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Review Article

Red Cell Indices, Iron Kinetics, and Erythropoietic Stress in Pregnancies Beyond 35 Years: A Narrative Review

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Abstract:

Advanced maternal age (≥35 years) is increasingly common and is associated with distinct hematologic challenges that extend beyond the physiological adaptations of normal pregnancy. This narrative review examines alterations in red cell indices, iron kinetics, and erythropoietic stress in pregnancies beyond 35 years. While gestation is characterized by plasma volume expansion and increased erythropoietic demand, older gravidas may exhibit reduced marrow responsiveness, higher prevalence of micronutrient deficiencies, and low-grade inflammatory states that disrupt iron homeostasis. Red cell indices—including hemoglobin, mean corpuscular volume, and red cell distribution width—remain essential screening tools but may mask functional iron deficiency when interpreted in isolation. Dysregulated hepcidin activity, impaired iron mobilization, and elevated soluble transferrin receptor levels may contribute to ineffective erythropoiesis in this population. These hematologic perturbations have implications for maternal fatigue, hypertensive disorders, placental insufficiency, and adverse neonatal outcomes. A biomarker-guided diagnostic framework integrating ferritin, transferrin saturation, reticulocyte parameters, and inflammatory markers is recommended to enhance risk stratification and therapeutic precision. Improved understanding of iron metabolism and erythropoietic dynamics in advanced maternal age is critical for optimizing maternal–fetal health outcomes.

Keywords: advanced maternal age; red cell indices; iron kinetics; erythropoietic stress; hepcidin

Introduction

Advanced maternal age (AMA), conventionally defined as pregnancy at or beyond 35 years, has become increasingly prevalent across both high- and low-resource settings. Sociodemographic transitions, delayed marriage, extended educational trajectories, career prioritization, and improved access to assisted reproductive technologies have contributed to a sustained upward shift in maternal age distribution. While many women in this age group experience uncomplicated pregnancies, epidemiologic data consistently associate AMA with increased risks of gestational hypertension, preeclampsia, gestational diabetes mellitus, placental dysfunction, operative delivery, and perinatal morbidity. Within this broader obstetric risk landscape, hematologic adaptation represents a critical yet underexplored domain in older gravidas [1-2]. Pregnancy imposes substantial physiologic demands on the hematopoietic system. Plasma volume expands by approximately 40–50%, red cell mass increases by 20–30%, and iron requirements escalate to support maternal erythropoiesis, placental development, and progressive fetal iron accretion—particularly during the third trimester. The resulting "physiologic anemia of pregnancy" reflects hemodilution rather than true deficiency, provided iron mobilization and marrow responsiveness remain intact. Efficient erythropoietic adaptation depends on coordinated suppression of hepcidin, enhanced intestinal iron absorption, augmented macrophage iron recycling, and erythropoietin-driven marrow expansion [3-4].

In women beyond 35 years, these adaptive mechanisms may intersect with age-related hematologic and metabolic alterations. Even in otherwise healthy individuals, advancing age is associated with subtle reductions in hematopoietic stem cell regenerative capacity, shifts in myeloid–erythroid lineage balance, increased oxidative stress, and a background state of low-grade inflammation often termed "inflammaging." Elevated pro-inflammatory cytokines—particularly interleukin-6—can upregulate hepcidin expression, thereby restricting iron egress from enterocytes and macrophages. This functional iron sequestration may impair effective erythropoiesis despite adequate or even elevated ferritin concentrations [5]. Moreover, cumulative micronutrient depletion over the reproductive lifespan may predispose older pregnant women to iron, folate, or vitamin B12 insufficiency at conception. Gastrointestinal absorption of vitamin B12 declines with age due to atrophic gastritis or reduced intrinsic factor activity, potentially contributing to macrocytosis or ineffective erythropoiesis. Iron

stores, particularly in women with previous pregnancies or heavy menstrual losses, may be suboptimal before gestation begins. These preconceptional factors are clinically significant because pregnancy rapidly unmasks marginal deficiencies [6-7].

Red cell indices—including hemoglobin concentration, hematocrit, mean corpuscular volume (MCV), and red cell distribution width (RDW)—remain foundational tools in antenatal screening. However, in AMA pregnancy, conventional indices may incompletely capture iron-restricted erythropoiesis or inflammatory-mediated functional deficiency. Emerging biomarkers such as soluble transferrin receptor (sTfR), reticulocyte hemoglobin content (Ret-He), and hepcidin provide additional mechanistic insight into iron kinetics and marrow activity. Their integration into obstetric practice may enhance diagnostic precision, particularly in older gravidas with coexisting metabolic or vascular comorbidities [8-9]. First, anemia and subclinical iron deficiency are linked to maternal fatigue, reduced physical resilience, and increased risk of postpartum hemorrhage. Second, impaired oxygen-carrying capacity may exacerbate placental hypoperfusion, potentially contributing to hypertensive disorders and fetal growth restriction. Third, inadequate maternal iron transfer affects neonatal iron endowment and early neurodevelopmental trajectories. In a population already at elevated obstetric risk, optimizing hematologic adaptation assumes heightened importance [10]. This narrative review aims to bridge that gap by examining current evidence on hematologic adaptations in AMA, highlighting diagnostic challenges, and proposing a biomarker-informed framework for risk stratification and individualized management.

Red Cell Indices in Advanced Maternal Age Pregnancy

Red cell indices remain the first-line laboratory parameters for evaluating hematologic adaptation in pregnancy. In women aged 35 years and above, interpretation of these indices requires a nuanced understanding of the interplay between physiologic hemodilution, iron availability, inflammatory tone, and age-related marrow dynamics. While the fundamental patterns of gestational hematology are preserved, advanced maternal age (AMA) may subtly modify both baseline values and their clinical implications [11]. Hemoglobin concentration and hematocrit typically decline during the second trimester due to disproportionate plasma volume expansion relative to red cell mass. In AMA pregnancies, this physiologic anemia may be superimposed on pre-existing marginal iron stores or chronic low-grade inflammation, increasing the likelihood of true anemia. Importantly, hemoglobin thresholds alone may underestimate iron-restricted erythropoiesis, particularly when inflammatory processes elevate ferritin and mask depleted bioavailable iron. Thus, a “normal” hemoglobin level in an older gravida does not invariably indicate optimal iron sufficiency or marrow performance [12].

Mean corpuscular volume (MCV) provides critical morphologic insight. In AMA pregnancy, microcytosis frequently reflects iron deficiency, either absolute or functional. Many women entering pregnancy beyond 35 years may have experienced cumulative reproductive iron losses, suboptimal dietary intake, or reduced iron absorption efficiency. Conversely, normocytic patterns may predominate when anemia is dilutional or related to inflammatory-mediated iron sequestration. Macrocytosis, although less common, warrants careful evaluation for vitamin B12 or folate deficiency—conditions that are more prevalent with advancing age due to gastrointestinal malabsorption, dietary insufficiency, or prior bariatric procedures. Even mild macrocytosis in pregnancy should prompt biochemical assessment, as ineffective erythropoiesis may compromise maternal oxygen delivery [13]. Mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) further characterize hemoglobinization of red cells. Hypochromia, reflected by reduced MCH or MCHC, supports iron-deficient erythropoiesis. In older pregnant women, this finding may precede overt anemia and signal early depletion of functional iron. Because iron demands increase substantially during the second and third trimesters, early detection of declining red cell hemoglobinization is clinically valuable [13].

Red cell distribution width (RDW) has gained attention as a dynamic marker of anisocytosis and erythropoietic stress. Elevated RDW in AMA pregnancy may indicate heterogeneous red cell populations resulting from combined nutritional deficiencies or fluctuating iron availability. Beyond its diagnostic utility in anemia classification, increased RDW has been associated in observational studies with systemic inflammation, endothelial dysfunction, and adverse obstetric outcomes such as preeclampsia and fetal growth restriction. Given that advanced maternal age itself correlates with higher cardiometabolic risk, RDW may serve as an integrative biomarker reflecting both hematologic and vascular perturbations [14]. Reticulocyte indices offer additional insight into marrow responsiveness. In the context of anemia, an appropriate reticulocyte response suggests effective erythropoietic compensation, whereas a blunted response may indicate insufficient substrate (iron, folate, vitamin B12), inflammatory inhibition, or reduced hematopoietic reserve. Age-related shifts in hematopoietic stem cell function, though subtle in healthy women, may influence the kinetics of marrow expansion under gestational stress. Reticulocyte hemoglobin content (Ret-He or CHr) is particularly informative, providing a real-time measure of iron incorporation into newly formed erythrocytes and enabling earlier detection of iron-restricted erythropoiesis than traditional indices [15]. Interpretation of red cell indices in AMA pregnancy must therefore be contextual and integrative. Physiologic hemodilution, inflammatory markers, nutritional status, and comorbid conditions such as hypertension or metabolic syndrome should inform diagnostic reasoning. Reliance solely on hemoglobin concentration may delay recognition of evolving deficiency states, whereas combined evaluation of MCV, RDW, reticulocyte parameters, and iron biomarkers enhances clinical precision [16].

Iron Kinetics and Regulation in Advanced Maternal Age Pregnancy

Iron metabolism during pregnancy is a tightly coordinated process designed to meet the competing demands of maternal erythropoiesis, placental development, and fetal growth. Across gestation, total maternal iron requirements approach 1000 mg, accounting for expansion of red cell mass, fetal and placental needs, and anticipated blood loss at delivery. In advanced maternal age (AMA) pregnancy, these physiologic demands intersect with age-related alterations in iron homeostasis, inflammatory signaling, and gastrointestinal absorption, creating a distinct kinetic landscape [17]. At the center of systemic iron regulation is hepcidin, a hepatic peptide hormone that governs intestinal iron absorption and macrophage iron release through degradation of the iron exporter ferroportin. In normal pregnancy, hepcidin levels decline—particularly during the second and third trimesters—facilitating enhanced dietary iron absorption and mobilization of stored iron to support accelerated erythropoiesis. This adaptive suppression ensures efficient iron flux toward the maternal bone marrow and fetoplacental unit [18]. In women beyond 35 years, however, baseline inflammatory tone may be modestly elevated due to age-associated cytokine activity, increased adiposity, or metabolic comorbidities. Interleukin-6 and related inflammatory mediators stimulate hepcidin transcription, potentially attenuating its physiologic suppression in pregnancy. The result can be functional iron deficiency, characterized by adequate or increased ferritin levels but restricted iron availability for erythropoiesis. In this scenario, iron becomes sequestered within macrophages and hepatocytes, limiting its incorporation into hemoglobin despite apparently sufficient stores [19].

Serum ferritin remains the most widely used biomarker of iron reserves. In AMA pregnancy, interpretation requires caution because ferritin behaves as an acute-phase reactant. Mild inflammatory states may elevate ferritin concentrations, masking depleted or inaccessible iron pools. Thus, ferritin

thresholds that define deficiency in younger, low-inflammatory populations may underestimate iron-restricted states in older gravidas. Serial monitoring, rather than single-point measurement, enhances interpretive accuracy [20]. Transferrin and transferrin saturation (TSAT) reflect circulating iron availability. During pregnancy, transferrin synthesis increases, expanding total iron-binding capacity. Low TSAT in the presence of normal or elevated ferritin suggests impaired iron mobilization rather than absolute deficiency. This distinction is clinically relevant because oral iron supplementation may be less effective when inflammatory blockade predominates, potentially necessitating parenteral strategies [21]. Soluble transferrin receptor (sTfR) offers additional mechanistic insight. Unlike ferritin, sTfR is minimally influenced by inflammation and correlates with cellular iron demand and erythropoietic activity. Elevated sTfR in AMA pregnancy indicates heightened marrow drive relative to iron supply. The sTfR–ferritin index further refines differentiation between absolute and functional deficiency, providing a more comprehensive view of iron kinetics in complex clinical settings [22].

Placental iron transport represents another critical regulatory axis. Iron crosses the placenta via transferrin receptor–mediated endocytosis, ensuring preferential fetal acquisition even when maternal stores are limited. However, in advanced maternal age, placental vascular aging or hypertensive disorders may impair efficient transfer. Maternal iron restriction in late gestation can therefore reduce neonatal iron endowment, with potential implications for early neurodevelopment and immune function [23]. Gastrointestinal absorption capacity may also influence iron kinetics in older pregnant women. Age-related changes in gastric acidity, subclinical atrophic gastritis, or prior bariatric surgery can diminish non-heme iron absorption. Concurrent use of proton pump inhibitors—more prevalent in older populations—may further compromise bioavailability. These factors underscore the importance of individualized supplementation strategies rather than uniform dosing [24]. Erythropoietin (EPO) plays a complementary regulatory role by stimulating erythroid progenitor proliferation in response to relative hypoxia. In pregnancy, EPO levels rise in parallel with expanding red cell mass. While most healthy women beyond 35 years maintain adequate EPO responsiveness, subtle age-associated reductions in hematopoietic stem cell proliferative potential may modulate the efficiency of iron utilization under stress conditions. When iron supply is inadequate or restricted, EPO-driven expansion can exacerbate iron depletion, perpetuating erythropoietic imbalance [25].

Erythropoietic Stress and Marrow Responsiveness in Advanced Maternal Age Pregnancy

Erythropoietic stress in pregnancy arises when the demand for red cell production exceeds the capacity of the bone marrow to deliver adequately hemoglobinized erythrocytes. In all pregnancies, erythropoiesis is physiologically upregulated to compensate for plasma volume expansion and to sustain maternal–fetal oxygen transport. In advanced maternal age (AMA), however, this adaptive process may be influenced by age-related hematopoietic dynamics, inflammatory signaling, micronutrient reserves, and coexisting metabolic conditions. The result is a more complex and potentially fragile erythropoietic equilibrium [26]. Under normal gestational conditions, rising erythropoietin (EPO) levels stimulate proliferation and differentiation of erythroid progenitors within the bone marrow. This expansion is highly dependent on sufficient iron availability, intact folate and vitamin B12 status, and effective marrow microenvironment support. In younger women, hematopoietic reserve is typically robust, enabling rapid scaling of red cell production. In contrast, women beyond 35 years may exhibit subtle declines in hematopoietic stem cell proliferative efficiency and altered marrow niche signaling. While these changes are usually subclinical, pregnancy represents a physiologic “stress test” that may unmask marginal reserve [27].

A central contributor to erythropoietic stress in AMA pregnancy is iron-restricted erythropoiesis. Even when total body iron stores are adequate, inflammatory-mediated hepcidin activity can limit iron egress from macrophages and reduce intestinal absorption. This creates a mismatch between EPO-driven marrow stimulation and iron supply, resulting in production of smaller, less hemoglobinized red cells. Over time, ineffective erythropoiesis may develop, characterized by increased erythroid precursor apoptosis and suboptimal reticulocyte output [28]. Reticulocyte parameters provide real-time insight into marrow responsiveness. An appropriate increase in reticulocyte count in the setting of anemia indicates preserved marrow compensatory capacity. However, in AMA pregnancy, reticulocyte responses may be blunted when iron, folate, or vitamin B12 substrates are insufficient, or when inflammatory cytokines suppress erythroid progenitor proliferation. Reticulocyte hemoglobin content (Ret-He or CHr) is particularly informative, reflecting the adequacy of iron incorporation into newly formed erythrocytes. Declining reticulocyte hemoglobin may precede overt anemia and signal emerging erythropoietic stress [29].

Age-related inflammatory changes further complicate marrow dynamics. The phenomenon of “inflammaging,” characterized by modest but persistent elevation of pro-inflammatory cytokines, can inhibit erythropoiesis both directly and indirectly. Cytokines such as interleukin-6 and tumor necrosis factor-α not only increase hepcidin expression but also suppress erythroid progenitor differentiation and shorten red cell lifespan. In the context of pregnancy—already a state of heightened immunologic modulation—this additional inflammatory burden may intensify erythropoietic strain [30]. Micronutrient status also plays a decisive role. Folate requirements rise substantially in pregnancy due to rapid cellular proliferation. Although supplementation is widely recommended, adherence and baseline reserves vary. Vitamin B12 deficiency, more common with advancing age because of malabsorption or dietary factors, may impair DNA synthesis in erythroid precursors, leading to ineffective erythropoiesis and macrocytosis. Combined iron and B12 deficiency may produce mixed morphologic patterns, further complicating interpretation of red cell indices [31].

Comorbid conditions prevalent in AMA—such as hypertension, insulin resistance, thyroid dysfunction, and obesity—can indirectly influence erythropoietic efficiency. Chronic kidney disease, even at early stages, may attenuate EPO production. Metabolic syndrome is associated with systemic inflammation, which may dampen marrow responsiveness and disrupt iron trafficking. These intersecting pathways underscore the need for comprehensive clinical assessment beyond routine hemoglobin measurement [32]. Clinically, unresolved erythropoietic stress in AMA pregnancy has implications for both maternal and fetal outcomes. Inadequate oxygen-carrying capacity may exacerbate placental hypoxia, potentially contributing to hypertensive disorders or fetal growth restriction. Maternal fatigue, reduced physical resilience, and increased susceptibility to postpartum anemia may also result from insufficient marrow compensation [33]. A structured evaluation of marrow responsiveness in older gravidas should integrate hemoglobin trends, reticulocyte count, reticulocyte hemoglobin content, iron biomarkers, and markers of inflammation. Early identification of suboptimal erythropoietic adaptation permits targeted nutritional correction or parenteral iron therapy when indicated. In selected cases, multidisciplinary management involving obstetricians and hematologists may be warranted [34].

Clinical Implications

The clinical implications of altered red cell indices, iron kinetics, and erythropoietic stress in pregnancies beyond 35 years extend beyond laboratory interpretation; they directly influence maternal functional status, obstetric risk profiles, and neonatal outcomes. Advanced maternal age (AMA) represents a demographic in which physiological gestational

adaptation intersects with age-related metabolic and vascular vulnerability. Within this context, even modest perturbations in hematologic equilibrium may carry amplified consequences [35]. Maternal anemia—whether absolute or functional—remains a central concern. In older gravidas, pre-existing marginal iron stores, inflammatory-mediated iron restriction, or micronutrient insufficiency may predispose to earlier onset or greater severity of gestational anemia. Clinically, this manifests as fatigue, reduced exercise tolerance, impaired cognitive focus, and diminished overall resilience. These symptoms, often normalized during pregnancy, may significantly affect quality of life and adherence to antenatal care. Furthermore, anemia increases susceptibility to peripartum complications, particularly postpartum hemorrhage and delayed hematologic recovery [36].

Beyond symptomatic burden, suboptimal oxygen-carrying capacity may influence placental function. Advanced maternal age is independently associated with endothelial dysfunction and increased risk of hypertensive disorders of pregnancy. Superimposed iron-restricted erythropoiesis may exacerbate placental hypoxia, contributing to maladaptive angiogenesis and impaired uteroplacental perfusion. Observational data have linked elevated red cell distribution width (RDW) and markers of inflammation with preeclampsia and fetal growth restriction, suggesting that hematologic dysregulation may participate in the pathophysiologic cascade rather than serving merely as a consequence [37]. Iron kinetics in AMA pregnancy also carry implications for fetal development. The fetus depends on active transplacental iron transfer, particularly in the third trimester when rapid brain growth occurs. Even in the setting of maternal anemia, placental mechanisms prioritize fetal iron delivery; however, sustained maternal deficiency can limit neonatal iron endowment. Infants born to iron-deficient mothers may exhibit lower ferritin concentrations at birth, predisposing to early-life iron deficiency and potential neurodevelopmental compromise. Given that pregnancies beyond 35 years may also carry increased risk of preterm birth, the window for adequate fetal iron accretion may be shortened, compounding vulnerability [38].

From a diagnostic standpoint, reliance solely on hemoglobin thresholds is insufficient in this age group. A normocytic, normochromic profile may conceal functional iron deficiency, particularly in the presence of inflammatory comorbidity. Incorporating ferritin, transferrin saturation, soluble transferrin receptor, and reticulocyte hemoglobin content into routine assessment enhances detection of early erythropoietic stress. Longitudinal monitoring across trimesters is particularly valuable, as iron requirements escalate progressively and compensatory mechanisms may falter late in gestation [39]. Therapeutically, individualized supplementation strategies assume heightened importance. While universal oral iron prophylaxis is common, gastrointestinal intolerance, reduced absorption efficiency, and inflammatory blockade may limit effectiveness in some older women. Intravenous iron formulations provide a safe and efficient alternative when oral therapy fails or when rapid correction is required. Timely intervention not only improves hematologic parameters but may reduce transfusion requirements and shorten postpartum recovery [40].

Preconception counseling offers an additional preventive opportunity. For women planning pregnancy beyond 35 years, evaluation of iron stores, vitamin B12, and folate status before conception allows correction of deficiencies prior to the onset of gestational demand. This proactive approach may mitigate early erythropoietic stress and support smoother hematologic adaptation [41]. At a systems level, the growing prevalence of advanced maternal age necessitates refinement of obstetric hematology guidelines. Age-stratified reference intervals, biomarker-guided algorithms, and integration of inflammatory assessment into anemia workup represent areas for protocol enhancement. Multidisciplinary collaboration between obstetricians, hematologists, and nutrition specialists may be particularly beneficial in complex cases [42].

Conclusion

Pregnancies beyond 35 years represent a distinct hematologic context in which physiological gestational adaptations converge with age-related alterations in iron metabolism, inflammatory regulation, and marrow reserve. While most older gravidas achieve adequate hematologic compensation, the margin for imbalance may be narrower. Subclinical iron depletion, functional iron deficiency mediated by hepcidin dysregulation, micronutrient insufficiency, and attenuated erythropoietic responsiveness can collectively predispose to anemia and ineffective red cell production. Red cell indices remain indispensable as initial screening tools; however, their interpretation in advanced maternal age requires integration with iron biomarkers and reticulocyte parameters to distinguish physiologic hemodilution from evolving erythropoietic stress. Ferritin, transferrin saturation, soluble transferrin receptor, and reticulocyte hemoglobin content provide complementary insight into iron availability and marrow performance. A biomarker-informed approach enhances diagnostic precision and enables earlier, targeted intervention. Clinically, optimizing iron kinetics and erythropoiesis in this population is essential not only for maternal functional capacity and peripartum safety but also for placental integrity and neonatal iron endowment. Given the global rise in advanced maternal age, refinement of screening algorithms, age-stratified reference standards, and individualized supplementation strategies is warranted. Future prospective studies should clarify hepcidin trajectories, define predictive biomarkers of adverse outcomes, and establish precision-based treatment frameworks.

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