclusion as a consensus (definitely include, maybe include, definitely exclude, or to review).

### 3 | RESULTS

Completed responses were obtained from all 12 experts in the first round of the Delphi survey. Results of the first round, including individual and group ratings, were analyzed and presented to the expert panel through a group meeting.

After the first round of the Delphi review, 49 out of 79 (62.0%) statements reached consensus, 29 (36.7%) statements were reviewed and modified (i.e. median score of  $\geq 7$ , but  $< 70\%$  of panel rated  $\geq 8$ , and  $< 100\%$  of panel understand the statement), and one statement was excluded. For statements that needed to be reviewed, the working group conducted a thorough discussion and refinements were proposed. The re-formulated statements were then put through a second round of Delphi survey. Of the 29 statements reviewed and re-formulated, all statements reached the threshold of

TABLE 1 Delphi technique inclusion criteria.

Statement result outcomes	Threshold applied
1. Definitely include (Consensus)	$\geq 80\%$ of panel rate statement as $\geq 8$ OR Median rating of $\geq 8$
2. Maybe include (Critical consensus)	$70\%$ of panel rate statement as $\geq 8$ OR Median rating of $\geq 6$
3. Definitely exclude	$< 70\%$ of panel rate statement as $\geq 8$ AND 100% of panel understand statement OR Median $\leq 5$ AND 100% of panel understand statement (i.e., low scores are not due to lack of understanding of item)
4. To review	Major revisions suggested OR $< 70\%$ of panel rate statement as $\geq 8$ AND $< 100\%$ of panel understand statement (i.e., low scores are due to lack of understanding of item)

inclusion and were accepted. In total, 78 statements reached consensus after reviewing, as shown in Table 2.

The final statements were collated to develop consensus recommendations on the need to raise awareness among physicians (Table 3), diagnosis of IDA in Asia (Table 4), management and treatment of IDA in pregnancy (Table 5) and postpartum period (Table 6), as well as management of IDA in heavy menstrual bleeding (Table 7), gynecologic cancer (Table 8), and preoperative anemia (Table 9). A brief summary of the implications of IDA and the need for consensus statements to optimize the diagnosis and management of IDA in each indication category has been described below.

#### 3.1 | Raising awareness about anemia and its consequences

Clinicians should keep abreast of advances in anemia management as it has important implications for the health, productivity, and well-being of society.<sup>5</sup> The management of anemia should be a key focus of clinical practice so as to reduce complications and improve productivity and quality of life in women.<sup>5</sup>

#### 3.2 | Diagnosis of iron deficiency

Iron is essential for key biologic functions such as respiration, energy production, DNA synthesis, and cell proliferation.<sup>23</sup> Iron also plays an important role in erythropoiesis and oxygen transport.<sup>15</sup> Iron deficiency frequently manifests clinically as anemia. While iron deficiency is the main cause and hence should be tested upon suspicion of anemia, iron stores can be reduced in the absence of anemia and hence easily overlooked.<sup>24</sup>

#### 3.3 | Iron deficiency anemia in pregnancy

During pregnancy, low existing iron stores and a steep increase in demand magnify the risk of IDA.<sup>25,26</sup> IDA during pregnancy can lead to maternal fatigue, reduced mental performance, reduced lactation, infection, and postpartum depression, and can increase the risk of blood transfusion.<sup>16</sup> IDA in the first and second trimesters of pregnancy is associated with a two-fold increased risk of preterm delivery and a three-fold increased risk of low-birth-weight baby. IDA in pregnancy is also associated with increased perinatal and neonatal mortality, and higher prevalence of disease in later life.<sup>5,6</sup>

#### 3.4 | Postpartum iron deficiency anemia

Despite being a major health concern in developing countries with a prevalence rate of 50%–80%, postpartum anemia is under-appreciated because of a lack of awareness and quick discharge of women following delivery.<sup>27,28</sup> Postpartum anemia impairs maternal cognitive

TABLE 2 Consolidated results of Delphi survey outcome for both rounds.

Section	Title	Delphi round 1					Delphi round 2 (Revised statements)					Final number
		Total statements	Definitely include	Maybe include	Definitely exclude	Review	Definitely include	Maybe include	Definitely exclude	Review		
Section 1	Raising awareness of IDA and its consequences	11	10			1	1					11
Section 2	Diagnosis of iron deficiency	7	6			1	1					7
Section 3	Treatment of IDA in pregnant women	16	6			10	10					16
Section 4	Treatment of IDA in postpartum women	11	3			8	8					11
Section 5	Treatment of IDA in heavy menstrual bleeding	10	6		1	3	3					9
Section 6	Treatment of IDA in women with gynecologic cancers	12	7			5	5					12
Section 7	Treatment and management of preoperative IDA	12	11			1	1					12
	Total	79	49		1	29	29					78

Abbreviation: IDA, iron deficiency anemia.

function and emotional stability, which is especially important during the critical period of maternal-child bonding.<sup>27</sup> Postpartum anemia can affect mother-infant interaction and consequently lead to cognitive delays in infants.<sup>29</sup> Furthermore, postpartum anemia increases risk of postpartum depression, risk of blood transfusion, length of hospital stay, and hospitalization costs.<sup>30,31</sup>

### 3.5 | Iron deficiency anemia associated with heavy menstrual bleeding

Heavy menstrual bleeding is defined as excessive menstrual blood loss that interferes with a woman's physical, social, or emotional quality of life.<sup>7</sup> At least one in four women are known to suffer from heavy menstrual bleeding; however, the numbers are expected to be much higher because of under-reporting of symptoms by patients.<sup>32</sup> Heavy menstrual bleeding-associated anemia increases the likelihood of blood transfusion, emergency admission, and overall costs in women hospitalized for gynecologic conditions.<sup>33</sup>

### 3.6 | Iron deficiency anemia in women with cancer

The incidence of anemia in patients with cancer varies from 20%–60% at the time of diagnosis to 60%–90% during cancer treatments.<sup>34</sup> The pathogenesis of IDA in cancer is multifactorial, ranging from inadequate dietary intake, inflammation, myelosuppression with chemotherapy and bone marrow infiltration by tumor cells to blood loss during surgery.<sup>8</sup> Anemia in these patients results in symptoms that affect quality of life, such as mental confusion, depression, nausea, and loss of appetite. It is also a strong predictor of poor survival.<sup>8,10</sup> Studies have also demonstrated that a decrease in the quality of life becomes apparent at hemoglobin levels of 10–11.5 g/dL.<sup>35,36</sup> Therefore, it is important for clinicians to be aware of the diagnosis considerations and treatment of patients even when anemia is mild.

### 3.7 | Preoperative iron deficiency anemia

Preoperative anemia increases the risk of postoperative morbidity and mortality and is a major problem in the Asia-Pacific region.<sup>11,12,37</sup> Preoperative IDA is an independent risk factor for 30-day postoperative adverse outcomes such as blood transfusion, surgical-site infection, and hospital re-admission in women undergoing procedures such as an elective hysterectomy or myomectomy.<sup>38,39</sup> Efforts must be taken to overcome reliance on blood transfusion for preoperative anemia correction, as it is a risk factor in itself for negative outcomes.

## 4 | DISCUSSION

This iron deficiency/IDA expert working group comprising leading obstetricians, gynecologists, and hematologists aimed to address

pertinent challenges in the diagnosis and management of iron deficiency/IDA in women. Similar to the use of the Delphi technique to drive previous consensus recommendations for conditions such as inflammatory bowel disease, pulmonary arterial hypertension, and anticoagulant therapy,<sup>40–42</sup> the current iterative Delphi approach reviewed current treatment options and clinical evidence, considered the real-world experience and expertise of the group, and facilitated robust discussions to drive agreement on these recommendations.<sup>43</sup> This is the first Delphi consensus to address iron deficiency/IDA among women in Asia.

### 4.1 | Iron deficiency/iron deficiency anemia and its implications in women

Iron deficiency/iron deficiency anemia is the leading cause of years lived with disability among women and is regularly encountered by clinicians. Iron deficiency can manifest clinically with or without anemia and can be asymptomatic. Symptoms of iron deficiency are typically not life-threatening and are often non-specific; these include fatigue, lethargy, alopecia, irritability, and pica. However, iron deficiency if left untreated can worsen the prognosis of patients with ischemic heart disease and heart failure. Similarly, preoperative anemia can lead to postoperative morbidity and mortality.

The expert consensus working group raised a call for increased awareness of this common condition to transform management approaches in obstetrical and gynecologic conditions. Clinicians need to be aware that iron deficiency/IDA can profoundly impair quality of life in women presenting with heavy menstrual bleeding, in postpartum women, and in gynecologic cancer patients. Diagnostic testing should be conducted as early as possible for women with heavy menstrual bleeding, placenta accreta, multiparity, or a short interval between pregnancies. Treatment of iron deficiency/IDA should be optimized and expected hematologic response rates achieved before any elective surgery/procedure, as preoperative iron deficiency/IDA is an independent predictor of perioperative blood transfusions, morbidity, and mortality. Interdisciplinary collaboration and awareness of patient blood management principles need to be customized and implemented especially for patients/procedures where blood loss is expected to be high, i.e., more than 500 mL, as this can positively impact patient outcomes. Regular education for clinicians on the risk-benefit of various iron therapies and other patient blood management concepts should be conducted to emphasize measures in anemia management.

### 4.2 | General considerations in diagnosis

The timely diagnosis of anemia allows for further prompt investigation of the underlying causes and choice of therapy option. In the various obstetrical and gynecologic conditions, slight variations in the definition of severe, moderate, and mild anemia in different

TABLE 3 Consensus on improving awareness on IDA.

1. It should be acknowledged that most pregnant women do not have adequate iron stores to meet the dramatic increase in requirements during the second and third trimester of pregnancy. The risk of IDA should be considered, and diagnostic testing should be prioritized in all pregnant women, especially in high-risk conditions such as history of heavy menstrual bleeding, multiparity, and short interval between pregnancies.
2. Postpartum anemia should be recognized as a significant problem, as it affects quality of life, cognitive function, and emotions and is linked to postpartum depression. Postpartum women should be followed up for early detection and treatment of IDA.
3. Clinicians should recognize heavy menstrual bleeding as a common cause of IDA affecting woman's physical, social, and emotional quality of life. Heavy menstrual bleeding increases the likelihood of blood transfusion, emergency admission, and costs in women hospitalized for gynecologic conditions.
4. Clinicians should be aware that ID without anemia is clinically relevant and can cause weakness and chronic fatigue and can impair quality of life in menstruating women.
5. Clinicians should be aware that preoperative anemia is a major, independent predictor of need for perioperative blood transfusion, and is linked to increased postoperative morbidity and mortality.
6. Clinicians should appreciate that preoperative iron deficiency anemia should be treated as early as possible before the scheduled surgical procedure in order to improve patient outcomes.
7. Interdisciplinary collaboration is essential for successful implementation of patient blood management strategies to reduce the need for transfusion and improve patient outcomes in anemic patients undergoing surgery.
8. Clinicians with expertise in patient blood management should advocate for and create awareness of the appropriate treatment of IDA in women of childbearing age, so as to reduce reliance on blood transfusions and avoid transfusion-related complications.
9. Clinicians should perceive the importance of anemia management in gynecologic cancer patients because it has a significant impact on quality of life and overall prognosis. Iron deficiency should be recognized as a major and potentially treatable contributor to anemia in cancer patients.
10. The limitations of oral iron treatment and efficacy of intravenous iron in increasing hematologic response rates and decreasing transfusions should be acknowledged. Continuing physician education is essential to improve familiarity with use of intravenous iron products.
11. Educational efforts should be directed towards highlighting the risk-benefit profile of oral and intravenous iron for adequate and timely anemia management.

Abbreviation: IDA, iron deficiency anemia.

Asian countries are acknowledged. The group agreed to adopt the WHO recommendations in defining anemia in women as hemoglobin of 11 g/dL or less. During pregnancy, there were slight differences in hemoglobin levels used to define anemia in available international guidelines. WHO defines anemia during pregnancy as hemoglobin of 11 g/dL or less,<sup>3</sup> the Center for Disease Control and Prevention has a cut-off of hemoglobin less than 11 g/dL in the first

and third trimesters and less than 10.5 g/dL in the second trimester,<sup>44</sup> and most recently, the British Society for Hematology guidelines defined anemia in pregnancy as hemoglobin less than 11 g/dL in the first trimester and less than 10.5 g/dL in the second and third trimesters.<sup>6</sup> Based on the diversity of practices in Asia, the group reached a consensus to adopt WHO recommendations in defining anemia in pregnancy as hemoglobin 11 g/dL or less.

There was a clear emphasis that clinicians should familiarize themselves with iron deficiency diagnosis methods and considerations as it is the leading cause of anemia. Serum ferritin is recognized as the mainstay for detecting iron deficiency, with a value of less than 30 ng/mL as highly suggestive of iron deficiency.<sup>18,45</sup> In pregnant women, hemoglobin above 11 g/dL and low serum ferritin (<30 ng/mL) are diagnostic of iron deficiency, whereas low hemoglobin (<11 g/dL) and low serum ferritin (<30 ng/mL) are diagnostic of IDA. The presence of iron deficiency even in the absence of symptoms is still significant because it predisposes women to depleting iron stores and impending IDA. Clinicians should also be aware that serum ferritin is an acute-phase reactant, which may be elevated (>30 ng/mL) during infection, liver disease, obesity, inflammation, surgery, or childbirth.<sup>18,46</sup> In situations where serum ferritin is unreliable as a single marker, measurement of transferrin saturation levels will be useful if iron deficiency/IDA is suspected in patients with low hemoglobin. For ferritin levels within the range of 30–50 ng/mL, a transferrin saturation less than 20% indicates iron deficiency.<sup>45</sup> Alternatively, where transferrin saturation testing is not readily available, a higher ferritin cut-off value of less than 100 ng/mL can be used to detect IDA when there is confirmed inflammation and/or cancer.<sup>23,47</sup>

Within certain regions in Asia, the thalassemia trait is prevalent and can be found in as much as 20% of the population.<sup>48</sup> Microcytosis (low mean corpuscular volume) and a low mean corpuscular hemoglobin concentration are present in both IDA and thalassemia trait. Hemoglobin is often low in these patients and confounds diagnosis between IDA and/or thalassemia. In such cases, serum ferritin should be measured to assess body iron stores and hemoglobin electrophoresis should be used to rule out thalassemia.<sup>49</sup> Specialized tests such as serum soluble transferrin receptor (sTfR) concentrations and the ferritin index (sTfR level/log ferritin) can be used. The main drawback here is that these assays are scarce, and thresholds have not been standardized. Obstetricians and gynecologists should work together with hematologists in the management of thalassemic women to reduce the risk of iron deficiency/IDA-related complications. Co-management by obstetricians, gynecologists, and hematologists should also be undertaken where intestinal worm colonization and malaria are suspected.

### 4.3 | Treatment options and general considerations

Oral iron is convenient, inexpensive, and is available in different doses and formulations.<sup>23</sup> It is still widely recommended as the first-line treatment in women with heavy menstrual bleeding,<sup>32</sup>

TABLE 4 Consensus on diagnosis of IDA in women.

1. Diagnostic screening for IDA should include hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, and serum ferritin levels.
2. Serum ferritin level has the highest sensitivity and specificity for detecting iron deficiency. Serum ferritin level of <30 ng/mL is diagnostic of iron deficiency.
3. As serum ferritin is an acute-phase reactant, it can be raised in inflammatory conditions or with suspected infections. Transferrin saturation, sTfR concentrations, and ferritin index (sTfR level/log ferritin) may be helpful for diagnosis in these situations.
4. All patients with suspected ID/IDA should be evaluated to determine underlying cause of anemia. Other causes of anemia such as thalassemia and vitamin B12 deficiency should be excluded. Presence of inflammation, malabsorption, and intestinal worm colonization should be considered.
5. Prevalence of thalassemia and malaria in some regions of Asia can confound the diagnosis of IDA. The cause of anemia should be identified before determining treatment.
6. Microcytosis and a low mean corpuscular hemoglobin concentration are present in both IDA and thalassemia traits. In these patients, serum ferritin levels should be measured to assess body iron stores and hemoglobin electrophoresis should be used to rule out thalassemia.
7. Iron deficiency and malaria can cause anemia during pregnancy, which increases the risk of poor maternal and fetal outcomes. In endemic areas, integrated interventions for malaria and anemia prevention in pregnant women are necessary.

Abbreviations: IDA, iron deficiency anemia; sTfR, soluble transferrin receptor.

for mild anemia in the first and second trimester of pregnancy, and in the postpartum period,<sup>6,45</sup> with dosing based on elemental iron content and bioavailability.<sup>18</sup> Traditionally, a daily dose of 100–200 mg of elemental iron is recommended.<sup>23</sup> However, these doses are associated with gastrointestinal symptoms in up to 70% of patients, which limits therapy compliance.<sup>50,51</sup> Patients should be counseled to avoid antacids and foods that bind iron and impair absorption.<sup>52</sup> Recently, findings have also cast doubt on the role of vitamin C in enhancing the absorption of oral iron,<sup>6</sup> as comparable hemoglobin increases were observed in patients taking oral iron with or without vitamin C.<sup>53</sup> Table 10 summarizes the available doses and elemental iron content of common oral iron preparations.<sup>54</sup>

The optimal oral iron regimen has also been redefined with increased knowledge of the role of hepcidin. Hepcidin is a peptide hormone secreted by the liver that maintains iron homeostasis by adjusting plasma iron fluctuations. A high level of iron stimulates hepcidin to reduce iron absorption, while iron deficiency inhibits hepcidin and thus, increases iron absorption.<sup>23</sup> Higher doses of oral iron in divided doses given twice or thrice daily are likely to be ineffective. Recent studies revealed higher iron absorption when (1) oral iron is given at 100 mg instead of 200 mg, and (2) alternate day dosing at 120 mg compared to 60 mg twice daily.<sup>55,56</sup> Daily or twice daily oral elemental iron more than 60 mg has been shown to increase hepcidin for up to 24 h and decreases oral iron

TABLE 5 Consensus on management of IDA in pregnancy.

1. Anemia in pregnancy should be defined as Hb <11 g/dL.
2. Pregnant women should be screened for anemia at the first prenatal visit and at the beginning of the third trimester. If anemia is detected, further investigations should be conducted to determine its underlying cause. Women should also be monitored for response after treatment.
3. Pregnant women with IDA should receive iron supplementation as IDA increases the risk of maternal morbidity, preterm delivery, and low-birth-weight babies.
4. Oral iron is the current standard of care for treatment of IDA in pregnancy as it is convenient, inexpensive, and easily available.
5. Oral iron should be the first-line therapy for mild anemia (Hb 9–10.5 g/dL) in the first and second trimester, with a target Hb of ≥11 g/dL.
6. Patients should receive counseling on the correct way to take oral iron to allow better absorption and avoid food interactions. It should be taken on an empty stomach, with water.
7. Over-the-counter prenatal multivitamins may not contain sufficient elemental iron to be adequate as sole therapy for IDA. Furthermore, multivitamins may have minerals that interfere with iron absorption. Identifying the amount of elemental iron in these preparations is important.
8. Judicious dosing of oral iron is essential. Daily or twice daily dosing of oral elemental iron >60 mg may increase hepcidin levels and decrease absorption of iron. Alternate-day dosing should be considered to optimize iron absorption.
9. Follow-up Hb levels should be measured after 2–3 weeks of oral iron therapy. Once Hb is normalized, oral iron should be continued for another 3 months or until at least 6 weeks postpartum to replenish iron stores.
10. A patient may be considered a poor responder to oral iron if the level of Hb does not increase by 1 g/dL after 2–3 weeks. After addressing causes for poor response, intravenous iron may be considered.
11. Intravenous iron can be considered in the second and third trimester if oral iron is not well tolerated, ineffective (increase in Hb <1 g/dL, or Hb remains <10 g/dL after 2–3 weeks of treatment), or if there is lack of compliance.
12. Intravenous iron should be recommended as first-line therapy in women presenting with IDA (Hb <10 g/dL) after 34 weeks of pregnancy. Rapid and effective anemia correction in these women is necessary to avoid the need for blood transfusion.
13. Intravenous iron may be considered when rapid repletion is necessary, in patients with risk factors such as coagulation disorders or placenta previa, and when complicated obstetrical surgery is anticipated.
14. Clinicians should be aware of the importance of judicious blood transfusion in anemic pregnant women as there is a higher risk of alloimmunization during pregnancy.
15. Blood transfusion may be considered in non-bleeding pregnant patients with symptomatic severe anemia, after taking clinical signs and symptoms into consideration.
16. If blood transfusion is deemed necessary in pregnant women with IDA, a single-unit transfusion should be followed by a clinical re-assessment to determine further management strategies.

Abbreviations: Hb, hemoglobin; IDA, iron deficiency anemia.

TABLE 6 Consensus on management of IDA in postpartum period.

1. Women with risk factors for postpartum hemorrhage should be considered at high risk of postpartum anemia.
2. Hemoglobin levels should be checked after delivery in cases of increased blood loss, in uncorrected anemia during the prenatal period, or in patients with symptoms of anemia.
3. Women presenting with postpartum depression should be screened for anemia within 6 weeks or during the first routine postpartum check-up, whichever is earlier.
4. Postpartum anemia can be defined as Hb  $\leq 10$  g/dL at 24–48 h post-delivery,  $< 11$  g/dL 1 week after delivery, and  $< 12$  g/dL 8 weeks after delivery.
5. Serum ferritin is not helpful in diagnosing postpartum iron deficiency, as it may be normal or elevated during the first 6 weeks post-delivery.
6. Mild postpartum IDA should be treated with oral iron, and patients should be monitored for treatment response until anemia is corrected.
7. A postpartum patient with IDA may be considered a poor responder to oral iron if Hb does not increase by 1 g/dL after 2–3 weeks. After addressing causes for poor response, she may be considered for intravenous iron.
8. Postpartum women who were previously intolerant or poor responders to oral iron should be considered for intravenous iron.
9. In postpartum women with moderate to severe IDA, intravenous iron should be considered as it confers a more rapid replenishment of iron stores and normalization of Hb levels.
10. Asymptomatic, severe postpartum anemia should be treated with intravenous iron. If response to intravenous iron is not rapid enough, judicious blood transfusion may be recommended.
11. The decision to transfuse women in the postpartum period should depend on the presence of bleeding risk, cardiac compromise, or symptoms requiring urgent attention.

Abbreviations: Hb, hemoglobin; IDA, iron deficiency anemia.

absorption the next day.<sup>57</sup> Further larger studies will be needed to define the optimal dose for alternate day dosing. The working group recognized that better understanding of hepcidin among clinicians would be beneficial in determining the optimal dosing of oral iron and suggested the use of alternate day dosing to optimize bioavailability of iron.

In terms of clinicians' expectations of treatment response to oral iron, the working group agreed that a patient might be considered a poor responder to oral iron if hemoglobin does not increase by 1 g/dL after 2–3 weeks, after addressing the cause for poor response. Poor response to oral iron could be due to inadequate intake (non-compliance, insufficient iron content in supplement) or inadequate absorption (concomitant consumption of inhibitors of iron absorption, intestinal mucosal disorders, *Helicobacter pylori* infection, impaired gastric acid secretion). Ongoing blood loss and coexisting conditions interfering with bone marrow response (vitamin B12 or folate deficiency, primary bone marrow disease, inflammation) may also contribute to a poor response.<sup>50</sup> For woman with factors known

TABLE 7 Consensus on IDA management in heavy menstrual bleeding.

1. Treatment of heavy menstrual bleeding-associated IDA should include addressing the underlying cause of heavy menstrual bleeding and correcting anemia with iron repletion therapy.
2. Oral iron should be used as first-line treatment for IDA in patients with heavy menstrual bleeding. Patients achieving increased Hb ( $\geq 1$  g/dL over 2–3 weeks) should continue oral iron to reach the target Hb  $\geq 12$  g/dL, serum ferritin  $\geq 30$  mg/L, and transferrin saturation  $> 20\%$ .
3. In the absence of active bleeding, a patient with IDA due to heavy menstrual bleeding is considered a poor responder or is non-compliant if her Hb does not increase by at least 1 g/dL after 2–3 weeks of oral iron treatment.
4. When planning surgery in anemic patients with heavy menstrual bleeding, clinicians should be aware of the time needed for oral iron to normalize Hb levels. Oral iron may not raise Hb levels sufficiently if time to surgery is limited.
5. High-dose intravenous iron may be recommended for patients who are intolerant or poorly responsive to oral iron, or when rapid repletion is necessary (e.g., short interval to surgery and severe IDA not requiring transfusion).
6. In patients with heavy menstrual bleeding scheduled for surgery in less than 1 month, high-dose intravenous iron should be recommended for its rapid replenishment of iron stores and correction of anemia.
7. The decision to transfuse patients with heavy menstrual bleeding should depend on the hemodynamic status and presence of active bleeding, not solely on the Hb level. Blood transfusion may be considered in asymptomatic patients with Hb  $\leq 5$  g/dL, and symptomatic patients with Hb  $\leq 6$  g/dL.
8. If a blood transfusion is medically necessary, transfusion of one unit of packed red cells is recommended, after which there should be a reassessment of hemodynamic status.
9. If transfusion is clinically indicated in women with heavy menstrual bleeding, restrictive transfusion is recommended to reduce transfusion-related complications and risk of hemolytic disease of newborn in future pregnancies.

Abbreviations: Hb, hemoglobin; IDA, iron deficiency anemia.

to limit their response to oral iron, intravenous iron may be considered after discussion with the patient.

Parenteral iron preparations are newer-generation treatment modalities that can be considered for patients who are intolerant or who respond poorly to oral therapy, or when rapid repletion is necessary (e.g., third trimester of pregnancy, postpartum, perioperative setting).<sup>45</sup> Table 11 summarizes the standard dosing of commonly available parenteral iron preparations.<sup>54</sup> Intravenous iron infusion rapidly replenishes iron stores, resulting in peak ferritin levels at 7–9 days. In most patients, hemoglobin levels should increase within 2–3 weeks.<sup>52</sup>

The efficacy and safety of high-dose intravenous iron has been demonstrated in a number of randomized controlled trials and meta-analyses, in which pregnant women receiving intravenous iron achieved target hemoglobin more often, had higher increases in hemoglobin level after 4 weeks, and experienced fewer adverse effects compared with oral iron.<sup>58,59</sup> In the postpartum period and

TABLE 8 Consensus on IDA management in gynecologic cancer.

1. Physicians should be aware that cancer-related anemia has a negative impact on quality of life and is an independent predictor of poor prognosis in cancer patients. Fatigue is the most debilitating symptom of anemia, along with impaired mental capacity, confusion, and depression.
2. Physicians should be aware that cancer-related anemia can result in delays in chemotherapy, limit the chemotherapy dose, and may affect survival.
3. There is a high prevalence of iron deficiency in patients with cancer. Iron studies should be conducted in anemic gynecologic cancer patients.
4. As patients with gynecologic cancers may have underlying liver dysfunction and/or inflammation, absolute iron deficiency should be defined as serum ferritin <100 ng/mL, and functional iron deficiency should be defined as serum ferritin >100 ng/mL with transferrin saturation <20%.
5. Oral iron therapy may not be suitable for treatment of anemia in patients with gynecologic cancers due to the underlying inflammation, gastrointestinal discomfort, malabsorption, and multiple concomitant oral medications.
6. Oral iron may be insufficient for correcting severe iron deficiency before commencement of chemotherapy/radiotherapy for gynecologic cancer.
7. Intravenous iron should be used in cancer patients with anemia (Hb < 11 g/dL) and absolute or functional iron deficiency, before or during administration of erythropoietin-stimulating agents.
8. Intravenous iron offers substantial benefits in treatment of anemia in cancer patients. Intravenous iron significantly increases hematopoietic response rate and decreases the rate of blood transfusions with or without erythropoiesis-stimulating agents.
9. Gynecologic cancer patients with IDA, and on chemotherapy, should receive high-dose intravenous iron. Intravenous iron may be given before or after chemotherapy, or at the end of a treatment cycle.
10. If erythropoietin stimulation agents are required to correct anemia, the targeted Hb level should be no higher than 12 g/dL. Hb levels beyond 15 g/dL may enhance tumor progression and increase risk of thromboembolic and cardiovascular adverse events.
11. Preoperative anemia before onco-surgery should be recognized as an indication for intravenous iron therapy with the objective of decreasing blood transfusions in the perioperative period.
12. Red blood cell transfusion increases the risk of thrombotic and anaphylactic events and may decrease survival. It should be reserved for patients with severe anemic symptoms in need of rapid Hb improvement.

Abbreviations: Hb, hemoglobin; IDA, iron deficiency anemia.

in patients with heavy menstrual bleeding, intravenous iron has similarly demonstrated more effective responses and fewer gastrointestinal effects.<sup>60–65</sup> Depending on the stability of the carbohydrate shell that encapsulates the iron core in these parenteral irons, the amount of iron that can be delivered differs. For example, iron sucrose has a less stable shell and hence about 200 mg can be delivered (i.e., low dose), whereas higher single doses can be delivered in shorter times with iron polymaltose (up to 2000 mg

TABLE 9 Consensus on management of preoperative IDA.

1. Preoperative anemia is an independent predictor of perioperative blood transfusion.
2. Preoperative anemia is associated with higher perioperative and postoperative morbidity and mortality.
3. The presence and cause of anemia should be investigated in all surgical procedures with an expected blood loss >500 mL.
4. Preoperative IDA increases the risk of surgical site infection and hospital re-admissions and is associated with higher incidence of major adverse cardiac and cerebrovascular events and longer hospital stay.
5. In the preoperative setting, efforts should be made to detect IDA as early as possible to allow enough time for correction before surgery.
6. There is a high incidence of ID/IDA in women scheduled for major elective surgery. Optimization of preoperative anemia management protocol is essential to attenuate the combined risks of preoperative ID/IDA and transfusions.
7. Intravenous iron is a key intervention in a preoperative IDA management protocol as it provides better correction of functional iron deficiency and offers faster repletion of iron stores compared with oral iron.
8. Patients without anemia but with low ferritin levels may benefit from preoperative iron supplementation, especially for procedures where substantial bleeding is anticipated. Treatment with oral iron along with nutritional advice should be initiated immediately in these patients.
9. If surgery is within 6 weeks after the diagnosis of IDA, a course of intravenous iron should be given no later than 3–4 weeks before the scheduled procedure. This can result in an improvement in reticulocyte counts and hemoglobin levels, and in reduced transfusion requirements.
10. Use of intravenous iron before surgery results in reduction in blood transfusions, higher hemoglobin 4 weeks after discharge, replenishment of iron stores, and reduced hospital stay.
11. Implementation of patient blood management strategies at institutional level should be prioritized to reduce the need for transfusion and improve patient outcome. Multi-specialty collaboration between obstetricians, gynecologists, hematologists, anesthesiologists, and gastroenterologists is essential to optimize preoperative anemia management.
12. It is important to enhance patient blood management education for doctors, nurses, and patients, and reinforce the pathways for oral and intravenous iron in order to conserve blood.

Abbreviations: ID, iron deficiency; IDA, iron deficiency anemia.

over 60–120 min) and ferric carboxymaltose (15–20 mg/kg up to 1000 mg over a 15-min infusion). The newer formulations of intravenous iron, which can be delivered in higher single doses within a shorter time, have the potential advantage of reducing the number of clinical admissions/consultations, compared with intravenous iron formulations with lower maximum single dose, and hence, may be more convenient to the patients. In addition, the choice between low- and high-dose intravenous iron also depends on the iron deficit to be replenished and the urgency to correct such a deficit. Randomized controlled trials comparing low-dose

**TABLE 10** Commonly available oral iron preparations for the treatment of IDA.

Oral iron formulation	Dose per tablet (mg)	Elemental iron per tablet (mg)
Ferrous sulfate	325	65
Ferrous fumarate	325	106
Ferrous gluconate	325	35
Iron protein succinylate	100	18

Abbreviation: IDA, iron deficiency anemia.

and high-dose intravenous iron in pregnant or postpartum women, or in women with heavy menstrual bleeding have consistently demonstrated that high-dose intravenous iron resulted in more rapid replenishment of iron stores with significantly higher hemoglobin levels, and with fewer hospital visits and total doses.<sup>56,66–69</sup> There were no differences in the rates of local or systemic adverse drug reactions.

Intravenous iron should also be considered as first-line therapy for the treatment of iron deficiency/IDA in women with gynecologic cancers, as the main form of iron deficiency present is functional iron deficiency. In this setting, patients frequently report fatigue as the most debilitating symptom, and cancer related anemia may delay the start of chemotherapy/radiotherapy, or limit the treatment dose, and therefore, affect survival. Intravenous iron has been shown to significantly improve hematopoietic response rate and decrease blood transfusions with or without erythropoiesis-stimulating agents, which is useful as there may be some concerns regarding the long-term safety of these agents.<sup>70</sup> Taking into consideration the results of intravenous iron studies, the recent European Society for Medical Oncology guidelines prefer the use of high-dose intravenous iron for IDA treatment in these patients, whereas the National Comprehensive Cancer Network guidelines do not show preference between low- and high-dose intravenous iron.<sup>47,71</sup>

#### 4.4 | Effective anemia management to support judicious use of transfusions

The working group raised a concern that blood transfusions are commonly relied on for treatment of anemia in Asia. This is probably due to a lack of awareness of transfusion-associated complications or a lack of knowledge of appropriate treatment options. The working group would like to advocate that blood transfusions should be limited to symptomatic and more severe cases of IDA.<sup>72,73</sup> Regardless of the clinical setting, if blood transfusion is indicated, a single-unit transfusion followed by clinical re-assessment should be undertaken to determine further management strategies. This can be broadly applied across obstetrical and gynecologic conditions and procedures. There are also suitable and effective alternatives to transfusions. Intravenous iron has demonstrated its efficacy in reducing blood transfusion when rapid correction of anemia before surgery

**TABLE 11** Commonly available parenteral iron preparations for the treatment of IDA.

Intravenous iron formulations	Dose (mg)	Dose required to replete iron deficit
Ferric carboxymaltose	500	1–2
Ferric derisomaltose	1000	1
Ferumoxytol	510	1–2
Iron sucrose	200–300	4–5
Iron dextran (LMW)	1000	1

Abbreviations: IDA, iron deficiency anemia; LMW, low molecular weight.

is essential.<sup>74</sup> Similarly in gynecologic cancer patients, treatment with intravenous iron can significantly reduce the amounts of blood transfused and should be considered as standard of care in cancer patients.<sup>75,76</sup> The working group also reached a consensus on the implementation of WHO-recommended patient blood management to optimize hemoglobin levels in anemic patients undergoing surgery. Without patient blood management, 30%–54% of patients undergoing surgery would need blood transfusions, putting additional strain on the shrinking blood donor pools.<sup>37</sup> Reduction in reliance on blood transfusion is of particular value in resource-limited settings where lack of blood may delay emergency operations or cause cancellation of elective surgeries.<sup>37</sup>

The group encouraged clinicians to conduct a review of how and when diagnosis, risk assessment, and interventions for iron deficiency/IDA management can be implemented in their clinical practice. For example, patient blood management during pregnancy can be optimized through correction of anemia during pregnancy and before delivery, and hence minimizes the risk of severe blood loss during pregnancy.<sup>77</sup> Previous cesarean section, placenta previa, older maternal age, multiparity, pregnancy-induced hypertension, and diabetes must be considered as risk factors for postpartum hemorrhage.<sup>78</sup> With concrete patient blood management implementation steps and support from the hospital administration, the rates of anemic women presenting at delivery, and hence the associated complications including transfusions, will decrease over time.<sup>72,79,80</sup>

#### 4.5 | Strengths and limitations of the consensus

Several international and Asia-Pacific guidelines and expert consensus exist regarding IDA in women. However, these guidelines tend to concentrate on particular aspects of IDA within the obstetrical and gynecologic domain, and there are limited guidelines that address IDA in the Asian population. This research presents a more comprehensive strategy for IDA that spans multiple gynecologic conditions and specifically focuses on Asian women. **Table 12** presents a detailed comparison of the current expert consensus with existing international guidelines.<sup>6,7,16,47,81–87</sup>

Despite the inputs and consensus among leading obstetricians, gynecologists, and hematologists within Asia to generate these

TABLE 12 Comparison of expert consensus on improving iron deficiency anemia management in obstetrics and gynecology in Asia with other international guidelines.

Society	Origin (year)	Guideline name	Covers IDA in pregnancy	Covers IDA in postpartum period	Covers IDA in heavy menstrual bleeding	Covers IDA in gynecologic cancer	Covers postoperative IDA	Applicable to Asian settings
BSH	UK (2019)	UK guidelines on the management of iron deficiency in pregnancy	Yes	Yes	No	No	No	No
USPSTF	USA (2015)	Final recommendation statement: Iron deficiency anemia in pregnant women: screening and supplementation	Yes	Yes	No	No	No	No
WHO	Global (2016)	WHO recommendations on prenatal care for a positive pregnancy experience	Yes	Yes	No	No	No	Yes
N/A	Asia-Pacific (2011)	Expert recommendations for the diagnosis and treatment of iron deficiency anemia during pregnancy and the postpartum period in the Asia-Pacific region	Yes	Yes	No	No	No	Yes
N/A	Turkey (2015)	Diagnosis and treatment of iron deficiency anemia during pregnancy and the postpartum period: Iron deficiency anemia working group consensus report	Yes	Yes	No	No	No	Yes
NATA	Europe (2018)	Patient blood management in obstetrics: management of anemia and haematinic deficiencies in pregnancy and in the postpartum period: NATA consensus statement	Yes	Yes	No	No	No	No
ASH	USA (2018)	Evaluation and management of heavy menstrual bleeding in adolescents: the role of the hematologist	No	No	Yes	No	No	No

(Continues)

TABLE 12 (Continued)

Society	Origin (year)	Guideline name	Covers IDA in pregnancy	Covers IDA in postpartum period	Covers IDA in heavy menstrual bleeding	Covers IDA in gynecologic cancer	Covers postoperative IDA	Applicable to Asian settings
ACOG	USA (2019)	Screening and management of bleeding disorders in adolescents with heavy menstrual bleeding	No	No	Yes	No	No	No
SOGC	Canada (2018)	Gynecological and obstetric management of women with inherited bleeding disorders	No	No	Yes	No	No	No
ESMO	Europe (2018)	Management of anemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines	No	No	No	Yes	No	No
N/A	Global (2016)	International consensus statement on the perioperative management of anemia and iron deficiency	No	No	No	No	Yes	Yes
N/A	Asia (2023)	Current expert consensus on improving iron deficiency anemia management in obstetrics and gynecology in Asia	Yes	Yes	Yes	Yes	Yes	Yes

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; ASH, American Society of Hematology; BSH, British Society for Hematology; ESMO, European Society for Medical Oncology; IDA, iron deficiency anemia; N/A, not applicable; NATA, Network for the Advancement of Patient Blood Management, Hemostasis and Thrombosis; SOGC, Society of Obstetricians and Gynecologists of Canada; USPSTF, U.S. Preventive Services Task Force; WHO, World Health Organization.

statements, this study is not without its limitations. The working group was not representative of all Asian countries. Furthermore, the Delphi technique may not meet the rigorous standards conferred by other methods. However, given the similarities in anemia prevalence, environmental and socioeconomic factors, and healthcare resources in the region, the consensus generated by such a method may be best applicable to provide guidance on iron deficiency/IDA among obstetrics and gynecology patients in Asia.

The final 78 consensus statements included topics on raising awareness on the consequences of iron deficiency/IDA, and approaches to the diagnosis and treatment of iron deficiency/IDA in women in various settings: pregnancy, postpartum, women with heavy menstrual bleeding, cancers, and perioperatively.

Iron deficiency/iron deficiency anemia is a major public health burden in Asian women, with important implications on patient outcomes and healthcare resources. The clinician-led consensus statements arising from this Delphi approach integrate the appropriate recommendations based on clinical evidence and clinical experience and are intended to guide decision making in the management of female patients with iron deficiency/IDA.

#### AUTHOR CONTRIBUTIONS

All authors contributed to data curation, writing the original draft, writing—review and editing, and visualization. Tsin Wah Leung, Jameela Sathar, and Unnop Jaisamrarn provided supervision and project administration.

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#### CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

#### DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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