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Review Article

Dynamic Trajectories of Hemoglobin Concentration Across Pregnancy: Physiological Adaptation or Early Marker of Maternal Risk

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Abstract:

Hemoglobin concentration undergoes dynamic and highly individualized changes throughout pregnancy, reflecting complex physiological adaptations alongside potential pathological processes. Traditionally, gestational declines in hemoglobin have been attributed primarily to plasma volume expansion and considered a normal feature of pregnancy. However, accumulating evidence indicates that deviations from expected hemoglobin trajectories—whether excessively low, persistently depressed, or unusually high—may serve as early markers of maternal risk. This narrative review examines the physiological basis of hemoglobin changes across pregnancy, with emphasis on trimester-specific patterns, erythropoietic responses, and iron metabolism. It further explores key determinants of hemoglobin variability, including nutritional status, infection, inflammation, genetic factors, and socioeconomic context. Importantly, the review highlights emerging data linking abnormal hemoglobin trajectories to adverse maternal and perinatal outcomes such as preeclampsia, preterm birth, fetal growth restriction, and maternal morbidity. By shifting focus from single time-point hemoglobin measurements to longitudinal patterns, this review underscores the clinical and public health relevance of dynamic hemoglobin monitoring. A trajectory-based approach may improve early risk stratification, guide targeted interventions, and inform the refinement of gestational hemoglobin reference ranges to optimize maternal and fetal health outcomes.

Keywords: hemoglobin; pregnancy; anemia; maternal health; hemodilution

Introduction

Hemoglobin concentration is a fundamental hematological parameter routinely assessed during antenatal care and serves as a primary tool for screening anemia in pregnancy [1-2]. Its clinical relevance extends beyond simple oxygen transport, reflecting the integrated effects of plasma volume regulation, erythropoiesis, iron metabolism, and systemic health. Pregnancy induces profound physiological changes in the maternal hematologic system, resulting in dynamic rather than static hemoglobin values across gestation. Consequently, interpretation of hemoglobin concentration in pregnancy requires careful consideration of gestational age and underlying maternal factors [3-5]. Traditionally, reductions in hemoglobin concentration during pregnancy have been regarded as a normal physiological phenomenon, largely attributed to plasma volume expansion that exceeds the increase in red blood cell mass. This process, often termed physiological hemodilution, is considered beneficial, as it improves uteroplacental perfusion, reduces blood viscosity, and provides a protective circulatory reserve for parturition. Based on this paradigm, gestational anemia has commonly been defined using fixed hemoglobin thresholds, with limited emphasis on temporal patterns or individual variability [6-7].

However, growing evidence from longitudinal cohorts and population-based studies challenges the adequacy of this simplified interpretation. Hemoglobin trajectories during pregnancy exhibit substantial interindividual and interpopulation variability, influenced by nutritional status, iron availability, inflammation, infection, genetic factors, and access to quality antenatal care [8-10]. Importantly, deviations from expected hemoglobin patterns—such as early pregnancy anemia, steep mid-gestational declines, failure of late gestational recovery, or persistently elevated hemoglobin levels—have been associated with adverse maternal and perinatal outcomes. These findings suggest that hemoglobin concentration may function not only as a marker of physiological adaptation but also as an early indicator of maternal risk [11-13]. In this context, there is increasing interest in moving beyond single time-point hemoglobin measurements toward a dynamic,

trajectory-based approach to assessment. Such an approach has the potential to enhance early risk stratification, guide targeted interventions, and improve pregnancy outcomes, particularly in settings with a high burden of anemia and limited diagnostic resources. This narrative review aims to synthesize current evidence on the dynamic trajectories of hemoglobin concentration across pregnancy, critically examining the balance between physiological adaptation and pathological change, and exploring the clinical and public health implications of longitudinal hemoglobin monitoring [14-15].

Physiological Basis of Hemoglobin Changes in Pregnancy

Hemoglobin concentration in pregnancy is determined by the dynamic interaction between plasma volume expansion, red blood cell mass accretion, erythropoietic regulation, and iron metabolism. These physiological adaptations are essential to meet the increased metabolic and oxygen demands of the growing fetus while maintaining maternal cardiovascular stability. Understanding these mechanisms is critical for distinguishing normal gestational changes from pathological alterations in hemoglobin concentration [16]. One of the earliest and most prominent hematological adaptations in pregnancy is plasma volume expansion. This process begins in the first trimester, accelerates during the second trimester, and typically reaches its peak by the late second or early third trimester. Overall, plasma volume may increase by approximately 40–50% above pre-pregnancy levels. In contrast, red blood cell mass increases more modestly, by about 20–30% in iron-replete women. The resulting imbalance leads to a dilutional reduction in hemoglobin concentration, commonly referred to as the physiological anemia of pregnancy [17].

This hemodilution is not a maladaptive process. Rather, it confers several physiological advantages, including reduced blood viscosity, improved uteroplacental blood flow, and the establishment of a circulatory reserve that protects the mother against the hemodynamic stress of labor and potential blood loss at delivery. Consequently, moderate declines in hemoglobin concentration, particularly during mid-pregnancy, are generally considered a normal and beneficial adaptation [18]. Pregnancy is associated with increased erythropoietic activity driven by elevated levels of erythropoietin, a hormone produced primarily by the kidneys in response to increased oxygen demand. This enhanced erythropoiesis supports the expansion of maternal red blood cell mass, which is necessary to compensate, at least partially, for plasma volume expansion and to ensure adequate oxygen delivery to maternal tissues and the developing fetus [19].

The efficiency of this erythropoietic response is highly dependent on iron availability. In women with sufficient iron stores, red blood cell mass expansion proceeds effectively, moderating the degree of hemoglobin decline. Conversely, in iron-deficient states, erythropoiesis is impaired, leading to a more pronounced and potentially pathological reduction in hemoglobin concentration [20]. Iron metabolism undergoes significant modulation during pregnancy. Total iron requirements increase substantially, particularly in the second and third trimesters, to support maternal erythropoiesis, placental development, and fetal iron accretion. These requirements often exceed what can be met through dietary intake alone, especially in settings with limited access to iron-rich foods or supplementation [21]. Physiological adaptations, including increased intestinal iron absorption and mobilization of iron stores, attempt to meet these heightened demands. However, when iron intake or absorption is inadequate, or when iron losses are increased, iron deficiency may develop or worsen, contributing to pathological anemia [22].

Pregnancy-related hormonal changes, including elevated levels of estrogen and progesterone, play a role in regulating plasma volume expansion and erythropoiesis. Additionally, inflammatory processes—whether pregnancy-related or due to concurrent infection or chronic disease—can influence hemoglobin concentration through the hepcidin-mediated sequestration of iron. Elevated hepcidin levels reduce iron absorption and limit iron availability for erythropoiesis, potentially exacerbating gestational anemia [23]. While declining hemoglobin concentration is a normal feature of pregnancy, the extent, timing, and pattern of change are critical. Excessive declines, early onset anemia, or failure of hemoglobin recovery in late pregnancy may indicate underlying pathology rather than physiological adaptation. Therefore, an understanding of the physiological basis of hemoglobin changes provides a necessary framework for interpreting hemoglobin trajectories and identifying women at increased risk of adverse pregnancy outcomes [24].

Trimester-Specific Hemoglobin Trajectories

Hemoglobin concentration follows a characteristic but highly variable pattern across the three trimesters of pregnancy. These trimester-specific trajectories reflect the timing and magnitude of plasma volume expansion, erythropoietic response, and iron availability. Appreciating these patterns is essential for distinguishing physiological adaptation from pathological deviation and for interpreting hemoglobin values in clinical and public health contexts (Table 1).

First Trimester: Baseline Status and Early Adaptation

During the first trimester, hemoglobin concentration largely reflects the woman's pre-pregnancy hematologic and nutritional status. Although plasma volume expansion begins early in gestation, its magnitude is relatively modest at this stage, and hemoglobin levels typically remain stable or show only a slight decline. Consequently, low hemoglobin concentrations detected in the first trimester are more likely to indicate pre-existing anemia, iron deficiency, chronic inflammatory conditions, or inherited hematologic disorders rather than physiological hemodilution [25]. Early pregnancy anemia has been consistently associated with adverse maternal and fetal outcomes, including increased risk of preterm birth and low birth weight. Therefore, hemoglobin measurements in the first trimester provide a critical opportunity for early risk identification and timely intervention.

Second Trimester: Peak Hemodilution and Hemoglobin Nadir

The second trimester is characterized by the most pronounced decline in hemoglobin concentration. This period coincides with rapid plasma volume expansion, which typically outpaces the increase in red blood cell mass despite heightened erythropoietic activity. As a result, hemoglobin concentration reaches its physiological nadir during mid-gestation [26]. This decline is often interpreted as a normal adaptation; however, the degree of hemoglobin reduction varies widely among individuals. Women with adequate iron stores and effective erythropoietic responses tend to experience moderate, transient declines, whereas those with iron deficiency, poor nutritional status, or concurrent infections may develop more severe anemia. Importantly, excessively low hemoglobin levels during the second trimester have been linked to adverse outcomes such as preterm delivery and impaired fetal growth, underscoring the need to differentiate physiological from pathological changes [27].

Third Trimester: Stabilization or Partial Recovery

In the third trimester, plasma volume expansion begins to plateau, while erythropoiesis continues in response to sustained oxygen demands and, in many cases, iron supplementation. As a result, hemoglobin concentration often stabilizes or shows a modest increase toward term. This partial recovery is considered a favorable trajectory and suggests adequate iron availability and effective hematologic adaptation [28]. Failure of hemoglobin concentration to stabilize or recover in late pregnancy may indicate persistent iron deficiency, ongoing inflammation, occult blood loss, or poor adherence to supplementation. Conversely, unusually high hemoglobin levels in the third trimester may reflect inadequate plasma

volume expansion and have been associated with hypertensive disorders of pregnancy, placental insufficiency, and fetal growth restriction [28].

Trimester	Hemoglobin Pattern	Physiological Basis	Clinical Significance / Risk Indicators
First Trimester	Stable or slight decline	Early plasma volume expansion; baseline maternal hemoglobin largely reflects pre-pregnancy status	Low hemoglobin may indicate pre-existing anemia, iron deficiency, or chronic disease; early intervention critical
Second Trimester	Pronounced decline (hemoglobin nadir)	Rapid plasma volume expansion outpaces red cell mass increase (physiological hemodilution); increased erythropoietic demand	Excessive decline may signal iron deficiency, poor nutrition, infection, or inflammation; associated with preterm birth, low birth weight
Third Trimester	Stabilization or modest recovery	Plasma volume plateaus; continued erythropoiesis; partial recovery with adequate iron and supplementation	Failure to recover suggests persistent anemia or ongoing pathology; unusually high hemoglobin may indicate inadequate plasma expansion, risk for preeclampsia or fetal growth restriction

Table 1: Trimester-Specific Hemoglobin Trajectories During Pregnancy

Clinical Significance of Trimester-Specific Patterns

Taken together, trimester-specific hemoglobin trajectories provide more clinically meaningful information than isolated measurements. Early low hemoglobin, excessive mid-gestational decline, lack of late gestational recovery, or persistently elevated hemoglobin levels may each signal distinct pathophysiological processes and maternal risks. Incorporating gestational age–specific interpretation into routine antenatal care may enhance early detection of at-risk pregnancies and improve maternal and perinatal outcomes [28].

Determinants of Hemoglobin Variability in Pregnancy

Hemoglobin trajectories during pregnancy exhibit substantial variability across individuals and populations. This heterogeneity reflects the interaction of biological, nutritional, environmental, and health system–related factors that influence plasma volume expansion, erythropoiesis, and iron metabolism (Table 2).

Maternal Nutritional Status and Iron Intake

Maternal nutritional status is a primary determinant of hemoglobin concentration in pregnancy. Adequate dietary intake of iron, folate, vitamin B_{12}, and protein is critical for effective erythropoiesis. Women who enter pregnancy with depleted iron stores are particularly vulnerable to gestational anemia, as pregnancy-related iron requirements increase substantially, especially in the second and third trimesters. Poor dietary diversity, food insecurity, and limited access to iron supplementation further exacerbate hemoglobin decline, particularly in low- and middle-income settings [29].

Iron Absorption, Inflammation, and Hepcidin Regulation

Iron absorption and utilization are tightly regulated by hepcidin, a hepatic hormone that controls intestinal iron uptake and iron release from stores. Inflammatory states, whether due to pregnancy-related conditions or concurrent infections, increase hepcidin levels, leading to functional iron deficiency despite adequate total body iron. This mechanism contributes to anemia of inflammation and explains why some women fail to respond adequately to oral iron supplementation during pregnancy [30].

Infections and Parasitic Diseases

Infectious diseases remain significant contributors to hemoglobin variability, particularly in regions with high endemic burdens. Malaria, helminth infections, HIV, and other chronic infections can cause hemolysis, impaired erythropoiesis, and increased inflammatory responses, all of which adversely affect hemoglobin concentration. Recurrent or untreated infections may lead to persistent or worsening anemia across gestation, altering expected hemoglobin trajectories [31].

Maternal Age, Parity, and Reproductive History

Maternal age and parity influence hemoglobin dynamics through their effects on nutritional reserves and physiological adaptation. Adolescents and women with high parity or short interpregnancy intervals are at increased risk of anemia due to inadequate replenishment of iron stores between pregnancies. Conversely, primigravidae may exhibit different patterns of plasma volume expansion and erythropoietic response, contributing to interindividual variability [32].

Genetic and Hematologic Factors

Inherited hemoglobinopathies and red blood cell disorders, such as sickle cell disease and thalassemias, significantly affect baseline hemoglobin levels and gestational trajectories. Even carrier states may influence hemoglobin concentration and complicate interpretation using standard reference ranges. Additionally, genetic variation in iron metabolism and erythropoietin responsiveness may contribute to observed differences in hemoglobin adaptation [32].

Socioeconomic and Health System Factors

Socioeconomic status, education, and access to quality antenatal care play critical roles in shaping hemoglobin trajectories. Early initiation of antenatal care, routine screening, timely treatment of infections, and adherence to iron supplementation are essential for maintaining optimal hemoglobin levels. In contrast, delayed or inadequate care increases the likelihood of unrecognized and untreated anemia, leading to unfavorable hemoglobin patterns [34].

Lifestyle and Environmental Influences

Lifestyle factors such as smoking, altitude of residence, and environmental exposures also affect hemoglobin concentration. Women living at high altitude typically have higher baseline hemoglobin levels, which may mask gestational declines or complicate anemia diagnosis if altitude-adjusted reference values are not applied [35].

Category	Determinant	Mechanism / Influence on Hemoglobin	Implications for Pregnancy
Nutritional Status	Iron, folate, vitamin B_{12}, protein intake	Supports erythropoiesis and red blood cell synthesis	Deficiency increases risk of anemia, low hemoglobin trajectories, and adverse maternal/fetal outcomes
Iron Absorption & Regulation	Hepcidin levels, inflammation	Inflammation elevates hepcidin, reducing iron absorption and utilization	Functional iron deficiency despite adequate intake; may blunt response to supplementation
Infections / Parasitic Diseases	Malaria, HIV, helminthiasis, chronic infections	Hemolysis, impaired erythropoiesis, inflammatory-mediated iron sequestration	Exacerbates hemoglobin decline; contributes to persistent anemia and poor pregnancy outcomes
Maternal Factors	Age, parity, interpregnancy interval	Adolescents and high-parity women have reduced iron stores; primigravidae may show different plasma volume expansion	Increases susceptibility to anemia and abnormal hemoglobin trajectories
Genetic / Hematologic Conditions	Hemoglobinopathies (sickle cell, thalassemias), inherited red cell disorders	Alter baseline hemoglobin and red cell dynamics	Complicates diagnosis and management of anemia; may alter gestational hemoglobin patterns
Socioeconomic & Healthcare Access	Education, income, antenatal care access	Affects nutrition, supplementation adherence, and infection management	Delayed or inadequate care increases risk of pathological hemoglobin trajectories
Lifestyle & Environmental Factors	Smoking, altitude, environmental exposures	Smoking may increase hemoglobin; high altitude stimulates erythropoiesis; environmental toxins can impair red cell production	Influences baseline and gestational hemoglobin levels; requires adjustment of reference ranges

Table 2: Determinants of Hemoglobin Variability in Pregnancy

Hemoglobin Trajectories as Early Markers of Maternal Risk

Emerging evidence suggests that hemoglobin concentration in pregnancy should be interpreted as a dynamic process rather than a static laboratory value. Longitudinal hemoglobin trajectories provide important prognostic information, offering insight into underlying physiological adaptation, nutritional adequacy, and disease processes. Deviations from expected gestational patterns may serve as early markers of maternal risk, often preceding overt clinical complications.

Low Hemoglobin Trajectories and Maternal Risk

Persistently low hemoglobin levels or steep declines early in pregnancy are strongly associated with adverse maternal outcomes. Early pregnancy anemia frequently reflects pre-existing iron deficiency, chronic infection, or inflammatory disease, all of which may compromise maternal reserves needed to support gestation. Longitudinal studies have shown that women whose hemoglobin levels are low in the first trimester and fail to improve with supplementation are at increased risk of severe anemia at delivery, postpartum hemorrhage, maternal fatigue, and reduced tolerance to blood loss [36]. Moreover, excessive hemoglobin decline during the second trimester has been linked to higher rates of preterm birth, low birth weight, and increased maternal morbidity. These associations underscore the importance of trajectory patterns, as single measurements may underestimate risk when hemoglobin decline is progressive or unrecognized.

High Hemoglobin Trajectories and Inadequate Plasma Expansion

While clinical attention has traditionally focused on low hemoglobin levels, persistently high hemoglobin concentrations during pregnancy have also been associated with adverse outcomes. Elevated hemoglobin in the second or third trimester may indicate inadequate plasma volume expansion, resulting in increased blood viscosity and reduced uteroplacental perfusion. Such patterns have been linked to hypertensive disorders of pregnancy, including preeclampsia, as well as fetal growth restriction and stillbirth [37]. High hemoglobin trajectories challenge the assumption that higher values uniformly reflect better maternal health and highlight the need for balanced interpretation that considers gestational physiology.

Nonlinear and Atypical Hemoglobin Patterns

Beyond persistently low or high levels, atypical hemoglobin trajectories—such as abrupt declines, minimal mid-gestational decline followed by late deterioration, or failure of late gestational recovery—may signal evolving pathology. These patterns can reflect poor adherence to supplementation, emerging inflammatory or infectious conditions, or occult blood loss. Recognition of such nonlinear trends requires repeated measurements and longitudinal analysis rather than reliance on fixed gestational thresholds [38].

Predictive Value for Maternal and Perinatal Outcomes

Several studies have demonstrated that hemoglobin trajectories are more predictive of adverse outcomes than single hemoglobin values. Trajectory-based models incorporating gestational timing and rate of change have shown improved ability to identify women at risk of preeclampsia, preterm delivery, and severe anemia compared with traditional screening approaches. This evidence supports the integration of longitudinal hemoglobin monitoring into routine antenatal care, particularly for high-risk populations [39-40].

Implications for Risk Stratification and Clinical Practice

Interpreting hemoglobin trajectories as early markers of maternal risk offers an opportunity to shift antenatal care from reactive to proactive management. Women exhibiting unfavorable hemoglobin patterns may benefit from intensified monitoring, targeted nutritional or therapeutic interventions, and closer obstetric surveillance. In resource-limited settings, where advanced diagnostics may be unavailable, trajectory-based assessment of hemoglobin could provide a practical and cost-effective tool for early risk identification [40].

Clinical and Public Health Implications

Recognition of hemoglobin concentration as a dynamic trajectory rather than a single diagnostic value has important clinical and public health implications for the management of pregnancy. Integrating longitudinal hemoglobin assessment into antenatal care can improve early risk identification, guide targeted interventions, and inform policy decisions aimed at reducing maternal and perinatal morbidity.

Implications for Clinical Practice

In clinical settings, routine hemoglobin measurement is often limited to isolated time points, with management decisions based on fixed gestational thresholds. A trajectory-based approach offers a more nuanced interpretation by accounting for gestational age, baseline hemoglobin status, and the rate of change across pregnancy. Early identification of unfavorable hemoglobin patterns—such as low first-trimester values, excessive mid-gestational decline, or failure of late gestational recovery—allows clinicians to intervene proactively rather than responding to advanced anemia [41]. Such interventions may include individualized iron supplementation strategies, evaluation for underlying infections or inflammatory conditions, assessment of adherence and tolerability of therapy, and closer maternal surveillance. Importantly, recognition of persistently high hemoglobin levels may prompt evaluation for inadequate plasma volume expansion and heightened monitoring for hypertensive disorders and placental insufficiency. Incorporating hemoglobin trajectories into clinical decision-making therefore supports more personalized and risk-informed antenatal care [41].

Implications for Antenatal Screening and Monitoring

From a public health perspective, longitudinal hemoglobin monitoring strengthens antenatal screening programs by improving the sensitivity of anemia detection and risk stratification. Repeated measurements across trimesters provide opportunities to assess response to supplementation and to adjust interventions in a timely manner. This is particularly relevant in settings with a high burden of anemia, where delayed recognition contributes to severe anemia at delivery and increased maternal mortality [42]. Trajectory-based monitoring may also inform the optimal timing of screening and supplementation, reinforcing the importance of early antenatal booking and continuity of care throughout pregnancy.

Policy and Guideline Development

Current guidelines for the diagnosis and management of anemia in pregnancy rely largely on fixed hemoglobin cut-offs that do not fully reflect gestational physiology or population diversity. Evidence supporting the prognostic value of hemoglobin trajectories highlights the need to reconsider existing definitions and to develop trimester-specific and context-specific reference ranges. Policymakers and professional bodies may need to incorporate longitudinal criteria into national and international recommendations to improve maternal health outcomes [43].

Implications for Resource-Limited Settings

In low- and middle-income countries, where access to advanced laboratory testing may be limited, hemoglobin measurement remains one of the most accessible and cost-effective diagnostic tools. A trajectory-based approach maximizes the utility of this simple test by extracting greater clinical value from repeated measurements. When integrated with basic clinical assessment, longitudinal hemoglobin monitoring can serve as a pragmatic early warning system for maternal risk, supporting targeted use of limited healthcare resources [44].

Public Health Surveillance and Research

At the population level, analysis of hemoglobin trajectories can enhance maternal health surveillance by identifying high-risk groups and informing programmatic interventions. Large-scale longitudinal data may also contribute to refining anemia prevention strategies, evaluating the effectiveness of supplementation programs, and guiding future research priorities [45].

Conclusion

Hemoglobin concentration during pregnancy reflects a complex interplay between physiological adaptation and pathological processes. While moderate declines in hemoglobin are a normal consequence of plasma volume expansion and enhanced circulatory demands, deviations from expected gestational trajectories may signal underlying nutritional deficiencies, inflammatory states, infections, or impaired maternal adaptation. Evidence increasingly demonstrates that hemoglobin patterns across pregnancy—rather than isolated measurements—carry important prognostic value for maternal and perinatal outcomes. A trajectory-based interpretation of hemoglobin offers a more clinically meaningful framework for antenatal assessment, enabling earlier identification of women at increased risk of adverse outcomes such as severe anemia, hypertensive disorders, preterm birth, and fetal growth restriction. This approach supports timely, targeted interventions and more individualized antenatal care, particularly in settings where hemoglobin measurement remains one of the most accessible diagnostic tools. From a public health perspective, incorporating longitudinal hemoglobin monitoring into routine antenatal programs may enhance screening effectiveness, inform policy development, and contribute to refining gestational hemoglobin reference ranges. Ultimately, re-framing hemoglobin concentration as a dynamic biomarker of maternal health rather than a static indicator of anemia has the potential to improve risk stratification, optimize resource use, and strengthen efforts to improve maternal and fetal health outcomes globally.

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