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Immune profiling in patients with recurrent miscarriage

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ABSTRACT

The central role of the maternal immune system for successful and disturbed pregnancies such as recurrent miscarriage (RM) is apparent. Recent studies have increased understanding of the complex interaction of the different immunological players and the adaptation of the maternal immune system to the semi-allogeneic embryo. There is growing evidence for immunological abnormalities in RM patients, including autoimmune and allogeneic factors. However, the question remains unsolved whether these changes represent the cause or the consequence of RM. As in half of the RM patients the underlying mechanism remains unknown, further diagnostic methods are urgently needed. Within this review we summarize (recent) literature on the immunological diagnosis in RM patients to find out current trends and to identify potential targets of therapy. As the exact mechanisms of feto-maternal tolerance have not yet been determined we suggest that the immunological diagnosis should be implemented only in well-designed clinical trials in specialized centers to establish a standardized immunological work-up in RM patients.

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1. Introduction

Recurrent miscarriage (RM) affects about 1–3% of all women during their reproductive years (Carrington et al., 2005). According to the Royal College of Obstetricians and Gynecologists, the American Society for Reproductive Medicine, and the German Society for Gynecology and Obstetrics there are several established risk factors concerning RM: parental genetic disorders, uterine anatomical malformations, endocrine dysfunction, and hemostatic disorders (Carrington et al., 2005; Franssen, 2005; Porcu et al., 2000; Rodger et al., 2008; Toth et al., 2010). With regard to the diagnostic of immunological changes, only screening for antiphospholipid syndrome is recommended in all guidelines (ACOG, 2002; Jauniaux et al., 2006). However, immunological mechanisms and maternal adaptation of the immune response to the semi-allogeneic embryo have been thought to play a role in successful pregnancy for a long time.

With the help of new and innovative diagnostic methods several studies described immunological parameters that differ between RM patients and healthy controls and might be associated with RM. Table 1 summarizes the potential immunological diagnostic in RM patients. Still, the question remains whether these changes indicate the cause or the consequence of the miscarriages. Research focuses on the decisive role of uterine and peripheral blood natural killer cells (uNK, pNK cells) during (early) gestation (Hanna et al., 2006; Seshadri and Sunkara, 2014; Tang et al., 2011), regulatory T-cells (Tregs) (Jin et al., 2009; Leber et al., 2010), KIR gene frequencies, and the HLA profiling of

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Table 1
Immunological diagnostic in recurrent miscarriage. Summary of the immunological disorders associated with recurrent miscarriage and the diagnostic procedures.

Immunological disorder	Diagnostic
Autoimmune factors	
Antiphosphoplipid syndrome	Clinical criteria: • Vascular thrombosis • Obstetrical disorders Laboratory criteria: • Lupus anticoagulant • Anticardiolipin antibody • Anti-b2 glycoprotein-I
Thyroid autoimmunity	Autoantibodies against thyroid peroxidase and/or thyroglobulin, hypothyreosis
Anti-nuclear antibodies	Anti-nuclear antibodies
Celiac disease	IgA antibodies against tissue transglutaminase
Allogeneic factors	
Cytokines	Plasma cytokine immunoassay
Regulatory T cells	Flow cytometry
NK cells	Peripheral NK cells • Flow cytometry Uterine NK cells • Immunohistochemical staining of tissue • Flow cytometry of cells after enzymatic digestion of tissue biopsy

affected couples (Hiby et al., 2008), TH1/TH2 imbalances with a shift to dominance of the TH1 cytokines (higher levels of IFN-γ/IL-4, TNF/IL-4, and TNF/IL-10) (Fukui et al., 2008; Nakashima et al., 2012), as well as TH17 cells (Lee et al., 2012).

However, data are limited because of the small size of the study population, the inclusion of patients with only two miscarriages, a mixture of several risk factors, and an incongruent definition of idiopathic recurrent miscarriages (iRM) (Seshadri and Sunkara, 2014; Tang et al., 2011).

Within this review we summarize (recent) literature on immunological diagnostics in RM to discover the current trends and to identify potential targets of therapy.

2. Autoimmune factors

2.1. Antiphosphoplipid syndrome

The antiphosphoplipid syndrome (APS) affects 2–15% of RM patients and is a well-established risk factor in all international guidelines (Miyakis et al., 2006; Perricone et al., 2012; Toth et al., 2010). It should be emphasized that it is mandatory to confirm elevated antiphospholipid antibodies (aPL) 12 weeks after the first measurement (Hughes, 2011). The pathogenic mechanisms on impaired obstetrical outcome are complex and involve not only the dysregulation of coagulation, but also direct effects on the trophoblast (Perricone et al., 2012). In addition, aPL may influence the synthesis of prostaglandins by decidual cells and cytokine patterns, increasing the expression and secretion of pro-inflammatory cytokines such as TNF, IL-1, and IL-6, resulting in placental apoptosis and activation of NK cells (Carp and Shoenfeld, 2007). Untreated patients with APS reach a live birth rate of only up to 10% (Huong et al., 2001; Rai et al., 1995). After diagnosis and appropriate treatment with low molecular weight heparin (LMWH) and acetylsalicylic acid the live birth rate is remarkably improved, but the occurrence of other obstetric complications, especially in the second and third trimesters, still remains high (Empson et al., 2005; Kwak-Kim et al., 2013; Toth et al., 2010).

2.2. Thyroid autoimmunity

Autoimmunity against thyroid tissue (e.g., autoantibodies against thyroid peroxidase and/or thyroglobulin) is the most prevalent autoimmunity, occurring in about 5–20% of normal pregnant women (Perricone et al., 2012). Several studies indicated a three- to five-fold increase in first-trimester miscarriages in the case of thyroid autoimmunity even without overt thyroid dysfunction (Perricone et al., 2012; Toth et al., 2010; Vaquero et al., 2000). In the case of Graves' disease, which has a prevalence of about 0.01–0.02% in pregnant women, the rate of miscarriages is also elevated (De Groot et al., 2012).

2.3. Anti-nuclear antibodies

Anti-nuclear antibodies can hint at autologous immune activation. These antibodies are present both in various autoimmune diseases such as systemic lupus erythematosus and in healthy individuals (Kurien and Scofield, 2006). Anti-nuclear antibodies are discussed controversially in the context of miscarriage, as some studies describe elevated and some normal levels in RM patients compared with healthy controls (Bustos et al., 2006; Shoenfeld et al., 2006).

2.4. Celiac disease

Celiac disease (CD, celiac sprue) is a chronic enteropathy and the most common autoimmune disease, with a prevalence of 1% in the general population worldwide. It is characterized by an abnormal immune response to gluten, the protein fraction of wheat, barley, and rye (Fasano et al., 2003; Tersigni et al., 2014). Only 20–50% of affected individuals show subjective symptoms (Bingley et al., 2004; Tatar et al., 2004). A recent meta-analysis described an odds ratio of 5.82 (95% confidence intervals [CI] 2.30–14.74) for celiac disease in women experiencing RM (Tersigni et al., 2014). It has been proposed that the autoantibodies increase the risk of adverse pregnancy outcome by direct binding to trophoblast cells as well as by inhibiting endometrial angiogenesis (Hadziselimovic et al., 2007; Tersigni et al., 2014). Thus, an association with miscarriage is possible and IgA antibodies against tissue transglutaminase can be determined, followed by a biopsy of the small intestine and a gluten-free diet (Tursi et al., 2008).

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