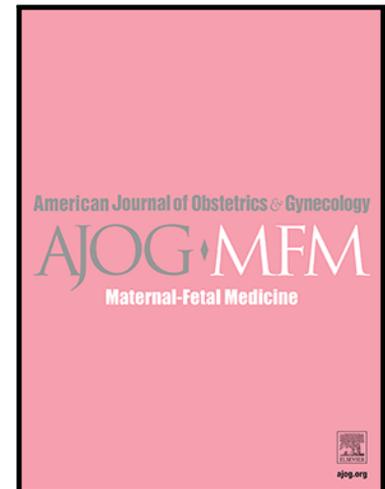# Journal Pre-proof

Recognizing who is at risk for postpartum hemorrhage: Targeting Anemic Women and Scoring Systems for Clinical Use

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Recognizing who is at risk for postpartum hemorrhage: Targeting Anemic Women and Scoring Systems for Clinical Use

Abstract

Iron deficiency anemia during pregnancy is a common concern, affecting 38% of women worldwide, and up to 50% in developing countries. It is defined differently throughout all three trimesters. It has several detrimental effects on pregnancy outcomes for both the mother and the fetus such as increasing the risk of postpartum depression, preterm delivery, cesarean delivery, preeclampsia and low birth weight. Management of iron deficiency anemia is done classically via oral iron supplementation. However, recent evidence has shown intravenous iron as a good alternative to oral iron if patients are unable to tolerate, not responding or present very late in pregnancy with new diagnosis. Management of iron deficiency anemia was demonstrated to be a protective against postpartum hemorrhage. Other ways to prevent postpartum hemorrhage include improving prediction tools that recognize who is at risk. Several risk assessment kits have been developed to estimate the risk of postpartum hemorrhage in patients and were proven to be useful in predicting patients at high risk of postpartum hemorrhage, despite limitations in low-risk groups. More comprehensive tools are also being explored, by determining clinically relevant factors through nomograms, with some proving their efficacy after implementation. Machine learning is also being utilized to form more complete tools, by including risk factors previously not accounted for. These newer tools however still require external validation before being adopted, despite promising results in testing conditions.

Introduction to IDA

Iron deficiency anemia (IDA) during pregnancy is a common concern, affecting 38% of women worldwide, and up to 50% in developing countries [1, 2]. During pregnancy, plasma volume expands, which expectedly decreases hemoglobin concentration [3]. Iron requirements in pregnancy exceed 1,000 mg, with 500 mg for red blood cell expansion, 350 mg for the developing fetus and 250 mg following blood losses during delivery [4, 5]. Pregnant patients suffering from IDA manifest similar symptoms to non-pregnant patients such as fatigue, palpitations, dyspnea, and dizziness [6]. IDA has several detrimental effects on pregnancy outcomes for both the mother and the fetus. It increases the risk of postpartum depression [7], preterm delivery [5], cesarean delivery [8], preeclampsia and low birth weight [9]. While some studies may show IDA adversely associated with neonatal neurodevelopmental outcomes [10], larger systematic reviews concluded this was not likely [11].

Diagnosis of IDA

IDA in pregnancy is defined differently throughout all three trimesters (Table 1). Hematocrit values below <33% in the first and third trimester and <32 % in the second trimester are also indicators of IDA [12]. Causes of anemia in pregnancy and postpartum period can be due to red blood cell loss, destruction, decreased production or mixed mechanisms [13]. Routine analysis of IDA in pregnancy shows low mean corpuscular volume (MCV) and mean cell hemoglobin concentration. MCV values, however, may be misleading due to a physiological rise of MCV during pregnancy or IDA combined with B12 deficiency [14]. Ferritin, another marker, is usually low in IDA; however, normal or elevated ferritin levels do not exclude anemia since it is an acute phase reactant which can be elevated in normal pregnancies, inflammation or chronic diseases [14]. In such cases, C-reactive protein (CRP) can help guide physicians in their diagnosis. An elevated CRP (> 10 mg/ L) is an indicator of inflammation, and ferritin values should be measured after the CRP value has been normalized [15]. Ferritin < 30 µg/l is the most used cutoff value for diagnosing IDA in

pregnancy [16]. Complete blood count and hemoglobin electrophoresis should be performed at the first obstetric exam, with routine labs repeated at 24-28 weeks if the previous tests are within normal range. If abnormalities are found and treatment initiated, labs should be repeated in 1 month to check the response (figure 1).

Prevention and management of IDA, Oral vs IV Iron:

Preventive therapeutic measures by the Institute of Medicine for nonanemic women planning a pregnancy that are at risk of IDA include iron-folate supplementation, or other multivitamins containing about 30 mg of iron; they are best taken between meals or at bedtime with water or juice [17]. Consumption of iron-rich foods and supplements, deworming and malaria prophylaxis (in at risk regions) during pregnancy in endemic areas result in improved birth outcomes for the mother and child [18]. Birth spacing and use of contraceptives have also been linked to improved overall health and nutrition. Women with heavy menstrual flow had significantly higher odds of being anemic when compared to women with normal flow [18].

Management of IDA in pregnancy is vital to prevent complications, since iron requirements increase throughout all three trimesters [19]. Women are advised to increase their dietary intake of iron throughout pregnancy by consuming iron-rich food. However, if a diagnosis of IDA is established, treatment is initiated as dietary supplements alone cannot compensate [14]. For women with low ferritin, and under 30 weeks of gestation, oral iron should be started every other day, while for those above 30 weeks, IV iron should be initiated (figure 1).

Oral iron is the first line treatment for IDA in pregnancy. There are several iron preparations available, including ferrous salts, ferric polymaltose complex and liposomal iron [20]. In their study, Gamad et al. compared four commonly used oral iron preparations: ferrous sulfate, ferrous fumarate, ferrous ascorbate, and carbonyl iron [21]. The outcomes of interest were rise of hemoglobin level to above 11 g/dL, anemia markers and indices, and drug adverse reactions. Patients assigned to ferrous fumarate had the highest proportion of reaching the

desired hemoglobin levels, but there were no statistically significant differences between the four groups. Moreover, all groups showed statistically significant rises in most anemia markers. Adverse effects, mainly gastrointestinal symptoms, were more common in the ferrous fumarate group, but no statistical difference was seen between the four cohorts [21]. Oral iron's side effects are well documented such as nausea, epigastric pain, and altered bowel habits [22]. When side effects become intolerable, dose reduction by using a formulation with less elemental iron (or every other day dosing with same formulation) is recommended [14].

Ferrous salts show better absorption and bioavailability than ferric salts [23]. The recommended daily dose ranges between 100 and 200 mg/day [15], and patients are usually advised to take the iron tablets between meals [24]. Reassessment of hemoglobin levels 2-4 weeks after initiation of oral iron is essential to monitor response to treatment; treatment should be continued at least 3 months after normal hemoglobin levels are reached and up to 6 months postpartum [25].Importantly, Stoffel et al. demonstrated in their randomized controlled trial that an alternate-day dosing resulted in 34% greater cumulative iron absorption when compared to daily dosing [26].

Ferric iron is not as commonly used as its ferrous counterpart, despite fewer side effects due to its slow release. Its use in pregnancy has not been extensively studied as other formulations, but they are safe to use in pregnant patients [27]. Liposomal iron on the other hand is a new generation oral iron composed of ferric pyrophosphate and ascorbic acid. Its use in pregnancy has not been evaluated [20], but it shows promising results with high bioavailability and low side effects.

Intravenous (IV) iron therapy is indicated in multiple scenarios, including minimal or absent response to oral iron, poor compliance/tolerability, and malabsorption disorders. The most common reason for IV therapy is IDA at >34 weeks requiring prompt treatment [28, 29].

Several studies have shown IV iron to be superior to oral iron in replenishing iron stores. Historically there were reservations on the use of IV iron due to undesirable side effects, mainly severe reactions and anaphylaxis [30]. The new generations of IV iron such as ferric carboxymaltose (FCM) and ferumoxytol, however, proved the risk of anaphylaxis to be rare at 1 in 1000 [31]. In addition, high doses of these preparations can be given over brief intervals of time [32-35]. Khalafallah et al. compared the efficacy of FCM given over 15 minutes to IV iron polymaltose (IPM) administered over 2 hours and oral iron ferrous sulfate [36]. Their main outcomes of interest were the change in hemoglobin and ferritin levels after 4 weeks of treatment and at predelivery. They also assessed adverse effects, tolerability, and the need for transfusion.

The level of hemoglobin after treatment was significantly higher in the FCM and IPM groups compared to the oral iron group by 4.35 and 4.08 g/L, respectively. Ferritin level was also higher in the FCM and IPM groups compared to the oral one. Similar patterns were seen in the pre-delivery measurements. No statistically significant difference between the two IV groups was noted.

Two patients in the oral group required blood transfusions, while no patients in the IV groups did. Undesirable side effects in the oral iron group led to lower compliance rates compared to the patients in the IV group. No serious adverse outcomes were reported among patients taking IV iron except for flu-like symptoms. The shorter duration for infusion in the FCM group was also a key element in patient satisfaction [36].

This study demonstrated that a single 1000 mg IV infusion was sufficient to raise hemoglobin levels significantly 4 weeks after treatment and until pre-delivery. The efficiency and low adverse effect profile of IV preparations make it a desirable method to treat IDA in pregnancy. Likewise, low-molecular iron dextran has shown promising results in repleting iron stores in a single 1-hour session in IDA patients not responding to oral treatment [35]. Other studies have shown IV iron can be used as along with oral preparations: IV iron is

used to elevate hemoglobin and iron levels to a normal level; whereas oral iron can then be used as a maintenance therapy approximately two weeks after last IV infusion [37].

Using data derived from studies evaluating workup and management of IDA in pregnancy [29, 38], the following algorithm was developed (figure 1).

Treatment of IDA as a protective factor against PPH

It is important to note that IDA during pregnancy puts the mother at risk of postpartum hemorrhage (PPH) [39]. IDA leads to impaired transport of hemoglobin and oxygen to the uterus causing cellular dysfunction [40, 41]. In fact, both impaired myometrial contractility and decreased uterine blood flow lead to inefficient uterine contractions and uterine atony resulting in PPH [40, 42, 43]. The latter hypothesis is mediated by low serum ferritin < 10 ng/mL (<100 µg/L) and therefore IDA [40]. Bivariate analyses demonstrated that increased blood loss at childbirth and postpartum was strongly associated with the severity of maternal anemia (p=0.02), while multivariate analyses showed that women with moderate-to-severe anemia had significantly greater total blood loss compared to non-anemic women (p<0.01) [40]. Significantly low hemoglobin can lead to severe PPH, and patients may require transfusion [25, 44]. Therefore, early diagnosis and treatment of IDA during pregnancy are protective factors against PPH. This is particularly true for low- and middle-income settings with less resources for blood transfusion and high income settings with smaller hospitals [45]. In fact, IDA and PPH together contribute to 40-43% of maternal deaths in Africa and Asia, as women with uncorrected moderate to severe anemia are often undiagnosed, until they seek hospital care when severe obstetric complications have developed [46, 47].

Sickle cell anemia is due to an inherited hemoglobinopathy affecting 100,000 persons in the United States, with most cases found among African Americans [48-50]. Sickle cell disease, through its underlying anemia and multi-organ dysfunction, can complicate pregnancy by affecting the cardiovascular, renal, hematologic, and respiratory systems [51-54]. Pregnant women with sickle cell disease have an increased risk of PPH (aPR 1.47, 95 % CI 1.17–

1.85) [55]. In this review, however, we will narrow our focus on the treatment of IDA as a protective factor against PPH.

Prevention of PPH by predicting PPH

PPH is an avertable cause of severe maternal morbidity and mortality [56]. Around 20% of maternal mortality in developing countries is caused by PPH. This percentage is lower in developed countries but still high at 8% [57]. PPH is prevalent in the United States contributing to 11% to maternal deaths, and the rate of PPH has almost doubled over the last two decades [58]. Moreover, the rate of blood transfusion and procedures to control bleeding caused by PPH has almost doubled over the span of twenty years [59]. The definition of PPH has been reviewed and updated. Previously, blood loss over 500 mL in a vaginal delivery or 1000 mL in a cesarean delivery (CD) would be classified as PPH (Table 1) but the more recent definition is blood loss leading to signs of hypovolemia regardless of the delivery type [60]. The most common type of PPH is primary PPH occurring during the first 24 hours of delivery. However, it can occur up to 12 weeks after delivery [61]. There are several risk factors for PPH including uterine atony in the majority of cases, as well as obstetrical lacerations during delivery, placental disorders, coagulopathies, and IDA [62].

Much like improving anemia can decrease cumulative risk of PPH and associated morbidity, optimizing prediction models can better raise awareness about PPH risk so patients get attention and care to reduce PPH morbidity. Risk assessment tool kits were devised to predict high-risk patients for PPH, based on risk factors identified by several studies [63] [64]. The commonly used assessment tools include the California Maternal Quality Care Collaborative (CMQCC), Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN), and New York Safety Bundle for Obstetric Hemorrhage (NYSBOH). Recent efforts have shown these kits may have partial capacity to predict PPH particularly with patients at low risk of PPH [65]. This pushed for the development of new risk assessment tools to capture additional risk factors not previously accounted for.

Risk assessment tools for PPH

The CMQCC risk assessment tool predicts PPH by categorizing patients into three cohorts (Table 2). This approach identifies patients who may require thorough management or even transfusion later [61]. It was developed based on data from experts and previous studies assessing PPH risk factors. In its first assessment it had low sensitivity and included two factors not significantly associated with PPH [66]. It was therefore updated, and body mass index and macrosomia were not considered risk factors [67].

Ruppel et al. conducted a retrospective cohort study to validate the updated version of CMQCC [68]. Their outcome of interest were PPH and severe PPH (Table 3) [61]. Patients were assigned to the low, medium, or high-risk cohorts based on CMQCC criteria.

Using the standard definition of PPH, the rate ranged from 3.2% in the low-risk group, up to 10.5% and 10.2% in the medium and high-risk groups, respectively. The sensitivity and specificity for PPH and severe PPH are described in Table 3. In the high-risk group, placenta previa, abnormal placental adhesions, hematocrit < 30%, and platelet count <100,000 were all statistically significant factors in severe PPH. Coagulopathy was not associated with severe PPH. However, the authors determined that since patients with coagulopathies receive treatment before and throughout pregnancy, coagulation disorders still pose a risk for severe PPH. On the other hand, prior CD, multiple gestation, uterine fibroids and chorioamnionitis were significant factors in the medium-risk group for severe PPH.

It is worth noting that out of the 13,479 PPH cases, 5,762 (or 43%) occurred in the low-risk group. Similarly, in the severe PPH group the low-risk group comprised 338 cases of the total 824. The characteristics in the low-risk group that predisposed patients to PPH were gestational age <37 weeks, pre-existing diabetes, hypertension, Laboratory and Acute Physiology score (LAPS2) >16, and Comorbidity Point Score (COPS2) >10. These findings are supported in other studies that show how comorbid conditions affect pregnancy [69] [70].

Colalillo et al. evaluated the AWHONN risk assessment for PPH [71]. The risk factors and classifications are shown in Table 2. The high-risk group had a greater chance of blood transfusion and of blood loss of >1000 mL compared to the low-risk group. The same trend was observed when comparing the medium-risk group to the low-risk groups. In addition, medium and high-risk patients were more likely to be admitted into the intensive care unit (ICU). The high-risk group comprised 48.4% of the patients requiring blood transfusion, in comparison to 9.3% of the low-risk group. AWHONN's specificity and sensitivity comparing the high vs low risk group are described in Table 3.

After AWHONN implementation in 19 hospitals, the incidence of blood loss >1000 mL decreased by almost 6% and the odds of any blood transfusion decreased by 0.66 [72]. Other studies have shown similar findings [65, 73, 74], suggesting these risk assessment tools can be used at admission to help reduce the number of patients requiring blood transfusion. It is important to note that risk assessment tools are likely part of a bundle of quality improvement interventions that helped to achieve the reduced blood transfusion outcome.

Kawakita et al. investigated the comparative utility of all three prediction tools in predicting PPH in patients undergoing CD [65]. They evaluated 6,301 patients who underwent a CD from January 2012 to December 2017. Their outcomes of interest were severe PPH defined as transfusion of > 4 packed RBCs along with any blood transfusion. AWHONN had the highest sensitivity, and CMQCC the highest specificity (Table 3). For severe PPH, the AUC of CMQCC was the highest at 0.77 (95% CI 0.71-0.84). For transfusion on the other hand, the AUCs were lower in all three assessment tools (0.69-0.77 vs 0.67-0.68).

Several conclusions were derived from this study. First, all three assessment tools were better at predicting severe PPH compared to blood transfusion, given it is a rarer outcome. In addition, they are limited at predicting patients at low risk of PPH. Finally, the authors found other risk factors for PPH not listed in the assessment tools including older age at

labor, early gestational age, active labor (natural or induced), general anesthesia, emergency CD, cesarean hysterectomy and hysterotomy type.

New efforts for PPH prediction models

Limitations of traditional assessment tools have driven the development of new prediction models (Table 4). Goad et al. performed a retrospective cohort study on both vaginal and CDs to create and validate a predictive model for PPH [75]. Measures of maternal morbidity consisted of maternal death, pulmonary edema, ICU admission, transfusion of > 4 units of blood, and emergency postpartum operative interventions such as uterine tamponade. These additional criteria were set by the ACOG Severe Maternal Morbidity Consensus [76].

The authors included several factors in their model based on clinically relevant risk factors of PPH, statistically significant risk factors can be found in Table 5. Patients at risk of PPH were also more likely to suffer from complications such as dilation arrest, chorioamnionitis, placental abruption, uterine rupture, and magnesium supplementation during delivery. In addition, Goad et al. were able to derive the following equation to predict the probability of PPH (Eq. 1) [75]. The sensitivity, specificity, AUC, positive and negative predictive values of the model can be found in Table 5. A score ≥ 6% classified patients as high risk for PPH. This model performed reasonably well. The authors included a large sample of patients undergoing both vaginal and CDs, and several risk factors were taken into consideration. However, a high false positive rate of the model of 25.9% adds a strain on the model.

Liu et al. developed a nomogram using multivariate logistic analysis to predict PPH in women undergoing vaginal delivery [77]. The authors determined a set of risk factors for severe PPH using multivariate logistic regression (Table 5) [77]. The nomogram determined the impact of each factor on the risk of PPH. For instance, a low-lying placenta contributes approximately "100" points to the nomogram, prior PPH contributes around "60", macrosomia score is "30", and so on. The total score would give the clinician the probability

of PPH in a certain patient. The C-index, which measures the ability of the nomogram to predict a certain outcome was high at 0.86.

Nomograms were also employed to determine the risk of PPH in CDs since they put patients at risk of PPH [78]. Du et al. conducted a retrospective cohort study to determine predictive models for severe PPH in repeat CDs [79]. They derived four models based on statistically significant risk factors (Table 5).

Du et al. then tested the validity of the models in a development and validation cohorts. The AUC for the full model, pre-operative simple, operative simple and the simple models in both cohorts are described in Table 5. The markers for each model differed based on the cutoff value used. For instance, if the threshold for PPH is ≥ 5%, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 0.84, 0.93, 0.21, 0.99 and 0.92, respectively, in the pre-operative model. Finally, the authors deduced nomograms for the pre-operative simple and simple models [79]. Like other nomograms, these models can be easily used by physicians to calculate a "risk score" for each patient.

Ahmadzia et al. used multivariable logistic regression to design a risk calculator for postpartum transfusion in women undergoing CD [39]. Model 1 used antepartum risk factors while Model 2 combined antepartum and intrapartum risk factors [39]. Both models were internally validated, with AUCs described in Table 5, and were accurate in predicting a patient's odds of receiving a transfusion during or after a CD. The models' strength lies in their applicability in daily practice [39]. This model is however limited to CDs, and still requires external validation with another cohort of patients.

Further efforts have integrated electronic medical records and machine learning to develop models to predict PPH. Zheutlin et al. derived an integrated machine model based on several machine learning methods [80]. They tested the validity of their model in a training and test samples. In the training sample, they narrowed down the relevant features to 24 raw

features, which achieved an AUC of 0.71 in the test set. These included lab results, diagnoses, vital signs, demographics, and medications (Table 5).

The authors used a Shapley score to determine the significance of each factor; the higher the score the more impact a factor has on a model. For instance, preeclampsia, anemia during pregnancy, and CDs had high Shapley scores.

Zheutlin et al. incorporated risk factors not usually used in classical models [80]. Systolic values above 132 mm Hg and diastolic values above 85 mm Hg increased the risk of PPH. They also included risk factors affecting vaginal and CDs differently with both hemoglobin < 10 g/dL and hematocrit < 30% increasing the odds of PPH. However their effect was more pronounced in CDs [80].

Venkatesh et al. used logistic regression and machine learning to predict PPH risk using 55 identified risk factors available on labor admission [81]. The extreme gradient boosting model, a machine learning derived model, had the best discriminative ability to predict PPH, followed by random forest, also machine learning derived, with a C statistic of 0.93 (95% CI 0.92-0.93) and 0.92 (95% CI 0.91-0.92) respectively [81]. These findings held with validation across both time and sites [81].

The future of model development including big data and machine learning methods likely requires the prospective creation and validation of models since retrospective aggregation of data from different data sets is confounded with issues of data heterogeneity.

Conclusion

In summary, IDA remains a burden on maternal morbidity and mortality, being also a risk factor for post-partum hemorrhage. In this review we discussed diagnosis, prevention and management of IDA as a protective factor against PPH, in addition to multiple PPH prediction models that can be used to prevent PPH. Early diagnosis and aggressive management of IDA are key in replenishing iron stores. New IV iron formulations that can be administered over a short period of time with low incidence of adverse effects present a

breakthrough in the management of ID despite oral iron still being the standard treatment for IDA. Several studies evaluated the capabilities and limitations of these widely used PPH prediction models. New assessment tools are being investigated to better capture the risk of PPH, but still require external validation. This review also highlights the importance of antenatal care particularly in underserved low to middle income countries, where modified screening strategies at key check points such as entry of care and at 28-30 weeks of gestation can screen for PPH risk factors. Adapting a prediction model that fits the population and data available would be optimal to help risk stratify patients so they can appropriately referred to tertiary care centers or interventions can be suggested such as IV iron prenatally.

$ln(p/1-p)$ = -3.79+0.02 (maternal BMI) +0.86 (number of fetuses) +3.19 (history of PPH) +1.12 (abnormal placentation) +1.33 (admission platelets <100,000/ mL) +0.38 (chorioamnionitis)+0.94 (arrest of descent) +1.17 (placental abruption) -0.35 (active labor duration: cesarean delivery no labor) -2.63(active labor duration: ≤4 hours) -2.50 (active labor duration: >4−≤8 hours) -2.17 (active labor duration: >8−≤12 hours) -1.61 (active labor duration: >12 hours) -1.65 (active labor duration: not collected) where p is the probability of PPH

Equation 1: Prediction of probability of Post-Partum Hemorrhage as per Goad et al.

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Guideline	PPH (mL)	Hgb 1st trimester (g/dL)	Hgb 2nd trimester (g/dL)	Hbg 3rd trimester (g/dL)	Hgb Postpartum (g/dL)
ACOG	≥1000	<11.0	<10.5	<11.0	-
CDC	-	<11.0	<10.5	<11.0	-
RCOG/UK	≥500/1000*	<11.0	<10.5	<10.5	<10.0
WHO	≥500	<11.0	<10.5	<11.0	-

Table 1: Definitions of Postpartum Hemorrhage and Iron deficiency anemia

*500mL for vaginal delivery and 1000mL for cesarean delivery

Risk Level	CMQCC	AWHONN	NYSBOH
Low Risk	No previous uterine incision	No previous uterine Incision	-
	Singleton pregnancy	Singleton pregnancy	-
	≤ 4 previous vaginal births	≤ 4 previous vaginal births	-
	No known bleeding Disorder	No known bleeding Disorder	-
	No history of PPH	No history of PPH	-
Medium Risk	Multiple gestation	Multiple gestation	Multiple gestation
	Prior cesarean birth or prior uterine incision	Prior cesarean birth or prior uterine incision	Prior cesarean birth, uterine incision, or multiple laparotomies
	>4 previous vaginal births	>4 previous vaginal births	>4 previous vaginal births
	History of 1 previous PPH	History of 1 previous PPH	History of previous PPH
	Large uterine fibroids	Large uterine fibroids	Large myoma
	Chorioamnionitis	Chorioamnionitis	Chorioamnionitis
	Polyhydramnios	Polyhydramnios	EFW >4,000 g
	Prolonged labor/Induction (>24 hours)	Induction of labor (with oxytocin)	Prolonged Oxytocin >24 hours
	HCT <30% (HGB <10)	Fetal demise	Hematocrit <30 %
	Gestational age <37 weeks or >41 weeks	Family history in first degree relatives who experienced PPH	Prolonged 2nd stage of labor
	Preeclampsia		Magnesium Sulfate
	Platelets 50-100,000		Obesity (BMI >40)
High Risk	≥2 Medium risk factor	≥2 Medium risk factor	≥2 Medium risk factor
	Abruption or active bleeding (greater than show)	Active bleeding more than "bloody show"	Active Bleeding

	Suspected/known placenta accreta or percreta	Suspected placenta accreta or percreta	Suspected placenta accreta/percreta
	Placenta previa	Placenta previa	Placenta previa
	Known coagulopathy	Known coagulopathy	Known coagulopathy
	Platelets <50,000	Platelets <100,000	Platelet <70,000
	HCT <28 (HGB <8)	HCT <30 AND other risk factors	
	History of >1 PPH	History of >1 PPH	
	HELLP Syndrome		
	Fetal demise		

Table 2: Comparison of risk factors in commonly used postpartum hemorrhage risk assessment tools

Researchers	Kit evaluated	Outcome	N=	Sensitivity for PPH	Specificity for PPH	Sensitivity for severe PPH	Specificity for severe PPH
Ruppel et al (52)	CMQCC	-Severe PPH (transfusion of > 4 units of blood, transfusion of 1-3 units of blood with haematocrit < 18%, blood loss of 1,500 ml with a haematocrit < 18%) - PPH (blood loss > 1,000 ml)	261,964	0.57	0.73	0.59	0.71
Colalillo et al (66)	AWHONN	- Obstetric hemorrhage (blood loss > 1,000 ml) - Blood transfusion - ICU admission - Additional hemorrhage-related complications	56,903	0.85	0.51	-	-
Kawakita et al (49)	CMQCC	- Severe PPH (transfusion of at least 4 units of blood) - Blood transfusion	6,301	-	-	Medium Risk: 0.91	Medium Risk: 0.25
				-	-	High Risk: 0.59	High Risk: 0.86
	AWHONN			-	-	Medium Risk: 0.97	Medium Risk: 0.08
				-	-	High Risk: 0.88	High Risk: 0.40
	NYSBOH			-	-	Medium Risk: 0.91	Medium Risk: 0.25
				-	-	High Risk: 0.77	High Risk: 0.64

Table 3: Evaluation of classical risk assessment tools

Assessment tool	Model development	Output	Commentary
CMQCC	Expert data and previous studies	Low, Medium, and High Risk	Good rule-out test Useful in high-risk patients
AWHONN	Expert data and previous studies	Low, Medium, and High Risk	Good rule-in test Useful in high-risk patients
NYSBOH	Expert data and previous studies	Medium and High Risk	-
Equation (Goad et al.) (59)	Clinically relevant risk factors for PPH	Probability of PPH	High false positive rate
Nomogram-NVD (Liu et al.) (61)	Clinically relevant risk factors for PPH	Score with probability	Limited to vaginal deliveries
Nomogram-CD (Du et al.) (63)	Statistically significant risk factors	Risk score	Limited to cesarean deliveries Multiple models for different scenarios
Equation-CD (Ahmadzia et al.) (37)	Statistically significant risk factors	Risk Score	Requires external verification
Integrated machine learning (Zheutlin et al.) (64)	Machine Learning	Risk score	Requires external validation Includes risk factors not used in other models
Integrated machine learning (Venkatesh et al.) (65)	Machine Learning	Probability	Missing patient data an issue External validation not successful

Table 4: Current and potential risk assessment tools

Researchers	Tool	Statistically significant risk factors	Outcome	Sensitivity	Specificity	AUC	Positive predictive value (%)	Negative predictive value (%)
Goad et al. (59)	Equation	- Older Age - High BMI - Platelet count <100,000 - Primiparous - History of PPH - History of C-section - Gestational hypertension/pre eclampsia - Multiple gestation	- PPH - Blood loss >3000 mL with measures of maternal morbidity	0.869	0.722	0.81	18.6%	98.8%
Liu et al. (61)	Nomogram	- Previous C-section - Prior PPH episode - In-vitro fertilization - IDA during pregnancy - Protracted Labor - Intrauterine death - Low lying placenta - Placental abruption - Placenta accreta - Macrosomia	- Severe PPH: Blood loss >1000 mL within 24 hours of childbirth	-	-	-	-	-
Du et al (63)	Nomogram	Simple Model*	- Severe PPH	0.841	0.929	Development: 0.858	21.9	99.5
						Validation: 0.925		
		Operative simple model**		0.841	0.922	Development: 0.864	20.8	99.6
						Validation: 0.928		
		Preoperative simple model***		0.795	0.926	Development: 0.888	21.1	99.7
						Validation: 0.921		
		Full Model****		0.795	0.928	Development: 0.9	20.7	99.6

						Validation : 0.914		
Ahmadzia et al. (37)	Logistic regression	Antepartum model ^	Need for transfusion	-	-	0.77	-	-
		Combined model ^^		-	-	0.83		
Zheutelin et al. (64)	Machine learning	- Lab results - Diagnoses - Vital signs - Demographic variables - Medications	- PPH	0.58	0.71	0.71	17	95
Venkatesh et al. (65)	Machine learning	Extreme gradient boosting '	- Blood loss >1,000 mL	-	-	-	-	-
		Random Forest ''		-	-	-	-	-
		Logistic regression with lasso regularization '''		-	-	-	-	-
		Logistic regression ''''		-	-	-	-	-

Table 5: Evaluation of new risk assessment tools

Simple model: Placenta previa and accreta, gestational weeks, endometrial injury

**Operative simple model: Simple Model + Pelvic adhesions and uterine incisions*

***Preoperative simple model: Placenta previa and accreta, gestational weeks, oligohydramnios, endometrial injury, endometrial injury, number of cesarean deliveries, time of repeat cesarean section, source (hospital patient vs referral)*

****Total Model: All previously mentioned factors*

^ Antepartum model: maternal age, BMI, platelet count, HCT, gestational hypertension/ preeclampsia, HELLP, history of asthma, abruption, race, coverage, heart disease, previous cesarean deliveries, previous terms deliveries, heart disease, gestational age

^^ Combined model: Antepartum model + abruption as indication for CD, general anesthesia, failure to progress, accreta/increta/percreta, intra-partum antibiotics, non-elective repeat CD, multiple births

' Extreme gradient boosting: Age, Pre-pregnancy weight, Pre-pregnancy BMI, Admission weight, Chronic hypertension, Parity, Anemia, Assisted reproductive technology, Breech presentation, Fetal macrosomia, Preeclampsia without severe features, Placental abruption, Small for gestational age, Large for gestational age, Antepartum vaginal bleeding, Placenta accreta, Gestational age at delivery, Admission systolic blood pressure, Trial of labor, Chorioamnionitis on admission, Maternal race, Gestational diabetes, Seizure disorder, Multiple gestation, Polyhydramnios, History of prior Cesarean delivery, Preeclampsia with severe features, Antenatal steroids, Placenta previa,

Threatened preterm labor, Admission temperature, Admission diastolic blood pressure, Spontaneous labor, Education status, Premature rupture of membranes, Marital status, Tobacco use, Drug use, Non-gestational diabetes, Gestational hypertension, Heart disease, Thyroid disease, Renal disease, Asthma, Depression, Gastrointestinal disease, History of seizures, History of prior preterm birth, Superimposed preeclampsia, Eclampsia, Fetal Demise, Maternal GBS colorization, Magnesium sulfate

'' Random forest: Age, Pre-pregnancy weight, Pre-pregnancy BMI, Admission weight, Chronic hypertension, Parity, Anemia, Assisted reproductive technology, Breech presentation, Fetal macrosomia, Preeclampsia without severe features, Placental abruption, Small for gestational age, Large for gestational age, Antepartum vaginal bleeding, Placenta accreta, Gestational age at delivery, Admission systolic blood pressure, Trial of labor, Chorioamnionitis on admission, Insurance status, Maternal race, Gestational diabetes, Seizure disorder, Multiple gestation, Polyhydramnios, History of prior Cesarean delivery, Preeclampsia with severe features, Antenatal steroids, Placenta previa, Threatened preterm labor, Admission temperature, Admission diastolic blood pressure, Spontaneous labor, Education status, Premature rupture of membranes, Marital status, Tobacco use, Drug use, Non-gestational diabetes, Gestational hypertension, Heart disease, Thyroid disease, Renal disease, Asthma, Depression, Gastrointestinal disease, History of seizures, History of prior preterm birth, , Eclampsia, Fetal Demise, Maternal GBS colorization, Magnesium sulfate

''' Logistic regression with lasso regularization: Age, Pre-Pregnancy weight, Anemia, Assisted reproductive technology, Breech presentation, Fetal macrosomia, Preeclampsia without severe features, Placental abruption, Small for gestational age, Large for gestational age, Antepartum vaginal bleeding, Placenta accreta, Gestational age at delivery, Admission systolic blood pressure, Trial of labor, Chorioamnionitis on admission, Insurance status, Maternal race, Gestational diabetes, Seizure disorder, Multiple gestation, Polyhydramnios, History of prior Cesarean delivery, Preeclampsia with severe features, Antenatal steroids, Placenta previa, Threatened preterm labor, Admission temperature, Admission diastolic blood pressure, Spontaneous labor, Education status

'''' Logistic regression: Age, Pre-pregnancy BMI, Admission weight, Chronic hypertension, Parity, Assisted reproductive technology, Breech presentation, Fetal macrosomia, Preeclampsia without severe features, Placental abruption, Small for gestational age, Large for gestational age, Antepartum vaginal bleeding, Placenta accreta, Gestational age at delivery, Admission systolic blood pressure, Trial of labor, Chorioamnionitis on admission, Insurance status, Maternal race, Seizure disorder, Antenatal steroids, Placenta previa, Threatened preterm labor, Admission diastolic blood pressure, Spontaneous labor, Prior antepartum hospitalization, Admission temperature, Premature rupture of membranes, Marital Status
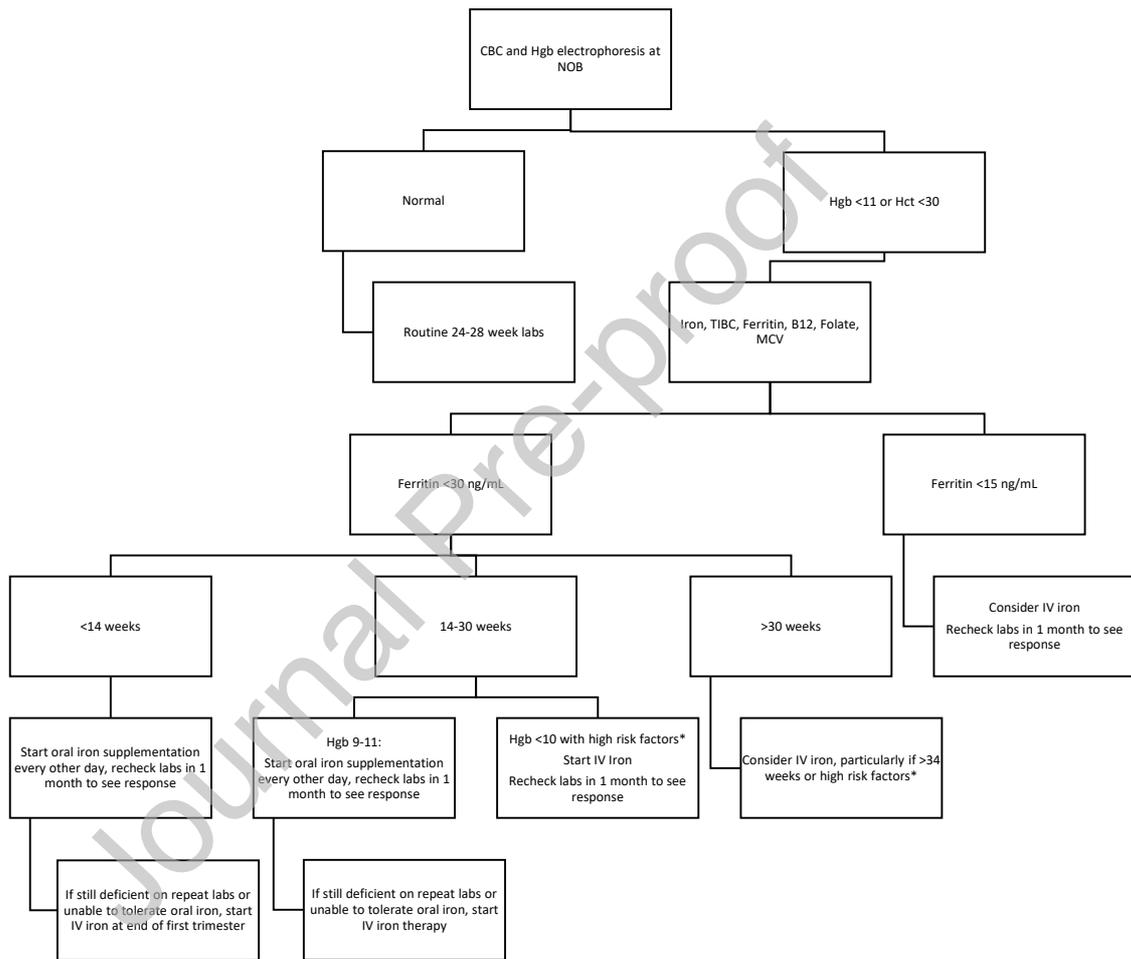
CBC and Hgb electrophoresis at NOB

- Normal
  - Routine 24-28 week labs
- Hgb <11 or Hct <30
  - Iron, TIBC, Ferritin, B12, Folate, MCV
    - Ferritin <30 ng/mL
      - <14 weeks
        - Start oral iron supplementation every other day, recheck labs in 1 month to see response
          - If still deficient on repeat labs or unable to tolerate oral iron, start IV iron at end of first trimester
      - 14-30 weeks
        - Hgb 9-11:
          Start oral iron supplementation every other day, recheck labs in 1 month to see response
          - If still deficient on repeat labs or unable to tolerate oral iron, start IV iron therapy
        - Hgb <10 with high risk factors*
          Start IV Iron
          Recheck labs in 1 month to see response
      - >30 weeks
        - Consider IV iron, particularly if >34 weeks or high risk factors*
    - Ferritin <15 ng/mL
      - Consider IV iron
        Recheck labs in 1 month to see response

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Figure 1: Algorithm for iron deficiency anemia workup and management (*Adapted from Govindappagari et al. *Contemporary OB/GYN Journal* 2021, Uptodate, James A. *Obstet Gynecol* 2021 and protocols from George Washington University Department of OB/Gyn)

*High risk factors: bleeding disorder, chronic placental abruption, history of gastric bypass, Jehovah's witness, multifetal gestation, placenta previa or accreta, physician discretion