

# IL-10, HLA-G and Neutrophil Extracellular Traps as Immune Regulators in Recurrent Pregnancy Loss

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## ABSTRACT

Recurrent pregnancy loss is a main reproductive health issue. There are several known causes such as endocrine and structural uterine abnormalities, chromosomal aberrations, genetic variants causing acquired thrombophilia and alloimmune rejection. A normal immunological homeostasis is needed to avoid reject of the fetus. Genetic polymorphisms in IL-10 and HLA-G as well as Neutrophil Extracellular Traps release could represent the underlying mechanisms of recurrent pregnancy loss, both spontaneous and after *in vitro* fertilization technique.

## Introduction

Recurrent pregnancy loss (RPL) is an important reproductive health issue defined as two and more failed pregnancies and it represents one of the most frustrating and difficult areas in reproductive medicine because the aetiology is often unknown and there are few evidence-based diagnostic and treatment strategies [1,2]. There are several known causes of RPL as karyotype, endocrine, structural uterine abnormalities as well as immunologic causes [3]. During pregnancy the immune responses must be rigorously controlled since the maternal immune system is in close contact with the cells of the semi-allogenic fetus and a normal immunological homeostasis is needed to avoid reject of the fetus [4,5].

### Interleukin 10 (IL-10)

The anti-inflammatory cytokine interleukin 10 (IL-10) is secreted by various innate and adaptive immune cells, such as Th1/2 lymphocytes, B lymphocytes and macrophages [6]. The IL-10 produced by cytotrophoblasts and decidual T cells plays a crucial role in human reproduction regulating the fetal-placental immune interface [7-9]. Some single nucleotide polymorphisms (SNPs) in the proximal region of the IL-10 gene were involved in the transcription rate of IL-10, directly affecting its production level

[10,11]. Among these, those correlated with the onset of abortive events are 1082 G/A, 819 C/T and 592 C/A [12]. The combinatorial haplotype of these 3 SNPs produces a lower plasma concentration of interleukin 10 in the bloodstream, resulting in pro-inflammatory signals at the placental maternal-fetal interface [13].

### Human Leucocyte Antigen-G (HLA-G)

Human Leucocyte Antigen-G (HLA-G) molecules have immunomodulatory, anti-inflammatory and tolerogenic functions [14]. HLA-G antigens play a key role in immune suppression at the maternal-fetal interface, they are expressed primarily by cytotrophoblast cells during the first trimester of pregnancy [15] and protect the semi-fetal allograft from lysis by maternal NK cells [16]. Relatively high levels of circulating HLA-G in maternal blood have been observed throughout pregnancy [17-19]. It has been reported that two polymorphisms in the untranslated region 3' (UTR) in exon 8, the insertion of 14 base pairs (bp) and the HLA-G G3142C polymorphism particularly affects the stability of HLA-G mRNA with lower levels or even absence of serum HLA-G [20-22]. This reduction leads to an immunological intolerance of the mother towards the embryo and therefore increases the probability of failure or abortion in the embryo implantation and recurrent miscarriage [23-26].

## Neutrophil Extracellular Traps (NETs)

Upon infection of viruses, bacteria and fungi, neutrophils become activated and in addition to the well-known mechanisms of phagocytosis and degranulation, they can extrude neutrophil extracellular traps (NETs) with a multistep process termed NETosis [27-29]. NETs are extracellular webs composed by double stranded DNA and decondensed chromatin and they are enriched of citrullinated histone H3 along with granules of myeloperoxidase and neutrophil elastase [30]. In addition to their function as a host defence mechanism, a growing body of evidences indicate that NETS could have a role in promoting thrombosis [31], cancer metastases [32-35] as well as different immunological conditions such as systemic lupus erythematosus (SLE) [36] and rheumatoid arthritis (RA) [37]. NETs appear to be involved in various stages of the reproductive cycle, with a crucial role in fertility as well as recurrent pregnancy loss [38]. During pregnancy, placenta can release inflammatory cytokines and debris activating neutrophils to form NETs, which may lead to an occlusion of the intervillous space and promote a condition of placental hypoxia leading to pregnancy loss [39]. Moreover, a growing area of research is now based on male factors that could be involved in the infertility. Neutrophils can interact with the semen in the female reproductive tract and in turn release NETs that could operate through a double effects consisting in phagocytize less motile spermatozoa or entrap them [38,40].

## Conclusion

Maternal immune system is crucial in recognizing the fetus as non-self. Genetic polymorphisms in immune key molecules such as IL-10 and HLA-G were associated with RPL and cortisone-based therapy at different dosology could be used. Role of NETs in women experienced RPL should be taken in account also because these traps could interfere with the physiological role of spermatozoa, highlighting the importance also of the male partner in the RPL pathophysiology.

## Competing Interests

No conflicts of interest exist.

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