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The impact of abnormal autoimmune function on reproduction: Maternal and fetal consequences

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Abstract

The impact of abnormal autoimmune function on reproductive success has remained a highly controversial issue. This is, at least partially, due to the relative lack of demographic data from women with established autoimmune diseases. We, therefore, investigated 163 women with proven autoimmune diseases and 73 controls in a demographic study of reproductive success and impact of abnormal autoimmunity on pregnancy and offspring. Women with autoimmune diseases experienced fewer pregnancies overall ($p = 0.04$) and fewer pregnancy losses ($p = 0.05$). Offspring from women with autoimmune diseases demonstrated a significantly increased prevalence of *confirmed* autoimmune diseases ($p = 0.04$; OR 3.759; 95%CL 1.04–1.27), which increased further if suspected, but not yet confirmed, cases were added ($p = 0.001$; OR 8.592; 95%CL 1.05–55.0). Women with autoimmune diseases exhibited a trend towards lower cesarean section delivery during their own birth and a significantly increased prevalence of disease in vaginally delivered offspring ($p = 0.014$; OR 6.041; 95%CL 1.32–38.22). Autoimmune diseases impair female fecundity even before the diseases become clinically overt. Offspring are at increased risk to develop autoimmune diseases, though they may differ from those of their mothers. This risk appears to correlate with mode of delivery and may be the consequence of varying cell traffic dynamics with vaginal and cesarean section deliveries.

Keywords: Autoimmune diseases; Fertility; Fecundity; Microchimerism; Cell traffic; Miscarriages

1. Introduction

The impact of abnormal autoimmune function on reproductive processes has remained under dispute. As a consequence, many basic questions, frequently asked by patients, have remained without answers. Amongst those, the most controversial is whether abnormal autoimmune function reduces the chance of reproductive success. Consensus has probably been reached that abnormal autoimmune function may increase the risk of pregnancy loss [1–4]. Whether the chance of conception is also affected has, however, remained subject to fierce disputes [5].

While it is well recognized that autoimmune diseases are *familial* in occurrence [6], the exact risk that children of mothers with autoimmune diseases carry to develop an autoimmune disease is not yet well defined. Moreover, it is unknown whether that risk is purely the consequence of polygenetic inheritance, the suspected mode of inheritance for most autoimmune diseases, or is also affected by environmental factors, which are potentially under men's control.

An environmental factor of potential significance is the mode of delivery. Whether a child is delivered by vaginal or cesarean section delivery, greatly affects the dynamics of cell traffic between maternal and fetal compartments [7–10]. Cell traffic, in turn, defines the subsequent chance and degree of

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microchimerism of donor cells within a recipient organism. Such *microchimerism* has recently been widely implicated as a possible contributing cause to the occurrence of autoimmune diseases [11,12], though it may also represent an absolute prerequisite for donor allograft transplant acceptance [13] and may, therefore, help in our understanding of the immunological acceptance of the fetal allograft by the maternal immune system.

This study was conceived to address all of these issues based on the controlled evaluation of a reasonably large number of middle-aged women with confirmed diagnoses of autoimmune disease and their offspring.

2. Materials and methods

A total of 346 women responded to print advertisements placed in Chicago newspapers, seeking out women with confirmed autoimmune diseases (Study group) and, separately, women with no medical problems (Control group). Both groups were asked to limit responses to women of an age range between 25 and 55 years and were solicited to respond to the advertisement with the statement that "*their participation would contribute to a better understanding of autoimmune diseases*". Amongst those who responded 236 (68%), after an initial confirmatory interview by a staff person, were considered eligible to participate as either Study or Control patients.

In order to qualify as a Study patient, the female (i) had to be able to name at least one autoimmune condition by name, she had been diagnosed with by a physician (some patients carried more than one disease diagnosis); (ii) had to be able to identify by name and address the physician who made the diagnosis of her autoimmune disease(s); and (iii) had to be able to name the year when her first diagnosis had been reached. Control patients, in order to qualify, had to confirm that (i) they suffered from no chronic medical conditions; (ii) were not under the active care of a physician; (iii) had not been under the active care and/or on any medication (beyond one week duration) over the preceding 5 years (except for pregnancy-related treatments); (iv) had not undergone hospitalizations (except pregnancy and/or accident related); and (v) specifically denied the past diagnosis of *any* medical condition. They were queried in detail on whether they were ever suspected and/or diagnosed with an autoimmune disease, autoimmune condition and autoimmune abnormality, and were read a list of specific autoimmune diseases for denial.

All interviews were conducted by a specifically trained staff person (R.W.) by telephone, following a written out script questionnaire. Amongst 236 qualified participants, 163 entered the Study- and 73 the Control-group. Both of these groups were statistically similar in ages (49.3 ± 11.9 and 49.4 ± 14.0 years; $p = 0.95$). They were also identical in racial distribution ($p = 0.91$) and in their degree of college education ($p = 0.96$).

All responses were recorded by the research assistant onto a questionnaire and then transferred into a computerized data bank. The data were analyzed using a standard statistical computer package, with comparisons between the groups made with independent 2×2 contingency tables and *t*-tests, where applicable. Significance was defined as $p < 0.05$.

3. Results

The 163 women with autoimmune diseases reported 184 specific autoimmune conditions (Table 1). Amongst those, 133 (72%) represented the four classical autoimmune diseases systemic lupus erythematosus, rheumatoid arthritis, scleroderma and Sjögren syndrome.

Women in the Study group reported significantly fewer pregnancies (2.3 ± 1.9) than Controls (3.0 ± 2.8; $p = 0.04$), though this difference lost statistical significance by the time of delivery when Study patients reported 2.8 ± 2.2 and Controls 2.3 ± 1.2 children ($p = 0.08$). This loss of significance was due to the surprising finding of a statistically higher rate of pregnancy loss in Controls (33.2%) than Study patients (30% $p = 0.05$), as shown in Table 2.

Offspring from women with autoimmune diseases demonstrated a significantly higher prevalence of autoimmune diseases (5.0%) than offspring of controls (1.4%; $p = 0.04$; OR 3.76; 95%CL 1.04–1.27). This finding became even more pronounced when symptomatic, though diagnostically yet not confirmed, children were added to the consideration. Such children were found in 5.7% of Study group offspring and 0% of Controls ($p = 0.001$), resulting in a combined prevalence of confirmed and suspected autoimmune diseases of 10% in Study offspring and 1.4% in Controls ($p = 0.001$; OR 8.592; CL 1.05–53.0), as also summarized in Table 3.

The autoimmune diseases reported in offspring, however, only rarely mimicked those of their mothers (Table 4). Only 4 out of 15 children with specific autoimmune diseases (27%) demonstrated the same disease as their mothers. All others exhibited other autoimmune diseases, with the high prevalence of Type-I diabetes mellitus (6/15; 40%) being of particular note.

Probably in a reflection of age, and the obstetrical practice patterns at that time, cesarean section deliveries for the mothers,

Table 1
Autoimmune diseases reported in Study group

Diagnosis	Number of cases[a]
Systemic lupus erythematosus	57
Rheumatoid arthritis and associated disorders	44
Scleroderma	20
Sjögren syndrome (Sicca syndrome)	12
Thyroid disease	7
Crest syndrome	6
Autoimmune liver disease	6
Dermatomyositis	5
Antiphospholipid antibody syndrome	5
Mixed connective tissue disease	4
Raynaud's syndrome	4
Polymyositis	4
Vitiligo	3
Myasthenia gravis	2
Immunologic thrombocytopenia	2
Type-I diabetes mellitus	2
Behcet's disease	1

[a] The number of diagnoses exceeds the number of patients since some patients reported more than one diagnosed autoimmune disease.