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Peer Review

Review of: "Gestational Inflammation: Its Foetal Control and the Proper Therapeutic Approach"

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The article offers an ambitious and thought-provoking reinterpretation of gestational inflammation, arguing that pregnancy is not merely a maternal process passively accommodating a semi-allogenic fetus, but rather a dynamic interaction actively modulated by the trophoblast. This core premise—that physiological pregnancy depends on the fetus's ability to control the maternal inflammatory response—challenges classical immunological paradigms and invites a reexamination of long-held assumptions about maternal tolerance and immune suppression. The article's strength lies in framing inflammation not as inherently pathological, but as a physiological and essential feature of implantation, vascular remodeling, and labor.

A major contribution of the text is its emphasis on the dual role of inflammatory mediators, which can be both protective and pathogenic depending on context. The discussion of the fMLP peptide, interleukin cascades, and the presence of receptors in amniotic tissue underscores the complex regulatory networks at play in gestation. However, while the article persuasively highlights the functional importance of these molecules, it would benefit from a more systematic organization of the evidence and clearer demarcation between experimental data and interpretive commentary. Additionally, the omission of regulatory immune cells such as Tregs, which play a pivotal role in maternal-fetal tolerance, leaves a conceptual gap in the otherwise thorough immunological narrative.

The exploration of trophoblastic invasion and its modulation of maternal vasculature is detailed and biologically sound. Drawing on Harold Fox's classic observations, the article demonstrates how trophoblasts suppress vasoconstriction and coagulation by remodeling spiral arteries and replacing endothelial linings. This section is particularly robust and well-supported by mechanistic explanations. The argument that fetal control of placental perfusion is essential for a successful pregnancy reinforces

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the article's central thesis and is a valuable framework for understanding complications like preeclampsia and fetal growth restriction.

A controversial aspect of the article is its stance on maternal vaccination. The claim that vaccines may exacerbate maternal inflammation and increase fetal loss is not well-balanced and lacks adequate reference to the broad literature demonstrating vaccine safety in pregnancy. While the author rightly calls for more research, the tone may unduly cast doubt on preventive health measures without sufficient evidence. The epidemiological argument that pregnant women are not at higher risk of ICU admission or death may also oversimplify a multifactorial issue influenced by access to care, comorbidities, and health system capacities.

The article excels in describing the shifting Th1/Th2 cytokine balance across gestation and its relevance to complications like preeclampsia. It explains how increased Th1 activity and associated cytokines (e.g., IL-12, IFN-γ) contribute to vascular dysfunction and oxidative stress. This immune shift is integrated with altered prostanoid balance (prostacyclin versus thromboxane), offering a comprehensive immunovascular model of disease progression. Nevertheless, some mechanisms remain underdeveloped, such as the role of angiogenic factors (e.g., sFlt-1, PlGF) or the downstream signaling effects of hypoxia-inducible pathways.

The discussion on platelet aggregation and aspirin therapy is insightful and well-contextualized. The article acknowledges the paradoxes surrounding in vitro and in vivo platelet function and challenges simplistic interpretations of aspirin's efficacy. This highlights the complexity of therapeutic strategies in obstetric care and the need for individualized, mechanistically informed interventions. However, the article could improve by addressing the diversity of patient responses and the pharmacogenetic variables that influence aspirin metabolism and prostanoid production.

An innovative contribution is the hypothesis that antibiotics may work not solely through antimicrobial activity but also through anti-inflammatory effects. This is supported by references to ampicillin's suppression of prostaglandins and IL-6 even in the absence of infection. Such claims, though speculative, open valuable avenues for future research into non-traditional uses of antibiotics in gestational medicine. They also raise important questions about current diagnostic frameworks, which often conflate inflammation with infection without robust microbiological confirmation.

The article also explores maternal and fetal genetic polymorphisms in inflammatory mediators and their association with miscarriage, preterm birth, and immune dysregulation. The author convincingly argues that both maternal and fetal genomes contribute to the trajectory of pregnancy. References to altered

expression of cytokines, adhesion molecules, and vasoactive peptides in aneuploid fetuses reinforce the idea that genetic programming directly shapes immune responses. Nonetheless, the article could be strengthened by more discussion on the epigenetic regulation of these pathways and environmental influences such as diet or infections.

By highlighting the limited attention given to fetal polymorphisms compared to maternal ones, the article encourages a shift toward a more balanced view of pregnancy immunology. This insight is crucial for the development of precision medicine approaches in obstetrics, which require a better understanding of fetal contributions to inflammatory balance and placental function. The case for including fetal genotyping in the risk assessment for gestational complications is well made and aligns with emerging trends in prenatal diagnostics.

In conclusion, the article makes a valuable theoretical and mechanistic contribution to the understanding of gestational inflammation, presenting pregnancy as an immunologically regulated state governed substantially by the fetus. While the breadth of topics covered is impressive, greater clarity in separating hypothesis from evidence, a more balanced treatment of controversial claims, and deeper engagement with recent molecular data would enhance the article's impact. Still, it succeeds in framing gestation as a finely tuned immune dialogue and sets the stage for further research into fetal-maternal immune cooperation and conflict.

Declarations

Potential competing interests: No potential competing interests to declare.