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Review Article

Relation between blood disorders in pregnancy and both mother and fetal health status

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ABSTRACT

Blood disorders in pregnancy, such as gestational thrombocytopenia and iron deficiency anemia (IDA), can have significant implications for both maternal and fetal health. This study aimed to investigate the association between blood disorders in pregnancy and their impact on the health of both the mother and the fetus. Gestational thrombocytopenia was found to have a low risk of maternal or fetal hemorrhage or bleeding complications. Iron deficiency anemia (IDA) was identified as a common cause of anemia in pregnant women, and investigating it is crucial if hemoglobin concentration falls below 11 g/dL. Nutritional interventions, such as increasing iron intake, were shown to significantly elevate hemoglobin levels in pregnant women during the first and second trimesters. In conclusion**,** managing blood disorders in pregnancy is essential for the health of both the mother and the fetus. Nutritional interventions, including increased iron intake, can help improve maternal hemoglobin levels and prevent complications associated with anemia. Gestational thrombocytopenia has a low risk of bleeding complications. Early detection and management of iron deficiency anemia are crucial to ensure optimal maternal and fetal health. In hemophilia cases, antifibrinolytic agents play a crucial role in managing bleeding risks during and after delivery.

Keywords: *pregnancy; anemia; iron deficiency; thrombocytopenia; venous thromboembolic disease; fetal health.*

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1. Introduction

Hematological disorders encompass a diverse group of clinical entities impacting the blood and its production pathways within the body. The severity spectrum of these disorders varies considerably, manifesting in a broad range of symptoms such as fatigue, asthenia, and dyspnea. Furthermore, they possess the potential to exert significant consequences on pregnancy and childbirth, affecting both maternal and fetal well-being **[1]**.

Pregnancy entails a cascade of physiological adaptations to support fetal growth and development **[2]**. These adaptations can influence the homeostasis of the blood and immune systems, potentially increasing the susceptibility of pregnant women to hematological disorders **[3]**. As per the World Health Organization (WHO), anemia affects approximately 42% of pregnancies globally, while thrombocytopenia complicates roughly 8% of these cases **[4]**.

Thrombocytopenia, defined as a platelet count below 150,000/µL, can occur in pregnancy due to various reasons. Gestational thrombocytopenia is the most common form, usually mild and occurring in the third trimester. It is generally benign and resolves postpartum. However, other causes such as immune thrombocytopenic purpura (ITP) and

preeclampsia-related thrombocytopenia can pose significant risks. Severe thrombocytopenia can lead to bleeding complications during delivery **[5]**.

Conditions such as deep vein thrombosis (DVT) and pulmonary embolism (PE) are more common during pregnancy. Inherited thrombophilias, such as Factor V Leiden mutation and prothrombin gene mutation, further increase this risk. Acquired conditions like antiphospholipid syndrome (APS) can also lead to recurrent pregnancy loss and other complications **[6]**.

Disseminated Intravascular Coagulation (DIC) is a severe condition characterized by widespread activation of the coagulation cascade, leading to the formation of blood clots throughout the body. It can be triggered by obstetric complications such as placental abruption, preeclampsia, and sepsis. DIC can result in severe bleeding, and organ failure, and is a medical emergency requiring prompt treatment **[7]**.

Inherited hemoglobin disorders, such as sickle cell disease and thalassemia, can complicate pregnancy. Sickle cell disease increases the risk of vaso-occlusive crises, infections, and preeclampsia. Thalassemia can lead to severe anemia and require regular blood transfusions. Both conditions necessitate specialized care and monitoring throughout pregnancy **[8]**.

Internists frequently encounter hematologic disorders during pregnancy, necessitating a thorough understanding of the underlying pathophysiology and clinical presentation of common disease processes. This article will review the diagnostic workup and management of different blood disorders, given their significant prevalence and potential consequences for both mother and fetus.

2. Methods

This review aimed to comprehensively assess the association between blood disorders and maternal and fetal health during pregnancy. A systematic search strategy was constructed utilizing Medical Subject Headings (MeSH) within the PubMed database. Search terms included "pregnancy", "anemia", "iron deficiency", "thrombocytopenia", and "venous thromboembolic disease." Studies published in English up to 2024 were included, with a particular emphasis on recent literature investigating this crucial relationship between mother and fetal health (**Fig. 1)**.

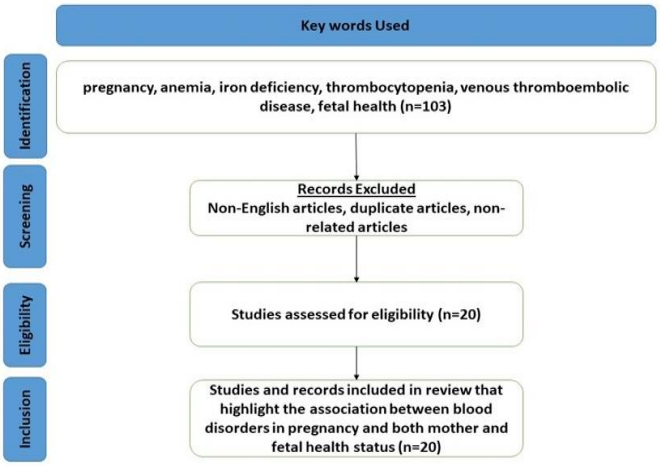

Fig. 1. Articles selection flow chart

3. Results and Discussion

3.1. Anemia

Anemia characterized by a diminution in the percentage of erythrocytes, signifies not a definitive diagnosis but rather the manifestation of an underlying etiology. The development of clinical manifestations is contingent upon the pathogenesis of the anemia, the rapidity of its onset, and the presence of concurrent medical conditions, particularly cardiovascular pathology. Typically, patients begin to experience clinical manifestations associated with anemia when the hemoglobin concentration falls below 7.0 g per

deciliter **[9]**.

Erythropoietin (EPO), synthesized within the kidneys, serves as the primary factor governing the generation of red blood cells (RBCs). Tissue hypoxia acts as the key instigator for EPO production, with its levels exhibiting an inverse relationship to hemoglobin concentration. In simpler terms, individuals experiencing anemia accompanied by low hemoglobin levels present with elevated EPO. However, this elevation is notably diminished in cases of anemic patients suffering from renal failure. In anemia of chronic disease (AOCD), EPO levels typically demonstrate a relative insufficiency, remaining elevated but failing to reach expected levels **[9]**.

Hemoglobin (Hgb) concentrations considered within the normal range may vary slightly across laboratories but generally adhere to the following parameters: **Males:** 13.5 - 18.0 g/dL, **Females:** 12.0 - 15.0 g/dL, **Children:** 11.0 - 16.0 g/dL, and **Pregnancy:** Values fluctuate depending on the trimester, typically exceeding 10.0 g/dL **[9] (Table 1)**.

Table 1. Classification of anemia according to the Mean cellular volume (MCV) [10]

MCV	Classification of Anemia	Possible Causes
Low MCV (<80 fl)	Microcytic anemia	Thalassemia syndromes, Iron deficiency anemia (IDA), Iron Refractory Iron Deficiency Anemia (IRIDA), Sideroblastic anemia
Normal MCV (80-99 fl)	Normocytic anemia	Anemia of chronic disease (ACD), chronic kidney disease (CKD), Sickle cell disease
High MCV (>100 fl)	Macrocytic anemia	Folate or vitamin B12 deficiency, Alcohol, Myelodysplastic syndromes (MDS), Chronic liver disease, Combined deficiency (for example iron + folate)

3.2. Iron Deficiency

Among the most prevalent hematological complications during gestation, anemia stands out. This phenomenon can be attributed to several normal physiological processes occurring during pregnancy, collectively termed "physiologic anemia of pregnancy." Notably, plasma volume undergoes a considerable expansion (40%–50%), whereas red blood cell mass experiences a comparatively smaller increase (20%–30%). This disparity in growth rates ultimately leads to a decrease in hemoglobin concentration **[11]**.

Nevertheless, should the hemoglobin concentration decline below 11 g/dL, an investigation into iron deficiency anemia (IDA) becomes imperative, as this etiology accounts for the majority of anemia diagnoses within the pregnant population. This heightened demand placed upon the bone marrow necessitates an increment in the daily iron intake, rising from 18 mg/day to 27 mg/day **[12]**.

Even in mild presentations, iron deficiency can induce the disruption of enzymatic function within tissues. This disruption manifests clinically as a constellation of symptoms including lassitude, dizziness, headache, and irritability **[13, 14]**.

Postpartum hemorrhage (PPH) in iron-deficient women is associated with significantly increased morbidity and mortality compared to iron-replete women. This increased risk manifests in several ways: a higher probability of requiring blood transfusions, a greater

susceptibility to sepsis, and ultimately, poorer overall clinical outcomes **[15]**.

3.2. Iron metabolism in pregnancy

The human body primarily utilizes two forms of iron: heme and non-heme. Heme iron carries two positive charges (Fe^{2+}) while non-heme iron can exist in either the ferrous (Fe^{2+}) or ferric (Fe^{3+}) states. Unlike non-heme iron, which typically constitutes the majority of dietary iron, heme forms a complex with protoporphyrin IX. Despite its smaller dietary presence, heme iron's superior bioavailability renders it a critical source for human physiological needs **[16]**.

Heme, primarily found in animal products, and non-heme, is predominantly present in plant sources. Enterocytes in the small intestine absorb approximately 15% of heme iron and 85% of non-heme iron via distinct mechanisms. Ascorbic acid and polyphenols in the diet can further influence non-heme iron absorption. At the apical membrane of enterocytes, ferric iron (Fe^{3+}) is reduced to ferrous iron (Fe^{2+}) by duodenal cytochrome B (DCYTB) and subsequently transported into the cell by divalent metal transporter 1 (DMT1). Intracellular Fe^{2+} can be stored in ferritin, a protein capable of accumulating up to 4,500 iron ions after oxidation. Alternatively, iron can be exported basolaterally into the bloodstream by ferroportin (SLC40A1, FPN). Within the vasculature, Fe^{2+} requires conversion to Fe^{3+} by a ferroxidase before binding to transferrin (TF), the primary iron transport protein in the body **[17] (Fig. 2).**

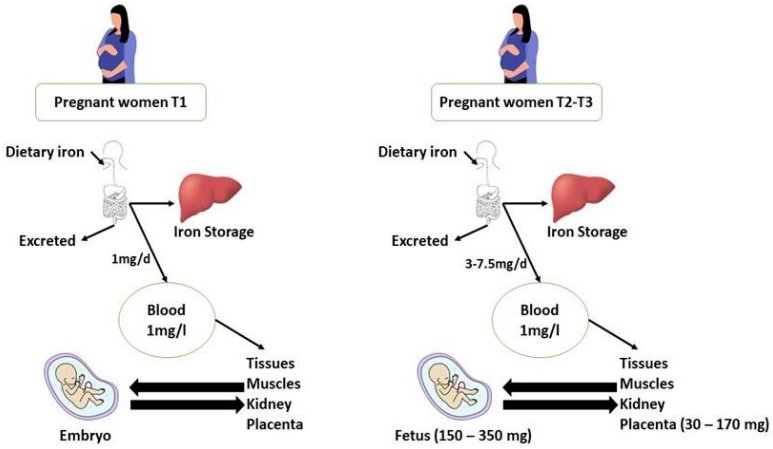

Fig. 2. Schematic description of Iron cycle during pregnancy

3.3. Role of hepcidin in systemic iron homeostasis

Hepcidin, a crucial regulatory peptide composed of 25 amino acids (aa), governs both intestinal iron absorption and distribution to various tissues. Primarily synthesized within hepatocytes, hepcidin expression also occurs at low levels in diverse cell types like macrophages, adipocytes, and even the brain. This localized expression suggests its potential role in the autocrine and paracrine regulation of iron fluxes, contributing to finely-tuned control beyond systemic regulation **[18]**.

Hepcidin antimicrobial peptide (HAMP) expression primarily relies on three regulatory pathways: the bone morphogenetic protein (BMP)-SMAD pathway, the inflammation-induced interleukin-6 (IL-6)/signal transducer and activator of transcription 3 (STAT3) pathways, and the hypoxia-responsive pathway **[19]**.

The BMP-SMAD pathway plays a central

role, focusing on BMP receptors. Liver sinusoidal endothelial cells contribute protein-6 (BMP-6), further activating the pathway. SMAD anchor molecules like endofin stabilize SMAD proteins within hepatocytes. Upon BMP binding to its receptors, Smad1/Smad5/Smad8 are phosphorylated and interact with the common mediator Smad4. This complex translocates to the nucleus where it acts as a transcription factor, modulating hepcidin expression. Mutations in key genes like HFE (human iron regulatory protein), TfR2 (transferrin receptor 2), and HJV (hemojuvelin), or disruption of the BMP receptor signaling pathway (e.g., BMP-6 deficiency, SMAD4 mutations) all lead to hepcidin downregulation **[19]**.

3.4. Iron requirements during pregnancy

Pregnancy demands substantial iron, estimated at 1000-1200 mg. Two-thirds support maternal needs (including increased red blood cell mass), while a third supports placental-fetal development. Iron requirements are dynamic, with lower needs in the first trimester (0.8 mg/day) but significantly increasing by the third (3.0-7.5 mg/day) due to accelerated hematopoiesis and fetal growth. Iron-replete women can partially meet this demand through stores and recycling (300 mg). However, approximately 750 mg of additional iron is needed even in iron-replete individuals. For women with depleted stores, 1000 mg or more might be necessary to ensure adequate iron supply for both mother and fetus **[20]**.

Although iron demand progressively increases throughout pregnancy, many developed countries maintain static reference intake values, neglecting this dynamic need. Countries like the US, Canada, Australia, and New Zealand advocate for a 150% higher iron intake from the start of pregnancy compared to non-pregnant women **(Table 2)**. Conversely, the UK, Europe, and WHO currently lack specific pregnancy recommendations, leading to international discrepancies. These reference intake values range from 7-22 mg/day (Estimated Average Requirement/Average Requirement) and 11.5-27 mg/day (Recommended Daily Allowance/Population Nutrient Intake/Recommended Nutrient Intake) to cater to 50% and 97.5% of the population, respectively **[20]**.

Table 2. Recommended Dietary Allowance (RDA) of iron for pregnant women, infants, and young children aged 12-23 months [21, 22, 23, 24, 25].

	Women of Reproductive Age	Pregnant Women	Infants			Young Children
			0 to 6 Months		6 to 12 Months	12 to 23 Months
			0 to 3	4 to 6		
United States & Canada (IOM [1])	8.1/18	22/27	0.26		6.9/11	3/7
Europe						
EFSA [2]	7/16	7/16	Not specified		8/11	5/7
UK (SACN [3])	11.4/14.8	11.4/14.8	1.3/1.7	2.3/3.3	6/7.9	5.3/6.9
Australia & New Zealand	8/18	22/27	0.2		7/11	4/9
WHO/FAO [4]	19.5/24.5/29.4/58.8	Not specified	Not specified		6.2/7.7/9.3/18.6	3.9/4.8/5.8/11.6

[1] Institute of Medicine (IOM); [2] European Food Safety Authority (EFSA); [3] Standing Advisory Committee on Nutrition (SACN); [4] Food and Agricultural Organization (FAO)/World Health Organization (WHO)

3.5. Maternal, fetal, and neonatal outcomes associated with iron deficiency anemia

Emerging evidence suggests a positive association between postpartum iron deficiency and increased incidence of depression, emotional lability, and cognitive dysfunction in new mothers **[13]**.

Multiple observational studies have established a strong association between severe anemia (hemoglobin <9 g/dL) during pregnancy and adverse pregnancy outcomes. This compelling evidence has led to the recommendation for universal iron supplementation during pregnancy at the Recommended Dietary Allowance (RDA) dose. Although the widespread implementation of prophylactic iron supplementation remains a subject of debate, several studies have demonstrated potential benefits **[26]**.

Research suggests that women receiving prophylactic iron supplementation during pregnancy experience longer gestation durations and have infants with higher birth weights compared to those receiving no supplementation. The risk of negative pregnancy outcomes appears to be particularly high when maternal anemia is detected early in pregnancy (first trimester). This may be due to the challenges in differentiating physiological anemia, a normal adaptation occurring during the first trimester, from iron deficiency anemia (IDA) in the later stages of pregnancy **[26]**.

While traditionally, postnatal iron deficiency (PID) in infants was attributed to a dual etiology of insufficient dietary iron intake and blood loss secondary to intestinal infections, recent evidence suggests a paradigm shift. A large randomized controlled trial conducted in a Chinese population with moderate maternal iron deficiency revealed that infant PID was primarily driven by their pre-birth iron status, reflecting the extent of fetal iron loading **[27]**.

Maternal iron deficiency anemia (IDA) during pregnancy poses a significant threat to both maternal and fetal health, manifesting in increased morbidity, perinatal complications, and fetal death. Affected mothers exhibit a constellation of symptoms including dyspnea, syncope, fatigue, palpitations, and sleep disturbances. Additionally, they display an enhanced susceptibility to perinatal infections, preeclampsia, and postpartum bleeding. Cognitive impairment and behavioral difficulties have also been observed in such mothers. Adverse perinatal outcomes directly linked to maternal IDA include intrauterine growth retardation, premature birth, and low birth weight, all significantly contributing to increased mortality risks, particularly in resource-limited settings. Importantly, IDA occurring in the first trimester exerts a more detrimental impact on fetal growth and risk of premature labor compared to anemia emerging later in gestation. Notably, socioeconomic factors heavily contribute to the multifaceted issues presented, exacerbating these interconnected challenges that disproportionately burden developing nations **[28] (Fig. 3)**.

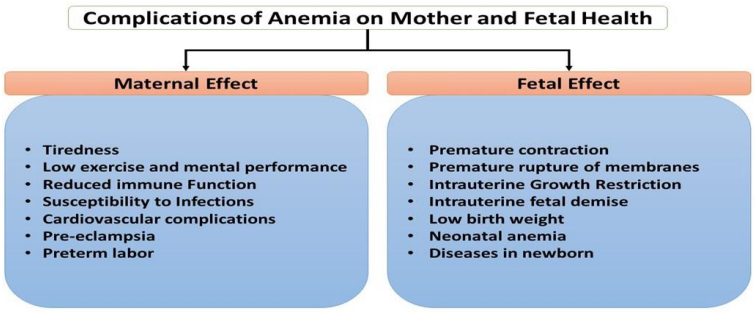

Fig. 3. Anemia Complications on Maternal and Fetal Health.

The INTERBIO-21st fetal study (Feb 2012 - Nov 2019), a prospective observational investigation conducted across diverse geographical settings (Brazil, Kenya, Pakistan, South Africa, and the UK), enrolled pregnant women meeting specific criteria. Inclusion criteria included age ≥18 years, singleton pregnancy resulting from natural conception, and initiation of antenatal care before 14 weeks gestation. A total of 2069 women with a mean age of 30.7 years (SD 5.0) participated **[29]**.

The pregnant women received at least one hemoglobin measurement (n= 4690) between 14-40 weeks. Compared to a 110 g/L cutoff, significantly increased risks were observed for pregnancy-induced hypertension (RR > 2.29) at ≥170 g/L hemoglobin, preterm birth (RR > 2.04) at both <70 g/L and ≥165 g/L hemoglobin, acute respiratory distress syndrome (RR > 2.84) at ≥165 g/L hemoglobin. This study supports the current WHO hemoglobin cutoffs in reducing adverse maternal and neonatal outcomes. However, a U-shaped association suggests exceeding high cutoffs also poses risks. Future guidelines should incorporate both minimum and maximum hemoglobin thresholds **[29]**.

WOMAN-2 trial (n= 10,561) investigated postpartum hemorrhage (PPH) risk in women with anemia across diverse settings (Pakistan, Nigeria, Tanzania, Zambia). Mean prebirth hemoglobin was 80.7 g/L, with 16.8% having severe anemia. PPH rate was 7.0%, higher in women with severe anemia (11.2% vs 6.2%). Each 10 g/L hemoglobin decrease increased PPH risk (aOR 1.23-1.29). Severe anemia had 7x higher odds of death/near miss (OR 7.25). This study highlights the strong association between anemia and PPH, emphasizing preventive and treatment measures in reproductive-age women **[30]**.

A prospective study found elevated iron deficiency anemia (IDA) prevalence (22%) in pregnant women. At delivery (39±1.65 weeks), IDA mothers had significantly lower hemoglobin (9.3±0.9 g/dL) and ferritin (15.4 ng/mL) compared to controls. Despite normal fetal iron levels, maternal and cord blood hepcidin showed no correlation with fetal iron status in IDA. Interestingly, placental iron transporters DMT1, FPN1, and GDF15 were upregulated in IDA, with GDF15 and ferroportin protein linked to fetal iron status. This suggests placental adaptation to maternal iron deficiency by enhancing iron transport to the fetus **[31]**.

3.6. Non-anaemic iron deficiency in pregnancy

While iron-deficiency anemia is a well-known concern during pregnancy, a lesser-known threat lurks non-anemic iron deficiency (NAID). Despite normal hemoglobin levels, women with NAID have depleted iron stores, impacting both their health and their baby's development **[32]**.

Pregnancy imposes progressive iron demands exceeding the absorption capacity of even optimal diets. This can lead to non-anemic iron deficiency (NAID) in previously iron-replete women. In women already facing iron deficiency, ongoing high demands further exacerbate the condition, ultimately progressing to iron deficiency anemia (IDA) **[32]**.

A clinical study in 31 non-anemic pregnant women analyzed the association between non-anemic iron deficiency (NAID) and postpartum depression. NAID, defined as serum ferritin <30 ng/mL, was present in 41.9% (n= 13) of participants at their first prenatal visit. Compared to women with normal ferritin levels (n= 18), the NAID group had significantly lower ferritin (18.5 vs. 74.7 ng/mL) but similar hemoglobin (12.7 vs. 12.8 g/dL). Notably, their Edinburgh Postpartum Depression Scale (EPDS) scores significantly increased from mid-pregnancy to 1 month postpartum, unlike the normal group. These findings suggest a potential link between NAID

in early pregnancy and decreased resilience to postpartum depression **[33]**.

3.7. Treatment strategies for iron deficiency anemia

3.7.1. Dietary Recommendations

Pregnant women in their third trimester have an increased Recommended Dietary Allowance (RDA) of iron, reaching 30 mg/day. Dietary modifications offer a cost-effective and culturally sensitive approach to meeting these requirements. Smartphone applications can be valuable tools, supporting women in (1) understanding their daily iron needs, (2) identifying the iron content of diverse food sources, and (3) monitoring their dietary iron intake **[34]**.

Three key dietary strategies have been identified to manage anemia and improve iron status in pregnant women: The first one is increased iron intake: This approach focuses on selecting iron-rich foods like meat, fish, legumes, and green leafy vegetables. Additionally, for young women with significant cereal intake, increasing whole-grain cereals can further boost iron content. Maximized Iron Absorption should be taken into consideration to enhance iron bioavailability. This involves incorporating iron absorption enhancers within meals, such as vitamin C and meat protein, while simultaneously limiting iron inhibitors like phytates, polyphenols, and calcium **[35]**.

Food fortification with iron, particularly in staple foods like wheat, maize, and rice, presents a strategic approach to addressing iron deficiency anemia (IDA) **[36]**. This intervention is recognized as a cost-effective and sustainable solution for minimizing IDA prevalence, especially in populations with inadequate dietary intake and limited food security **[37]**. The choice of fortification vehicles needs careful consideration, prioritizing affordability and consistent consumption within the target population **[38]**. This strategy holds particular promise for low-income countries grappling with widespread IDA and food supply challenges **[39]**.

Dietary counseling emerges as a potential strategy for anemia management; The World Health Organization (WHO) recommends comprehensive counseling for pregnant women concerning healthy dietary practices and regular physical activity throughout pregnancy **[40]** **(Table 3)**.

Table 3. Effect of Dietary Interventions in Prevention and Treatment of Iron-Deficiency Anemia in Pregnant Women

Ref.	Applied Intervention	Duration	Vitamin C Intake within the Diet	Iron Intake within the Diet	Conclusions
[41]	(1) Dietary intervention with a fortified beverage: This intervention involves the daily consumption of a powdered beverage mix flavored with orange and fortified with eleven essential micronutrients. These micronutrients include iron (10.8 mg/day), iodine, zinc, vitamin A, vitamin C (144 mg/day), vitamin E, riboflavin, niacin, vitamin B6, folic acid, and vitamin B12. The beverage provides approximately 176 kilocalories (kcal) per day. (2) Placebo beverage (176 kcal/day)	2 months	Not specified	Not specified	The consumption of a micronutrient-fortified beverage presents a potentially valuable and practical preventive intervention. This intervention holds the capacity to enhance the nutritional status of women, both before and throughout pregnancy. Consequently, it may contribute to the mitigation of certain potential maternal and fetal health complications arising from micronutrient deficiencies.
[42]	(1) Dietary intervention with iron-fortified milk powder: Daily consumption of 400 mL of milk powder fortified with 15 mg of iron, vitamin C, and folic acid. (2) Dietary intervention with non-iron-fortified milk powder: Daily consumption of 400 mL of milk powder not fortified with iron, but	4 months	At baseline: 41.1–50.4 mg/day, depending on group	At baseline: 9.7–10.3 mg/day, depending on group	The implementation of an intervention combining iron-fortified milk and iron tablet supplementation holds the potential to mitigate declines in iron status.

	supplemented with vitamin C and folic acid. (3) Oral supplementation with an iron-folic acid combination tablet: Daily intake of a single tablet containing 60 mg of iron and 250 micrograms of folic acid. (4) Placebo tablet				
[43]	(1) Dietary intervention with personalized counseling: This intervention involves personalized counseling sessions focusing on increased intake of calcium, iron, folic acid, vitamins C and E, and other antioxidants through the consumption of dairy products, vegetables, and fruits. Additionally, it recommends the removal of fluoride from ingested sources such as drinking water, food, and other dietary contributors. (2) Control: no dietary intervention	5 months	Not specified	Not specified	Data from a nutritional intervention study revealed a significant elevation in hemoglobin levels in 73% of pregnant women during the first trimester and 83% during the second trimester.
[44]	(1) Dietary intervention with a weekly supplementary food package: This intervention provides participants with a weekly allotment of a supplementary food product containing 600g of tempeh, 30g each of meat, dry anchovies, and chicken liver, 350g of guava, 300g of papaya, and 100g of orange. This combination delivers an estimated daily intake of 3.97mg of iron and 173mg of vitamin C. Additionally, participants have unlimited access to iron-folic acid tablets containing 60mg of iron and 250mg of folic acid. (2) Control: no dietary intervention; free access to receive tablets containing 60 mg of Fe and 250 mg of folic acid	Not specified	Not specified	Not specified	The inclusion of a daily supplementary food combining tempeh and vitamin C-rich fruits in the maternal diet during pregnancy may offer beneficial effects in mitigating iron deficiency.
[45]	(1) Dietary intervention utilizing the Trials of Improved Practices (TIPs) framework: This intervention involves three home visits, each serving a specific purpose. The first visit focuses on a comprehensive nutritional assessment. The second visit facilitates personalized dietary counseling and negotiation based on the individual's needs and preferences. Finally, the third visit evaluates the effectiveness of the implemented dietary practices and provides further guidance as needed. (2) Control: no dietary intervention applied within TIPs	3 months	Not controlled *	At baseline: Diet: 19 ± 7.02 mg/day; control: 19.05 ± 6.63 mg/day. After intervention: Diet: 21.58 ± 7.25 mg/day; control: 19.96 ± 6.59 mg/day	Statistically significant improvement in the nutritional status of pregnant women residing in the study area.
[46]	(1) Dietary intervention with a multi-pronged approach: **Counseling:** Participants received personalized counseling throughout pregnancy, focusing on evidence-based dietary practices for optimal nutrition, anemia prevention, and management. **Supplementation:** From the first trimester until	6–8 months	Not specified	Not specified	Corn Soya Blend Plus, a fortified dietary supplement, demonstrated efficacy in significantly reducing the prevalence of maternal anemia in late gestation among pregnant women in Cambodia, compared to those consuming a standard diet.

	delivery, participants were provided with: **Corn Soya Blend Plus (CSB Plus):** A total of 6.75 kg of CSB Plus was distributed, with a monthly ration of 200 g providing 850 kcal, 13 mg of iron, and 200 mg of vitamin C. **Vitamin A and D-fortified palm olein oil:** 300 mL of the oil was provided initially, with 10 mL added during daily cooking throughout the pregnancy. **Iron and folic acid supplementation:** All participants received daily tablets containing 60 mg iron and 400 mg folic acid. Anemic individuals received additional support with two iron-folic acid tablets daily for 14 days. (2) Control: Participants received dietary counseling focused on iron-rich foods and optimizing iron absorption to prevent and manage anemia. Daily iron (60 mg) and folic acid (400 mg) supplements were provided, with a temporary increase to double the dose for individuals diagnosed with anemia for 14 days.				
[47]	(1) Dietary intervention with pineapple-flavored lactoferrin and health education: Supplementation: Participants were provided with pineapple-flavored lactoferrin oral sachets (100 mg) twice daily for four weeks. Health education: Participants received comprehensive health education focused on: Anemia management during pregnancy: This included strategies for identifying and addressing anemia during pregnancy, potentially including additional medical interventions. Dietary modifications: Participants were educated on incorporating iron-rich and vitamin C-rich foods into their diet to enhance iron absorption. Dietary restrictions: Participants were advised to limit coffee and tea consumption, particularly close to meals, as these beverages can inhibit iron absorption (2) A total dose infusion of low-molecular-weight iron dextran will be administered intravenously, the dosage individually determined using the Ganzoni formula. Abstention from coffee and tea, particularly immediately postprandially, is advised. Dietary intake of iron-rich and vitamin C-rich foods should be augmented.	1 month	Not controlled *	Not controlled *	For pregnant women with IDA, supplementation with pineapple-flavored lactoferrin oral sachets alongside health education represents a promising alternative to TDI iron dextran. This treatment strategy achieved significant clinical and laboratory improvements in iron deficiency after one month.

3.7.2. Effects of Probiotic Species on Iron Absorption

A systematic review and meta-analysis of 15 studies (N= 950) identified in 12 articles investigated the influence of the probiotic strain Lactobacillus plantarum 299v (Lp299v) on iron absorption and status. A random-effects meta-analysis of eight studies revealed a significant increase in iron absorption with Lp299v supplementation, with a pooled standardized mean difference of 0.55 (95% CI: 0.22-0.88, p= 0.001). However, of the seven randomized and non-randomized clinical trials examining various probiotic species and iron status, only one study using Lp299v demonstrated improvement in serum iron. No other studies reported significant changes in iron status-related indices after probiotic treatment. The present findings suggest that Lp299v significantly enhances iron absorption in humans. Future investigations should assess the impact of Lp299v on iron absorption and status in populations with high iron deficiency risk, such as pregnant women **[48]**.

3.7.3. Iron supplementation via Oral route

The presented data underscores the significance of maintaining optimal hemoglobin (Hb) levels in pregnant women, avoiding both deficiency and excess. During pregnancy, daily iron requirements rise from the baseline of 1 mg to a peak of 20-30 mg/day. While animal-derived foods offer simpler pathways to achieving these requirements, a well-planned and strategically prepared vegetarian diet can also fulfill the iron needs of this population **[49]**.

While dietary supplements are frequently utilized during pregnancy, their necessity beyond folic acid and iodine remains contested. This is exemplified by Femibion, a popular prenatal supplement in Austria, containing 10-14 mg iron per tablet, potentially exceeding 71-100% of the daily recommended intake even before pregnancy confirmation or anemia diagnosis. Interestingly, 46.5% of pregnant women in Austria initiate iron "substitution" pre-emptively, and 28.1% begin even before pregnancy confirmation, highlighting the prevalence of supplementation without established diagnoses. Notably, 88.6% of iron supplementation instances occur upon physician recommendation **[50]**.

Oral iron supplementation constitutes the first-line therapy for women experiencing mild to moderate anemia. Currently, available oral medications often exceed daily iron requirements, with examples like Ferretab (containing 100 mg bivalent iron), Ferro Sanol Duodenal (100 mg iron), and Ratiopharm iron tablets (100 mg iron). While generally well-tolerated, a subset of patients experiences side effects, potentially leading to discontinuation **[51]**.

3.7.4. Intravenous iron supplementation

In cases of severe anemia requiring rapid response, red blood cell transfusions remain an option, though alternative approaches are gaining traction. This is exemplified by the rising number of publications and marketing efforts surrounding intravenous iron preparations. For instance, Ferinject, containing 1000 mg iron, offers efficacy within 4 weeks of therapy initiation, with product information claiming fetal safety from the second trimester onward **[52, 53]**.

3.8. Thrombocytopenia in pregnancy

Approximately 8-10% of pregnancies experience gestational thrombocytopenia, a decrease in platelet count secondary to physiological adaptations during gestation. These adaptations include increased blood volume, enhanced platelet activation, and accelerated platelet clearance. Gestational thrombocytopenia typically manifests as mild thrombocytopenia (100,000-150,000 platelets/μL) and rarely poses

health risks to the mother or baby **[26, 54]**.

A recent retrospective cohort study demonstrated a significantly elevated risk of gestational thrombocytopenia in women with a history of the condition compared to those without prior experience. Specifically, the study found a 14.2-fold increase in the risk of gestational thrombocytopenia among women with a previous occurrence **[55]**.

Studies utilizing umbilical cord blood platelet counts suggest that the incidence of neonatal thrombocytopenia in infants born to mothers with gestational thrombocytopenia ranges from 0.1% to 2.3%. This data indicates a low risk of maternal or fetal hemorrhage or bleeding complications associated solely with gestational thrombocytopenia **[56]**.

Causes of Thrombocytopenia in Pregnancy includes Gestational thrombocytopenia, Hypertension in pregnancy (Preeclampsia, HELLP syndrome), Primary immune thrombocytopenia, Secondary immune thrombocytopenia (Antiphospholipid syndrome, Systemic lupus erythematosus, Infectious (such as HIV, hepatitis C virus, cytomegalovirus, Helicobacter pylori), Drug-induced thrombocytopenia (use of drugs such as heparins, antimicrobials, anticonvulsants, analgesic agents)), Association with systemic conditions (Disseminated intravascular coagulation, Thrombotic thrombocytopenia/hemolytic uremic syndrome, Splenic sequestration, Bone marrow disorders, Nutritional deficiencies), Congenital thrombocytopenia **[57]**.

Gestational thrombocytopenia typically occurs in the third trimester and is thought to result from hemodilution, increased platelet clearance, and hormonal changes. The exact cause remains unclear, but it is generally benign and resolves postpartum. Gestational thrombocytopenia is usually asymptomatic and discovered incidentally during routine blood tests. Platelet counts are mildly reduced, rarely falling below 70,000/µL **[58]**.

Preeclampsia, characterized by hypertension and proteinuria, can lead to HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets). The pathogenesis involves endothelial dysfunction, systemic inflammation, and platelet activation, leading to microangiopathic hemolysis and thrombocytopenia **[59]**.

HELLP syndrome presents with right upper quadrant pain, nausea, vomiting, and significant thrombocytopenia. It is a severe condition requiring immediate medical intervention **[59]**.

Conditions like preeclampsia and HELLP syndrome can impair placental function, leading to reduced nutrient and oxygen supply to the fetus. This can result in intrauterine growth restriction, preterm birth, and low birth weight **[60]**. Moreover, preeclampsia often necessitates early delivery to protect maternal and fetal health. Preterm birth can lead to complications such as respiratory distress syndrome and developmental delays **[61]**.

3.9. Management and Treatment

The parturient's clinical status dictates the mode of parturition. Vaginal delivery is generally preferred from a hemorrhagic standpoint due to its lower associated risk of bleeding; however, this is not the sole determinant. Administration of neuraxial analgesia (epidural anesthesia) presents a challenge in this context. The American College of Obstetrics and Gynecology recommends a thrombocyte concentration of 80 x 10^9/L (Grade C recommendation) as the threshold for the safe administration of epidural analgesia. The platelet goal for parturition itself is greater than 50 x 10^9/L, particularly when anticipating a cesarean section **[62, 63]**.

Gestational thrombocytopenia (GT) is

characterized by a mild decrease in thrombocyte count (rarely below 70 x 10^9/L) that typically resolves spontaneously 4-8 weeks postpartum. No intervention is necessary for isolated GT due to its benign course. However, a thrombocyte count <70 x 10^9/L warrants investigation for possible superimposed immune thrombocytopenia (ITP). While treatment with corticosteroids or intravenous immune globulin (IVIG) is ineffective in GT alone, it may be beneficial in individuals with coexisting ITP. Notably, neonatal outcomes are excellent, with no reported cases of thrombocytopenia in infants born to mothers with GT **[62, 63, 64]**.

Immune thrombocytopenia (ITP) during pregnancy presents a complex challenge in balancing fetal and maternal well-being. Therapeutic intervention is generally unnecessary unless the thrombocyte count falls below 20-30 x 10^9/L in the first or second trimester. The presence of bleeding manifestations, regardless of platelet count, also necessitates intervention. The management approach in the third trimester is guided by the planned mode of delivery and the patient's suitability for neuraxial analgesia (epidural anesthesia) **[64]**.

In pregnant patients with ITP, corticosteroids serve as the first-line therapy, typically yielding a response within 3-7 days. Intravenous immunoglobulins (IVIG) administered as a single 1000 mg/kg dose can induce a rapid increase in platelets within 24 hours, although the effect wanes after 2-3 weeks. Repeat dosing, either alone or combined with steroids, is possible if the initial response is inadequate **[65]**.

Rituximab emerges as a safe option during pregnancy, associated with minimal maternal complications. However, transient neonatal B-cell lymphopenia, resolving by 6 months of age, has been reported. Other treatment options include azathioprine and cyclosporine, while chemotherapeutic agents like cyclophosphamide and vincristine are generally contraindicated in pregnancy **[65]**.

In Paroxysmal Nocturnal Hemoglobinuria (PNH), eculizumab, a humanized monoclonal IgG1 antibody, targets complement component C5, specifically inhibiting its cleavage into C5a and C5b. This action subsequently blocks the formation of the membrane attack complex (MAC), ultimately leading to a reduction in intravascular hemolysis mediated by the complement system and a potential improvement in platelet count **[66]**.

3.10. Bleeding Disorders

Pregnant women can experience bleeding complications due to either inherited or acquired coagulopathies. While inherited conditions present from birth, acquired bleeding disorders during pregnancy typically manifest acutely post-partum, after failing interventions like uterotonics or sutures for massive hemorrhage. Interestingly, within 1-4 months postpartum, some women develop acquired hemophilia, characterized by the presence of autoantibodies against specific coagulation factors **[26]**.

Pregnancy and childbirth significantly increase the likelihood of clinical manifestations for previously undiagnosed bleeding disorders. Hematologists evaluating women experiencing pregnancy-related bleeding complications should maintain a high index of suspicion for such conditions. A history of menorrhagia or specific gynecological complications (hemorrhagic ovarian cysts, endometriosis, endometrial hyperplasia) may serve as red flags, as undiagnosed bleeding disorders reach a prevalence of 20% in this population. While von Willebrand disease (VWD) and hemophilia carriership comprise the majority of cryptic bleeding disorders affecting women, a small subset may present with platelet dysfunction or rare factor deficiencies. Case reports document

various bleeding events associated with these disorders in women, including subchorionic hemorrhage, miscarriage, placental abruption, placenta previa, and secondary or delayed postpartum hemorrhage **[67, 68]**.

3.10.1. Venous Thromboembolic Disease

Pregnancy and puerperium are established risk factors for venous thromboembolic disease (VTE), with a 5-fold increase in risk compared to non-pregnant women during pregnancy and a further 30-60-fold increase postpartum **[69, 70]**. VTE incidence in these periods significantly exceeds that in age-matched controls, necessitating heightened clinical suspicion for pregnancy-specific risk factors **[70]**. Management of limb- or life-threatening VTE in antepartum or postpartum women requires a multidisciplinary approach to optimize both maternal and fetal outcomes **[71]**.

Interestingly, the distribution of VTE events differs by period: deep vein thrombosis (DVT) is more prevalent during pregnancy, while pulmonary embolism (PE) is more likely to occur postpartum **[72]**. DVT itself poses significant obstetric risks, contributing to increased maternal morbidity (e.g., higher post-thrombotic syndrome incidence) and mortality **[73]**.

Pregnancy induces a progressive hypercoagulable state through a physiological rise in various clotting factors, including von Willebrand factor, fibrinogen (which notably increases by 50%), factors II, VII, VIII, IX, and X, from conception to delivery. Though aimed at facilitating postpartum hemostasis, these changes affect prothrombin time (PT) and partial thromboplastin time (PTT), potentially complicating anticoagulation monitoring in pregnant women **[74]**.

Hyperestrogenism during pregnancy contributes to decreased protein S activity, which counterbalances factors Va and VIIIa through interaction with protein C. This effect occurs directly, due to reduced production, and indirectly, via increased C4b-binding protein. Additionally, elevated levels and activity of thrombin-activated fibrinolysis inhibitor (TAFI), plasminogen activator inhibitor-1 (PAI-1), and plasminogen activator inhibitor-2 (PAI-2) suppress fibrinolysis **[74]**.

Three key factors contribute to venous stasis and hypertension during pregnancy, parturition, and puerperium: (i) decreased venous tone mediated by endothelial-derived nitric oxide (upregulated by estradiol and vasodilatory prostaglandins like PGI2), (ii) compression of the inferior vena cava and iliac veins by the gravid uterus, and (iii) endothelial injury to pelvic veins during childbirth **[74]**.

3.10.2. Management/Prophylaxis of venous thromboembolic disease in pregnancy

Although organizations may differ in specific recommendations and strategies, the guiding principles for venous thromboembolism (VTE) prophylaxis in pregnant and postpartum women remain consistent. Early in pregnancy, and whenever risk factors change, a comprehensive and documented risk assessment of each patient should form the foundation for all clinical decisions regarding VTE prevention, both during pregnancy and the postpartum period. Several VTE risk scores have been devised to guide clinical decision-making **[75]**, some of which have demonstrated clinical significance in guiding appropriate thromboprophylaxis **[76]** and reducing the incidence of VTE **[77]**.

Despite individual studies demonstrating the potential efficacy of thromboprophylaxis in reducing VTE risk within the obstetric population **[78]**, a recent systematic review failed to identify conclusive evidence supporting these recommendations **[79]**. Consequently, all existing reports on this topic warrant critical appraisal by

healthcare professionals due to inherent methodological limitations (**Table 4)**.

Table 4. Prophylaxis and therapeutic dosing for VTE in the obstetric population [80]

Feature	Unfractionated Heparin	Certoparin	Dalteparin	Enoxaparin	Nadroparin	Tinzaparin	Fondaparinux	Danaparoid
FDA Pregnancy Category	C	B	B	B	C	B	B	B
Half-life	0.5-2 h	4.6 h	2-2.3 h	4.5 h	3.7 h	3.3-3.5 h	17-21 h	25 h
Molecular Weight	15,000	5600	5000	4500	4300	6500	1728	6000
Prophylaxis Dose	3 x 5000 U/day 2 x 7500 U/day	1 x 3000 U/day	1 x 5000 U/day	1 x 40 mg/day	1 x 2850 U/day	1 x 3500 U/day	1 x 2.5 mg/day	2 x 750 U/day
Treatment Dose	Iv (PPT 60–80 s)	2 x 8000 U/day	1 x 200 U/kg/day	2 x 1 mg/kg/day	2 x 90 U/kg/day	1 x 175 U/kg/day	1 x 5 mg/day	Iv (anti-Xa level 0.5–0.80 IU/mL)

Anticoagulant therapy is sufficient for the majority of venous thromboembolism (VTE) instances during pregnancy. Nevertheless, in scenarios involving massive pulmonary embolism (acute PE associated with systemic hypotension, absence of pulse, or ongoing bradycardia presenting with signs and symptoms of shock), more sophisticated interventions are necessary. These interventions encompass systemic thrombolysis, surgical thrombectomy, catheter-directed thrombectomy/thrombolysis, or extracorporeal membrane oxygenation (ECMO). Catheter-directed thrombolysis or thrombectomy presents a viable option for individuals experiencing limb-threatening proximal deep vein thrombosis (DVT). Furthermore, advanced therapeutic approaches may be contemplated in cases of sub-massive PE (characterized by right ventricular dysfunction or myocardial necrosis in the absence of hypotension) **[81]**.

3.10.3. Hemophilia in Pregnancy

Peripartum hemorrhage accompanied by an extended activated partial thromboplastin time (aPTT) in women lacking previous personal or familial bleeding history warrants investigation for acquired hemophilia. This autoimmune disorder involves the generation of autoantibodies targeting coagulation factors, often factor VIII, and manifests as life-threatening bleeding in most patients. Prompt diagnosis and intervention are crucial. While commonly associated with pregnancy, acquired hemophilia may also arise in the context of malignancies and autoimmune diseases **[82]**.

In contrast to congenital hemophilia, where musculoskeletal manifestations like hemarthroses and deep muscle bleeds predominate, acquired hemophilia primarily present with spontaneous bleeding at mucosal surfaces (gastrointestinal, pulmonary, and genitourinary) and in subcutaneous tissues. Additionally, life-threatening events such as retroperitoneal and intracranial hemorrhages are more common in acquired forms **[83]**.

Acquired hemophilia typically manifests within the post-partum period, ranging from 21 to 120 days following delivery. However, delayed diagnoses suggest that the onset could also occur antepartum **[84]**.

Women who are carriers of hemophilia have one affected X chromosome, which can lead to reduced levels of clotting factors. These women may experience mild to moderate bleeding tendencies, similar to those seen in mild hemophilia. During pregnancy, the physiological changes can exacerbate these tendencies,

increasing the risk of bleeding complications. These women must receive specialized care from a multidisciplinary team, including hematologists, obstetricians, and anesthesiologists **[85]**.

Pre-pregnancy genetic counseling is essential for women who are carriers of hemophilia. This counseling helps assess the risk of transmitting the disorder to the offspring and provides information on available diagnostic options. Prenatal diagnostic procedures, such as chorionic villus sampling (CVS) or amniocentesis, can determine the fetal hemophilia status. These procedures, however, carry a risk of bleeding and should be performed in specialized centers **[86]**.

3.10.4. Management of Hemophilia during Pregnancy

Management of hemophilia carriers during pregnancy involves regular monitoring of clotting factor levels. As pregnancy progresses, levels of clotting factors VIII and IX may increase naturally, reducing the risk of bleeding. However, some women may still require prophylactic treatment with clotting factor concentrates to maintain adequate levels of clotting factors **[87]**. Alternatives such as desmopressin and antifibrinolytic agents (e.g., tranexamic acid) may also be used to manage bleeding risks **[88]**.

Delivery planning involves careful coordination among healthcare providers. Vaginal delivery is preferred if clotting factor levels are adequate, as it reduces the risk of surgical bleeding. However, cesarean delivery may be necessary for obstetric indications. In such cases, clotting factor concentrates should be administered before the procedure to ensure hemostasis. The use of regional anesthesia, such as epidurals, should be carefully considered and managed by an experienced anesthesiologist **[88]**.

The postpartum period is critical due to the risk of postpartum hemorrhage (PPH). PPH can occur even if clotting factor levels were adequate during delivery. Close monitoring and prompt administration of clotting factor concentrates are essential to manage bleeding. Women should be educated about the signs of PPH and the importance of seeking immediate medical attention if they experience excessive bleeding **[89]**.

Antifibrinolytic agents, such as tranexamic acid and aminocaproic acid, help prevent the breakdown of blood clots. These medications are used to manage bleeding episodes and are particularly useful during and after delivery to reduce the risk of postpartum hemorrhage. They can be administered orally or intravenously **[90]** **(Fig. 4)**.

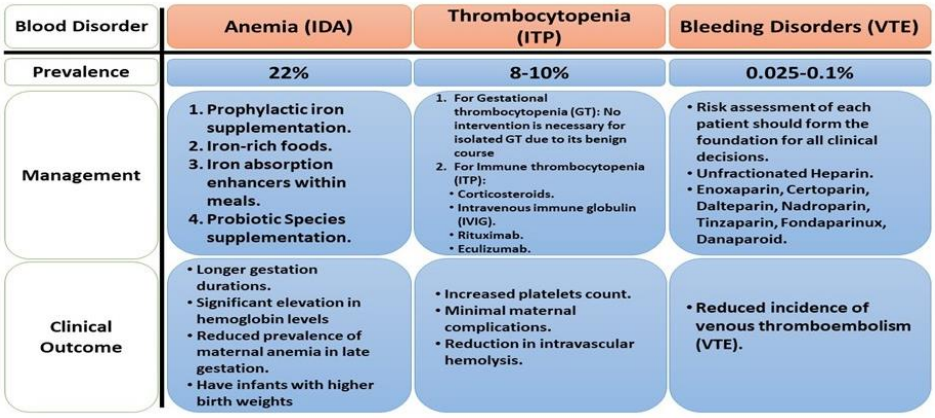

Fig. 4. Different Types of Blood Disorders and their Management Outcomes

Conclusion

It can be concluded that hematological abnormalities during pregnancy are prevalent. While gestational thrombocytopenia may not significantly increase bleeding risks, venous thromboembolism (VTE) risk surges fivefold during pregnancy and further during postpartum. Iron deficiency anemia (IDA), particularly in the first trimester, is detrimental for both the mother (depression, fatigue) and the infant (prematurity, mortality). Socioeconomic factors exacerbate these issues. Nutritional interventions, including iron supplementation and dietary management via smartphone apps, can significantly improve maternal and fetal health outcomes. Managing hemophilia in pregnancy requires vigilant monitoring and a multidisciplinary approach. Antifibrinolytic agents play a crucial role in managing bleeding risks during and after delivery.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent to Publish

All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article in the main manuscript.

Competing Interests

The authors declare that no competing interests exist.

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Authors' Contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Lina Mohamed Nabil. The first draft of the manuscript was written by Lina Mohamed Nabil and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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