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Preeclampsia-associated nephropathy; current insights into renal histopathology and molecular mechanisms

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ABSTRACT

Preeclampsia-associated nephropathy represents a distinct form of pregnancy-induced kidney injury characterized by proteinuria, hypertension, and endothelial dysfunction, posing significant risks to both maternal and fetal health. Historically defined by the hallmark lesion of glomerular endotheliosis, contemporary histopathological analyses have expanded this paradigm to reveal widespread podocyte effacement, mesangial expansion, and subtle tubulointerstitial alterations that correlate with disease severity and postpartum renal recovery trajectories. At the molecular level, recent insights emphasize a profound angiogenic imbalance driven by excessive placental release of anti-angiogenic factors, particularly soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin, which disrupt glomerular capillary integrity and impair endothelial nitric oxide signaling. Concurrently, oxidative stress, complement activation, and dysregulated inflammatory cascades amplify endothelial injury, while emerging evidence highlights mitochondrial dysfunction and epigenetic modifications as critical contributors to sustained podocyte damage and maladaptive repair. Integrative multi-omics approaches have further identified dysregulated lipid metabolism, extracellular matrix remodeling, and autophagy impairment as pivotal pathways linking systemic vascular stress to localized nephropathy. Despite these advances, the precise temporal sequence of molecular events and their translation into targeted therapeutics remain unresolved. Current research is increasingly focused on biomarker validation, noninvasive imaging correlates, and repurposing angiogenic or complement-modulating agents to mitigate renal injury. Translational efforts are now prioritizing interventions that restore vascular homeostasis and preserve podocyte architecture, alongside longitudinal cohorts designed to delineate long-term renal sequelae. Finally, a deeper mechanistic understanding of preeclampsia-associated nephropathy refines risk stratification, informs postpartum monitoring, and illuminates broader paradigms of endothelial-driven kidney disease across the lifespan.

Review

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Implication for health policy/practice/research/medical education:
Preeclampsia is a pregnancy-specific hypertensive disorder frequently complicated by renal involvement, termed preeclampsia-associated nephropathy. Recent advances have clarified its characteristic histopathological features, most notably glomerular endotheliosis, characterized by swollen, vacuolated endothelial cells, podocyte foot process effacement, and subendothelial fibrinoid deposits. At the molecular level, dysregulated angiogenic signaling, particularly an imbalance between soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor, drives widespread endothelial dysfunction and oxidative stress. Complement activation, proinflammatory cytokine release, and diminished nitric oxide bioavailability further exacerbate glomerular injury. Emerging evidence highlights podocyte-specific cytoskeletal disruptions, including down-regulation of nephrin and synaptopodin, alongside mitochondrial impairment and epigenetic alterations that sustain renal damage. Although structural lesions typically regress postpartum, severe or recurrent episodes may accelerate long-term chronic kidney disease. Integrating precise histopathological assessment with circulating molecular biomarkers promises to enhance early risk stratification, guide targeted interventions, and optimize maternal renal prognosis. Ongoing research continues to elucidate novel therapeutic targets that may mitigate progressive renal decline.
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Introduction

Preeclampsia-associated nephropathy remains one of the most clinically consequential manifestations of hypertensive pregnancy disorders, representing a complex intersection of placental dysfunction, systemic endothelial injury, and targeted renal damage (1). The kidney serves as both a primary victim and a critical diagnostic window into the broader pathophysiology of preeclampsia, as its structural and functional alterations often precede or parallel the onset of severe maternal complications (2). Contemporary understanding of this condition has evolved substantially from earlier descriptive models, transitioning into a mechanistic framework that integrates precise histomorphologic observations with dynamic molecular pathways (3). At the heart of this paradigm is the recognition that preeclampsia-induced renal injury is not merely a passive consequence of hypertension but rather an active, multifactorial process driven by circulating anti-angiogenic factors, inflammatory mediators, oxidative stress, complement activation, and direct placental-renal cross-talk (4). The morphologic hallmark of this disease, glomerular endotheliosis, has been recognized for decades, yet modern investigative approaches have revealed that this seemingly localized lesion is the visible endpoint of a systemic molecular cascade that disrupts the glomerular filtration barrier, alters podocyte architecture, perturbs tubulointerstitial homeostasis, and compromises renal microvascular integrity (5,6). Current insights emphasize that the renal phenotype in preeclampsia exists on a spectrum, varying in severity based on gestational timing, genetic susceptibility, pre-existing renal reserve, and the magnitude of placental-derived toxic factors (7,8). Understanding this spectrum requires a seamless integration of histopathologic detail with molecular biology, as the structural changes observed under light and electron microscopy directly reflect the underlying biochemical and signaling derangements that define the disease (7). Here, we therefore aim to discuss on preeclampsia-associated nephropathy, across with evaluation of current insights into renal histopathology and molecular mechanisms.

Search strategy

For this review, a comprehensive literature search was conducted in major electronic databases, including PubMed, Web of Science, EBSCO, Scopus, Embase, Google Scholar, and the Directory of Open Access Journals (DOAJ). The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords related to renal disease and pregnancy complications, such as kidney disease, nephropathy, preeclampsia, hypertension, and renal histopathology, which were used individually and in various Boolean combinations (AND, OR) to maximize sensitivity and specificity. Where relevant, reference lists of retrieved articles and pertinent reviews were also screened manually to identify additional eligible studies.

Morphologic lesions of preeclampsia-associated nephropathy

The defining histopathologic feature of preeclampsia-associated nephropathy is glomerular endotheliosis, a lesion characterized by swelling of the glomerular capillary endothelial cells, narrowing or obliteration of capillary lumens, and detachment of the endothelium from the glomerular basement membrane (6). Under light microscopy, affected glomeruli appear enlarged and bloodless, with capillary walls thickened by pale, eosinophilic material that corresponds to endothelial cytoplasmic expansion and subendothelial matrix deposition (9). Electron microscopy reveals the true extent of the injury: endothelial cells lose their fenestrations, become vacuolated, and develop prominent intracellular

organelles such as dilated endoplasmic reticulum and mitochondria, reflecting a state of metabolic stress and impaired protein handling (6,10). The glomerular basement membrane itself may appear subtly thickened or wrinkled, not due to true hyperfiltration-related remodeling but rather to mechanical stress from endothelial swelling and altered hemodynamics (11). Importantly, this endothelial injury is remarkably selective; it predominantly affects the renal glomeruli while sparing other vascular beds, a phenomenon that has long puzzled investigators until recent molecular studies clarified the unique dependence of glomerular endothelial cells on continuous vascular endothelial growth factor signaling for fenestration maintenance and survival (6). The absence of significant immune complex deposition or cellular crescents distinguishes preeclampsia-associated nephropathy from primary glomerulonephritides, reinforcing its classification as a secondary, hemodynamically and biochemically driven endotheliopathy (4). Beyond the endothelium, podocytes exhibit parallel but distinct morphologic alterations (12). While not as dramatically swollen as endothelial cells, podocytes undergo foot process effacement, detachment from the glomerular basement membrane, and redistribution of slit diaphragm proteins (12). Immunofluorescence and ultrastructural studies frequently demonstrate reduced expression or mislocalization of nephrin, podocin, and synaptopodin, with corresponding cytoskeletal disarray (13,14). These changes are not merely secondary to endothelial swelling but represent an independent, parallel injury pathway that directly compromises the size and charge selectivity of the filtration barrier, explaining the characteristic proteinuria that often heralds clinical diagnosis (9). Tubulointerstitial changes, though historically considered minor, are increasingly recognized as clinically relevant. Mild tubular epithelial cell vacuolization, focal atrophy, and interstitial edema can be observed, particularly in severe or prolonged cases (2). These alterations likely reflect ischemic stress from upstream glomerular hypoperfusion, oxidative damage, and the toxic effects of filtered proteins that overwhelm proximal tubular reabsorptive capacity (4). Vascular lesions, including arteriolar narrowing, medial hypertrophy, and occasional fibrinoid necrosis, mirror the systemic vasoconstrictive state but are less specific and often overlap with chronic hypertensive changes (15,16). The morphologic landscape, therefore, is not static but evolves with disease duration, severity, and maternal comorbidities, making biopsy interpretation highly context-dependent (17). Nevertheless, the consistent presence of endotheliosis, podocyte injury, and filtration barrier disruption across diverse patient cohorts underscores a unified pathogenic core that modern research continues to decode at the molecular level (12).

From histologic observation to molecular mechanisms

The transition from histologic observation to molecular mechanism reveals that preeclampsia-associated nephropathy is fundamentally an angiogenic crisis localized to the renal microvasculature (18,19). The most extensively validated pathway involves the dysregulated balance between pro-angiogenic and anti-angiogenic factors, primarily driven by placental overproduction of soluble fms-like tyrosine kinase-1 (sFlt-1) (15,20). Recent studies showed that, sFlt-1 acts as a circulating decoy receptor that binds and neutralizes vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), depriving glomerular endothelial cells of their essential survival and differentiation signals (21). Preliminary studies detected that, VEGF is constitutively expressed by podocytes and is critical for maintaining endothelial fenestrations, regulating nitric oxide and prostacyclin synthesis, and preventing endothelial apoptosis (22). When sFlt-1 levels rise, typically in the late second or third trimester, VEGF signaling is abruptly suppressed, triggering endothelial cell swelling, loss of fenestrations, and detachment from the basement membrane (23). This molecular mechanism directly explains the histologic appearance of endotheliosis and the accompanying increase in glomerular permeability (23,24). Recent studies have refined this model by demonstrating that the sFlt-1/PlGF ratio not only correlates with disease severity but also predicts renal involvement before clinical symptoms manifest (25). Furthermore, recent studies indicated that sFlt-1 exists in multiple isoforms with varying tissue affinities (25). It should remember that, the VEGF axis does not operate in isolation; it intersects with endothelin-1 signaling, which becomes upregulated in response to endothelial stress and further exacerbates vasoconstriction and podocyte injury (26). Endothelin-1 receptors are densely expressed on both endothelial cells and podocytes, and their activation promotes cytoskeletal contraction, reduces nitric oxide bioavailability, and stimulates pro-fibrotic pathways that may contribute to persistent renal dysfunction even after pregnancy resolution (27). The angiogenic imbalance model has thus evolved from a simple ligand-receptor paradigm into a dynamic network involving multiple receptor tyrosine kinases, co-receptors, and downstream signaling cascades that collectively dictate endothelial phenotype and barrier integrity (28).

Podocyte injury in preeclampsia

Podocyte injury in preeclampsia extends well beyond the indirect effects of VEGF deprivation and involves direct molecular destabilization of the slit diaphragm and actin cytoskeleton (29). The slit diaphragm, a specialized intercellular junction between podocyte foot processes,

functions as a size-selective filter and signaling hub (30). Key structural proteins such as nephrin, podocin, and CD2AP form a molecular complex that transduces mechanical and biochemical signals into intracellular responses (31). In preeclampsia, reduced nephrin expression and altered phosphorylation status disrupt this complex, leading to foot process retraction and effacement (32). Current insights implicate several signaling pathways in this process, including the activation of Rho-family GTPases such as RhoA and Rac1, which regulate actin polymerization and stress fiber formation (33). Excessive RhoA activity, often triggered by angiotensin II, endothelin-1, and oxidative stress, promotes actin contractility and podocyte detachment, while diminished Rac1 signaling impairs lamellipodial extension and barrier repair (33). Transient receptor potential canonical channel 6 (TRPC6) has emerged as a critical mediator of podocyte calcium dysregulation in preeclampsia (34). Upregulated TRPC6 expression leads to sustained intracellular calcium influx, activating calcineurin and downstream effectors that promote cytoskeletal collapse and apoptosis (35). Notably, pharmacologic inhibition of TRPC6 or calcineurin in experimental models attenuates proteinuria and preserves podocyte architecture, suggesting a direct therapeutic target (36). Integrin-mediated adhesion to the glomerular basement membrane is similarly compromised (36). Meanwhile, α3β1 integrin, as the the primary podocyte receptor for laminin-521, undergoes internalization or reduced surface expression under angiogenic stress, weakening cell-matrix attachment and predisposing to detachment and urinary loss (37). Recent single-cell RNA sequencing studies of renal tissue from preeclamptic pregnancies have identified distinct podocyte subpopulations exhibiting upregulated stress-response genes, including heat shock proteins, unfolded protein response markers, and senescence-associated secretory phenotype factors (38). These findings indicate that podocytes do not merely degenerate passively but actively participate in a maladaptive stress response that may perpetuate injury even after the initial trigger subsides (39). The molecular crosstalk between podocytes and endothelial cells further amplifies renal dysfunction (40). Podocyte-derived VEGF normally maintains endothelial health, while endothelial-derived nitric oxide and prostaglandins modulate podocyte contractility and survival (41). In preeclampsia, this reciprocal signaling is severed, creating a vicious cycle of mutual deterioration that manifests histologically as combined endotheliosis and podocytopathy (42).

Focus on oxidative stress

Oxidative stress operates as both a primary instigator and a secondary amplifier of renal injury in preeclampsia, bridging placental ischemia with glomerular damage (4). The placenta, particularly when shallowly implanted or subjected to abnormal spiral artery remodeling, experiences intermittent hypoxia-reperfusion, generating reactive oxygen species (ROS) that spill into the maternal circulation (15). Systemic oxidative stress overwhelms endogenous antioxidant defenses, including superoxide dismutase, catalase, and glutathione, leading to lipid peroxidation, protein carbonylation, and DNA damage within renal cells (43). Glomerular endothelial cells are especially vulnerable due to their high metabolic rate, extensive surface area, and reliance on redox-sensitive signaling pathways (44). Notably, ROS directly inactivate endothelial nitric oxide synthase (eNOS) by uncoupling it, shifting its function from nitric oxide production to superoxide generation, thereby exacerbating vasoconstriction and inflammation (45). Mitochondrial dysfunction within podocytes and tubular epithelial cells further compounds oxidative injury (46). Recent studies demonstrate that preeclampsia is associated with fragmented mitochondrial networks, reduced ATP production, and increased mitophagy in renal tissue (47). The accumulation of damaged mitochondria triggers the release of mitochondrial DNA and formyl peptides, which act as damage-associated molecular patterns that activate toll-like receptors and inflammasome complexes (48). The NLRP3 inflammasome, in particular, has been implicated in preeclampsia-associated renal injury, as its activation in podocytes and endothelial cells promotes caspase-1 cleavage, IL-1β and IL-18 secretion, and pyroptotic cell death (49). Pharmacologic or genetic inhibition of NLRP3 in animal models significantly reduces proteinuria, preserves glomerular architecture, and attenuates inflammatory infiltration, highlighting its potential as a therapeutic target (50). Oxidative stress also modulates epigenetic regulation in renal cells (51). On the other hand, DNA methylation, histone acetylation, and non-coding RNA expression are highly sensitive to redox status, since preeclampsia has been associated with aberrant methylation of genes involved in endothelial function, podocyte differentiation, and antioxidant defense (52,53). It should remember that, the epigenetic alterations may persist postpartum, offering a molecular explanation for the well-documented increased risk of chronic kidney disease and cardiovascular disease in women with a history of preeclampsia (54).

Inflammatory setting in preeclampsia-associated nephropathy

The inflammatory milieu in preeclampsia-associated nephropathy has shifted from being viewed as a secondary phenomenon to a central driver of renal pathology (2). Activated maternal immune cells, particularly

neutrophils, monocytes, and natural killer cells, infiltrate the renal interstitium and glomeruli, releasing cytokines, chemokines, and proteolytic enzymes that degrade the filtration barrier (55,56). Tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interferon-gamma (IFN-γ) are consistently elevated in preeclamptic serum and directly impair endothelial and podocyte function by downregulating tight junction proteins, increasing vascular permeability, and promoting apoptotic signaling (4,57). Macrophage polarization plays a critical role; while M2 macrophages support tissue repair and angiogenesis, preeclampsia skews the balance toward M1 dominance, which secretes pro-inflammatory mediators and reactive nitrogen species that exacerbate glomerular injury (58,59). Complement system activation has emerged as one of the most significant recent insights in preeclampsia pathophysiology (60). The alternative complement pathway is excessively activated in preeclampsia, with elevated levels of C3a, C5a, and the membrane attack complex (C5b-9) detected in both maternal circulation and renal tissue (61). Complement activation products directly damage glomerular endothelial cells by inducing calcium influx, promoting vesiculation, and triggering apoptosis (61). C5a receptor (C5aR) signaling on podocytes and tubular cells amplifies inflammatory cytokine production and upregulates adhesion molecules that recruit additional leukocytes (62). Genetic polymorphisms in complement regulatory proteins, such as factor H and membrane cofactor protein, have been associated with increased susceptibility to severe preeclampsia and persistent renal dysfunction (63,64). Therapeutic complement inhibition, particularly at the C5 level, has shown promise in preclinical models by reducing proteinuria, preserving glomerular architecture, and improving placental perfusion, though clinical translation remains cautious due to infection risks and pregnancy-specific pharmacokinetics (61). The complement system does not act alone; it intersects with the coagulation cascade, as tissue factor expression on damaged endothelium initiates microthrombus formation that further compromises glomerular blood flow (65). Fibrin deposition in capillary lumens, occasionally seen on histology, reflects this prothrombotic shift and contributes to ischemic injury (66).

A short look at the renin-angiotensin-aldosterone system

Renin-angiotensin-aldosterone system (RAAS) dysregulation in preeclampsia presents a paradox, as pregnancy normally induces physiological RAAS activation to support volume expansion and placental perfusion, yet preeclampsia is characterized by a state of functional angiotensin II hypersensitivity despite elevated circulating levels (67). Angiotensin II type 1 receptor (AT1R) signaling is amplified by oxidative stress, inflammatory cytokines, and autoantibodies that stabilize the receptor in an active conformation (68). These AT1R autoantibodies, frequently detected in preeclamptic serum, bind to the receptor's second extracellular loop, mimicking angiotensin II effects and promoting vasoconstriction, sodium retention, and endothelial dysfunction (69). In the kidney, AT1R activation on efferent arterioles increases glomerular capillary pressure, initially maintaining filtration rate but ultimately exacerbating endothelial shear stress and protein leakage (70). Angiotensin II also directly stimulates podocyte apoptosis and cytoskeletal collapse via NADPH oxidase-derived ROS and TGF-β1 upregulation (71). The interplay between RAAS and endothelin-1 is particularly deleterious; each system potentiates the other's expression and receptor sensitivity, creating a self-sustaining cycle of vasoconstriction and barrier disruption (72). Aldosterone, traditionally viewed as a mineralocorticoid, has gained recognition for its pro-fibrotic and pro-inflammatory effects in preeclampsia-associated nephropathy (67,73). Mineralocorticoid receptor activation in renal tubular cells and podocytes promotes sodium channel expression, potassium wasting, and extracellular matrix deposition, contributing to both acute injury and long-term structural remodeling (74,75). It is possible that selective mineralocorticoid receptor antagonists in pregnancy-complicated hypertension have demonstrated improved renal hemodynamics and reduced albuminuria without compromising fetal growth, suggesting a potential niche for targeted RAAS modulation (76,77). The endothelin system mirrors these findings, with endothelin-1 levels correlating strongly with proteinuria severity and glomerular endothelial swelling (78). Endothelin receptor antagonists have shown efficacy in reducing blood pressure and preserving renal function in experimental preeclampsia, though their use in human pregnancy remains limited by teratogenicity concerns and the need for rigorous safety profiling (79,80).

Role of trophoblasts and decidual cells

Placental-derived extracellular vesicles and microRNAs represent a rapidly advancing frontier in understanding renal involvement in preeclampsia (81,82). Trophoblasts and decidual cells continuously release exosomes, microvesicles, and apoptotic bodies into the maternal circulation, carrying proteins, lipids, mRNAs, and non-coding RNAs that modulate systemic endothelial and immune function (83). In preeclampsia, the quantity and cargo of these vesicles are altered, with an enrichment of pro-inflammatory, pro-angiogenic inhibitory, and oxidative stress-inducing molecules (84). Specific microRNAs, such as miR-210, miR-155, and miR-223, are consistently upregulated in preeclamptic plasma and have been shown to target renal endothelial and

podocyte transcripts involved in barrier maintenance, antioxidant defense, and apoptosis (85). Accordingly, miR-210, hypoxia-inducible and highly expressed in preeclampsia, downregulates ephrin-A3 and ISCU, impairing mitochondrial respiration and promoting ROS generation in glomerular cells (86,87). Likewise, miR-155 targets SOCS1 and SHIP1, removing negative regulators of inflammatory signaling and amplifying cytokine-driven endothelial activation (88). Exosomal transfer of these microRNAs to renal cells has been demonstrated in vitro and in vivo, confirming a direct placental-renal communication pathway that operates independently of circulating protein factors (89). Proteomic analysis of preeclamptic exosomes reveals enrichment of sFlt-1, endoglin, complement fragments, and oxidized phospholipids, all of which contribute to renal endothelial injury (60, 90). The diagnostic and prognostic potential of exosomal biomarkers is actively being explored, as their cargo reflects real-time placental stress and may precede clinical renal dysfunction by weeks (91). Therapeutic strategies aimed at neutralizing pathogenic exosomes or modulating their biogenesis are in early developmental stages but hold promise for interrupting the placental-renal injury axis without systemic immunosuppression (92,93). Genetic susceptibility and epigenetic reprogramming further shape the renal phenotype in preeclampsia, explaining the variable penetrance and severity observed across populations (94,95). Genome-wide association studies have identified numerous loci associated with preeclampsia risk, many of which encode proteins involved in angiogenesis, coagulation, immune regulation, and renal development (96,97). Variants in FLT1, ENG, STOX1, and LEP have been linked to both placental dysfunction and renal vulnerability, suggesting shared genetic pathways that predispose to multi-organ involvement (96,98). Epigenetic modifications, particularly DNA methylation and histone acetylation, mediate environmental and gestational influences on gene expression in renal tissue (99). Preeclampsia is associated with global hypomethylation in leukocytes but hypermethylation in specific renal promoters, reflecting tissue-specific epigenetic programming in response to oxidative and inflammatory stress (100,101). These modifications can persist postpartum, contributing to the well-documented long-term risk of chronic kidney disease, hypertension, and cardiovascular morbidity in affected women (102). Emerging research into transgenerational epigenetic inheritance suggests that maternal preeclampsia may influence fetal renal development and adult disease susceptibility through in utero programming of renal stem cell populations and vascular precursor cells (101). This underscores the importance of viewing preeclampsia-associated nephropathy not merely as an acute pregnancy complication but as a window into lifelong renal and cardiovascular health trends (16).

Integrating of morphologic lesions with molecular biomarkers

Contemporary clinical and research approaches increasingly emphasize the integration of histopathologic findings with molecular biomarkers to enable early detection, risk stratification, and targeted intervention (103). Renal biopsy, though rarely performed during pregnancy due to safety concerns, remains invaluable in atypical cases where primary glomerular disease must be excluded or when postpartum renal dysfunction persists (104,105). When obtained, biopsy specimens consistently demonstrate endotheliosis, podocyte injury, and variable tubulointerstitial changes, with severity correlating strongly with proteinuria magnitude, blood pressure control, and placental angiogenic markers (32). Non-invasive biomarkers such as the sFlt-1/PlGF ratio, urine albumin-to-creatinine ratio, and complement split products are now routinely used to monitor renal involvement and guide clinical management (106). Emerging omics technologies, including single-cell transcriptomics, spatial proteomics, and metabolomic profiling, are revealing previously unrecognized cellular heterogeneity and pathway crosstalk within the preeclamptic kidney (107,108). These approaches have identified distinct endothelial subpopulations exhibiting varying degrees of stress response, repair capacity, and apoptotic susceptibility, offering new targets for precision therapeutics (109). Animal models, particularly those utilizing adenoviral sFlt-1 overexpression, complement activation, and genetic knockout strategies, continue to validate molecular pathways and test novel interventions (110). Pharmacologic strategies under investigation include VEGF supplementation via controlled-release formulations, sFlt-1 apheresis, complement inhibitors, endothelin receptor modulators, TRPC6 antagonists, and antioxidant or Nrf2 activators (20). While none have yet achieved widespread clinical approval, several have demonstrated remarkable efficacy in preclinical studies by preserving glomerular architecture, reducing proteinuria, and improving maternal-fetal outcomes (111). The ultimate goal remains the development of pregnancy-safe, targeted therapies that interrupt pathogenic molecular cascades without compromising placental perfusion or fetal development (112,113). The ongoing refinement of our understanding of preeclampsia-associated nephropathy underscores the necessity of viewing renal injury not as an isolated event but as the renal manifestation of a systemic pregnancy-specific syndrome (4,38). The morphologic lesions observed in biopsy specimens are direct readouts of molecular disruptions

that originate in the placenta, propagate through the circulation, and selectively target the glomerular filtration barrier (111). Endotheliosis, podocyte effacement, and tubulointerstitial stress are not static endpoints but dynamic processes that evolve in response to angiogenic imbalance, oxidative burden, inflammatory signaling, complement activation, and genetic predisposition (9,114). Current insights have transformed preeclampsia from a purely clinical diagnosis into a molecularly defined entity, enabling risk prediction, mechanistic classification, and pathway-specific intervention (115). Yet significant challenges remain, including the need for pregnancy-compatible therapeutics, standardized histomolecular correlation protocols, and long-term renal outcome tracking in affected women (116). As research continues to unravel the intricate crosstalk between placental factors, systemic endothelium, and renal parenchyma, the hope is that preeclampsia-associated nephropathy will transition from a feared complication to a preventable and treatable condition (117). The integration of histopathology with molecular biology has already yielded unprecedented clarity, and future advances will undoubtedly rely on continued cross-disciplinary collaboration, innovative biomarker development, and patient-centered therapeutic design that prioritizes both maternal renal health and fetal well-being (6,118).

Conclusion

Preeclampsia-associated nephropathy remains a critical manifestation of systemic endothelial dysfunction, with contemporary research steadily clarifying its distinctive renal histopathology and underlying molecular architecture. The characteristic glomerular lesion, termed endotheliosis, reflects profound capillary endothelial swelling and podocyte foot-process effacement driven primarily by a systemic shift toward anti-angiogenic signaling. Circulating sFlt-1 and soluble endoglin sequester vascular endothelial growth factor and placental growth factor, thereby disrupting the maintenance of fenestrated glomerular endothelium and precipitating significant proteinuria. This angiogenic imbalance is further compounded by oxidative stress, aberrant complement activation, and pro-inflammatory cytokine networks that collectively exacerbate tubulointerstitial inflammation and promote podocyte detachment. While these histological alterations classically resolve following placental delivery, emerging longitudinal data indicate that residual microvascular scarring, subclinical podocyte loss, and maladaptive fibrotic remodeling may persist, substantially elevating lifetime risks for chronic kidney disease and cardiovascular complications. Recent advances in single-cell transcriptomics and spatial proteomics have begun to map these pathophysiological cascades with unprecedented resolution, identifying novel mediators such as disrupted autophagy, mitochondrial dysfunction, and dysregulated Wnt/β-catenin signaling. Translating these insights into clinical practice demands integrated, multicenter cohorts that bridge molecular phenotyping with long-term renal outcomes, alongside the validation of noninvasive biomarkers for early disease stratification. Eventually, refining our mechanistic understanding of preeclampsia-associated nephropathy will not only enhance postpartum surveillance strategies but also catalyze the development of targeted, renoprotective therapies capable of restoring angiogenic equilibrium, mitigating irreversible structural damage, and safeguarding maternal kidney health well beyond the acute hypertensive crisis of pregnancy.

Authors' contribution

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Writing–original draft: All authors.
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The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

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