Tumor Necrosis Factor-Alpha

Subjects: Immunology

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TNF-α anti-TNF-α placental transfer procreation fertility pregnancy

1. The Role of TNF-α in Pregnancy

Tumor necrosis factor-alpha (TNF-α) is a multifunctional Th1 cytokine and one of the most important inflammatory cytokines. It is produced by macrophages during inflammation and can also be activated by the endotoxin lipopolysaccharide (LPS). TNF-α controls the growth of normal and neoplastic cells, has a profound effect on the expression of genes related to cell differentiation, and influences the function of different cells.

TNF-α has been shown to play a role in the pathogenesis of various inflammatory diseases, such as rheumatoid arthritis, Crohn's disease, spondyloarthropathies, psoriasis, systemic lupus erythematosus (SLE) or antiphospholipid syndrome, as well as in atherosclerosis, diabetes mellitus, and metabolic syndrome [1]. In pregnancy, TNF-α influences hormone synthesis, placental architecture, and embryonic development [2]. It was also shown that increased levels of TNF-α are associated with pregnancy loss [3] and preeclampsia [4].

The mother-fetus interaction requires a perfect synergy between the maternal immune system and inflammatory responses, which allows for the immune adaptation of the fetus and, at the same time, maintains immune responses at a level that confers protection from potential infections.

TH1 and TH2 cytokine homeostasis allows for embryo implantation and normal pregnancy outcomes. At the early stages of normal pregnancy, Th1 pro-inflammatory cytokines are necessary for the stimulation of new vessels for successful embryo implantation [5]. However, prolonged exposure to Th1 cytokines may result in a cell-mediated immune response, which is harmful to the fetus and may cause spontaneous abortion [6].

It was noted at the beginning of the twenty-first century that the expression of Th2 cytokines, the anti-inflammatory interleukin IL10 in particular [7][8][9], was increased in normal pregnancy, whereas women after pregnancy loss presented a higher expression of Th1 cytokines [10]. The expression of cytokines, as well as the resulting immune response, may also be the result of cytokine gene polymorphism. Thus, cytokine gene polymorphisms can potentially contribute to the risk of recurrent miscarriage, especially gene polymorphisms associated with pro-inflammatory cytokines such as TNF-α, Il-1, Il-6, and IFNG [11][12][13][14][15]. TNF-α may directly promote tissue

damage in pregnancy, as suggested by in vitro studies where TNF-α activated maternal monocytes bound to LFA-1 on placental syncytiotrophoblasts and induced apoptosis [16]. Maternal blood levels of TNF-α during pregnancy increase in direct proportion to the stage of pregnancy, as well as in the postpartum period [17][18].

Increased TNF-α levels have been shown to be associated with a number of adverse effects, such as gestational hypertension and gestational diabetes mellitus (GDM) [18][19]. Increased TNF-α levels in complicated pregnancy draw attention to trophoblast biology, especially migratory activity, syncytialisation, and endocrine function [20][21].

Additionally, elevated TNF-α levels may affect the maternal-fetal relationship by altering the secretory profile of placental immunomodulatory factors, which in turn affects maternal immune cells. Indeed, literature data suggest that trophoblast-derived factors can induce the differentiation of peripheral blood monocytes into macrophages [22], as well as increasing recruitment and differentiation of inducible regulatory T cells (Treg) [23].

To conclude, the placenta is an immunomodulatory organ that regulates both local (embryo implantation) and systemic immune responses [24]. The highly differentiated syncytiotrophoblast is an integral part of the placenta, and the barrier connecting the placental villi with the maternal blood directly exposes the fetus to maternal cytokines.

Diseases that release inflammatory (e.g., TNF-α) and immunomodulatory factors, such as chronic inflammatory rheumatic, gastroenterological, or dermatological diseases, may result in the abnormal release of cytokines and chemokines in syncytiotrophoblasts. There is growing evidence that metabolic/pro-inflammatory cytokines can program early placental functions and growth in the first trimester of pregnancy [25]. Furthermore, early pregnancy placenta has a direct impact on fetal development and the maternal immune system [26]. Homeostasis of pro-and anti-inflammatory cytokines is the subject of interest of many scientific studies. Maintaining this fragile balance between pro- and anti-inflammatory factors is crucial for successful implantation and normal pregnancy outcomes. Recent studies have shown a shift in the cytokine profile of the human placenta in the first trimester of pregnancy towards increased levels of GM-CSF, CCL5, and IL10 in response to increased maternal TNF-α levels, while IL-6 and IL-8 remain unchanged [27].

2. Rheumatic and Gastroenterological Diseases in Pregnancy

A total of 80% of patients with chronic inflammatory rheumatic, gastroenterological and dermatological diseases are at a reproductive age.

Pregnancy poses a challenge in the treatment of chronic disease in patients who plan to have children. The activity of the disease, the impact of pregnancy on the course of the disease, and the safety of pharmacotherapy, including anti-rheumatic agents, in pregnancy, should be considered.

Sustained clinical remission of the underlying disease is the ideal time for conception. A recently published meta-analysis in pregnant patients with rheumatoid arthritis (RA), which was based on 10 different studies (a total of 237 pregnant and 135 puerperal patients), showed that the activity of RA decreased in an average of 60% (40% to 90%) of pregnant patients, whereas exacerbation was observed in 46.7% (39% to 70%) of puerperal patients [28][29].

The majority of retrospective studies showed no effects of RA activity on pregnancy. It should be noted that further studies (at least three) have shown that infants born to mothers with RA present with lower birth weight, although the majority are within the normal range [30][31][32]. A relationship was found between RA exacerbation during pregnancy and the low birth weight of the child. Data on psoriatic arthritis are very limited and are based on single, prospective studies where exacerbations were reported for approximately 22%, unchanged psoriatic arthritis (PsA) activity for 50%, and reduced symptoms for 28% of pregnant women [33].

For seronegative spondyloarthritis (SpA), literature reviews (mainly retrospective studies) have shown highly varied, controversial, and ambiguous data [34]. About 80% of pregnant patients with SpA present with stable disease activity or worsening of symptoms, which often improve during the third trimester. However, deterioration is observed after delivery (6–12 weeks after delivery) [35][36]. Zbiden et al. showed that 78% of women with axial spondyloarthritis (axSpA) experienced disease exacerbation in pregnancy, especially in the second trimester [37]. This risk is increased in patients who are not in remission at conception, those with elevated acute-phase protein (CRP), especially at 20 weeks gestation (second trimester), and women who discontinued anti-TNF-α therapy once pregnancy was confirmed [38][39].

Discontinuation of TNF-α inhibitor treatment itself causes a 3.08-fold increase in the risk of disease exacerbation throughout pregnancy in women with axSpA. Interestingly, patients without preconception exposure to anti-TNF-α also experienced high persistent disease activity from the preconception period until postpartum [40].

The Visual Analog Scale (VAS) indicated more severe pain in pregnant patients with ankylosing spondylitis (AS) compared to those with RA [29]. It should also be emphasized that standard methods for pain measurement are of no use in pregnancy because the non-specific lumbosacral pain may worsen, especially in the third trimester [29].

Studies on inflammatory bowel diseases (IBDs) deliver much more epidemiological data.

A large prospective multicenter study (PIANO), which included over 1475 pregnant women with IBD, showed a higher rate of ulcerative colitis activity compared to Crohn's disease activity during pregnancy [41][42]. A hypothesis of overlapping immune pathways, including the production of pro-inflammatory cytokines by the placenta [43], was proposed as a potential explanation [43].

Additionally, the risk of exacerbation during pregnancy was 20% for Crohn's disease and 33% for ulcerative colitis among women with IBDs who had remission of their underlying disease at conception [42][43].

A meta-analysis in 1475 patients with IBD (PIANO) showed a strong correlation between disease activity during pregnancy and disease activity in general [42][43]. Disease exacerbation affects 46% to 55% of women who conceived during active IBD compared to 23% to 29% of pregnancies started during remission. The rates of IBD relapse during pregnancy are generally similar to those for non-pregnant women [44]. Exacerbation during pregnancy and puerperium may be associated with discontinuation of disease-modifying therapy [45][46]. Therefore, optimized care, patient awareness, appropriate disease treatment, and control prior to conception helps maintain IBD remission throughout pregnancy.

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