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Review

Cutting edge assessment of the impact of autoimmunity on female reproductive success☆

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ABSTRACT

There, likely, is no more controversial issue in reproductive medicine than the effects of autoimmunity on female reproductive success. Published studies are, therefore, often biased. We performed PubMed, Google Scholar and Medline searches for the years 2000–2010 under various key words and phrases, referring to effects of autoimmunity/autoimmune diseases on pregnancy/pregnancy outcomes/pregnancy rates/reproduction/reproductive outcomes/fertility/infertility/fertility treatments/infertility treatments, and a number of similar terms. Reference lists of selected manuscripts were evaluated for additional, potential references. All selected manuscripts were reviewed by at least one author (N.G.). Opinions were reached based on preferential review of only selected studies, which offered data, primarily developed in pursuit of unrelated scientific questions. Data from various medical fields point, surprisingly effectively, toward significant impacts of autoimmunity on female reproductive success. Autoimmunity not only increases miscarriage risks but also reduces female fecundity and infertility treatment success. A, likely, reason why differences of opinion have persisted is that effects are primarily observed in genetically predisposed women, with specific fragile X mental retardation 1 (*FMR1*) genotypes. This discovery coincides with recently increasing appreciation of the importance of the long arm of the X chromosome (Xq) in control of functional ovarian reserve (reflective of female fertility) and autoimmunity, with *FMR1* at Xq27.3, located at cross roads of both. Autoimmune effects on female reproductive success deserve recognition. Further investigations must not ignore patient stratification, based on ovarian *FMR1* genotypes. Genetic definition of high-risk patients should lead to development of successful therapeutic interventions.

1. Introduction

Few subjects in reproductive medicine have over decades remained as controversial as the topic of this manuscript. Repeatedly reviewed [1,2], including by these authors [3–5], profound disagreements have not been overcome [6]. Since whether autoimmunity affects reproductive success is difficult to study, creative approaches may help. Studies with unrelated purposes, at times, offer unintended contributions. Here presented review will concentrate on such studies.

This will, therefore, not be yet another all-encompassing review of the subject but, by design, a selective review of data, often generated by investigators in unrelated medical fields, not influenced by prevailing conflicts amongst reproductive endocrinologists, rheumatologists and immunologists [6].

The concept for this review arose based on personal experiences of these authors, who in pursuit of completely unrelated research interests, unexpectedly, developed relevant information to this subject, published elsewhere [7], but included in this review.

Abbreviations: BM15, bone morphogenic protein-15 gene; *FMR1*, fragile X mental retardation 1; FoxP3, Forkhead Box p3; *het*, heterozygous; HIGM, immunodeficiency with hyper-IgM; HLA, histocompatibility locus antigen; *hom*, homozygous; IPEX, Immunodysregulation Polyendocrinopathy and Enteropathy; IVF, in vitro fertilization; MHC, mixed histocompatibility complex; *norm*, normal; PCO, polycystic ovary; POF, premature ovarian failure; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; POI, primary ovarian insufficiency; WAS, Wiskott-Aldrich syndrome.

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2. Materials and methods

This manuscript presents a selective review of, in principle, between 2000–2010 published studies, addressing the question whether autoimmunity affects spontaneous female reproductive success and success after fertility treatments. Literature review was selective because it concentrated on interpretation of data, not developed in scientific pursuit of this question and, therefore, considered, likely, less biased.

The medical literature was searched via PubMed, Google Scholar and Medline under key words and phrases, referring to effects of autoimmunity/autoimmune diseases on pregnancy/pregnancy outcomes/pregnancy rates/reproduction/reproductive outcomes/fertility/infertility/fertility treatments/infertility treatments, and a number of similar terms. The references of so discovered studies were then further reviewed for additional relevant papers. More than one author reviewed most of the selected manuscripts, but all were reviewed by N.G. Data selection for presentation in this manuscript was unanimous.

Because of its format, this study did not require prior review and approval by the center's Institutional Review Board.

3. Some basic facts about autoimmunity in reproduction

Definition of pregnancy as a semi-allograft is the most basic building stone in discussing autoimmunity and reproduction [8]. Embryo implantation is immunologically akin to transplantation of a complex tissue allograft into a recipient. Since most pregnancies deliver without complications, tolerance induction apparently works impeccably in most.

Since all physiological processes do, however, fail sometimes, it is virtually certain that tolerance induction in pregnancy will so, too [9,10]. Such failure has to be clinically expressed, and will vary depending on time of gestation when failure of tolerance occurs.

Clinical manifestations of allogeneic tissue transplants failure are well described [11]. Similarities with failure to develop normal tolerance toward the fetal semi-allograft can be expected. For example, early immunologically-induced pregnancy loss and preeclampsia/eclampsia, likely, represent tolerance failures, and compare to graft versus host disease [11].

Disturbed allogeneic transplantation tolerance is often accompanied by autoimmune phenomena [9]. Pregnancy, too, appears in genetically predisposed women associated with increased autoimmunity, inducible by implantation, and leading to miscarriages [9,11]. Similarly, preeclampsia/eclampsia is associated with autoimmune laboratory findings [9].

Original observations, linking autoimmunity to reproductive success, were first made on a medical ward, noting excessive miscarriages in women with lupus anticoagulant, hospitalized for thrombotic events [12]. Associations were then expanded to other anti-phospholipid antibodies and polyclonal B lymphocyte activation, in general [13].

Even skeptics about autoimmunity accept an association between autoimmunity and increased miscarriage risks [1,2]. Disagreements commence about how close this association is, and whether it also applies to conception; i.e., whether autoimmunity adversely affects fecundity and fertility treatment success.

Uninterested parties in the dispute have reported considerable evidence that fecundity is decreased with different autoimmune diseases [14], and that this decrease precedes clinical diagnosis of disease by years [15]. Even subclinical autoimmunity, therefore, appears capable of reducing fecundity [15]. Highest decibels between opposing opinions were, however, reached because nobody was able to demonstrate effects of autoimmunity on infertility treatment outcomes [16–18]. Development of such evidence could, therefore, potentially change minds.

4. Tolerance induction

Sir Peter Brian Medawar (Nobel Prize in Medicine and Physiology in 1960), by many considered father of transplantation immunology and clinical organ transplantation, already in 1953 pointed out that pregnancy requires tolerance against paternal antigens, expressed by the fetal-placental unit [19]. More recently, the liver transplantation pioneer, Thomas Starz (and co-workers), discovered that long-term cell chimerism in donor organs and recipients, likely, is essential for graft success [20].

Bi-directional chimerism has also attracted attention in pregnancy physiology and in association with autoimmunity. Both subjects, indeed, intertwine because microchimerism is suspected of inducing autoimmunity [9,11,21], and a possible cause for the high autoimmune prevalence in women [22]. In analogy to Starzl's hypothesis in liver transplants, bi-directional microchimerism between mother and offspring can, therefore, be presumed essential for tolerance of the semi-allograft of pregnancy [21].

So-called Tregs, $CD4^{+}CD25^{+}$T regulatory cells, represent a specific subpopulation of T lymphocytes, with great importance in preventing autoimmunity and affecting tolerance in allogeneic transplantations [23–25]. Forkhead box p3 (*FOXP3*) is an essential transcription factor for the induction and the development of Tregs [26]. Mutations in *FOXP3* are associated with severe immune dysregulation, including autoimmune manifestations, like polyendocrinopathies [5] and the X-linked Immunodysregulation, Polyendocrinopathy and Enteropathy (IPEX, MIM: 304930) syndrome (see also below, the X chromosome) [27].

Reaffirming the functional closeness of autoimmunity with tolerance of the semi-allograft of pregnancy, $CD4^{+}CD25^{high}$ T cells increase early in normal pregnancy [28,29] and then fall again after delivery [30]. Mei et al. recently reaffirmed characteristically low-$CD4^{+}CD25^{high}$ T cells and *FOXP3* expression in unexplained repeat aborters [31]. Tregs, thus, appear to play a significant role in tolerance of the semi-allograft of pregnancy [8].

Pregnancy tolerance appears to favor HLA incompatibility between both parents, as excessive compatibility has been associated with miscarriage risk [32] and induction of autoimmunity in predisposed females [33]. While in allogeneic transplantation good HLA matches between donor and recipient used to be considered essential, this is no longer the case [34,35].

The most important difference between these two states of immunological tolerance may, however, lie in the temporary nature of the pregnancy semi-allograft. The intent of allogeneic surgical transplants is induction of permanent tolerance toward the graft. The biological intent of tolerance of the products of conception is temporary tolerance for an average period of only approximately nine months.

Indeed, reversal of tolerance has been suggested as a potential labor-inducing event [11,36,37]. That the induction of labor may, indeed, be related to immunological processes, is supported by a number of recently published studies, investigating premature labor. For example, autoimmune diseases are, almost uniformly, associated with increased prematurity risk [36]. And twin pregnancies, involving a male offspring, have shorter pregnancies than twin pregnancies involving only female fetuses [38,39]. Yet, studies of fetal microchimeric implants from offspring demonstrate that they can survive in maternal tissues for decades, and have been suggested to lead to autoimmunity [21].

An immune system, attempting to induce/maintain tolerance, thus, appears at significant risk for autoimmunity. In tissue transplantations this is reflected in autoimmune manifestations with