Placental Abruption

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Placental abruption is the separation of the placenta from the lining of the uterus before childbirth. It is an infrequent perinatal complication with serious after-effects and a marked risk of maternal and fetal mortality. Despite the fact that numerous placental abruption risk factors are known, the pathophysiology of this issue is multifactorial and not entirely clear.

placental abruption decidua endometrium myometrium placenta maternal–fetal interface immunology

1. Placental Abruption—Overview and Epidemiology

Placental abruption is defined as the early complete or partial separation of the placenta from the lining of the uterus with the development of a retroplacental hematoma before delivery [1]. Placental abruption is a relatively infrequent perinatal complication. However, it is associated with a marked risk of maternal and fetal mortality and requires emergent management [2]. The complication is characterized by a sudden onset and frequently occurs when a patient is not in the hospital. An analysis by Ananth et al. (2015) showed that placental abruption rates tended to decline in the majority of developed countries [3] where the incidence ranged from 0.4 to 1% [1]. As regards to developing countries, the reported risk was higher [4], especially in the case of multiparas, or patients with a history of cesarean section, previous abortion, or placental abruption [5]. Placental abruption patients are more commonly referred to tertiary centers, but actually, each obstetrician may face such a complication in gestations which were initially physiological. This is due to the fact that placental abruption may also occur in patients in labor (about 0.3% of all term deliveries) [6].

Placental abruption may be associated with a variety of complications, even in the case of an instant availability of highly qualified medical personnel and efficiency in saving the mother and the child. The complications are related to iatrogenic prematurity, poor condition of the newborn at birth necessitating hospitalization in the neonatal intensive care unit, prolonged hospital stay and an intervention in the mother. The examples of more common complications of placental abruption include severe hemorrhage, fetal demise, maternal death, premature labor, low birth weight, repetitive transfusions, coagulopathy, or invasive procedures including hysterectomy [1]. According to a systematic review by Downes et al. (2017) placental abruption might also be associated with the elevated risk of sepsis, amniotic fluid embolism, acute kidney injury, severe respiratory distress, encephalopathy, and maternal intensive care unit admission [7]. It also affects a long term prognosis—placental abruption is a significant risk factor for long term maternal cardiovascular disease mortality in a follow-up period of over a decade [8][9].

The exact cause of placental abruption is not entirely clear, and several risk factors are known. Overall, the risk factors of developing placental abruption include advanced maternal age, a history of placental abruption, the use of stimulants, increased arterial pressure (with its sequelae, such as preeclampsia (PE), or fetal growth restriction (FGR)), infectious agents, polyhydramnios, preterm or prolonged rupture of membranes, a history of cesarean section, multiple pregnancies or thrombophilia [1][10]. As regards the cases of placental abruption at term, it was demonstrated that they were significantly associated with pregnancy-induced hypertension, non-vertex presentation, FGR, polyhydramnios and advanced maternal age [6]. Placental abruption may also occur in the case of an abdominal injury in a pregnant woman, e.g., during a vehicle accident or a fall. Some authors also reported the possible influence of stress [11], or heavy physical exertion [12]. Furthermore, several genetic loci were identified that might play a part in placental abruption risk change.

For example, Qiu et al. found that rs2899663 single nucleotide polymorphism of the *RORA* gene was associated with a 21% reduction in the odds of placental abruption. Most of the data in this area have been summarized recently. According to a well performed genome-wide association study and a meta-analysis of genome-wide association studies by Workalemahu et al. from 2018, the genetic loci suggestively associated with placental abruption included rs4148646 and rs2074311 in *ABCC8*, rs7249210, rs7250184, rs7249100 and rs10401828 in *ZNF28*, rs11133659 in *CTNND2*, and rs2074314 and rs35271178 near *KCNJ11*, rs76258369 near *IRX1*, and rs7094759 and rs12264492 in *ADAM12*. Additional analyses performed by the authors revealed that the majority those genes are connected to trophoblast-like cell interaction, or in the endocrine or cardiovascular systems or cellular function pathways. However, their role still needs further research [13].

2. Placental Abruption—Pathophysiology

The etiopathogenesis of placental abruption is multifactorial. According to the current concept of ischemic placental disease, placental abruption is one of the manifestations of impaired placental function comprising PE and FGR. According to the available literature, the pathophysiological mechanisms leading to the occurrence of such complications include uteroplacental ischemia (the placenta becoming underperfused) and placental insufficiency beginning during placental implantation [14][15]. It is believed that those various conditions represent the same disease processes with advancing gestation [14][15].

In the majority of cases, placental diseases are related to the abnormalities of the vascular and immune system. The disruptions lead to necrosis, inflammation, vascular problems and, ultimately, to placental abruption [16][17]. Physiological changes in the immune tolerance process are observed during each stage of pregnancy and labor [17]. The first reports considering labor as a non-infectious inflammatory process were published a long time ago, but the issue is still valid and insufficiently studied due to its multifactorial character. It is currently known that it is the temporary activation of the maternal immune system in which unique suppression is maintained throughout pregnancy [18][19].

Immune tolerance is necessary at the interface between the mother and fetus [20]. The maternal–fetal interface includes the extravillous trophoblast, the decidual stromal cells that house the maternal immune cells (i.e., T cells,

uterine natural killer cells, macrophages, dendritic cells) and the uterine vessels with their endothelium. Each of the components may individually participate in the pathogenesis of preterm birth [21]. The immune system cells and functional regulation are involved in controlling the normally silent inflammatory process of the human uterine decidua, which is a state of very delicate balance [18][22]. Immune cells, such as decidual natural killer (dNK) cells, macrophages, B cells, T cells, dendritic cells, and natural killer T cells (NKTs), are the key players in this process [22]. It is known that chronic placental inflammation might occur in even 10% of pregnancies. However, this inflammation is generally not associated with a documented infection [23]. Numerous authors claimed that placental abruption was associated with a chronic non-infectious inflammatory process in which placental abruption was an easily observable end point, and not an acute phenomenon occurring in isolation [14]. Inflammatory disorders affecting the placenta represent a diverse category of pathological processes leading to adverse perinatal outcomes. For example, maternal and fetal inflammatory responses are related to the clinical diagnosis of chorioamnionitis (CA), an acute type of inflammation that might be associated with potential respiratory and neurological diseases. Conversely, the following chronic placental inflammations may occur: chronic villitis of unknown etiology, chronic deciduitis, chorionitis or intervillositis [24].

The immunological alterations occurring in placental abruption remain mostly unknown, yet some of them have already been established. The disruption of the NKs and T cell balance may result in preterm placental abruption [16][17]. According to the available data, an increased risk of placental abruption was observed to be accompanied by an increased infiltration of macrophages and neutrophilic cells in the uterus [25][26][27][28][29][30]. A high proportion of experts claimed that placental abruption was particularly related to the accumulation of cytotoxic response resulting from the insufficient immunosuppressive activity of the decidua [30][31].

Recent studies also suggested an important role of the cytosolic multiprotein oligomers responsible for the activation of inflammatory responses. Therefore, they were called inflammasomes in the pathophysiology of placental abruption. Many different factors are connected with the fine-tuned regulation of inflammasome assembly and the final effect [32] in this area. For example, NOD-like receptor proteins (NLRPs), e.g., NLRP7, are important in reproductive losses [33]. According to Abi Nahed et al. (2019), NLRP7 was expressed by trophoblast cells and regulated by hypoxia. NLRP7 was found to play a key role in trophoblastic cell proliferation, migration, and invasion. NLRP7 deregulation was suggested to be connected to the occurrence of severe pregnancy outcomes which might precede placental abruption.

It is worth mentioning the abnormal separation of the placental tissue, which may partially be included in placenta accreta spectrum, i.e., a range of the pathologic adherence of the placenta, including placenta increta, placenta percreta, and placenta accreta [34][35]. The spectrum and the described situations are currently referred to as the concept of the biologically defective decidua rather than the primarily abnormally invasive trophoblast [35]. Conversely, it is worth presenting the condition opposite to placental abruption—the retained placental tissue (RPT) in which, for an unclear reason, some placental tissue is not completely separated from the uterine wall. RPT is a condition in which all or a part of the placenta or membranes failed to separate from the uterine lining and were retained within the uterus [36]. It also includes the abovementioned placenta accreta spectrum [37]. A high proportion of those situations are probably associated with the insufficient accumulation of cytotoxic response factors resulting

from the immunosuppressive hyperactivity of the decidua [17][29]. Therefore, a comparison between the immunological picture of the decidua in the case of placental abruption and RPT seems to be an interesting issue in available and future research.

A successful pregnancy involves various interactions between trophoblasts and maternal immune cells. These interactions allow the development of a new life in the uterus while the mother's immune system remains intact [31]. The planned systematic review aims at the determination of the molecular basis of the clinical diagnosis of placental abruption and identifying pathways and factors leading to this complication. The obtained data will facilitate a better understanding of the phenomenon and the improvement of diagnostic and therapeutic opportunities for patients at risk of developing placental abruption.

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