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The Contribution of Complement Protein C1q in COVID-19 and HIV Infection Comorbid with Preeclampsia: A Review

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Keywords
Component 1q · Complement · COVID-19 · Human immunodeficiency virus · Preeclampsia

Abstract
Dysregulation in component 1q (C1q) levels is associated with weak placental development in preeclampsia (PE). Human immunodeficiency virus infection (HIV-1) triggers the C1q complex, resulting in opsonization of healthy host cells, contributing to their removal, and augmented progression of HIV disease. In coronavirus disease 2019 (COVID-19)-infected patients, the deposition of C1q activates the complement. Considering the paucity of data, this review highlights a significant gap in the potential of C1q in the immunocompromised state of preeclamptic HIV-infected women and COVID-19 infection. In PE, C1q is downregulated; while in antiretroviral treatment-treated HIV/COVID-19 infected patients, C1q is upregulated. It is plausible that C1q is augmented in the triad and may exacerbate severity of disease. This thereby provides a foundation for future intended research which involves the investigation of single nucleotide polymorphism expression of the C1q gene, specifically in these diseases.

Introduction

In December 2019, a severe threat to human well-being originated in Wuhan, China, and rapidly spread across the globe [1]. This outbreak of acute atypical respiratory disease caused by the novel coronavirus was named the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2, 3]. The World Health Organization declared the coronavirus disease (COVID-19), a pandemic [1]. Similar to other coronaviruses such as SARS-CoV-1 and MERS-CoV, the human-to-human transmission was implicated in the outbreak [4]. Up until April 5, 2022, approximately 490,853,129 cases were confirmed worldwide with 6,155,344 deaths [5]. Most patients with COVID-19 exhibit mild to moderate symptoms but approximately 15% progress to severe pneumonia, and about 5% develop an acute respiratory distress syndrome (ARDS) and/or multiple organ failure [6]. The high mortality and morbidity rate of COVID-19 has caused severe disruptions to public health, the economy, and medical communities across the world [3]. Moreover, human immunodeficiency virus (HIV) infection, diabetes, and hy-

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pertension predispose severe COVID-19 illness and are associated with high morbidity and mortality [7, 8].

The COVID-19 challenge to public health was superimposed upon an existing HIV pandemic. In fact, in 2021, 36.3 million (27.2 million–47.8 million) people were already living with HIV infection [9]. More than two-thirds of HIV infections occur in Africa. South Africa has a high (18.9%) prevalence of adult HIV infection [10]. Importantly, antiretroviral therapy (ART) has increased the life expectancy of HIV-infected individuals [11]. South Africa has the largest ART rollout in the world [12]. The risk of dying from COVID-19 among people with HIV infection is twice that of the general population [9]. Hence, it is a concern that up until July 2021, only 3% of individuals residing in Africa had received one dose of a COVID-19 vaccine [9]. Also, since 85% of HIV-infected pregnant women receive ARTs to prevent HIV transmission to the neonate, it is uncertain whether the administration of ART may alter their susceptibility to SARS-CoV-2 infection [13].

In the face of both pandemics, hypertensive disorders of pregnancy such as hemolysis, elevated liver enzymes, low platelet count syndrome; preeclampsia (PE), and eclampsia are still the commonest direct cause of maternal mortality and morbidity [14]. PE is a pregnancy-specific disorder associated with a new-onset high blood pressure of ≥140/90 mm Hg occurring after 20 weeks of gestation [15] and accounts for 4–41% of maternal deaths depending on the economic status of the country [16–18]. PE may be accompanied by proteinuria and/or evidence of multi-organ dysfunction (hematological complications, acute kidney injury, and neurological complications) [15]. Fetal complications include intrauterine growth restriction, placental abruption, and perinatal death [19].

Pregnant women are more susceptible to viral infection due to a change in immune response occurring across the later stages of pregnancy [20]. The risk for severe SARS-CoV-2 infection in the third trimester is linked to the mechanical upward movement of the diaphragm with resultant compression of the lungs causing poor gaseous exchange. This reduced lung mechanics favors the development of pneumonia/pneumonitis and therefore promotes the severity of infection [21, 22]. This increases the risk of contracting COVID-19 infection in the duality of HIV-associated PE and may amplify adverse maternal and fetal outcomes such as preterm birth, miscarriage, and small for gestational age neonates, and mothers may require intensive care management.

The Complement System

The complement system plays a central role in the host's immune defense by linking innate response to adaptive immunity [23]. Complement components are activated by three different pathways viz., the classical, lectin, and alternative pathways (CP, LP, and AP, respectively). All three pathways share the common step of activating the central C3 component, but they differ according to the nature of recognition [24]. Component 1q (C1q) of the CP together with C1r and C1s form the C1 complex (shown in Fig. 1). Activation of this complex leads to the stimulation of C2–C9 components of the CP with resultant formation of the membrane attack complex (MAC) [27]. The consequence of complement activation is the opsonization of pathogens and their removal by phagocytes, inflammation, mobilization of immune cells, and cell lysis. Complement activity is firmly controlled by complement regulators given their potential to harm host tissue. Uncontrolled complement activation would lead to acute and chronic inflammation (acute phase proteins increase), intravascular coagulation and cell injury terminating in multiple organ failure, and death [28].

Complement C1q

The C1q is a target recognition protein that links innate immunity to adaptive immunity by binding to Immunoglobulin G (IgG) and Immunoglobulin M (IgM) immune complexes [29]. This interaction triggers conformational changes within the C1 complex (shown in Fig. 1) which result in the activation of the CP [30].

C1q is responsible for an antibody (Ab)-dependent and -independent immune function mediated by cell signaling on effector cell surfaces [31, 32]. It also regulates immune cell differentiation, cytokine discharge, phagocytosis, and macrophage divergence thereby mediating a tolerogenic phenotype [33], thus endorsing a pregnant women's innate immune response [34, 35]. C1q also maintains this immune tolerance via virus inactivation [36] through induction of proinflammatory cytokines [37]. Apart from C1q-facilitated phagocytosis of apoptotic debris, it mediates uptake of apoptotic lymphocytes by macrophages and dendritic cells (DC) [38]. C1q-exposed macrophages and dendritic cells have a depressed competence to promote T helper (Th) 1/Th17 response with a tendency to sustain regulatory T cells [32].

The normal circulating C1q levels of nonpregnant women (199.4 ± 35.4 mg/L) are very similar to that of pregnant women 202 ± 42.4 mg/L (95% CI for mean:

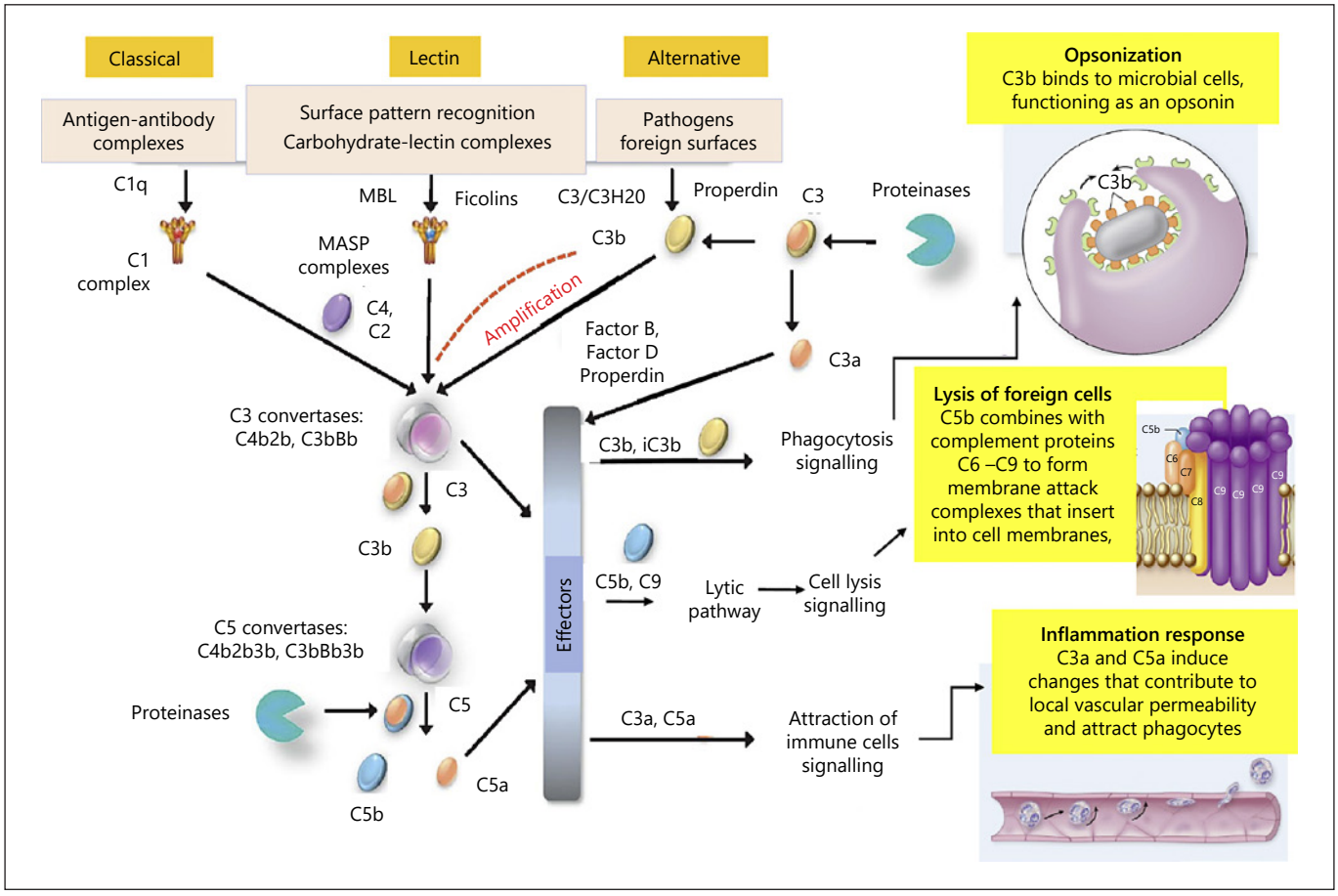

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Fig. 1. Schematic diagram showing the activation and regulation of the complement cascade. Complement activation occurs via three pathways, CP, AP, and LP. The CP is activated by Ab binding to cell surfaces which exposes a C1q-binding site, the LP is activated when ficolin or (MBL which binds to carbohydrate moieties found on pathogen surfaces, and the AP is activated when component 3 (C3) is spontaneously hydrolyzed to form C3(H_2O). All three pathways form a C3 convertase, cleaving component 3a (C3a) and component 3b (C3b), resulting in an MAC with resultant cell lysis and opsonization (modified from Kovanen and Meri [25]; Orsini et al. [26]).

196.6–208.5 mg/L) and remain stable across pregnancy trimesters [39]. In light of the increased susceptibility of HIV-infected pregnant women to COVID-19 infection, this narrative review explores and outlines the diverse role of C1q in both HIV and SARS-CoV-2 infection of normotensive pregnant and PE. It serves as a foundation to elucidate the role of C1q in this deadly triad of inflammatory-related conditions.

The Complement System in COVID-19 Infection

Complement response is a double-edged sword of our immune system; it may be protective by favoring viral clearance, but its uncontrolled activation predisposes acute and chronic inflammation, tissue injury, and coagulation [40]. SARS-CoV similar to SARS-CoV-2 activates C3 and leads to ARDS [41]. SARS-CoV-infected C3-deficient mice display decreased respiratory function with lung pathology accompanied by a decline of cytokines and chemokines (e.g., interleukin 1 alpha [IL-1α], interleukin 5 [IL-5], interleukin 6 [IL-6], tumor necrosis factor alpha [TNF-α], and granulocyte-colony stimulating factor [G-CSF]) compared to their wild-type littermates [41]. This finding validates that C3 inhibition would decrease the severity of ARDS in SARS-CoV-2 infection [42].

More specifically, low levels of mannose-binding lectin (MBL) or its deficiency predispose the acquisition of COVID-19. When SARS-CoV interacts with MBL, it activates the mannose-binding protein-associated serine protease 2 (MASP-2) [43]. This initiates cleavage of C2

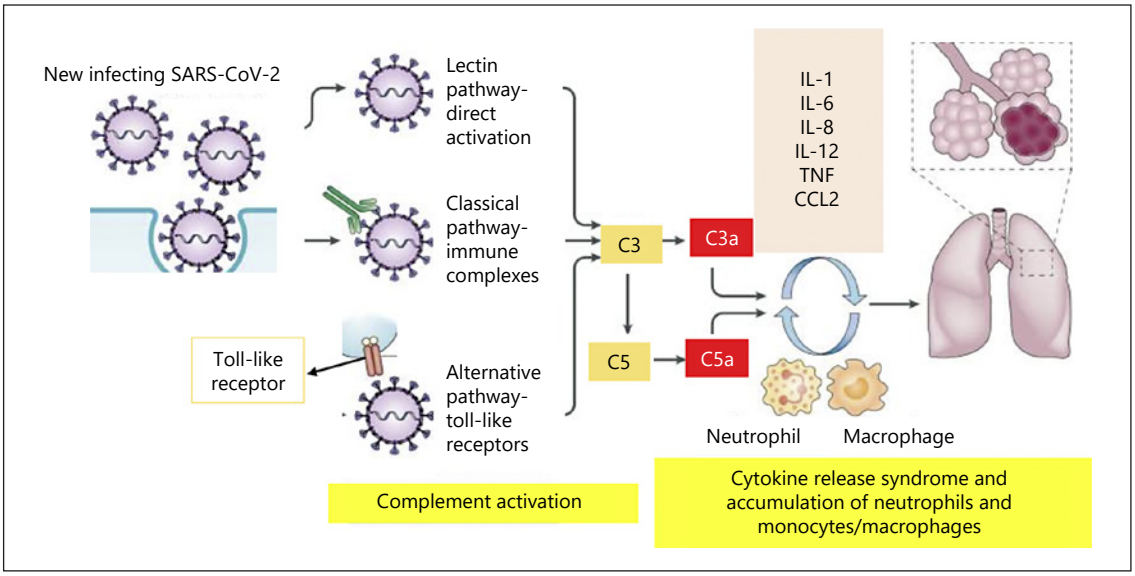

Fig. 2. Complement activation in SARS-CoV-2. Excessive activation of the complement system plays a significant role in severe COVID-19 patients. Complement activation triggers the LP, CP, and AP. Excess levels of proinflammatory cytokines are produced by inflammatory macrophages in the event of component 3a (C3a) and component 5a (C5a) stimulation. C5a and MAC result in the formation of thrombus as a result of endothelial cell activation (modified from Risitano et al. [42]).

and C4 promoting the action of the LP (shown in Fig. 2) [28]. Furthermore, an elevated deposition of C4-activation fragments occurs when MBL adheres to infected SARS-CoV cells [43].

Moreover, strong immunohistochemical staining for MBL, MASP-2, C4a, C3, and MAC colocalize with SARS-CoV-2 nucleocapsid protein in patients with severe COVID-19 [44]. Also, transcriptomic studies on bronchoalveolar lavage fluid from severe COVID-19 patients show higher ficolin 1 levels in monocyte-derived macrophages which support MBL pathway activation (shown in Fig. 2) [44]. These findings highlight that both MBL opsonization and deposition of C3 and C4 onto virions are required for SARS-CoV-2 neutralization [45]. Interestingly, the significance of the MBL pathway in SARS-CoV infection is controversial. Patients with low serum MBL expression are at a greater risk of becoming infected with SARS-CoV, suggesting that MBL activation will promote defense against infection [43]. In contrast, other studies found no association between MBL genotypes/haplotypes and their susceptibility to SARS-CoV infection and disease development [46, 47]. Mechanistic studies on the role of various complement components in SARS and MERS infections suggest broad immune functions that affect multiple organs during coronavirus infection.

C1q and COVID-19

IgM autoantibodies that recognize angiotensin-converting enzyme-2 (ACE2) on endothelial cells (ECs) do not class-switch to IgG, suggesting a T-independent Ab response [48]. This immune response activates the CP and stimulates an inflammatory response observed in severe COVID-19 patients [49, 50]. Moreover, there is an enhanced deposition of IgG and IgM and complement components C1q and C4d on lung tissue [51]. The complement cascade, which is crucial in pathogen removal also influences major complications of COVID-19, including coagulopathy and multi-organ failure [52]. This deposition activates the CP where C3b forms C5 leading to its split into terminal complement products, C5a and C5b-C9. This activation is accompanied by ischemia, trauma, bacterial and viral pneumonia, and ARDS [53–56]. In SARS and MERS infection [57, 58], a consequence of this activation is lung inflammation and respiratory failure [59].

Complement in HIV Infection

Several pathogens mutate as a strategy to evade complement attack. These stratagems include the integration of cell-derived complement regulators into viral particles

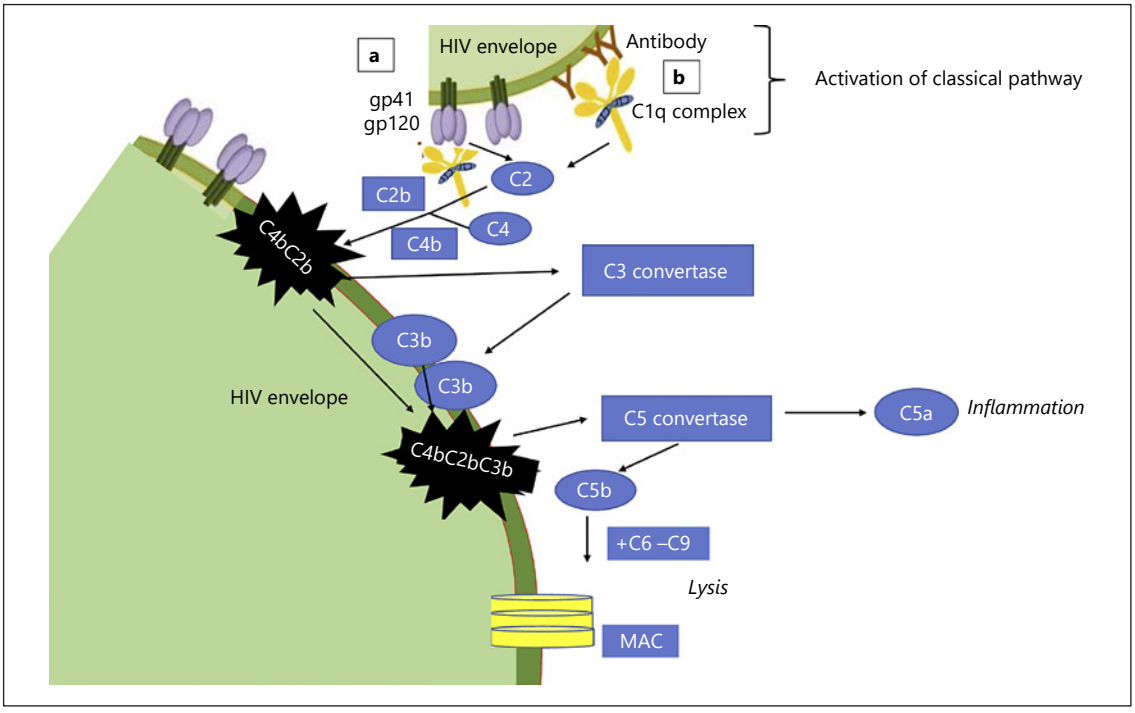

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Fig. 3. Schematic diagram showing the role of complement C1q in the complement system of HIV. **a** The CP can activate the complement system in an Ab-independent manner. This complement-activating capability of HIV-1 resides in gp41 which triggers the component 1 (C1) complex. This results in the lysis of healthy host cells and contributes to C1q removal, consequently, increasing the progression of HIV disease. **b** Similar homologous structures of gp120 and C1q enable the interaction for the same sites on gp41 and the cross-reactivity of antibodies against gp120 with C1q. Antibodies against the envelope protein cross-react with C1q. They are therefore liable for the significantly low C1q levels. Activation of the CP results in the deposition of component 3 (C3) fragments on the viral surface and thereafter lysis of the target host cell.

and/or the parody of negative regulators of complement activation. Moreover, some viruses may exploit complement molecules by utilizing complement receptors as sites for entry. HIV has exploited these strategies to achieve maximal replication and dissemination during infection [60].

The entry of HIV-1 into host cells is dependent on envelope proteins glycoprotein 120 (gp120) and glycoprotein 41 (gp41) that form a noncovalent complex at the viral surface. Sequentially, the outer envelope protein of HIV, gp120, attaches to the CD4 receptor and a chemokine coreceptor on the target cell. The transmembrane envelope protein of HIV, gp41, mediates fusion between the viral and target cell membranes [36].

Complement activation is triggered directly without antigen/Ab interaction in the initial stages of HIV-1 infection [61]. HIV-1 gp41 attaches to C1q and activates the CP [62, 63]. MBL binds to the gp120/gp41 complex to activate complement activity and promote viral clearance and neutralization by tissue macrophages and also augment Ab-mediated neutralization [64]. Notably, susceptibility to HIV-1 infection and disease progression correlates with MBL deficiency [65, 66]. The LP also prohibits viral entry into susceptible cells [67]. Additionally, the CP is triggered by HIV-1-specific antibodies [62]. However, C1q- or C3-deficient serum does not activate the CP, while C3 deficiency does not activate the terminal pathway, hence negating their antiviral effect. Furthermore, the coating of virions by complement components contributes to the viral inactivation [68].

C1q in HIV Infection

Clq binds directly to the transmembrane protein gp41 at amino acid (aa) residues 601-613 [62]. Clq binds to the immunodominant site in gp41 [36]. Additional regions (aa 625-655 and aa 526-538) also facilitate the binding between C1q and gp41 [69]. The adhering site for gp41 is located within the globular regions of C1q [36]. Calcium

ions are necessary for the binding of rsgp41 and Clq, whereas the interaction between rsgp41 and gp120 occurs independent of divalent cations [70].

A functional and structural homology between C1q and gp120 exists showing mimicry and competition with each other for the same sites. Both proteins can successfully adhere to the exact or at least overlapping sites on gp41 [69, 71]. Purified intact HIV-1 virus and recombinant gp41 adhere to purified C1q, activating the complement cascade [62, 72].

Furthermore, isolated HIV-1-infected cells stimulate the activation of the CP in an Ab-independent manner (shown in Fig. 3a) [73], thereby augmenting HIV-1 infection of complement receptor-positive cells. This complement-activating capability of HIV-1 resides in gp41, which triggers the C1 complex [69]. Following complement activation, the resultant opsonization of healthy host cells may contribute to their removal, consequently, increasing the progression of HIV disease (shown in Fig. 3a) [36].

The homology between gp120 and C1q further suggests that individual gp120 may associate directly with the collectin receptor to facilitate the entry of HIV into macrophages in a CD4-independent manner. Similarly, gp120 could induce an oxidative burst, as was shown to be the case for C1q [74]. Stoiber et al. [69] demonstrated that apart from the direct effect of gp120, antibodies against this envelope protein also cross-react with C1q (shown in Fig. 3b). They are therefore accountable for the significantly low C1q expression in HIV1-positive sera. Since C1q is liable for the removal of insoluble immune complexes [75], its absence may contribute to significantly high levels of insoluble immune complexes in HIV-infected individuals [76].

These results propose that homologous structures of gp120 and C1q mediate their competition for the same sites on gp41 and expound the cross-reactivity of antibodies against gp120 with C1q (shown in Fig. 3b). This homology represents an example of an autoimmune phenomenon resulting from molecular mimicry in acquired immunodeficiency syndrome [69].

Complement activity is stimulated by highly active antiretroviral therapy administration; notably in the absence of highly active ART, complement components are consumed by the constant interaction between viral antigens and antiviral antibodies as well as by direct interaction between C1q and gp41. Under therapy, the viral production decreases dramatically, resulting in reduced viral antigens and antibodies and consequently in an elevation of complement components C4 and C3 [77, 78].

Complement Activation in Pregnancy

In pregnancy, there is an enhanced activation of the complement system as a result of complement deposition on placental tissue [79, 80]. At the fetal-maternal interface, this deposition serves as protection against pathogens [81, 82]. Complement components C3, C4, and C1q are deposited onto trophoblast cells [83].

Maternal tolerance is established via the deposition of complement products on placental tissues [80, 84]. These are expressed locally on the surface of the cytotrophoblast, syncytiotrophoblast, and extravillous trophoblast cells [85]. The invasion of extravillous trophoblast cells into maternal tissues is challenged by both complement activation and its regulation [86]. More specifically, endovascular trophoblast cells migrate down the luminal walls of the spiral arteries enabling vascular remodeling of the spiral arteries, with ultimate migration through the decidua into the myometrium. This invasion into maternal tissue produces apoptotic debris that promotes complement activation with minor placental damage challenging complement regulation [87, 88].

During pregnancy, the fetus is protected from harm by complement regulatory proteins that regulate complement activation [82]. However, excessive complement activation is restricted to ensure a successful pregnancy [89, 90]. Complement regulators include decay-accelerating factor (DAF), membrane cofactor protein (MCP), and CD59. DAF halts C3 convertase formation and increases decay of preformed C3 convertase; MCP cleaves C3b and C4b into their active forms, while CD59 functions downstream to inhibit the formation of MAC [91]. Thus, the complement system at the feto-maternal interface protects both the mother and the fetus against invading pathogens while also protecting the fetus from the maternal immune system via maintenance of tolerance.

Chow et al. [91] demonstrated that activated C3 played a crucial role in early pregnancy in mice. In this in vitro study using mouse embryos iC3b, the derivative of C3 displayed embryotrophic activity, which stimulates blastulation and hatching rates. Furthermore, C3-deficient mice displayed extended estrous cycle and elevated resorption rates, thus suggesting that impaired placental development induces fetal outcome [91, 92].

C1q in Pregnancy

In pregnancy, C1q mediates immunotolerance by promoting implantation and is functional throughout gestation [93]. It promotes angiogenesis by acting on ECs at

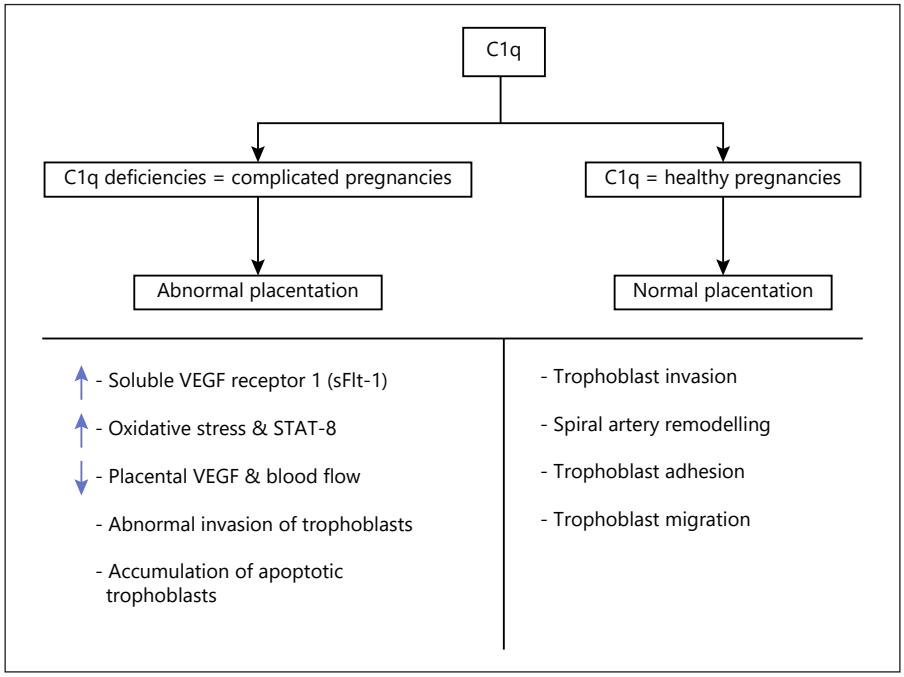

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Fig. 4. The function of C1q in normal placentation and adverse pregnancy outcomes. Deficiency of C1q results in an abnormal invasion of fetal trophoblast into the decidua. C1q deficiency surges oxidative stress and build-up of apoptotic trophoblasts. This has an unfavorable influence on the placenta preventing the generation of vascular endothelial growth factor (VEGF) and blood flow, consequently, causing implantation malfunction and difficulties in pregnancy such as pregnancy loss, miscarriage, and preeclampsia.

the embryo implantation site [94, 95]. C1q plays an important role in placentation where it influences trophoblast invasion and the physiological remodeling of spiral arteries (shown in Fig. 4) [96]. The deposition of C1q is absent on uterine microvascular ECs from nonpregnant uterus, hence binding of C1q to decidual ECs is a pregnancy-associated process [84].

Moreover, the presence of C1q at the feto-maternal interface may influence the regulation of trophoblast and stromal cell lineage differentiation occurring at the beginning of pregnancy such as implantation and placentation. Trophoblast cells express C1q in the first trimester decidual cells and in macrophages suggesting multiple protective functions, including eliminating pathogens, apoptotic materials, and simultaneously, modulating the immune response during early pregnancy [93, 97].

C1q in PE

Excessive complement activation results in adverse pregnancy outcomes such as miscarriage, preterm delivery, and PE [89, 98, 99]. C1q deficiency is linked to dysfunctional placental formation, trophoblast invasion, impaired angiogenic balance, and poor fetal outcome [95, 96]. C1q knockout mice display defective removal of apoptotic cells [95, 100]. These results indicate that apoptotic cell clearance is affected by C1q deficiency in PE development [85]. C1q expression is reduced in PE compared to normotensive pregnant women thereby affecting the outcome [101].

In contrast, an early study reported that C1q placental expression is amplified in PE compared to normotensive pregnancy [102]. Elevated apoptosis has been reported in the placental bed of PE compared to normotensive women [103, 104]. C1q attaches to apoptotic cells via its globular head [105].

C1q-deficient mice also display key features of PE such as hypertension and albuminuria together with a reduction in placental growth factor and vascular endothelial growth factors (PIGF and VEGF) with concomitant amplified levels of soluble VEGF receptor-1 [106]. The onset of PE in C1q-deficient mice is prevented by pravastatin that acts on endothelial function and the expression of VEGF [107], heightened oxidative stress, diminished blood flow, increased fetal death, reduced litter size, defective invasion of trophoblasts, and amplified STAT-8 expression (inhibitor of trophoblast migration) (shown in Fig. 5) [85, 96].

Lokki et al. [108] established that women with early-onset PE displayed higher C1q placental deposits than those with late-onset PE. The former study demonstrated a reduced mRNA expression of the C1q gene in placental tissue from PE compared to healthy matched controls. However, in another study, C1q mRNA placental expression was similar between preeclamptic versus normal

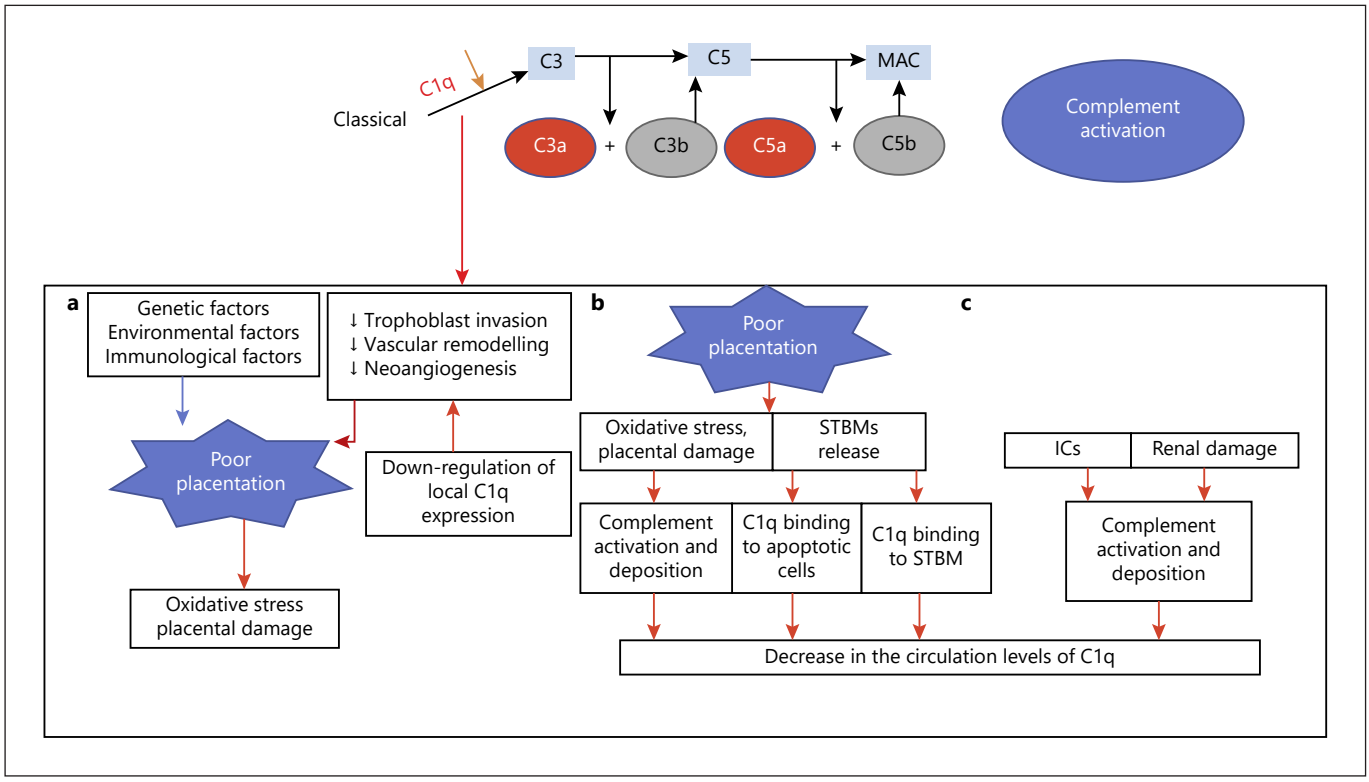

Fig. 5. Significance of C1q in the pathogenesis of preeclampsia. C1q deficiency is a contributing factor to complement dysregulation and as a result a role in the clinical presentation of preeclampsia. **a** Decreased C1q production results in impaired placentation by defective trophoblast invasion, vascular remodeling, and neoangiogenesis. **b** Complement system is triggered by placental injury and at a placental level the accumulation of C1q and other complement components. C1q adheres to apoptotic cells, which results in elevated placental expression. It also binds to circulating STBM with resultant reduced serum expression of C1q in preeclampsia. **c** The decreased expression of C1q observed in C1q may be the result of consumption of C1q, therefore triggering the CP. The C1q consumption may emanate from circulating immune complexes in preeclampsia. This may also rapidly progress to multi-organ dysfunction such as acute renal failure (modified from Agostinis et al. [107]).

control patients [109]. It is plausible that the environmental milieu within the hypoxic oxidatively stressed placenta may account for the lowered C1q expression in PE.

Syncytiotrophoblast microvesicles (STBM) are proinflammatory and circulate in amplified quantities in PE (shown in Fig. 5b). C1q was noted to be one of the 538 proteins unique to preeclamptic STBMs [93, 110]. C1q is deposited onto STBMs and released into the maternal circulation [111]. No significant difference in C1q levels on STBMs between normal and PE was noted [111]. Nonetheless, it is established that preeclamptic placentas release an excessive amount of debris and move STBMs with C1q deposits into circulation [112]. Based on this finding, one may assume that C1q expression mirrors a downstream effect of tissue damage associated with PE development [101]. Nonetheless, dysregulation in C1q levels results in irregular placental development [103].

C1q in HIV-Associated PE and COVID-19

While it is well-established that C1q plays a role in viral infection, there is a lack of data on C1q immune response in the triad of HIV and SARS-CoV-2 infection of pregnant women with PE. From this narrative investigation of C1q, it is understood that the complement system is vital in the protection against HIV infection, however, it may also augment infection [113]. Moreover, C1q expression is intensified in HIV infection. Gp41 adhering to C1q triggers the complement CP, C5a increases and promotes the release of TNF-α and IL-6 that stimulate HIV-1 infection [114]. Of note, HIV-infected individuals receiving ART have an increased rate of non-acquired immunodeficiency related-related comorbidities, which may be due to increased systemic immune activation [115, 116]. However, it is also plausible that HIV itself,

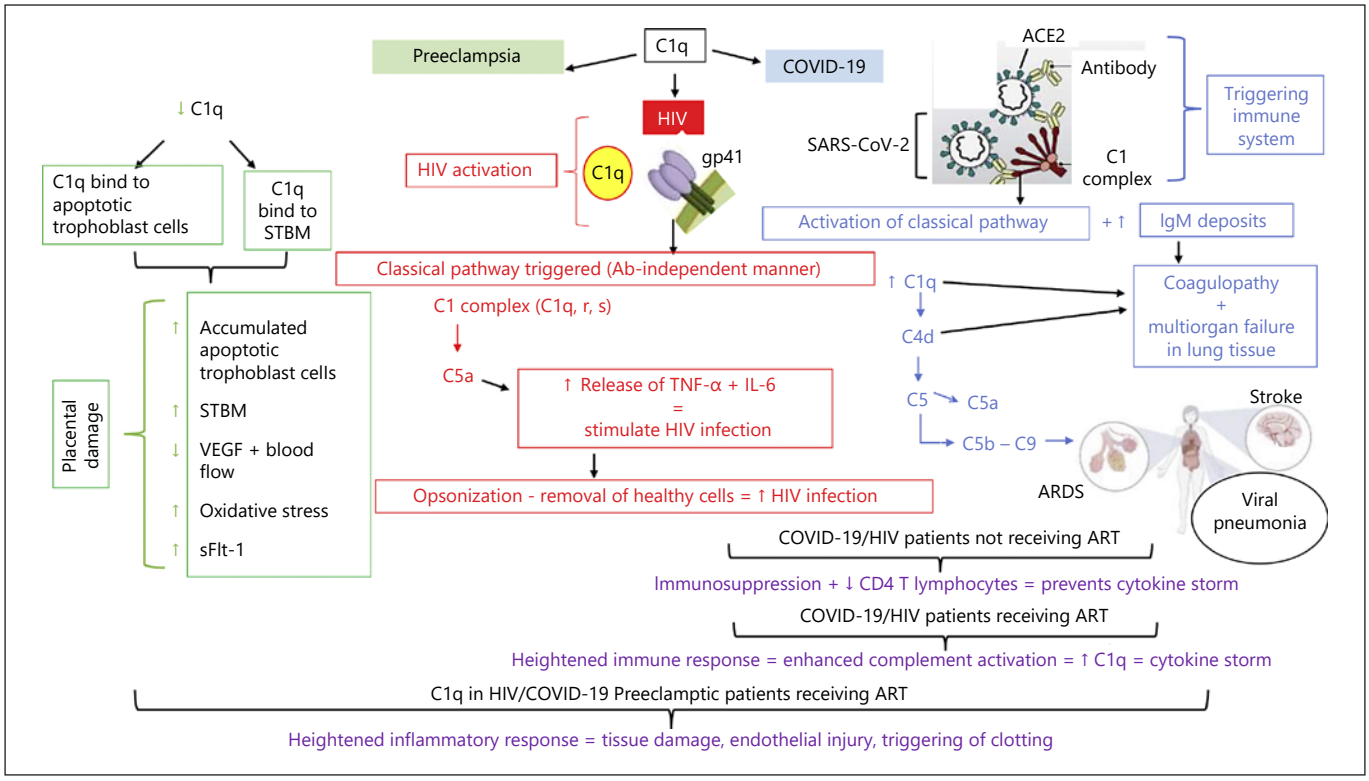

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Fig. 6. The role of C1q in the triad of diseases. In preeclampsia, C1q is downregulated; while in ART-treated HIV/COVID-19-infected patients, C1q is amplified. Excessive C1q activation in this pathological triad exacerbates the severity of disease by promoting endothelial cell injury and ARDS.

obesity, or aging are associated with inflammation that elevates the risk of noncommunicable diseases as opposed to ART.

Despite evidence suggesting that C1q enhances complement activation in COVID-19/HIV-infected patients receiving ART [51, 76]. Immunosuppression and low CD4 T lymphocytes (CD4) prevent HIV-infected individuals from developing the cytokine storm observed in COVID-19 patients [117, 118]. Therefore, ARTs and resultant immune reconstitution would directly promote a cytokine storm in the duality of HIV/COVID-19 infection.

Nonetheless, there is a dire scarcity of information on the immune response to SARS-CoV-2 in pregnant women, although general evidence from prior coronavirus pandemics indicates that pregnancy may increase the risk of infection and susceptibility to death compared with nonpregnant women [119]. Furthermore, COVID-19 mimics PE as the SARS-CoV-2 infection exploits ACE2 entry [120].

Additionally, heightened complement activation occurs in HIV patients receiving ART. This response also occurs in COVID-19-infected patients and women diagnosed with PE promoting tissue damage as a result of EC injury, vascular leakage, and triggering of the clotting cascade leading to thrombosis (shown in Fig. 6) [115, 121–124].

Conclusion

The complement system is a vital protagonist in the rapid host innate immune response against bacterial, viral, and fungal infections. Despite its efficacy in protecting the host against viral infections, it may also be pathogenic against both coronavirus and HIV infections. This narrative review demonstrates for the first time the expression and function of C1q in HIV infection, COVID-19 comorbid with PE. In PE, C1q may be reduced as it clears out the excessive apoptotic debris. Alternatively, it may be reduced due to heightened C1q attachment to

STBM in the sera of PE patients. Excessive C1q activation in this pathological triad negatively impacts placentation, vascular remodeling, and neoangiogenesis. This ultimately leads to tissue damage such as EC injury and vessel leakage that exacerbates adverse pregnancy outcomes such as miscarriage, small for gestational age infants, and preterm delivery. Moreover, intensified complement activation in patients receiving ART promotes EC injury and ARDS. Further large-scale laboratory-based studies that explicitly examine the expression of individual components of the complement cascade are urgently required to help unravel this conundrum.

Future Recommendation

Complement inhibition may be a potential target in the treatment of COVID-19.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Miss Sumeshree Govender wrote the first draft and Professor Thajasvarie Naicker read, edited, and approved the final manuscript.

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