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Immunological Issues in Recurrent Spontaneous Abortion

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Abstract:Recurrent spontaneous abortion (RSA) is a serious reproductive disorder of pregnancy that presents an unresolved issue in the fields of gynecology and obstetrics. RSA is usually defined as a woman suffering from ≥3 spontaneous abortions with the same sexual partner. The incidence rate of RSA ranges from 1 to 5% in women of childbearing age .[1]. The WHO defines recurrent pregnancy loss (RPL) as 3 or more consecutive pregnancy losses before the 20th week of pregnancy, while the American Society for Reproductive Medicine (ASRM) defines RPL after two pregnancy losses with clinical evidence of pregnancy (sonographic or histopathological evidence of pregnancy) [1,2]. About 1–5% of couples are affected by RPL, with significant consequences concerning their partnership and quality of life [3]. In the last years, the European Society of Reproduction and Embryology (ESHRE) [4], ASRM [5], German/Austrian/Swiss Society of Obstetrics and Gynecology (DGGG/OEGGG/SGGG) [6] and the Royal College of Obstetricians and Gynecologists (RCOG) [7] have developed guidelines to define a diagnostic and therapeutic work-up in RPL patients .Recent research has determined that the etiology of RSA is extremely varied, chiefly advanced high maternal age, inheritable genetic abnormalities, anatomical factors, infections, and endocrine dysfunctions .However, in most patients, the cause is unclear. Immune dysfunction accounts for more than half of these cases, and is usually referred to as immune-related RSA .A successful pregnancy requires an accurate immunologic dialogue at the maternal-fetal immune interface in the endometrium. [2] During early gestation, the occurrence of immunologic events over bilateral communication between the mother and fetus is extremely elaborate, and encompasses a great deal of immunocytes,including innate lymphocytes (ILC), macrophages, decidual dendritic cells (DCs), and T cells. These cells play a crucial role in establishing a balance between the inflammatory response and immune tolerance. [3]Existing evidence indicates that disorders occurring in the endometrial immune microenvironment are related to severe crucial reproductive disorders, which involve recurrent implantation failure (RIF) and RSA with inexplicable etiology. Innate Lymphoid Cells Innate lymphoid cells (ILCs) play significant roles in membrane immunity, tissue equilibrium, and metabolism regulation, and have inspired much research in recent years.Protocols which includes both drugs and Immunotherapy has been found to reduce the miscarriage rate and achieve a higher rate of live births in women. [1-39]

Key words:Recurrent Abortion,Immunologic Abortion, Pregnancyloss, SpontaneousAbortion, Pregnancy,Infertility

IMMUNOLOGY IN PREGNANCY LOSS

Researchers have identified that ILCs exist in the human decidua and are crucial at the maternal-fetal interface. ILCs with short antigen receptors substantiate a classical lymphoid cell morphology, depending on two important components (cytokine receptor γ-chain and the transcriptional repressor inhibitor of DNA binding2 Based on distinct developmental pathways, they are classified into two subfields: natural killer (NK) cells and non-cytotoxic helper ILCs, including ILC1s, ILC2s, and ILC3s.Decidual natural killer (dNK) cells are the only subset of ILCs with cytotoxicity. [6] Maladjustment of cytotoxic regulation transforms dNK cells into harmful cells and leads to reproductive disorders, including RSA. Itsinternal mechanisms have been extensivelyresearched, including the unbalanced expression ofactivating and inhibiting receptors on the surface ofdNK cellsThis includes the increased presentation ofNKG2D and the lack of KIR, the combination ofwhich causes adverse pregnancy outcomes. Furthermore, it has been found that in the mouseuterus, dNK cell cytotoxicity is usually altered bythe unbalanced expression between TumorNecrosis Factor-Like Weak Inducer of ApoptosisTWEAK and its receptors, which could result inabortion.[7]

UNEXPLAINED PREGNANCY LOSS

More than half of the women who experience RSA arediagnosed with unexplained recurrent pregnancy loss. Some of them may suffer immune defects, such asdisorganized NK cells or abnormal NK cell subpopulations .The quantity and viability of peripheral blood NK(pNK) cells may also play an important role in RSAdevelopment.Women who suffer from RSA generally have higheractive performance in the quantity and viability of Pnkcells compared with normal pregnant women[8]. This may be related to the high cytotoxic activityof pNK . Human NK cells are categorized into fourtypes, including NK1, NK2, NK3, and NKrl subsets,based on cytokine production. Among them, NK1 produces IFN-γ and TNF-α, andNK2 excretes IL-4, IL-5, and IL-13 NK3 cellsproduce TGF-β; and NKr1 cells produce IL-10 .In order to achieve a good pregnancy outcome,NK cells may change from type 1 to type 2immune responses . [9] A previous study presentedan obvious type 1 shift in pNK cells in patientswith recurrent implantation failure (RIF) or RSA. This suggests that the

growth in the NK1/NK2 ratiomay be an indicator for the probability of pregnancyfailure. [10]

In addition, CD56bright/CD16 accounts for almost90% of uterine NK (uNK) cells .Cells with low cytotoxic activity produce morecytokines. Women with RSA had a smaller number ofuNK than fertile controls, indicating that recurrentspontaneous abortion is closely associated with anabnormal proportion of uNKcells . [11]It is well known that uNK cells are indispensable forcontrolling trophoblast invasion and proliferationSuccessful pregnancy depends on correct spiral arterremodeling. During the process of placentation, thepurpose of invasive extravilloustrophoblasts (EVTs)moving to the uterus is to remodel vessels. Spiralartery remodeling by EVTs plays an important role inadapting blood flow and delivering nutrients todeveloping fetuses .Impaired spiral artery remodeling has been linked toearly miscarriage. uNK cells are the major source ofvarious cytokines, including GM-CSF, CSF-1, TNF-α,IFN-γ, TGF-β [23], and angiogenic growth factors. [12]

A previous study has shown that in women with RSA, theexpression profile of angiogenicfactors in CD56bright uNK cellsdisplays a significant overexpression of angiogenin, bFGF, andVEGF-A.This may be relevant to the overactive oxygenation and oxidativestress in the mother and fetal immune interface of patients withRSAOverexpressed angiogenic growth factors cause aberrantendometrial angiogenesis and vascular disorder, includingprecocious development of endometrial blood vessels andlowered resistance of uterine artery to blood flow andmicrovessel density, which above have been found to accumulatein women with RSA . [13]A recent study has shown that obesity is associated with adversereproductive outcomes. This is because a high-fat diet, which isrelated to impaired vascular remodeling within the uterus,promotes NK cell activation during pregnancy and altered uNKgene expression . [1,14]

AUTOPHAGY IN PREGNANCY LOSS

In recent years, research on autophagy has become popular in theimmunological field. Autophagy, a firmly controlled catabolic approach ofcellular self-degradation, is defined as a non-apoptotic form withrelevance in over stimulated programmed cell death resulting from thestimuli-initiation, and it is substantially a cellular tension reaction andquality regulation mechanism. [15]Autophagy has an important effect onembryonic growth during the early stage of pregnancy. This developmentis usually associated with reproductive disorders, including abortion andpreeclampsia [13]. A recent study reported that the level of autophagy in thevilli of RSA sufferers was remarkably lower than that of selectivetermination in pregnant women, and suggested that the suppression oftrophoblast autophagy causes RSA via IGF-2 secretion and PEG10reduction. [16] This study demonstrated that a high level of IGF-2 leads to NKcell transformation into a special category of cell with high cytotoxicactivity, which then attacks normal cells at the immune interface. [17]Thelatter has a negative influence on the process of vascular invasion, whichinduces pregnancy failure. Uterine Dendritic Cells. In the decidua, uterine DCs are believed to play a key role inthe delicate equilibrium involved in maternal recognition ofpaternal antigens. It has been suggested that in the aspectof differentiation of endometrial stromal cell, DCs play apositive role positive tropism, in proliferation, and localangiogenesis. [18]

They are considered major regulators of the immuneresponse, augmenting T cell–mediated immunity, andstimulating regulatory T cell induction. It is suggested thatdecidual DCs may also play a crucial role in the etiology ofRSA . Any disturbance in their distribution, maturationstate, or function might have a negative impact onpregnancy outcome, leading to adverse pregnancyoutcomes [19]

In recent human studies, the following findings have beendemonstrated: [1-4,25-30]
(1) Compared with the control group, the levels of myeloid DCs(MDCs), and CD86+ DCs in the RSA group were increasedsignificantly, and CD200 expression on peripheral blood DCs wassignificantly lower in the RSA group;
(2) An elevated number of mature DCs and a decreased quantityof immature DCs may be associated with RSA;
(3) And compared with controls, ILT4+ DCs in the peripheral bloodand endometrium were decreased in women with RSA,[1,3,16]

MYELOID-DERIVED SUPPRESSOR CELLS

Myeloid-derived suppressor cells (MDSCs) haveemerged as a new immune regulator at thematernal-fetal interface. They participate in regulatingother immune cells, especially on T cells, bysuppressing their activities .We have two categories based on phenotypes: MDSCs(MO-MDSCs) and granulocytic MDSCs (GR-MDSCs).Recent studies have shown that GR-MDSCs generallyaccumulate at the maternal-fetal immune interface,and that their immune modulatory properties may besignificant for fetal-maternal toleranceIn one study, researchers demonstrated that GR-MDSCsaccumulated in the human placenta in healthy pregnancies,while they were remarkably diminished in patients sufferingspontaneous abortion. [11, 15-20]MDSCs are likely to function in RSA by regulatinghypoxia-inducible factor 1α (HIF-1α).Previous research has also shown that HIF-1α expressionwas lower in the missed abortion group than in the electiveabortion group .Furthermore, scientists have extensively investigated the relationship between HIF-1α, MDSCs, and RSA, and recentresearch provides a reasonable explanation for the above phenomena.

Myeloid cells with deficient HIF-1α cause a diminishingaccumulation of MDSCs, diminish the suppressive activity ofMDSCs, increase the apoptotic rates of MDSCs, andenhance the abortion rate [1,31]. It is also known that MDSCsare myeloid cells with suppressive activity on other immunecells. Therefore, the alteration of the number and functionof MDSCs has a negative influence on fetal-maternalimmune tolerance. Furthermore, research clearly suggeststhat in early miscarriage (EM) patients, the decline inG-MDSCs is related to a decline in estrogen (E2) andprogesterone (P4) .

Women suffering from EM alsogenerally experience poor endometrial receptivity, due tothe downregulation of ER-α and contra variant expression ofcaspase-3 in endometrium

decidua Neovascularization is crucial for decidualization andestablishment of the placenta. Previous research hasreported that MDSCs are associated with the progression ofneovascularization [2,32]. They facilitate nonimmunereactions such as angiogenesis by secreting the keypro-angiogenesis inducer VEGF during pregnancy. Thus, wespeculated that in RSA patients, the reduction of GR-MDSCsmight lead to deovascularization disorder and embryo loss.A study confirmed this speculation, demonstrating that higher early miscarriage incidence is associated with adecrease in suppressive monocyte levels in the peripheralblood and endometrium of pregnant mice and women. [3, 33]Immune cells always form an interactive networkrather than being isolated in the immune system. For example, pregnancy loss as a possible result ofmyeloid-derived suppressor cell depletion isassociated with the upregulation of decidual NK cellcytotoxicity [6,34]. Meanwhile, a remarkable feature ofa successful pregnancy is the higher frequency ofnon-cytotoxic NK cells and lower number of cytotoxicNK cells present at the maternal-fetal interface [34-37].Some studies show that MDSCs could not onlysuppress DC and T cell maturation but also supported NK cells and resting macrophage development [34-36].It has also been documented that MDSCs can induceFoxp3+ T regulatory (Treg) cells by activating TGF-β viathe TGF-β/β-catenin signaling pathway [1,35]. Theproportion of uNK cells and Treg cells was therefore significantly upregulated, revealing that as a newimmunosuppressive network system, theMDSCs-NK-Treg axis plays a complex and crucial role inregulating fetal-maternal immune tolerance.MDSC-tolerogenic dendritic cells and Treg cells play acrucial role in supporting normal pregnancy andplacenta formation, and may represent a new networksystem in maternal-fetal immunity . [1-6]

Another study has shown that MDSCs not only suppressed T cellsvia reactive oxygen species (ROS) production but were alsocapable of inducing a shift toward Th2 cell subtypes in a cell-cellcontact manner [6]. Moreover, these cells could reduce thepresentation of L-selectin on immature T cells, inhibiting theirtrafficking toward lymph nodes and sustaining fetal-maternaltolerance Placental GR-MDSCs play a negative regulatory rolein T cell responses by expressing arginase I and producing ROS[1,2,34]. In fact, GR-MDSCs can be sensitized at the immune interfacebetween mother and embryo through interaction withtrophoblasts. Moreover, GR-MDSCs isolated from placentapolarized CD4+ T cells toward a Th2 cytokine response. Asmentioned above, due to the importance of MDSCs in pregnancy,their absence or dysregulation may cause complications.[37,38].Here Special attention was drawn to recommendations in the guidelines regarding diagnostic factors such as autoantibodies, natural killer cells, regulatory T cells, dendritic cells, plasma cells, and human leukocyte antigen system (HLA)-sharing as well as treatment options in Immunologic Pregnancy loss .All these information open ways for more results and success of unexplained or immunologic recurrent pregnancy loss treatments .

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