Autoimmune pathology and pregnancy: crucial issues

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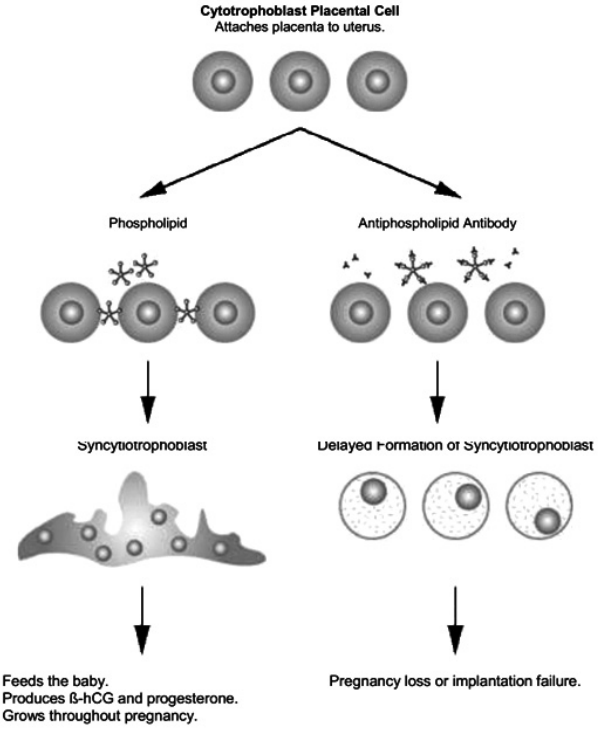
Autoimmune diseases, do not begin at the time of clinical appearance, but rather many years before that. The identification of positive autoantibody serology in an asymptomatic individual might allow immunological treatment whereby disease is prevented. New prospective studies are needed in order to assess the predictive value of antibody testing, as well as the means to apply them to clinical management of healthy population and high-risk individuals.
Kew words: *autoimmune diseases, autoantibody serology, immunological treatment, antibody testing.*

In XXI century autoimmune diseases, taken as a group, are the third leading cause of morbidity and mortality in the industrialized world, only surpassed by cancer and heart disease [1, 2, 5]. The great attention attracted to autoantibodies and autoimmune pathology is being explained that many autoimmune diseases are characterized by the presence of autoantibodies that **precede the overt disease** by months or years [6]. For example, the presence of two islet cell antibodies (ICA) are associated with a 50% risk of future development of diabetes mellitus in 5 years, anticyclic citrullinated (anti-CCP) antibodies are found in the sera samples of rheumatoid arthritis (RA) patients a median of 4.5 years before the overt disease, and in systemic lupus erythematosus (SLE), patients the specific antibodies are stated before 3–4 years prior to the clinical symptoms. So the screening healthy women for autoantibodies could help in prediction of autoimmune diseases, or rather their clinical manifestations [1, 2, 5, 6].

Autoimmune pathology appears to play the decisive role in adverse pregnancy outcomes. It was found out, that certain autoimmune disorderss, such as SLE, are associated with pregnancy loss. Since the end of the XX century physicians paid attention on negative pregnancy outcomes in women with antiphospholipid antibodies (APLA) and the antiphospholipid antibody syndrome (APS) (Picture 1).

The APS diagnosis is being established on the background of clinical and laboratory data, including fetal wastage in the presence of high levels of anticardiolipin antibodies. Afterwards it was raising interest in investigation of other autoimmune pathology and various specific autoantibodies as possible causes of pregnancy loss. It was an attempt to establish a linkage between recurrent pregnancy loss and the presence of a specific type autoantibody or patterns of autoantibodies [1, 2].

It is greatly important that some primary APS patients may develop SLE or any other autoimmune diseases, so having secondary APS. A retrospective study following 128 primary APS patients for a mean follow-up period of 9 years has investigated this notion. The data testify that during the follow-up and after a median disease duration of 8.2 years (range, 1–14 years), 11 (8%) patients developed SLE, 6 (5%) – lupus-like disease, and 1 (1%) – myasthenia gravis. In future 110 patients (86%) continued to have primary APS. Analysis of the risk factors related to the development of other autoimmune diseases showed, that only the presence of Coomb's positivity had statistical significance (odds ratio, 66.4; 95% confidence interval [CI], 1.6–2714; P=0.027) and was associated with the development of SLE. The study also testified that progression from primary APS to SLE or lupus-like disease is looking like unusual [4, 7].



Picture 1. Role of APLA in pregnancy loss

The modern laboratory diagnostics of systemic lupus erythematosus (SLE) corresponding to autoimmune nature of diseases during pre-pregnancy and pregnancy period includes: test for anti-Ro/SSA and anti-La/SSB antibodies, lupus anticoagulant and anticardiolipin antibody studies, anti-double-stranded DNA (anti-dsDNA) test, complement studies (CH50 or C3 and C4 [6, 7].

In women with connective tissue disorders, taking into consideration SLE and some other autoimmune disorders (Sjogren's syndrome and rheumatoid arthritis), anti-Ro/SSA antibody (as the main pathogenic factor of congenital heart block) has been evaluated recently in the pathogenesis not only of disease's severity but of pregnancy loss [8].

For nowadays it is proved that anti-Ro/SSA-positive serum sample may contain two sets of antibodies, including a 60 kDa (Ro60) and a 52 kDa (Ro52) polypeptidic component of the Ro molecule. Additionally, there is a hypothesis, that IgG antibodies against a 57 kDa protein (p57) could become an additional risk factor in the pathogenesis of neonatal lupus syndrome.

The results of [8] testified about a correlation between recurrent pregnancy loss and the levels of Ro/SSA peptides, revealed in the samples of the sera of autoimmune women. The authors proved, that the rates of recurrent pregnancy losses differed significantly from 0% among women with no Ro/SSA peptides to 75% among women with all three peptides. In the same study it was identified that thyroid and cardiolipin autoantibodies didn't influence on the correlation between these proteins with adverse pregnancy outcomes.

These results could be considered as highly important,

Table 1

Autoantibodies as predictors of specific disease manifestations in SLE

Antibody	SLE manifestation
Anti-Heparin sulphate	lupus nephritis
Antinucleosome	lupus nephritis
Anti-Ro	neonatal lupus, congenital heart block
Anti-PL	pregnancy loss*, fetal growth retardation*, premature deliveries*, strokes*
Antiribosomal P protein	cerebritis, psychosis, depression

* – Disease manifestations when antibody is present during pregnancy.

Table 2

Pattern of appearance of autoantibodies predictive of SLE

Antibody	Mean years prior to clinical manifestation
Anti-PL	3.4 years
Anti-Ro	3.4 years
Anti-La	3.4 years
Anti-dsDNA	2. 2 years
Anti-Sm	1.2 years
Antinuclear ribonucleoprotein (anti-RNP)	1.2 years

because predominantly recurrent pregnancy losses in women with autoimmune pathology were absolutely associated with APLA [1, 6, 8]. The data obtained in the study [6, 8, 12] proved that namely anti-Ro/SSA patterns and antibodies against thyroglobulin, were greatly associated with pregnancy losses.

In pregnant women with SLE, the presence of anti-Ro antibodies also becomes a significant risk factor for neonatal lupus and congenital heart block, prompting more careful monitoring. Monitoring APLA has great significance in pregnancy due to increased risk of antenatal fetal death, IUGR, fetal loss and premature deliveries. It was shown that positive serology in pregnant women for anti-Ro and anti-La, has been found to be linked to future development of SLE and Sjogren's syndrome. The great importance of antibodies screening is that most of the mothers with such serological findings being clinically healthy at the time of delivery, will develop clinical SLE or SjËogren's syndrome in long-term follow-up (table 1, 2) [6, 9, 11].

Great attention has been paid to antinuclear antibodies (ANA) and their role in pregnancy loss, contributing in 22% of women with recurrent pregnancy losses and nearly 50% of women with infertility and IVF failures. The mechanism of action is that women with this problem make antibodies to DNA, or DNA breakdown products in the embryo or in the pregnancy. These types of antibodies form first in the blood as IgM, afterwards they appear as IgG and live in the lymphatic system and lymph nodes. These antibodies can be against pure double stranded DNA (ds – DNA), single stranded DNA (ss-DNA), or polynucleotides and histones that make up the single strands (Picture 2) [9, 12].

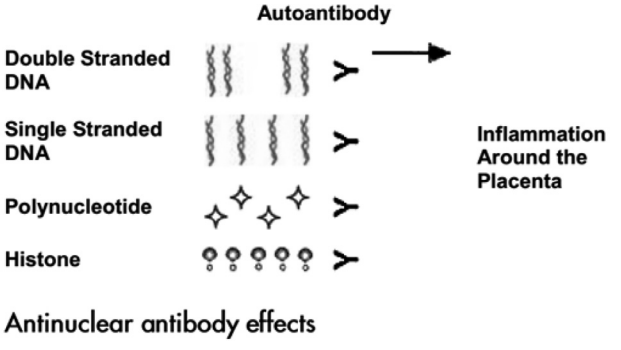
Any titer of ANA above 1:40 is clinically significant, sometimes the titers can get into the thousands such as 1:2,500 and they could be positive in women with lupus, rheumatoid arthritis, Crohn's disease and some other autoimmune diseases [6]. ANA directed against nuclear components of the cell are the most characteristic of SLE, but they have limited specificity [6, 9, 11].

Ticconi C. et al obtained the data those antinuclear antibodies (ANA) at titers ≥1:80 were detected in 97 (50%) women with recurrent pregnancy loss versus in 16 (16%) control women. Moreover, elevated ANA titers (≥11:180) were detected only in women with recurrent pregnancy loss, but all control women had ANA titers no more than 1:80 [10].

The effect of antiDNA antibodies for pregnancy development are explained by the exposure of human placentas to anti-DNA, which was previously shown to cross-react with laminin-1, resulted in significant disorders of trophoblast attachment and migration. Laminins are considered as basement membrane glycoproteins and believed to play an important role in the remodeling of endometrial stroma, which is the crucial step of the egg implantation into the uterus wall. The anti-DNA antibodies by their cross-reaction with laminin-1 (inhibiting this process) became the cause of pregnancy loss in SLE patients [10, 12].

Corrado A. et al. evaluated the prevalence of recurrent pregnancy loss in systemic sclerosis (SSc) patients and investigated the relationship with organ involvement, autoantibody profile and capillaroscopic abnormalities in these patients. As SSc is an autoimmune connective tissue disease, main features of which are: fibrosis, autoimmunity and marked microangiopathy, great attention should be paid to vascular damage, including digital ulcers, pulmonary arterial hypertension and scleroderma renal pathology. Otherwise, the increased risk of pregnancy complications, particularly pregnancy loss, and preeclampsia has been reported in patients with SSc, but there is lack of knowledge concerning the pathogenic mechanisms of these events and the potential role of microvascular disorders and autoimmunity is still unclear [3].

Their data obtained suggested that microvascular damage could be related with recurrent pregnancy loss in SSc, especially in anti SCL70+ and ACA+ patients. The authors concluded that antiphospholipid syndrome played a prominent role pre-



Picture 2. Role of ANA in pregnancy loss

dominantly in a subgroup of patients, revealed for particular autoantibody profile (Ab-), which presented less severe microvascular involvement [9, 11].

It is worse discussing the autoimmune thyroid diseases (AITD), which include Hashimoto's thyroiditis, juvenile thyroiditis, and Graves' disease. The meaningful feature for all AITD is a variable degree of lymphocytic infiltration of the thyroid gland along with antibody to thyroid tissue production.

There are the most important thyroid autoantibodies which are directed against: thyroglobulin (TG), thyroid peroxidase (TPO), and the TSH-receptor (TSH-R). The results of several studies have confirmed the prognostic value of anti-TG and antiTPO antibodies in prediction of autoimmune hypothyroidism [6, 7].

The odds ratio of developing hypothyroidism in individuals with positive thyroid antibodies and normal TSH has been shown in a 20-year follow-up: 8 for women and 25 for men. The predictive values increased to 38 and 173, respectively, in cases of subclinical hypothyroidism (elevated TSH levels and normal free T4). Pregnant women with anti-TPO antibodies found appeared to be in high risk of postpartum AITD, some data testified that in 50% of pregnant women with positive anti-TPO antibodies postpartum thyroiditis had been diagnosed [6].

The level of anti-TPO antibodies in a titer of 1:1600 or more at third trimester and delivery was proved to have a 97% sensitivity and 91% specificity for postpartum AITD. The data obtained became the background foro suggestions that all pregnant women should be offered antenatal screening for TPO autoantibodies, but there is still no any consensus on this issue. The presence of antibodies for thyroid tissue could be considered as a risk factor for the future development of AITD, and demands the careful TSH follow-up. It should be emphasized that the benefits of AbTPO screening in the general population or cohort of pregnant women have not been established [2].

Outcomes

1. The autoimmune diseases, considerably to the end-organ pathologies they could cause, do not begin at the time of clinical manifestation, but many years before.

2. The pregnancy period could exacerbate the course of autoimmune diseases and become the trigger for the development of somatic disorders, which might have the negative influence on the maternal and fetal health state, pregnancy outcome and perinatal morbidity.

3. The identification of autoimmune diseases in their latent preclinical stage has become feasible by autoantibody testing. which would allow to implement this ability for the treatment and possible prevention of autoimmune diseases. However, appropriate prospective studies are necessary for proper assessment of the predictive value of antibody testing, as well as for the means to apply this approach from «bench-to bedside» for clinical management of healthy population and high-risk cohort.

Аутоімунна патологія та вагітність: актуальні питання

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Процес розвитку автоімунних захворювань розпочинається значно раніше, ніж з'являються перші клінічні ознаки. Виявлення автоімунних антитіл за відсутності клінічних ознак захворювання дозволяє почати специфічну імуносупресивну терапію значно раніше, а також розробити відповідні методи профілактики. Необхідні подальші проспективні дослідження для оцінювання прогностичного значення антитіл-тестування у доклінічній фазі захворювання, особливо в групах високого ризику.

Ключові слова: *автоімунні захворювання, антитіл-тестування, імунологічне лікування.*

Аутоиммунная патология и беременность: актуальные вопросы

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Процесс развития аутоиммунных заболеваний начинается значительно раньше, чем появляются первые клинические признаки. Выявление аутоиммунных антител при отсутствии клинических признаков заболевания позволяет начать специфическую иммуносупрессивную терапию значительно раньше, а также разработать соответствующие методы профилактики. Необходимы дальнейшие проспективные исследования для оценки прогностического значения антител-тестирования в доклинической фазе заболевания и в группах высокого риска.

Ключевые слова: *аутоиммунные антитела, тестирование антител, иммунологическое лечение.*

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Статья поступила в редакцию 12.10.2014