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Placenta, platelets, and podocytes; the triad of renal injury in pregnant women with antiphospholipid syndrome

Maryam Kazemi[1], Arina Shikarchi[2], Azam Moridi[3], Mahnaz Kayyal[4], Zahra Hamidi Madani[5], Sadaf Rassouli[6], Zeinab Zamanpour[7], Nazanin Farzaneh[8*]

[1]Department of Obstetrics and Gynecology, Imam Hossein Hospital, Faculty of Medicine, Shahid Beheshti University of Medical Science, Tehran, Iran
[2]Women's Health Research Center, Islamic Azad University of Medical Sciences, Tabriz Branch, Tabriz, Iran
[3]Mother and Child Welfare Research Center, Hormozgan University of Medical Science, Bandar Abbas, Iran
[4]Department of Nursing, Shahid Mostafa Khomeini Hospital of Tabas, Birjand University of Medical Sciences, Birjand, Iran
[5]Department of Obstetrics and Gynecology, Reproductive Health Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
[6]Department of Gynecology and Obstetrics, Imam Khomeini Hospital, School of Medicine, Sari University of Medical Sciences, Sari, Iran
[7]Department of Gynecology and Obstetrics, Fertility, Infertility, and Perinatology Research Center, Jundishapur University of Medical Sciences, Ahvaz, Iran
[8]Department of Obstetrics and Gynecology, Taleghani General Hospital, Faculty of Medicine, Shahid Beheshti University of Medical Science, Tehran, Iran

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ABSTRACT

The intricate triad of placenta, platelets, and podocytes represents a central framework for understanding the multifactorial renal injury associated with antiphospholipid syndrome (APS) during pregnancy. This triadic interaction underscores a pathophysiological continuum driven by thrombosis, inflammation, and endothelial dysfunction that disrupts both placental and renal homeostasis. In pregnant women with APS, the placenta functions as a key initiator of systemic disturbances through procoagulant and proinflammatory mediators that alter vascular tone and promote immune activation. These placental signals propagate into the maternal circulation, stimulating platelet activation and aggregation that intensify microvascular thrombotic damage. Activated platelets further contribute to endothelial injury by releasing cytokines, chemokines, and growth factors that perpetuate inflammatory cascades and coagulative imbalance. At the renal glomerular level, podocytes serve as critical yet vulnerable responders within this network. They experience direct insults from circulating antiphospholipid antibodies and secondary injury from ischemic and hemodynamic stress induced by microthrombi and endothelial derangement. The consequent podocyte depletion and barrier disruption lead to proteinuria and progressive glomerular dysfunction characteristic of APS nephropathy. This integrative model highlights how maternal, hematologic, and renal compartments intersect in a self-reinforcing cycle of injury, illuminating potential therapeutic targets that modulate platelet activation, placental inflammation, and podocyte resilience.

Implication for health policy/practice/research/medical education:
The conjunction of placental insufficiency, platelet hyperactivity, and podocyte injury creates a vicious cycle of kidney injury in pregnant women with APS. Placental thrombosis and ischemia release antiangiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1), which further impair endothelial function and podocyte integrity. Platelet-derived microparticles exacerbate this injury by promoting inflammation and coagulation within the glomeruli. Podocyte loss, in turn, leads to proteinuria and nephrotic syndrome, which can worsen hypertension and further compromise placental perfusion.

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Introduction

Antiphospholipid syndrome (APS), an autoimmune disorder characterized by the persistent presence of antiphospholipid antibodies (aPL), predisposes individuals to thrombotic events and pregnancy complications (1). Though APS is widely recognized for its role in recurrent miscarriages, preeclampsia, and intrauterine growth restriction, its impact on the kidney, particularly in the

***Corresponding author**: Nazanin Farzaneh, Email: nznnfarzaneh@gmail.com

context of pregnancy, has only recently gathered focused attention (2). The kidney, a highly vascularized organ with intricate filtration mechanisms, becomes a critical target in APS due to its susceptibility to microvascular thrombosis, immune-mediated inflammation, and endothelial dysfunction (3). In pregnant women, this vulnerability is amplified by the physiological demands of gestation, which include increased renal plasma flow, glomerular hyperfiltration, and heightened coagulability (4). Within this milieu, the placenta, platelets, and podocytes emerge not merely as isolated components but as interconnected players in a pathological cascade that culminates in renal injury (5).

Search strategy

For this narrative review, we conducted a comprehensive literature search across PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ), and Embase, employing a range of relevant keywords including; antiphospholipid syndrome, pregnancy, renal injury, placenta, platelets, podocytes, proteinuria, thrombotic microangiopathy, autoimmune disease and glomerular damage.

The role of the placenta in APS-related nephropathy during pregnancy

The placenta, often described as the interface between mother and fetus, serves as both a lifeline and a battleground in APS (6). In healthy pregnancies, the placenta orchestrates nutrient and gas exchange, modulates immune tolerance, and secretes hormones essential for maintaining gestation (7). However, in women with APS, the placenta becomes a focal point of thrombotic and inflammatory injury (1). Antiphospholipid antibodies, primarily lupus anticoagulant, anticardiolipin antibodies, and anti-β2-glycoprotein I antibodies, bind to phospholipid-binding proteins on trophoblasts and endothelial cells within the placental vasculature (8, 9). This binding triggers a cascade of prothrombotic and proinflammatory responses. β2-glycoprotein I (β2GPI), the primary antigenic target in APS, is expressed on the surface of syncytiotrophoblasts, and its interaction with aPL activates complement pathways, particularly C5a, which recruits neutrophils and monocytes, leading to oxidative stress and tissue damage (10). Moreover, aPL binding inhibits trophoblast invasion and differentiation, impairing spiral artery remodeling, a process critical for establishing low-resistance uteroplacental circulation (10,11). The resulting placental hypoperfusion and ischemia not only compromise fetal development but also initiate a systemic inflammatory response that spills over into maternal organs, including the kidneys (12). This placental dysfunction is intrinsically linked to the development of preeclampsia, a hypertensive disorder of pregnancy that shares overlapping features with APS nephropathy (13). In fact, many women with obstetric APS present with early-onset, severe preeclampsia, often before 34 weeks of gestation (14). The placenta in these cases releases antiangiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin, which antagonize vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β) signaling (15-17). The consequent endothelial dysfunction manifests systemically as hypertension, proteinuria, and multiorgan involvement, including renal injury (18,19). Importantly, the renal manifestations in APS-associated preeclampsia may mimic or coexist with antiphospholipid antibody–associated nephropathy (aPL nephropathy), a distinct histopathological entity characterized by thrombotic microangiopathy (TMA), fibrous intimal hyperplasia, and arterial occlusions (20,21). Thus, the placenta, far from being a passive victim, actively contributes to renal pathology through the release of vasoactive and inflammatory mediators that disrupt glomerular and tubular homeostasis (22,23).

The role of platelets in APS-related nephropathy during pregnancy

Platelets, the second component of this triad, serve as both effectors and amplifiers of thrombotic injury in APS (24). Since, traditionally viewed as cellular fragments involved in hemostasis, platelets in APS exhibit a hyperactivated phenotype driven by aPL-mediated signaling (24,25). Antiphospholipid antibodies bind to platelet surface receptors such as apolipoprotein E receptor 2 (ApoER2) and glycoprotein Ibα, triggering intracellular signaling cascades that increase cytosolic calcium, promote phosphatidylserine exposure, and enhance thromboxane A2 production (25,26). This leads to platelet aggregation, adhesion to endothelial cells, and the formation of microthrombi, particularly in the renal microvasculature (27,28). In pregnancy, the baseline state of physiological thrombocytopenia and increased platelet turnover further sensitizes the system to aPL-induced activation (29,30). Moreover, activated platelets release microparticles and proinflammatory cytokines (e.g., IL-1β, CD40L) that exacerbate endothelial injury and promote leukocyte recruitment (31,32). These platelet-derived mediators not only sustain a prothrombotic milieu but also directly impair glomerular filtration by occluding capillaries and inducing mesangial cell proliferation (32,33).

The renal microcirculation is especially vulnerable to platelet-mediated thrombosis due to its high blood flow and fenestrated endothelium (33,34). In APS nephropathy, histological examination often reveals glomerular capillary thrombi, endothelial swelling, and double contours of the glomerular basement membrane, hallmarks of TMA (20,35). Platelet activation also contributes to the development of cortical infarcts and interstitial fibrosis over time (36,37). Critically, the interaction between platelets and the complement system creates a vicious cycle: complement activation (particularly C5a) enhances

platelet reactivity, while platelet microparticles activate the alternative complement pathway (38,39). This synergy is particularly detrimental in pregnancy, where complement regulation is already delicately balanced to prevent fetal rejection (40). Dysregulation in this setting accelerates renal damage and may explain the rapid progression of proteinuria and hypertension observed in some pregnant women with APS (41,42).

The role of podocytes in APS-related nephropathy during pregnancy

Podocytes, the third and perhaps most specialized element of the triad, are terminally differentiated epithelial cells that form the final barrier of the glomerular filtration apparatus (43). Their interdigitating foot processes and slit diaphragms, composed of proteins like nephrin, podocin, and CD2-associated protein (CD2AP), are essential for maintaining selective permeability to proteins (44,45). In APS, podocytes are directly and indirectly targeted, leading to foot process effacement, detachment, and proteinuria (46,47). Emerging evidence suggests that aPL can bind directly to podocytes via annexin A2 and other surface receptors, activating intracellular kinases such as p38 MAPK and Src family kinases (48). This activation disrupts the actin cytoskeleton, destabilizes slit diaphragm complexes, and induces apoptosis (49). Additionally, the proinflammatory and prothrombotic environment generated by placental dysfunction and platelet activation indirectly harms podocytes (50). For instance, reduced VEGF bioavailability, due to elevated sFlt-1 from the ischemic placenta, compromises podocyte survival, as VEGF is a critical autocrine factor for these cells (51). Similarly, oxidative stress from activated neutrophils and macrophages damages podocyte mitochondria and impairs energy metabolism (52). The consequences of podocyte injury in pregnant women with APS are profound (53,54). Proteinuria, often the earliest clinical sign of renal involvement, reflects the breakdown of the glomerular filtration barrier (55). Unlike the transient proteinuria seen in normal pregnancy, proteinuria in APS is typically persistent, progressive, and associated with declining renal function (56,57). Histologically, podocyte loss correlates with glomerulosclerosis and tubulointerstitial fibrosis, irreversible changes that may persist postpartum and increase the risk of chronic kidney disease (53). Furthermore, podocyte-derived urinary biomarkers such as podocalyxin and nephrin have been detected in the urine of APS patients with active nephropathy, offering potential tools for early diagnosis and monitoring (58). The vulnerability of podocytes is magnified during pregnancy due to the increased mechanical and metabolic stress on the glomerulus (59,60); hyperfiltration stretches the capillary loops, placing additional strain on already compromised podocytes (59,61). This explains why renal manifestations of APS often worsen during gestation and may first become clinically apparent in pregnancy (21).

Focus on kidney injury in APS patients in pregnancy

The conjunction of placental, platelet, and podocyte pathologies in APS creates a self-perpetuating cycle of renal injury (62-64). Placental ischemia initiates systemic inflammation and endothelial dysfunction, which activate platelets and promote micro-thrombosis in the renal vasculature (12, 65,66). Platelet-derived mediators and thrombotic occlusions impair glomerular perfusion, leading to hypoxia and oxidative stress that further damage podocytes (33). Injured podocytes, in turn, release proinflammatory cytokines and fail to maintain the filtration barrier, exacerbating proteinuria and activating tubulointerstitial inflammation (67). This triad is not merely additive but synergistic; each component amplifies the others, accelerating renal decline. For example, complement activation, a central mechanism in APS, links all three: it is triggered by aPL binding to the placenta, enhances platelet reactivity, and directly injures podocytes via the membrane attack complex (C5b-9). Similarly, the renin-angiotensin-aldosterone system (RAAS), often dysregulated in preeclampsia and APS, contributes to vasoconstriction, glomerular hypertension, and podocyte stress. It should be remembered that, diagnosis of renal involvement in pregnant women with APS remains challenging due to overlapping features with preeclampsia, lupus nephritis (in cases of secondary APS), and other causes of proteinuria in pregnancy. Current guidelines recommend screening for proteinuria and hypertension at every prenatal visit, but distinguishing APS nephropathy from preeclampsia requires a nuanced approach. The presence of thrombocytopenia, hemolytic anemia, elevated lactate dehydrogenase, and schistocytes on peripheral smear may suggest TMA, a hallmark of aPL nephropathy. Renal biopsy, though rarely performed during pregnancy due to bleeding risks, can reveal characteristic lesions such as arterial fibrinoid necrosis, intimal proliferation, and glomerular microthrombi. Postpartum biopsy is more feasible and often shows chronic changes like fibrous intimal thickening and glomerular scarring. Serological testing for aPL, performed on two occasions at least 12 weeks apart, is essential for confirming APS, though transient aPL can occur in infections and should not be misinterpreted.

Long-term complications of APS-related nephropathy beyond pregnancy

Long-term implications of APS-related renal injury extend beyond pregnancy. Women who experience nephropathy during gestation are at increased risk of developing chronic kidney disease, end-stage renal disease, and recurrent thrombotic events postpartum (68). Persistent proteinuria after delivery necessitates prompt nephrology evaluation and consideration of renal biopsy. Moreover, the presence of renal involvement in APS is a marker of severe disease and may influence decisions regarding future

pregnancies (69). Preconception counseling, optimization of anticoagulation, and tight control of cardiovascular risk factors are detailed components of postpartum care (70).

Focus on biomarkers

Biomarkers elucidating the triad's dynamics are under intense investigation. Urinary podocytes and nephrin fragments reflect active glomerular injury. Circulating sFlt-1, endoglin, and platelet-derived microparticles track placental and platelet dysregulation. Complement split products such as C5a and Bb may indicate the immunologic activation driving both organ damages (71). Meanwhile, novel biomarkers (e.g., urinary VEGF, soluble urokinase plasminogen activator receptor [suPAR]) can provide real-time insights into the status of the triad (72,73). Moreover, the timely initiation of therapy, particularly with anticoagulants and secondary-line medications like HCQ for patients with triple aPL positivity, can significantly reduce adverse obstetric events. The integration of these biomarkers with antibody titers could enable stratification of women at risk of renal and obstetric complications, allowing personalized therapy intensity (74). Emerging noninvasive imaging of placental perfusion through Doppler ultrasonography or MRI may serve as additional surrogate markers of efficacy (75).

Treatment modalities

Management of renal injury in pregnant women with APS hinges on early recognition and multidisciplinary care (76). The cornerstone of therapy is anticoagulation, typically with low-molecular-weight heparin (LMWH) combined with low-dose aspirin (77). LMWH not only prevents thrombosis but also exhibits pleiotropic effects: it inhibits complement activation, protects trophoblasts from aPL-induced injury, and may stabilize the glomerular barrier by preserving heparan sulfate proteoglycans on podocytes. Aspirin, by inhibiting thromboxane A2 synthesis, reduces platelet aggregation and may improve placental perfusion (78). In refractory cases, additional therapies such as hydroxychloroquine, known to inhibit Toll-like receptor signaling and reduce aPL binding, have shown promise in stabilizing renal function (79). For women with severe TMA or rapidly progressive nephropathy, plasma exchange or complement inhibitors (e.g., eculizumab) may be considered, though data in pregnancy are limited (80). Blood pressure control with safe antihypertensives (e.g., labetalol, nifedipine) is crucial to mitigate glomerular hypertension and podocyte stress (81). Hence close observing of kidney function tests, including serum creatinine, proteinuria, and blood pressure, is essential for early detection and intervention (82).

Conclusion

In summary, the intricate interplay among the placenta, platelets, and podocytes forms a pathogenic triad that underpins renal injury in pregnant women with APS. This triad operates through converging mechanisms like thrombosis, inflammation, and endothelial dysfunction, which collectively drive maternal renal compromise. The placenta, far from being a passive organ, acts as a central instigator: in APS, it becomes a source of prothrombotic and proinflammatory mediators that disrupt systemic vascular homeostasis. These perturbations spill into the maternal circulation, triggering widespread endothelial activation. Platelets, in turn, respond by aggregating at sites of vascular injury, propagating microthrombi and releasing cytokines that exacerbate inflammation and further impair endothelial function. This microvascular thrombosis directly threatens renal perfusion and glomerular filtration. Meanwhile, podocytes are uniquely vulnerable; since, they suffer both direct assault from antiphospholipid antibodies, which can bind to surface antigens and disrupt cytoskeletal integrity, and indirect damage from altered hemodynamics and inflammatory mediators. The resulting podocyte injury manifests as proteinuria and, in severe cases, contributes to the development of TMA or preeclampsia-like syndromes. Understanding this triad not only clarifies the multifactorial nature of renal pathology in obstetric APS but also highlights potential therapeutic targets.

Authors' contribution

Conceptualization: Azam Moridi and Mahnaz Kayyal.
Data curation: Maryam Kazemi and Arina Shikarchi.
Investigation: Nazanin Farzaneh and Zeinab Zamanpour.
Supervision: All authors.
Validation: Zahra Hamidi Madani and Sadaf Rassouli.
Visualization: Nazanin Farzaneh and Maryam Kazemi.
W**riting–original draft:** All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity.ai and Grammarly.com 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 accuracy and content of the publication.

Ethical issues

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

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