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Redefining Maternal Shock: Cytokine Release Syndrome in Severe Postpartum Hemorrhage

***Emmanuel Ifeanyi Obeagu[1,2] and Amarachi Suzzy-Martins Ezekwunem[3]**

[1]Division of Haematology, Department of Biomedical and Laboratory Science, Africa University, Zimbabwe.

[2]Department of Molecular Medicine and Haematology, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[3]Department of Medical Laboratory Sciences, Madonna University, Elele, Rivers State, Nigeria

*Corresponding author: Emmanuel Ifeanyi Obeagu, Department of Biomedical and Laboratory Science, Africa University, Zimbabwe, emmanuelobeagu@yahoo.com,

ORCID: 0000-0002-4538-0161

Abstract

Severe postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality worldwide and has traditionally been understood as a purely hypovolemic form of shock. However, increasing clinical and immunological evidence suggests that a subset of women with severe PPH develop a dysregulated systemic inflammatory response consistent with cytokine release syndrome (CRS). This hyperinflammatory state is driven by hemorrhage-induced tissue hypoxia, endothelial injury, innate immune activation, and transfusion-related immunomodulation, culminating in capillary leak, refractory hypotension, coagulopathy, and multiorgan dysfunction. Such presentations often persist despite adequate hemorrhage control and volume resuscitation, challenging conventional management paradigms. This narrative review redefines maternal shock in severe PPH by integrating immunopathophysiological mechanisms of CRS with emerging clinical observations. We highlight key diagnostic considerations, potential biomarkers, and therapeutic implications, emphasizing the need for combined hemodynamic and immunomodulatory strategies in maternal critical care. Recognizing CRS as a contributor to maternal shock may improve risk stratification, guide targeted interventions, and ultimately enhance maternal outcomes in obstetric emergencies.

Keywords: Postpartum hemorrhage; Cytokine release syndrome; Maternal shock; Endothelial dysfunction; Obstetric critical care

Expanded Introduction

Postpartum hemorrhage (PPH) remains one of the most formidable challenges in modern obstetrics and continues to account for a substantial proportion of maternal morbidity and mortality worldwide, particularly in low- and middle-income countries [1-2]. Despite major advances in antenatal risk stratification, active management of the third stage of labor, surgical techniques, and transfusion medicine, severe PPH can still progress rapidly to maternal shock and multiorgan failure. Conventionally, this deterioration has been attributed almost exclusively to hypovolemia and impaired oxygen delivery resulting from acute blood loss. While this paradigm adequately explains early hemodynamic compromise, it fails to fully account for clinical scenarios in which maternal instability persists or worsens despite timely hemorrhage control and appropriate volume resuscitation [3-4].Pregnancy itself represents a unique immunological state characterized by tightly regulated inflammatory and anti-inflammatory phases that support fetal tolerance while preserving maternal host defense. Labor and delivery are associated with a physiological surge in inflammatory mediators, facilitating uterine contractions, placental separation, and tissue repair. In the setting of severe PPH, however, this finely balanced immune environment may be abruptly overwhelmed. Massive blood loss, tissue hypoxia, ischemia–reperfusion injury, and extensive endothelial activation converge to trigger an exaggerated innate immune response. This response closely resembles cytokine release syndrome (CRS), a hyperinflammatory condition well described in sepsis, trauma, and immunotherapy-related complications but only recently considered in obstetric emergencies [5-6].

Cytokine release syndrome is characterized by uncontrolled release of pro-inflammatory cytokines such as interleukin-6, tumor necrosis factor-α, and interleukin-1β, leading to systemic inflammation, endothelial dysfunction, capillary leak, coagulopathy, and organ injury. In severe PPH, these mechanisms may be further amplified by obstetric interventions, including massive transfusion of blood products, uterotonic agents, and surgical trauma. Transfusion-related immunomodulation and exposure to bioactive mediators within stored blood products may intensify immune activation, creating a self-perpetuating inflammatory cascade that extends well beyond the initial hemorrhagic insult [7-9].Clinically, the overlap between hypovolemic shock, septic shock, and CRS-related inflammatory shock presents a significant diagnostic challenge. Women with severe PPH may demonstrate refractory hypotension, metabolic acidosis, acute respiratory distress, renal impairment, and coagulopathy that are disproportionate to measured blood loss or hemoglobin decline. These features suggest that immune-mediated vascular and organ dysfunction may play a central role in maternal deterioration. Failure to recognize this inflammatory component risks over-reliance on aggressive fluid resuscitation, which may exacerbate endothelial leak, pulmonary edema, and tissue hypoxia [10-11].

Reconceptualizing maternal shock in severe PPH as a composite syndrome—encompassing both circulatory collapse and cytokine-driven inflammation—has profound implications for obstetric practice. It calls for a shift from a purely volume-centric resuscitation model toward a more integrated approach that incorporates immunopathophysiological insight, early identification of inflammatory biomarkers, and timely escalation to critical care. This expanded perspective also opens avenues for targeted therapeutic strategies aimed at modulating excessive inflammation and preserving endothelial integrity [12-14].In this narrative review, the paper explored the emerging concept of cytokine release syndrome as a key contributor to maternal shock in severe postpartum hemorrhage. We examine the immunological and vascular mechanisms underlying this phenomenon, discuss its clinical manifestations and diagnostic challenges, and consider the potential implications for management and future research. By redefining maternal shock through the lens of CRS, this review seeks to advance a more comprehensive and biologically informed framework for understanding and managing one of the most life-threatening obstetric emergencies.

Pathophysiological Link Between Postpartum Hemorrhage and Cytokine Release Syndrome

Severe postpartum hemorrhage represents far more than an episode of acute blood loss; it is a profound systemic insult capable of initiating complex immunological and vascular cascades. The pathophysiological link between postpartum hemorrhage (PPH) and cytokine release syndrome (CRS) is rooted in the convergence of tissue injury, hypoxia, innate immune activation, endothelial dysfunction, and iatrogenic factors associated with resuscitation and transfusion. Together, these processes transform a primarily hemodynamic emergency into a state of dysregulated inflammation resembling classical cytokine storm syndromes [15-16].Acute and massive blood loss in PPH leads to global tissue hypoperfusion and cellular hypoxia. As oxygen delivery falls below critical thresholds, affected tissues undergo metabolic stress, mitochondrial dysfunction, and ultimately cellular injury or necrosis. These damaged cells release damage-associated molecular patterns (DAMPs), including high-mobility group box 1 protein, heat shock proteins, mitochondrial DNA, and extracellular ATP. DAMPs act as endogenous danger signals, engaging pattern recognition receptors such as Toll-like receptors and NOD-like receptors on monocytes, macrophages, neutrophils, and dendritic cells. This interaction rapidly activates intracellular signaling pathways that culminate in nuclear factor-κB–mediated transcription of pro-inflammatory cytokines [17-18].

The innate immune response triggered by hemorrhage-induced tissue injury is further amplified during reperfusion following volume resuscitation. Ischemia–reperfusion injury promotes oxidative stress through the generation of reactive oxygen species, which directly damage endothelial and parenchymal cells while also serving as secondary inflammatory signals. This process intensifies cytokine production, particularly interleukin-6, tumor necrosis factor-α, and interleukin-1β, creating a feed-forward loop of immune activation characteristic of CRS [19-21].Endothelial dysfunction is central to the transition from hemorrhagic shock to cytokine-mediated inflammatory shock. In pregnancy, the endothelium is already primed by physiological adaptations that favor vasodilation and increased permeability. Under the influence of inflammatory cytokines, endothelial cells lose their barrier integrity, upregulate adhesion molecules, and shift toward a procoagulant phenotype. This results in capillary leak, intravascular volume depletion that is disproportionate to blood loss, microvascular thrombosis, and impaired tissue oxygenation. The ensuing vascular instability often manifests as hypotension refractory to fluid resuscitation, a defining feature of CRS-related shock [22-23].

Coagulation abnormalities provide another mechanistic bridge between PPH and CRS. Severe hemorrhage activates the coagulation cascade while simultaneously consuming clotting factors and platelets. Pro-inflammatory cytokines further disrupt hemostatic balance by suppressing natural anticoagulant pathways and impairing fibrinolysis regulation. The resulting coagulopathy is not merely consumptive but inflammatory in nature, closely resembling the immunothrombotic processes observed in sepsis and other cytokine-driven conditions. This interplay between inflammation and coagulation perpetuates ongoing bleeding, endothelial injury, and organ dysfunction [24-25].Resuscitative interventions, particularly massive transfusion of blood products, can exacerbate cytokine release. Stored red blood cells, plasma, and platelets contain bioactive substances, including cytokines, chemokines, extracellular vesicles, and free hemoglobin, which can stimulate recipient immune cells. Transfusion-related immunomodulation may thus amplify pre-existing inflammation, accelerating the progression toward CRS. Additionally, surgical interventions for hemorrhage control introduce further tissue injury, compounding the inflammatory burden [26-28].Pregnancy-specific immune adaptations may further influence susceptibility to CRS in severe PPH. The maternal immune system undergoes dynamic shifts between pro-inflammatory and anti-inflammatory states across gestation and parturition. The abrupt transition from the inflammatory milieu of labor to the physiological resolution phase may be disrupted

by massive hemorrhage, tipping the balance toward uncontrolled inflammation. This unique immunological context helps explain why some women develop profound systemic inflammatory responses disproportionate to the apparent severity of blood loss [29-30].

Clinical Manifestations of Cytokine Release Syndrome in Severe Postpartum Hemorrhage

The clinical presentation of cytokine release syndrome (CRS) in the setting of severe postpartum hemorrhage (PPH) is often complex, evolving, and easily mistaken for other causes of maternal deterioration. While early features may overlap with classical hypovolemic shock, CRS introduces a distinct inflammatory dimension that alters the trajectory of illness and contributes to persistent or worsening maternal instability despite adequate hemorrhage control. Recognizing these manifestations is essential for timely diagnosis and appropriate escalation of care.In the acute phase, women with severe PPH may initially present with tachycardia, hypotension, pallor, and altered mental status, findings traditionally attributed to blood loss. However, in CRS-associated cases, these signs often persist or recur after apparent hemodynamic stabilization. Hypotension may become refractory to fluid resuscitation, reflecting cytokine-mediated vasodilation and endothelial dysfunction rather than ongoing intravascular volume depletion. This vasoplegic state frequently necessitates early vasopressor support and intensive monitoring [31-32].

Systemic inflammatory features are a hallmark of CRS in severe PPH. Maternal temperature dysregulation is common and may manifest as fever, hypothermia, or wide fluctuations in core temperature, independent of infection. These abnormalities are driven by circulating pyrogenic cytokines and hypothalamic dysregulation. Concurrently, women may exhibit malaise, agitation, or reduced consciousness, reflecting cerebral hypoperfusion, metabolic derangements, and inflammatory effects on the central nervous system [33].Respiratory manifestations are particularly prominent due to cytokine-induced capillary leak and increased pulmonary vascular permeability. Clinically, this may present as tachypnea, hypoxemia, and progressive oxygen requirement, even in the absence of overt cardiopulmonary disease. In severe cases, non-cardiogenic pulmonary edema and acute respiratory distress syndrome–like features may develop, complicating fluid management and mechanical ventilation strategies [34].

Renal involvement is another frequent manifestation of CRS in the context of severe PPH. Acute kidney injury may occur despite restoration of circulating volume and blood pressure, underscoring the role of inflammatory microvascular injury and renal endothelial dysfunction. Oliguria, rising serum creatinine, and electrolyte imbalances are commonly observed and often correlate with the severity of systemic inflammation [35].Hepatic dysfunction may also emerge as part of the multiorgan involvement seen in CRS. Elevated transaminases, hyperbilirubinemia, and impaired synthetic function can occur due to hepatic hypoperfusion, sinusoidal endothelial injury, and direct cytokine-mediated hepatocellular stress. These abnormalities may mimic or coexist with pregnancy-related liver disorders, further complicating diagnostic assessment [36].

Coagulation disturbances represent a critical and clinically consequential manifestation of CRS in severe PPH. Inflammatory cytokines disrupt the balance between coagulation and fibrinolysis, leading to thrombocytopenia, hypofibrinogenemia, and prolonged clotting times that are often disproportionate to ongoing blood loss. This inflammatory coagulopathy not only worsens hemorrhage but also increases the risk of microvascular thrombosis and organ ischemia [37].A defining clinical feature of CRS in severe PPH is its dynamic and sometimes biphasic course. Some women demonstrate initial improvement following hemorrhage control, only to deteriorate hours later as inflammatory pathways become fully activated. This delayed worsening, characterized by escalating vasopressor requirements, rising inflammatory markers, and progressive organ dysfunction, is a key clue to the presence of CRS rather than isolated hypovolemic shock [38].

Diagnostic Considerations and Biomarkers

Diagnosing cytokine release syndrome (CRS) in the context of severe postpartum hemorrhage (PPH) is inherently challenging, as its clinical features overlap extensively with hypovolemic shock, sepsis, transfusion reactions, and pregnancy-related coagulopathies. Unlike infectious or cardiogenic shock, CRS lacks obstetric-specific diagnostic criteria, requiring clinicians to rely on a combination of clinical judgment, exclusion of alternative diagnoses, and supportive laboratory evidence. A high index of suspicion is therefore essential, particularly when maternal deterioration persists despite adequate hemorrhage control and appropriate resuscitation [39].From a clinical standpoint, the key diagnostic clue lies in the dissociation between hemodynamic instability and measurable blood loss. Persistent hypotension, escalating vasopressor requirements, and progressive organ dysfunction following correction of hypovolemia should prompt consideration of an inflammatory etiology. Temporal patterns are also informative; CRS often manifests after an initial period of stabilization, reflecting delayed immune activation rather than ongoing hemorrhage. This biphasic course distinguishes CRS from purely hemorrhagic shock and highlights the need for continued vigilance in the postpartum period [40].
Laboratory biomarkers play an increasingly important role in supporting the diagnosis of CRS in severe PPH. Elevated inflammatory markers are a central feature, with interleukin-6 emerging as a particularly informative cytokine due to its strong association with disease severity and vascular permeability. Although routine cytokine profiling is not widely available in obstetric practice, surrogate markers such as C-reactive protein and ferritin can provide indirect evidence of systemic inflammation when interpreted in the appropriate clinical context. Disproportionately high levels of these markers relative to blood loss or infection burden should raise suspicion of CRS [41-42].Markers of endothelial injury and vascular dysfunction offer additional diagnostic insight. Elevated serum lactate, despite adequate perfusion pressures, reflects microcirculatory failure and impaired oxygen utilization rather than simple hypovolemia. Increased levels of angiopoietin-2, von Willebrand factor, and soluble thrombomodulin—where available—indicate endothelial activation and damage, key pathophysiological features of CRS. Clinically, these abnormalities correlate with capillary leak, tissue edema, and refractory shock [43].

Coagulation parameters are particularly informative in differentiating CRS-associated inflammatory coagulopathy from dilutional or consumptive coagulopathy due solely to hemorrhage. Hypofibrinogenemia, thrombocytopenia, and prolonged clotting times that persist or worsen after transfusion suggest cytokine-driven dysregulation of hemostasis. Viscoelastic testing, where accessible, may reveal impaired clot strength and fibrinolytic abnormalities reflective of inflammatory rather than purely hemorrhagic processes [44].Organ-specific biomarkers further support the diagnosis. Rising creatinine and reduced urine output in the absence of ongoing hypovolemia point toward inflammatory renal microvascular injury. Elevated transaminases and bilirubin suggest hepatic involvement mediated by cytokine-induced endothelial and hepatocellular stress. Cardiac biomarkers, such as troponin and natriuretic peptides, may also be modestly elevated due to myocardial inflammation and stress, even in the absence of primary cardiac pathology [45].Importantly, CRS remains a diagnosis of integration rather than exclusion alone. While infection must always be considered and appropriately investigated in postpartum women, the absence of a clear infectious source, negative cultures, and poor response to antimicrobial therapy should prompt reconsideration of the underlying pathophysiology. Differentiating CRS from sepsis is particularly difficult, as both conditions share inflammatory signatures; however, the temporal relationship to hemorrhage and transfusion, along with rapid cytokine escalation, favors CRS.

Therapeutic and Management Implications

Recognizing cytokine release syndrome (CRS) as a contributor to maternal shock in severe postpartum hemorrhage (PPH) has significant implications for clinical management, as it

challenges traditional volume-centric resuscitation strategies and calls for a more integrated, physiology-driven approach. While rapid control of bleeding and restoration of circulating volume remain fundamental, failure to address the inflammatory component of shock may lead to persistent hemodynamic instability, organ dysfunction, and increased maternal morbidity [46].Initial management must continue to prioritize prompt hemorrhage control through uterotonics, surgical or interventional radiologic procedures, and correction of coagulopathy. However, once bleeding is controlled, ongoing hypotension should prompt careful reassessment rather than reflexive escalation of fluid administration. In CRS-associated shock, excessive fluid resuscitation may worsen endothelial leak, pulmonary edema, and tissue hypoxia. Early initiation of vasopressor support, particularly in women with evidence of vasoplegia and capillary leak, is often necessary to maintain adequate perfusion while minimizing fluid overload [47].

Transfusion strategies also require refinement in the context of CRS. Balanced transfusion protocols remain essential for managing severe PPH, yet clinicians should be aware of the immunomodulatory effects of massive transfusion. Close monitoring for inflammatory escalation following transfusion is warranted, and transfusion should be guided by clinical status and laboratory parameters rather than fixed ratios alone. Where available, viscoelastic testing can support targeted correction of coagulation abnormalities, reducing unnecessary exposure to blood products and potentially limiting inflammatory amplification [48].Supportive care in a critical care setting is central to managing CRS in severe PPH. Early admission to high-dependency or intensive care units allows for continuous hemodynamic monitoring, timely organ support, and multidisciplinary input. Respiratory support may be required to manage hypoxemia resulting from capillary leak or inflammatory lung injury, with careful attention to fluid balance and ventilatory strategies that minimize further endothelial stress. Renal support, including renal replacement therapy, may be necessary in cases of inflammatory acute kidney injury unresponsive to conventional measures [49].

The potential role of immunomodulatory therapy represents an important, though still evolving, aspect of management. Corticosteroids may offer benefit by dampening excessive cytokine production and stabilizing endothelial function, particularly in cases of refractory shock with clear inflammatory features. However, evidence specific to obstetric populations remains limited, and the risks and benefits must be weighed carefully. Targeted cytokine-directed therapies, such as interleukin-6 pathway inhibitors, have demonstrated efficacy in other CRS settings but require rigorous evaluation before routine use in severe PPH [50].Endothelial protection and modulation of the inflammatory–coagulatory axis are emerging therapeutic considerations. Strategies aimed at preserving glycocalyx integrity, optimizing oxygen delivery, and minimizing oxidative stress may help attenuate microvascular dysfunction. Early recognition and treatment of inflammatory coagulopathy are essential to break the cycle of bleeding, thrombosis, and immune activation that characterizes CRS-associated maternal shock.
Effective management of CRS in severe PPH also depends on coordinated, multidisciplinary care. Obstetricians, anesthesiologists, intensivists, hematologists, and transfusion specialists must work collaboratively to balance hemostasis, hemodynamics, and immune modulation. Protocols that incorporate early identification of inflammatory shock patterns and clear escalation pathways can improve decision-making and reduce delays in care [51].Ultimately, acknowledging CRS as a key driver of maternal deterioration in severe postpartum hemorrhage broadens the therapeutic focus beyond hemorrhage control alone. Integrating immunopathophysiological insight into obstetric critical care offers an opportunity to individualize treatment, avoid iatrogenic harm, and improve maternal outcomes. Continued research is essential to define optimal therapeutic strategies and to translate emerging immunomodulatory approaches into safe and effective clinical practice for women experiencing this life-threatening obstetric emergency [52].

Conclusion

Severe postpartum hemorrhage is traditionally viewed as a purely hypovolemic emergency; however, accumulating clinical and biological evidence indicates that this perspective is incomplete. In a subset of women, severe PPH acts as a powerful trigger for cytokine release syndrome, transforming maternal shock into a complex, immune-mediated condition characterized by systemic inflammation, endothelial dysfunction, coagulopathy, and multiorgan impairment. This inflammatory dimension helps explain persistent or worsening maternal instability despite timely hemorrhage control and adequate volume resuscitation. Redefining maternal shock through the lens of cytokine release syndrome has important implications for obstetric practice. It emphasizes the need for heightened clinical vigilance, early recognition of inflammatory patterns, and diagnostic approaches that integrate hemodynamic assessment with biomarkers of immune activation and endothelial injury. Therapeutically, it supports a shift from exclusive reliance on aggressive fluid resuscitation toward balanced strategies that incorporate vasopressor support, targeted transfusion, organ support, and, in selected cases, immunomodulatory interventions.

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