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Commentary

Pathogenetic link between postpartum hemorrhage and renal cortical necrosis

Adarsh Kumar[1,*]

[1]Department of Nephrology and Renal Transplant, VMMC & SJH, New Delhi, India

*Author for correspondence: Email: adarshnephro081@gmail.com

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Abstract

Renal cortical necrosis (RCN) is a catastrophic form of pregnancy-related acute kidney injury (AKI) and is significantly more prevalent in developing countries than in developed nations. Among obstetric complications, postpartum hemorrhage (PPH) remains a major etiological factor associated with RCN. Conventionally, its pathogenesis has been attributed to massive blood loss leading to severe renal ischemia, often compounded by disseminated intravascular coagulation (DIC) and sepsis. However, emerging evidence suggests that the underlying mechanisms are more complex and extend beyond hypoperfusion alone, with endothelial injury, microvascular thrombosis, and dysregulation of the complement pathway increasingly recognized as key contributors.

Keywords: Renal cortical necrosis, Acute kidney injury, Postpartum hemorrhage, Obstetric complications

Introduction

Renal cortical necrosis (RCN) is a devastating form of pregnancy-related acute kidney injury (AKI), still encountered more frequently in developing countries [1–4]. Among obstetric complications, postpartum hemorrhage (PPH) remains a major etiological factor for RCN [1–6]. Conventionally, the pathogenetic link has been attributed to massive blood loss leading to severe renal ischemia, often compounded by disseminated intravascular coagulation (DIC) and sepsis. However, emerging evidence suggests that the underlying mechanisms extend beyond hypoperfusion alone, implicating microvascular injury and endothelial dysfunction [1–3].

A focused literature search was performed using PubMed and Google Scholar with relevant keywords. Case reports and studies without specific mention of both RCN and PPH were excluded. Relevant articles were screened, and key studies reporting RCN in association with PPH are summarized in **Table 1**.

Pathogenetic Mechanism

Ischemic and microcirculatory factors

The renal cortex, despite receiving nearly a quarter of cardiac output, is uniquely susceptible to ischemic injury due to its high metabolic demand and microvascular architecture [7–9]. Experimental studies demonstrate that cortical perfusion falls disproportionately during hypovolemic shock [10,11], which may partly explain the association between obstetric hemorrhage and RCN. However, accumulating clinical evidence challenges the notion that hypoperfusion alone accounts for the high incidence of RCN following PPH, suggesting the involvement of additional pathophysiological mechanisms.

Hemostatic disturbances and endothelial injury

RCN following obstetric hemorrhage often occurs in the setting of DIC or sepsis, with endothelial damage and intrarenal thrombosis playing a central role [1–3,12,13]. In the case series

Table 1. Studies reporting postpartum hemorrhage and renal cortical necrosis.

Author	Study/Population	Prevalence of PPH in RCN Cases	Relevant Findings
Frimat *et al.* [1]	18 patients with pregnancy-related AKI secondary to PPH (France)	100% (pure PPH cohort)	All patients had thrombocytopenia, and >50% demonstrated hemolysis, suggesting a role of DIC and possible contribution of antifibrinolytic therapy.
Ramachandran *et al.* [2]	21 patients with pregnancy-related RCN (India)	43%	RCN has historically been attributed to hemorrhage and sepsis; however, ~60% of patients demonstrated activation of the alternative complement pathway, suggesting a possible role of aHUS.
Kumar *et al.* [3]	Histopathological review of 25 cases of postpartum RCN (India)	28%	Findings were consistent with TMA rather than DIC, suggesting predominant endothelial injury. Notably, even mild to moderate PPH was associated with the development of RCN.
Bhaduaria *et al.* [4]	Obstetric AKI cohort, 1999–2014 (India)	9.09% (among obstetric AKI)	Postpartum TMA was the most important cause of RCN, observed in 48.7% of patients.
Jiang *et al.* [5]	9 patients with pregnancy-related RCN (China)	66.7%	All patients exhibited features of TMA/ probable aHUS, and all required kidney replacement therapy.
Wang *et al.* [6]	23 patients with RCN (China)	65%	Pregnancy-associated TMA was identified as the predominant mechanism, suggesting that RCN is not solely due to ischemia.
Prakash *et al.* [12]	RCN patients, 1982–2014 (India)	–	The prevalence of RCN among obstetric AKI was 5.8%, with an observed declining trend over time.
Chug *et al.* [13]	RCN patients, 1964–1992 (India)	10.5% (due to PPH)	Obstetric causes accounted for 56.6% of ACN cases.
Islam *et al.* [14]	Case series of RCN associated with PPH and septicemia (Bangladesh)	100% (pure PPH cohort)	All patients developed septicemia following PPH and required prolonged hemodialysis (>21 days). Histology showed 60% patchy and 40% diffuse RCN.
Kaufeld *et al.* [21]	5 patients with RCN following PPH (Germany)	100% (pure PPH cohort)	Four of five patients received complement inhibition with partial recovery of renal function, suggesting a potential therapeutic role of complement blockade.

Abbreviations: RCN: Renal Cortical Necrosis; PPH: Postpartum Hemorrhage; AKI: Acute Kidney Injury; DIC: Disseminated Intravascular Coagulation; TMA: Thrombotic Microangiopathy; aHUS: Atypical Hemolytic Uremic Syndrome

by Frimat *et al.* [1], thrombocytopenia and hemolysis were frequent, and the use of antifibrinolytic agents was observed to potentially increase the risk of uncontrolled microvascular thrombosis in the renal cortex. Similarly, Islam *et al.* [14] noted that septicemia commonly followed hemorrhage in patients who developed RCN, with histology revealing patchy or diffuse necrosis.

Emerging role of thrombotic microangiopathy and complement activation

Recent studies have highlighted that RCN not merely as a consequence of hypoperfusion but as part of the spectrum of thrombotic microangiopathies (TMAs). Ramachandran *et al.* [2] demonstrated that nearly 60% of affected women showed activation of the alternative complement pathway, raising the possibility of atypical hemolytic uremic syndrome (aHUS) in this context. Similarly, Jiang *et al.* [5] and Wang *et al.* [6] identified pregnancy-associated TMAs, including complement-mediated forms, as significant contributors to RCN in women with PPH. In our recent study [3], RCN was observed even in women with mild-to-moderate PPH, in the absence of DIC as defined by the modified ISTH scoring criteria [15]. Instead, histological and laboratory findings were consistent with TMA, suggesting that hemorrhage may act as a trigger for endothelial injury and complement activation rather than a simple ischemic insult. Importantly, heme released during hemorrhage is a potent activator of the alternative complement pathway in genetically predisposed individuals [16].

Postpartum immune dynamics and complement dysregulation

Pregnancy is characterized by upregulation of complement regulatory proteins (CD55, CD59, MCP) that protect maternal endothelium and placental tissue from excessive complement activation. The abrupt postpartum withdrawal of this protection, combined with increased circulating complement proteins, may unmask underlying genetic defects and precipitate complement-mediated TMA [17]. This immunological shift provides a plausible mechanistic explanation for why PPH frequently precipitates RCN in susceptible women in the immediate postpartum period.

PPH and Risk of Cardiovascular Disease

PPH, beyond being an important precipitant of renal cortical necrosis, has also been increasingly linked to adverse cardiovascular outcomes. Emerging evidence from population-based cohort studies and recent systematic reviews suggests that women experiencing PPH may have an elevated risk of both short-term and long-term cardiovascular disease (CVD) [18–20]. The proposed mechanisms include endothelial dysfunction, systemic inflammation, and coagulation abnormalities, which may overlap with the pathophysiological pathways implicated in RCN, such as microvascular injury and complement activation. These observations highlight the need for a broader perspective, wherein targeted interventions aimed at preventing or mitigating RCN in PPH should also consider the potential long-term cardiovascular implications in this subset of the population.

Therapeutic Implications

The recognition of complement-mediated mechanisms has direct therapeutic relevance. Recent reports describe partial renal recovery in women with PPH-associated RCN who received complement inhibitors such as eculizumab [21]. This highlights the need to move beyond supportive care and consider targeted therapies in select patients. Genetic testing for complement pathway variants may help identify women at risk and guide precision-based management in the future [2].

Conclusion

RCN following PPH represents a complex interplay of hemodynamic, endothelial, and immunological factors. While ischemia and DIC remain important contributors, emerging evidence strongly supports the role of complement dysregulation and TMA in its pathogenesis. Recognition of this link provides a framework for early diagnosis and targeted intervention, with complement inhibition offering a potential therapeutic strategy. Further prospective studies are required to elucidate these mechanisms and optimize outcomes for affected women.

Limitations and Future Research Directions

Current evidence on RCN in the setting of PPH is limited by predominantly retrospective designs, small sample sizes, and heterogeneity in diagnostic approaches. Mechanistic data on endothelial injury, thrombotic microangiopathy, and complement dysregulation remain limited, with scarce use of genetic and functional assays. Additionally, long-term renal and cardiovascular outcomes are inadequately studied.

Future research should prioritize prospective multicenter studies with standardized diagnostic criteria and incorporation of complement and endothelial biomarkers. Further evaluation of targeted therapies, including complement inhibition, and longitudinal assessment of renal and cardiovascular outcomes are essential to improve understanding and management of this condition.

Declarations

Conflict of interest

The author declares no conflicts of interest.

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Author contributions

Kumar A contributed to the conception, literature review, drafting, and critical revision of the manuscript, and approved the final version.

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