

The Dual Role of the Complement System in Pregnancy

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چکیده فارسی

سیستم کمپلمان به عنوان بخشی از ایمنی ذاتی، نقشی حیاتی و دوگانه در بارداری ایفا می کند. از یک سو، فعال سازی کنترل شده این سیستم برای لانه گزینی، تهاجم تروفوبلاست ها و بازسازی عروق مارپیچی رحم ضروری است؛ از سوی دیگر، فعال سازی بیش از حد کمپلمان می تواند به آسیب بافتی جفت، سقط مکرر، پره اکلامپسی و محدودیت رشد داخل رحمی (IUGR) منجر شود. سطح تروفوبلاست با بیان پروتئین های تنظیمی غشایی مانند CD46، CD55 و CD59 از تشکیل کمپلکس حمله غشایی (MAC) محافظت می شود (Salmon and Girardi, 2008). سندرم آنتی فسفولیپید (APS) نمونه بارز پاتولوژی کمپلمان محور است و با فعال سازی بیش از حد مسیر پایانی C5 همراه است؛ هدف گیری این مسیر می تواند نتایج بارداری را بهبود دهد (Girardi et al., 2006). این مقاله مکانیسم های فیزیولوژیک و پاتولوژیک سیستم کمپلمان در بارداری را بر اساس مرورهای منتشر شده (Regal et al., 2015) مرور می کند.

Keywords (کلیدواژه ها)

Complement system, Pregnancy, Trophoblast, Preeclampsia, Recurrent **Keywords:** Pregnancy Loss (RPL), Ant phospholipid Syndrome (APS), and Complement Regulators.

کلیدواژه ها: سیستم کمپلمان، بارداری، تروفوبلاست، پره اکلامپسی، سقط مکرر، سندرم آنتی فسفولیپید، مهارکننده های کمپلمان.

Abstract

The complement system is a critical component of the innate immune response, acting as a double-edged sword during pregnancy. While controlled activation of complement is

required for placental development, trophoblast invasion, and spiral artery remodeling (Regal et al., 2015), uncontrolled activation is a potent driver of pregnancy complications, including recurrent pregnancy loss, preeclampsia, and intrauterine growth restriction (Girardi et al., 2006). This article reviews the balance between complement activation and its membrane-bound (CD46, CD55, CD59) and soluble regulators, and highlights the clinical implications of complement dysregulation, with particular attention to the antiphospholipid syndrome, where blockade of C5 has proven therapeutic potential (Salmon and Girardi, 2008).

Introduction

During pregnancy, the maternal immune system must tolerate the semi-allogeneic fetus — which expresses paternal antigens — while maintaining host defense against pathogens. The complement system, comprising more than 50 soluble and membrane-bound proteins, operates at a low steady state of activation and can be amplified through the classical, lectin, and alternative pathways. Its effector products, C3a and C5a (anaphylatoxins) and the membrane attack complex C5b-9, must therefore be carefully controlled at the fetal-maternal interface, where fetal trophoblasts are the only fetal cells in direct contact with maternal blood and circulating complement (Regal et al., 2015).

Traditionally viewed as a lytic pathway for pathogen clearance, complement is now recognized as a key mediator of tissue remodeling and placentation. The survival of the fetus depends on a finely tuned equilibrium: too little activation impairs placental vascular development, whereas excessive activation — particularly of the terminal C5-dependent pathway — places the fetus at risk of rejection, growth restriction, or death (Girardi et al., 2006). This review summarizes the physiological and pathological roles of complement in pregnancy.

Physiological Role of Complement in Placental Development

Complement activation is not exclusively deleterious; it is required for normal placental development. In early pregnancy, the uterine wall transforms into decidual tissue, and inflammation accompanies trophoblast invasion and successful implantation. Activated C3 participates in the phagocytic activity of trophoblasts in vitro, suggesting that C3 assists trophoblast invasion of the decidua and endometrial blood vessels (Regal et al., 2015). Decidual endothelial cells secrete C1q, which localizes at the contact sites between endovascular trophoblasts and maternal vessels and likely acts as a bridge enabling adhesion and migration of trophoblasts up the spiral arteries, converting them into high-flow, low-resistance vessels. Notably, no C4 co-localizes with C1q at these sites, indicating that C1q acts there as a scaffold rather than as an activator of the classical pathway. C1q-deficient mice show reduced placental labyrinth development, defective spiral artery remodeling, reduced litter size and fetal weight, and even a preeclampsia-like phenotype with hypertension and proteinuria, underscoring the critical importance of C1q for a normal pregnancy (Regal et al., 2015).

In parallel, the anaphylatoxins C3a and C5a, through their G protein-coupled receptors, assist the vascular changes needed to ensure adequate placental perfusion. However, excessive activation has the opposite effect: complement activation induces dysregulation of angiogenic factors and causes fetal rejection and growth restriction in experimental models (Girardi et al., 2006).

Molecular Mechanisms of Complement Regulation at the Fetal-Maternal Interface

The fetal-maternal interface is protected by a specialized shield of membrane-bound complement regulatory proteins (mCRPs) expressed on the trophoblast surface. These molecules are the primary defense against spontaneous or antibody-driven activation:

- acts as a cofactor for Factor I- **CD46 (Membrane Cofactor Protein, MCP)**: mediated cleavage of C3b and C4b, preventing the propagation of C3 convertase.
- disrupts the stability of both C3 and C5 **CD55 (Decay-Accelerating Factor, DAF)**: convertases, slowing the cascade before it reaches the terminal pathway.
- directly inhibits the final assembly of the membrane attack **CD59 (Protectin)**: complex (C5b-9) by preventing the binding of C9 to the C5b-8 complex.

The synergy of these three regulators allows the placenta to persist in a pro-inflammatory environment without being destroyed by the mother's own innate defenses. Soluble regulators such as Factor H, C4-binding protein, and C1-inhibitor provide additional control in plasma, while the murine analog Crry fulfills a role comparable to CD46 and CD55 in rodent models (Regal et al., 2015).

Trophoblast cells themselves also produce complement components, and their synthesis can be modulated by pro-inflammatory cytokines (Pierik et al., 2020). When these regulatory mechanisms fail or are overwhelmed — for instance, by high titers of activating antibodies — the resulting terminal pathway activation causes direct lysis and sublytic injury of endothelial and trophoblast cells, an event that underlies several pregnancy pathologies.

Complement Dysregulation and Antiphospholipid Syndrome

One of the most significant clinical manifestations of complement dysregulation is seen in **antiphospholipid syndrome (APS)**. In obstetric APS, autoantibodies against β 2-glycoprotein I do not merely trigger coagulation; they directly activate the classical complement pathway at the placenta. This leads to excessive production of C5a and C5b-9, recruitment and activation of neutrophils, endothelial damage, thrombosis, and placental infarction.

In a landmark mouse model of APS-associated pregnancy loss, heparin treatment prevented fetal loss at doses that inhibited complement activation, whereas low molecular weight and unfractionated heparin (but not direct anticoagulation alone) rescued pregnancies — establishing complement inhibition as the key mechanism of its therapeutic effect (Girardi et al., 2005). Studies have further shown that blocking the C5a-C5aR1 axis, or antibody-

mediated neutralization of C5, significantly improves pregnancy outcomes in APS models, highlighting C5 as the primary therapeutic target (Salmon and Girardi, 2008). These findings have reshaped the management of APS: the clinical benefit of heparin in recurrent pregnancy loss is now attributed largely to its anti-complement and anti-inflammatory properties rather than to anticoagulation alone.

Clinical Pathologies: Preeclampsia and IUGR

- characterized by new-onset hypertension and proteinuria after 20 weeks of gestation, preeclampsia affects 3-6% of pregnancies and is associated with increased circulating levels of C3a, C5a, and the soluble terminal complex sC5b-9, suggesting a systemic breakdown in local complement control. Defective spiral artery remodeling — the process in which C1q plays a constructive role — is a central histological finding (Regal et al., 2015).
- chronic, low-level complement activation leads to dysregulation of placental angiogenic factors, suboptimal placental perfusion, and failure of the fetus to reach its growth potential (Girardi G, Yarilin D, Thurman JM, Holers VM, Salmon JE, 2006, *Journal of Experimental Medicine*).
- in women with antiphospholipid antibodies, excessive placental deposition of C4d and C5b-9 correlates with adverse outcomes, making complement split products candidate biomarkers for risk stratification (Pierik et al., 2020).

Discussion and Conclusion

The complement system's role in pregnancy is a delicate equilibrium between necessity and toxicity. While essential for vascularizing the placenta and enabling trophoblast invasion, its over-activation is a common denominator in the major pregnancy pathologies — preeclampsia, intrauterine growth restriction (IUGR), and recurrent pregnancy loss.

Complement activation is known to induce dysregulation of angiogenic factors and cause fetal rejection and growth restriction in experimental models (Girardi et al., 2006). The key insight of the past two decades is that the clinical benefit of therapies such as heparin derives largely from complement inhibition, not anticoagulation alone (Girardi et al., 2005; Salmon and Girardi, 2008).

rather than "complement modulation" Future therapeutic strategies may focus on targeted total suppression — for example, C5 blockade with eculizumab or selective C5a receptor antagonism — aiming to preserve the constructive functions of complement in placentation while preventing the terminal lytic damage that causes fetal loss. Complement split products (C3a, C5a, sC5b-9, and placental C4d deposition) hold promise as biomarkers for identifying pregnancies at risk, although their clinical validation is still in progress (Regal et al., 2015; Pierik et al., 2020).

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