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Immunological mechanisms of preterm abruption of the normally located placenta

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ABSTRACT

Data from the modern scientific literature concerning the etiology and pathogenesis of preterm abruption of normally located placenta were analyzed. Preterm placental abruption is a rare but very dangerous condition for the mother and fetus. This clinical situation occurs very quickly, and its consequences can be fatal. Because placental abruption can cause disability of the mother and fetus, it should be classified as a social problem.

This review included data from international and Russian articles published over the past decade. This literature review aimed to examine modern theories about molecular changes in the fetoplacental complex that occur during placental abruption. Available evidence suggests that disruption of immunological processes at the maternal–fetal interface is of key significance in the pathophysiology of placental abruption. The reviewed studies described signs of chronic noninfectious inflammation and an enhanced immunological cytotoxic response in placental abruption. Currently, obstetrics is a risk-based approach to medical care for pregnant women. Thus, understanding the predictors and mechanisms of the formation of this pregnancy complication is the key to predicting complications and providing highly competent medical care to patients.

Keywords: immunological reactions; preterm abruption of normally located placenta (PANLP); inflammation.

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Иммунологические механизмы преждевременной отслойки нормально расположенной плаценты

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АННОТАЦИЯ

Проведён анализ данных современной научной литературы, касающихся вопросов этиологии и патогенеза преждевременной отслойки нормально расположенной плаценты. Преждевременная отслойка плаценты — редкое, но очень опасное состояние как для матери, так и для плода. Данная клиническая ситуация развивается всегда молниеносно и последствия её бывают фатальными. Отслойка плаценты может привести к инвалидизации матери и плода, что позволяет отнести данную проблему к категории социальных.

В обзор включены данные зарубежных и отечественных статей, опубликованных за последние 10 лет. Целью данного обзора литературы стало изучение современных теорий о молекулярных изменениях в фетоплацентарном комплексе, происходящих при отслойке плаценты. Имеющиеся данные свидетельствуют о том, что нарушение иммунологических процессов на границе организмов матери и плода играет решающую роль в патофизиологии отслойки плаценты.

В проанализированных исследованиях описываются признаки хронического неинфекционного воспаления и усиленного иммунологического цитотоксического ответа при отслойке плаценты.

Акушерство сегодня — это риск-ориентированный подход к медицинской помощи беременным. Понимание предикторов и механизмов формирования данного осложнения беременности — ключ к возможности прогнозирования осложнений и оказания высококомпетентной медицинской помощи пациенткам.

Ключевые слова: иммунологические реакции; преждевременная отслойка нормально расположенной плаценты (ПОНРП); воспаление.

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INTRODUCTION

Placental abruption (PA) is a life-threatening complication of pregnancy. This is a rare pregnancy complication, with the reported incidence of 0.3% to 0.4% in Russia and up to 1% in the USA [1, 2]. According to Ananth et al., severe placental abruption with blood loss of more than 1,000 mL accounted for 0.65% of pregnancies [2].

Over the years, PA has remained the leading cause of obstetric emergency ("near-miss") and may be associated with a number of complications, including hemorrhagic shock (20%), uteroplacental apoplexy, also known as Couvelaire uterus (16.5%), and disseminated intravascular coagulation (5.8%) [3]. It should be highlighted that the maternal mortality rate from these causes is seven times higher than in the general population [4]. A literature review reveals that women with a history of PA have an increased risk of cardiovascular diseases [5].

GENERAL INFORMATION

The etiopathogenesis of PA is multifactorial. The term "ischemic placental disease" is frequently used in the current literature. It is defined as uteroplacental ischemia resulting from inadequate physiological transformation of the uteroplacental spiral arteries, poor trophoblast invasion, and subsequent impaired placental perfusion. Ischemic placental disease is the underlying cause of a number of major obstetric syndromes, such as PA, pre-eclampsia, and fetal growth restriction (FGR) [5]. PA is commonly associated with vascular and immune disorders leading to necrosis, inflammation, endothelial dysfunction, and ultimately to PA [5].

The maternal immune system changes significantly during pregnancy due to physiological immune suppression. Literature evidence suggests that parturition is a non-infectious inflammatory process with maternal immune activation subsequent to the pregnancy-induced suppression.

Immune tolerance is an essential part of the maternal-placental-fetal interface [6]. The decidual stromal cells of the fetoplacental unit are invaded by extravillous trophoblasts, with maternal immune cells (T cells, uterine natural killer cells, macrophages, and dendritic cells) residing in the decidua. The fetoplacental unit comprises the uterine vasculature and vascular endothelium. Each of these components can independently contribute to the pathogenesis of premature birth [7]. Immune cells and functional regulation play a role in controlling the normally silent decidual inflammatory response, which remains in a precarious equilibrium [8].

Mhatre et al. [9] elucidated the mechanism by which bacterial lipopolysaccharide (LPS) and endogenous thrombin (Thr, F2) synergetically augment the inflammatory response associated with chorioamnionitis that may be associated with the pathogenesis of placental abruption. The effect of the Thr release from the amnion is potentiated in response to bacterial LPS. Thr may activate matrix metalloproteinase (MMP), which cleaves the extracellular matrix and induces PA. Furthermore, Thr has been demonstrated to inhibit the activity of progesterone receptors. Nishimura et al. (2020) [10] found that Thr induced myometrial contractions via two mechanisms: direct activation of myosin and increased prostaglandin (PG) synthesis.

The pathogenesis of PA is attributed to various factors, including intercellular matrix cleavage, inhibition of progesterone receptors, and myometrial contractile activity, and can be manifested by external bleeding or retroplacental hematomas and imbibition of blood into the myometrium. This, in turn, increases the Thr release, forming a vicious circle.

It is important to highlight the role of arachidonic acid metabolism via the cyclooxygenase pathway. Arachidonic acid is released from cell membrane phospholipids by phospholipase A2 and subsequently converted to PGs by two enzymes: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). The role of COX-1 and COX-2 at the time of implantation and during pregnancy is well established, with successful implantation being associated with PG induction by COX-1 and COX-2 [11]. A precise balance between COX-negative and COX-positive cells is essential for the adequate production of PGs and the physiological evolution of pregnancy [12]. The available evidence indicates that COX-1 and COX-2 placental activity is lower in women with pre-eclampsia. Additionally, the polymorphism in the COX-2 gene is associated with FGR. Thus, COX-1 and COX-2 play a role in the pathogenesis of ischemic placental disease [11]. Nevertheless, the role of COX-1 and COX-2 in the pathogenesis of PA remains to be elucidated.

Singh et al. (2019) demonstrated an up-regulation of COX-2 expression in the amnion of pregnant women with PA [13]. Furthermore, Nishimura et al. (2020) observed the up-regulated expression of COX-2 in Thr-treated myometrium [10].

The international literature demonstrates that placenta of patients with chorioamnionitis contains nitric oxide and peroxynitrite, with an increased expression of nitric oxide synthase, which are indicative of inflammation and may also be found in samples from patients with PA. A placental injury pathway appears to be comparable between chorioamnionitis and PA, with a significant involvement of nitric oxide and its metabolites produced by activated macrophages and polymorphonuclear leukocytes [11]. They may be observed in both clinical situations.

The decidual tissue plays a crucial role in human reproduction. Normal placentation is characterized by adequate invasion of trophoblasts into the decidualized endometrium and uterine spiral artery remodeling. Disturbances in these processes can lead to major obstetric syndromes, as previously mentioned. Decidualization is known to induce changes in the expression of tissue factor, type-1 plasminogen activator inhibitor (PAI-1), and MMPs in endometrial stromal cells [14]. The decidua also exhibits a physiological phenomenon of unique coexistence of activated immune cells and decidual stromal cells. It regulates immune cell infiltration

and activity [11]. These cellular interactions are essential for maintaining the immune tolerance required for successful pregnancy outcomes. Both PA and childbirth are associated with inadequate immune suppression by decidual cells and accumulation of cytotoxic immune cells following a decrease in the immunomodulatory effects of membrane proteins [15]. Placental abruption is defined as a premature cessation of molecular changes at the maternal-fetal interface, prior to the onset of labor.

CONCLUSION

The pathophysiology of PA is significantly influenced by immunological disorders within the fetoplacental unit. Identifying the mechanisms responsible for alterations in immune tolerance may provide insight into reference immunotherapeutic strategies in patients with high-risk pregnancies. The first steps have already been taken, but the majority of the subject remains to be investigated.

ADDITIONAL INFO

Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. The concept and design of the study — Fatkullina I.B.; collection and processing of the material — Lazareva A.Yu.; writing of the text — Lazareva A.Yu.; editing — Lazareva A.Yu., Fatkullina I.B.
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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией. Концепция и дизайн исследования — Фаткуллина И.Б.; сбор и обработка материала — Лазарева А.Ю.; написание текста — Лазарева А.Ю.; редактирование — Лазарева А.Ю., Фаткуллина И.Б.
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