

Maternal Immunity, Pregnancy and Child's Health

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1. Introduction

Why do women live longer, than men? Is gender-connected lifespan related to woman's ability to give a new life and partly depend on persistence of fetal cells in maternal tissues (microchimerism) [O'Donoghue, 2008]? On opposite side, childlessness leads to shortening of an average lifespan of women (<http://www.moscowuniversityclub.ru/home.asp?artId=5742>). Some believes, that pregnancy (if happens not too often) leads to mobilizing of the biologic reserves in woman organism and improves the general health state. The phenomenon could be related to positive influence of fetal and placental trophic factors, and besides, to receiving of fetal stem-cell powerful reparative-regenerative potencies. In any case, if result of pregnancy is appearance of a new life (child) and strengthening of the woman's health and longevity, then this phenomenon principally can not be considered from viewpoint of pathology. Accordingly, it seems quite incorrect to habitual using some of "fetal invasion", "maternal aggression", or similar terms, semantically associated with rather negative (pathological) events. Normal pregnancy should not be considered from confrontational positions, because such approach distort the biological sense of pregnancy. Maternal organism does not struggle against new life, but helps embryo with implantation, growth, development and maturation of the last. Moira Howes provides refined arguments for idea that maternal immune influences upon the fetus are principally lacking of aggressiveness, because during gestation mother and fetus are in essence not two but rather one complicated organism [Howes, 2007]. Pregnancy seems to be peculiar example of mutually beneficial co-assistance of two biological systems temporally functioning in frame of united super-organism.

Ideology of this kind may became very useful for explanation of many not yet explained facets of pregnancy, including immune phenomena related to maternal-fetal interactions. First of all, we should decline an habitual attitude to the pregnancy as situation of immune conflict between mother and fetus. From such point of view any forms of mutual aggression should be considered as the pathology which may lead to pregnancy losses.

Is any absurd in this view? Hardly so. Besides we have other bright and widespread phenomena, similar to some extend. For example, any healthy human organism together with its obligatory inhabitants (permanently presented variants of normal micro-flora:

“domestic” microbes) also may be considered as super-organism, whose biologically antigenic components function for mutual benefit. Commensal microflora of gut play principal role in digestion and utilization of food as well as in production of vitamins [Grubb et al., 1989]. It is worth mentioning, that only allied microorganisms provide us with vitamin B12, which plays a key role in the normal functioning of the brain and nervous system, and plays great role for the formation of blood. Vitamin B12 is normally involved in the metabolism of every cell of the body, especially affecting not only DNA synthesis and regulation, but also fatty acid synthesis and energy production [Lieberman, & Marks, 2008; Zaichik, & Churilov, 2008]. Interestingly, B12 can be produced only through bacterial fermentation-synthesis in digestive tract of animals and humans [De Baets et al., 2000].

Today we don't know the most of important details about mechanisms and principles of co-existence with our micro-inhabitants, in spite of fact that symbiotic microorganisms compose nearly 10% of human body weight [Levinson, & Jawetz, 2000]. Fortunately, genetic and antigenic foreignness of such “components” of our body per se, does not imply obligatory mutual struggle [Pradeu T., Carosella, 2006]. Moreover, biologic non-relative organism (normal microflora and host-organism), as well as partly relative (mother and fetus) components forms a new entity – quasi-united superorganism. Of special interest is the fact, that immune system provides the main instrument not for rejection, but for peaceful and mutually useful integration of different and autonomous organisms under the guidance of alive host super-organism [Parnes, 2004].

Due to the system mother-fetus could be considered as peculiar and specialized example of super-organism there is no immunological or any other conflict between integrated components (maternal and fetal compartments) *in normal condition*. In case of united superorganism there is no “foreignness” of integrated components. Nevertheless, in some pathological situations maternal-fetal interactions can become abnormal and can lead to pathology of pregnancy development. Unfortunately obstetricians meet with such pathological cases too often, and comprehension of the main aspects of maternal-fetal interactions from immunological point of view may be practically important.

2. Maternal immunity and pregnancy

Probably up to 40% of all desired pregnancies is interrupted spontaneously during initial 1-3 weeks after fertilization [Radhupathy, 1997]. Additionally 10-15% loss of pregnancies occurs later. Many pregnancies, interrupted at the initial stages, can be related to genetic aberrations [Balakhonov, 2001], but further losses seems related mostly to epigenetic reasons [Poletaev, 2008]. In general most of authors believe that genetic abnormalities are reasonable for nearly 5-13% of unfavorably results and nearly 90% of such cases is based upon other reasons, including changes in immune mechanisms [Radhupathy, 1997; Poletaev, 2008; Sukhikh & Van'ko, 2003]. Participation of the immune mechanisms in regulation of pregnancy is far from being fairly understood yet. However it should be noted that many of cytokines (interleukins, interferons, chemokines) and autoantibodies seem to be important factors involved in mechanisms of tissue's regeneration, growth and cells differentiation [Khaitov, 2002; Poletaev, 2010]. These observations may become a key for the future understanding of the issue from viewpoint of constructive (not destructive) impact of immunity in pregnancy development and fetus formation and maturation.

Historically, immunology emerged as a branch of applied microbiology, therefore “microbiological” approaches and accents have persisted for decades due to the fact that generations of specialists in immunology have been educated by microbiologists. From habitual (microbiological) point of view the pregnancy is a paradox. For solution of this puzzle more than half of century ago Peter Medawar proposed the hypothesis about inability to adequate recognize the “alien” fetus by the immune system of pregnant women – Medawar proposed that this phenomenon could be based upon combined mechanisms of maternal immune suppression and maternal-fetal immune tolerance [Medawar, 1953]. Unfortunately this speculation was too seriously perceived by many obstetricians as rather elevated activity of the immune system during pregnancy [Sacks et al., 1999; Kaštelan et al., 2010]. In his review Entrican specially noted, that pregnancy is accompanied by changes in different components of the immune system, but these changes should not be considered as signs of immune suppression [Entrican, 2002].

Evidently at early 50th Medawar could not think out of frames of traditional views – that is about activity of the immune system aimed to and restricted by searching and destruction of aliens. But now many immunologists re-evaluate the main predestination of the immune system. Nearly half of century ago Pierre Grabar proposed a homeostatic function of the immune system mediated by the natural autoantibodies [Grabar, 1968]. Some earlier, in thirtieths, an idea of the regulatory autoantibodies was mentioned by Karl Landsteiner [Landsteiner, Scher, 1936]. However the main prophet of the new immunological views became Elia Metchnikoff. He had claimed that it would be wrong to consider the immune system mainly as a gendarme of an organism. Its participation in a constant struggle Host-against-Parasite is no more a particular case of much more wide biological predestination of the immune system – dynamic participation in self-maintenance, self-reparation, self-optimization, and maintenance of organism’ harmony state under the constant pressure of the Environment [Metchnikoff, 1901]. Not *War but Peace* – or providing general homeostasis or “harmony” in Mechnikoff terms seems to be the main feature the immune activity [Matzinger, 2002; Poletaev, 2010]. Developing fetus is not inspected by the immune system as something hazard and does not became an object for attack in spite of evident non-selfness, but is considered by maternal organism as an object for integration. In this connection active maternal immune recognition of the fetus is an important and necessary condition for normal development of pregnancy [Howes, 2007]. In opposite side, if “the rate of recognition” of embryo and fetus by maternal immune system is too low - it may be reason for pregnancy losses. The last is typical for women with immune suppression related to different causes [Nyukhnin, 2007]. Moreover frequency of miscarriages is directly related to intensity of maternal immune suppression [Poletaev & Morozov, 2000].

More often general immune suppression in fertile women can be induced by chronic opportunistic infections (such as *Herpes viridae*, *Chlamidia*, etc.), and besides – by prolonged usage of some medicines, chronic intoxications, and chronic psychogenic stresses [Poletaev, 2008]. Situation of immune suppression may be associated with incomplete or insufficient fetal recognition by maternal immune system and with pregnancy loss. Frequent miscarriages are also common for women with genetical similarities to her spouse (in cases of marriage between relatives) because excessive similarities in MHC genes between spouses do not permit maternal immune system to recognize clearly the fetal-paternal antigens [Roberts et al., 1996]. Thus (in case of similarities in MHC patterns of mother, father

and fetus) women's immune system turns out to be lacking of full-fledged recognition of the fetus as well as an ability to provide an active maintenance for growth and development of the later.

3. Natural autoantibodies and the health state of the human organism

In recent twenty years clinical immunology was characterized by emerge of paradoxes *sui generis* contradicting to adopted positions of many physicians. As an example, puzzle of natural serum autoantibodies may be noted. The generation of autoantibodies against self-antigens is a common phenomenon in humans. Elevated autoantibody level earlier has been associated directly and exclusively with the pathogenesis of autoimmune diseases. Now it is common place that the rise of serum content of many autoantibodies also occur in the context of other diseases, not belonging to autoimmune ones, including strike, cancer, or complicated pregnancy [Backes et al., 2011; Poletaev, 2010]. Moreover, it was clearly demonstrated that natural a-Abs of IgG, and IgM classes against very different self-antigens had been permanently presented in the blood serum of any healthy person [Lacroix-Desmazes et al., 1998]. Experimental data indicates for roughly equal serum content of a-Abs with the same specificity in the vast majority of healthy individuals [Lacroix-Desmazes et al., 1998], and conversely, indicates notably deviations in production and serum content of particular a-Abs, related to primary molecular changes in the certain cell populations in different tissues and organs, accompanying the plurality of diseases [Poletaev & Churilov, 2010]. It is proved that production and secretion of natural a-Abs is regulated directly by the quantity/availability of respective antigens (by feed-back principle [Kovaliov & Polevaya, 1985]. It is based on the fact, that although expression/degradation rates of any cytoplasmic, membrane, or nuclear antigens in any specialized cells are individual, but at the same time they are similar and represent same relative level/pattern in any healthy person (with slight variation between individuals). Only minor variability in serum level of a-Abs with different specificity is typical for humans in the normal (healthy) state, but not for cases of pathology. Plurality of very different chronic diseases has been connected directly to steady abnormal changes in rates of apoptotic, necroptotic, or necrotic events, as well as to abnormalities in expression/secretion of multiple autoantigens. Such events lead to the changes in a-Abs serum content with according specificity (feed-back principle).

In other words versatile set of natural autoantibodies with different specificity, can be considered as immune fingerprints of molecular content of an entire organism, and mirrors the functional state of the different populations of cells. The general system of autoantibodies has been named earlier as "Immunologic Homunculus" [Cohen & Young, 1991], or "Immunculus" [Poletaev & Osipenko, 2003; Poletaev & Churilov 2010]. Immunculus can be considered as an internal image of the current functional-metabolic state of the body expressed in the terms (language) of quantitative alterations in the content of different autoantibodies. To some extent the Immunculus concept is similar to the concept of Neurological Homunculus, which is an internal image of the body's anatomical/physiological state reflected by the nervous system in the language of the spikes activity of the brain's neuronal nets [Cohen & Young, 1991]. However, in contrast to the dimensionally fixed and morphologically structured neuronal nets, the Immunculus is a dissipative system constructed not by the cellular but by the highly mobile molecular elements: very different autoantibodies presented in the blood, lymph, and interstitial fluid

in any spatial compartment of the body. Therefore, the content of autoantibodies with the different antigenic specificity may be considered as roughly the same in various compartments of the bloodstream. This feature permits us (at least potentially) to evaluate the functional-metabolic state of any organ (the heart, brain, liver, etc.) by measuring the content of autoantibodies with respected AG specificity (directed against cordial, brain, or hepatic AGs), presented in the same sample of the serum. Besides natural autoantibodies interacting with molecular structures of the self organism, represent one of the main instruments by which the immune system takes part in the control upon organism's homeostasis [Poletaev & Osipenko, 2003; Poletaev & Churilov 2010]. That is reflected by set of autoantibodies not only as passive "mirror" of the organism's state, but also as an active participator in tuning of the different physiologic functions, including clearance of organism from excessive producing molecular components and debris of dying cells [Poletaev, 2010]. The active regulatory function of the Immunculus has been clearly demonstrated by its participation in the mechanisms of regeneration of injured tissues [Poletaev, 2010]. The control and "tuning" functions of the Immunculus have been visible also in the processes of cellular differentiation and morphogenesis during early (fetal) ontogenetic development [Poletaev, 2008]. Regulatory, reparatory, and/or managerial functions of the Immunculus are illustrated by positive effects of the IVIG therapy in different pathologies (oncology, infection diseases, intoxications, neurology diseases, etc.) [Poletaev, 2008]. This kind of treatment, based on massive administration to the patient of immunoglobulines (autoantibodies), obtained from thousands of healthy donors, leads to the correction of the homeostasis and mitigates very different metabolic and functional deviations.

Serum content of various different autoantibodies is maintained in relatively common ranges (different for autoantibodies with each defined antigenic specificity) in any healthy person - in men and women. In opposite side, constant abnormal elevation or decreasing of some autoantibodies may be secondary reflection of primary tissue or organ pathology and may be used for estimation of clearance effectiveness in injured organ [Poletaev & Churilov, 2010]. More rarely primary abnormal rise of definite autoantibodies may become the background for autoimmune disease [Poletaev, 2010].

Bearing in mind the systemic (not summative) organization of autoantibody Network (Immunculus), it may be easily to comprehend, how it may reflect innumerable multiplicity of functional states of whole organism and its compartments. In this way, we would assume that reflection-recognition process of changeable and innumerable "antigenic images" of the body is based not upon changes of independent elements, but upon the whole immune network (Immunculus). In this context I would like to appeal to only two of quotations: "...The initial paradigm "one autoantibody for one disease" does not appear to be useful any longer. An autoantibody profile does seem to offer more diagnostic and prognostic power than the determination of single autoantibody specificity. The consequence is the use of new assays to detect different autoantibodies" [Meroni et al., 2007]. Backes C. and other [2011] wrote: "Instead of allocating single antigens to a specific group of diseases and even to a specific disease, it appears more appropriate to allocate seroreactivity patterns". This idea identification of autoantibody reactivity patterns, also addressed as autoantibody signatures that are highly specific for various diseases as shown by us and others". The main question is: how soon we will begin to learn very specific language which used the immune system for telling the wonderful story of dynamic changes of ours bodies?

4. Embryotropic antibodies

Serum content of any “embryotropic” autoantibodies [Poletaev, 2008] in healthy women was restricted by narrow limits (as well as for any other regulatory molecules). But at least in 90% of women suffered from habitual miscarriages, still births, or other forms of pathology of pregnancy, these parameters were changed prominently, and more prominent deviations in autoantibodies accompanied more often and severe reproductive problems [Poletaev & Morozov, 2000; Poletaev et al., 2007]. This phenomenon was successfully used for prognosis of result of planned pregnancy [Poletaev, 2010]. Question is – which of maternal autoantibodies of IgG class should be analyzed first of all (between thousands presented)? In accordance to reproductive function, it seems that abnormal changes in serum content of very different (practically any?) maternal autoantibodies may be causal factors of infertility, miscarriages, or other forms of pregnant pathology. That is to say, that plurality of autoantibodies (with any antigenic specificity) synthesized in mother’s organism could be considered as “embryotropic” if they belonged to IgG class. Nor IgM, nor IgA, or IgE penetrate the placental barrier [Landor, 1995]. However some of them could be more important.

Systemic autoimmune disorders, SLE in particular, are accompanied by prominent rise of infertility and pregnancy losses. The last phenomenon was so typical, that Gleicher as well as Sherer and Shoenfeld have recommended to consider the recurring miscarriages as indication for supposed autoimmune disorder yet undiagnosed in observed woman [Gleicher et al., 1995; Sherer & Shoenfeld, 2004]. Therefore obstetricians can’t overlook such a common marker of SLE and other systemic autoimmune disorders as elevated production of autoantibodies against DNA. Lot of publications about negative influences of anti-DNA autoantibodies upon pregnancy development appears yearly. However it is clear now that situation of excess of anti-DNA autoantibodies is no more than particular example of pathogenic immune influences in pregnancy.

Soon after having described antiphospholipid syndrome (APS) as defined nosology form, attention of obstetricians was draw to autoantibodies against phospholipides (cardiolipin, phosphatidilserin, phosphoinisitol, etc.) and against phospholipid-binding serum protein β 2-Glycoprotein I; antibodies against the last seemed to be the most informative marker of APS [Sherer & Shoenfeld, 2004; Roubey, 2006]. It should be noted, obstetricians had met APS long before the syndrome was described by G.R.V. Hughes. Because abnormal elevation of anti-cardiolipin autoantibodies was typical for patients with syphilis, and many years was used for diagnostic of syphilis (since 1906: Wasserman’ reaction). On other hand, it was known for decades that maternal syphilis was accompanied with rise of still-birth and miscarriage frequency in affected patients [Borisenko et al., 1998].

Fertility is strictly dependent on serum autoantibody level against DNA or cardiolipin, but also depends on changes in autoantibodies against luteinizing hormone, FSH, prolactin [Talwar, 1997], chorionic gonadotropin [Shatavi et al., 2006]. Premature ovarian failure can be accompanied by excessive production of autoantibodies against specific ovarian antigens [Tuohy & Altunas, 2007] and also autoantibodies against chorionic gonadotropin [Shatavi et al., 2006]. Relation to pathology of pregnancy could be associated with autoantibodies against PSG (pregnancy-specific glycoproteins) [Finkenzeller et al., 2000], against Mater (Maternal Antigen that Embryos Require) [Tong et al., 2004; Tuohy et al., 2007], and many others.

If we will take in mind that autoantibodies are biologically active regulatory molecules it will be evident, not only excessive production, but also shortages in many (any?) autoantibodies could lead to multiple deviations in gestation process, miscarriages and still-birth formation [Poletaev, 2008].

5. Opportunistic microflora as a cause of deviations in serum content of embryotropic antibodies

A lot of wide spreading conditionally pathogenic or opportunistic viruses and bacteria does not belong to the friendly or normal microflora. These inhabitants of the human organism are the most common ground for deviations of the immune system activity and steady changes in production and serum content of embryotropic autoantibodies. Such microbial agents can activate the different clones of immune competent cells, because members of *Herpesviridae* family (Herpes simplex virus, Epstein-Barr virus, Cytomegalovirus, etc) may implement the role of co-stimulators for CD4⁺ T-cells, and in their turn, lead to polyclonal activation of antibody-producing B-lymphocytes. Such intracellular bacteria as *Chlamydia*, *Mycoplasmae* and other, may activate B-cells directly (T-cell independent activation) by using mechanism of superantigens [Khaitov et al., 2002]. On the other hand the same microbes in one woman will induce immune deviations nearly inevitably, but in other one microbial influence will be minimal or nearly absent. This difference probably depends on individual genetic background, in particular from individual set of MHC molecules [Poletaev, 2008]. Therefore the fact of revealing of Herpes simplex viruses, Cytomegaloviruses, or *Mycoplasma hominis*, etc., by serological methods or by PCR is not the cause for obligatory prescription of treatment, but revealing of infection agents combined with induced immune changes should be. The situation provided the possibility of monitoring for antiviral or antibacterial treatment effectiveness by dynamic measuring of embryotropic autoantibodies [Poletaev, 2008]. In accordance to clinical observations in women suffered from habitual miscarriages [Serova, 2000] treatment directed to etiology can be the most effective if combined with the control on embryotropic autoantibodies in blood; and improvement of according immune parameters indicates for efficacy and sufficiency of used therapy [Serova, 2000].

Opportunistic microbial flora may induce not only abnormal immune activation, but also become direct cause of pathologic immune suppression, due to usage by microbes multiple molecular instruments for declining general activity of the immune system as important component of strategy of survival in the host-organism [Mayanskiy, 1999]. In their turn prominent maternal immune suppression may influence negatively the pregnancy development and sometimes can be fatal for the fetus [Poletaev, 2010].

Changes in serum content of autoantibodies, if appeared transitory (up to 2-4 weeks), do not influence prominently the fetus development, but long-term or constant prolonged changes may interrupts the pregnancy. Constant abnormal changes in serum content of autoantibodies is typical feature of many women with unexplained infertility (nearly 80-90% of all cases), including ones repeatedly unsuccessfully used IVF [Poletaev, 2010]. In such cases the immune anomalies can interrupt zygote implantation, as well as embryo development. Besides abnormal elevation many of maternal autoantibodies may be reason of pathology in fetus and deviations in child health, because direct action of autoantibodies, or indirectly, by mechanism of maternal immune imprinting (see below) [Lemke & Lange, 1999].

As well as opportunistic viruses and bacteria presented in woman organism may trigger for abnormal production of embryotropic autoantibodies, successful anti-microbial treatment of women with chronic infection will lead to normalization the immune parameters in most cases. It is interestingly to note that nearly 30% of recently infertile women had become pregnant during the first six months after anti-bacterial or anti-viral treatment if therapy was accompanied by normalization of serum content of embryotropic autoantibodies [Serova, 2000]. These observations indicate: some women with “unexplained infertility” in essence are fertile, and their pregnancy may happens often but interrupts at early stages (usually before diagnosing) because severe but reversible immune deviations. This deviations has been reflected and may be detected by quantitative measuring of changes in blood serum content of embryotropic autoantibodies.

Obstetricians often arise the question, which seems to be difficult: why did some women with opportunistic infection suffer from repeated miscarriages and other reproductive problems, but reproductive functions of some other women with the same herpetic or mycoplasmic infection was not disturbed? Serova [2000], and Litvak [2001] in observed patients, and Cronise and Kelly [1999] in experiments with laboratory mice show clearly: the cause of opportunistic (potentially pathogenic) microbial factor does induce systemic immune deviations, such situation is usually associated with reproductive problems. On opposite, the situation usually does not influence negatively the pregnancy course if presence of the same microbial factor has not associates with notable immune changes. These empirical data and conclusions are close to aphoristic idea of the founder of the modern microbiology Louis Pasteur: “microbe is nothing, background (that is reactivity of the host-organism) is everything” [Mayanskiy, 1999]. In this context investigation of serum level of embryotropic autoantibodies may became a useful instrument for evaluation of individual risk of pathology in pregnancy if some viruses or bacteria persist in organism of woman. Such observing is suitable for decision on necessity or its contradictions of antimicrobial treatment before planned pregnancy in each individual case.

6. Human papilloma viruses and reproductive health

Numerous human papilloma viruses (HPV; *papovaviridae*) belong to DNA-viruses. All species of HPV induce typical changes in mitotic activity of flat epithelial cells, and lead to appearance of neoplasm in skin and mucosa. Some variants of HPV are high oncogenic, especially types 16, 18, 31, 33, some other also may induce rare malignancy. Oncogenic variants of HPV may be found in more then 50% of melanomas [Dréau et al., 2000].

Clinical consequences of HPV infection is not restricted by risk of malignancy and cosmetic problems, but by influence on gestation process. In abortions’ tissues HPV can be found nearly in 60% of cases of spontaneous abortions, but in 20% of cases, if we have deal with medical abortions [Spandorfer et al., 2006]. HPV prominently decreases the successes of IVF [Spandorfer et al., 2006]. Besides, clinical problems, concerned to inborn malformations of the nervous system, described to be related with HPV. Frequency of neural defects (very different) is arisen 10-12 times in children born by HPV infected women [Poletaev, 2008].

Influence of HPV infection on embryo and fetus development is supposedly related to induction of elevated serum level of autoantibodies against S100 proteins by mechanism of molecular mimicry. Common epitopes in molecules of S100 and few viral antigens were

described [Poletaev, 2008]. Two dozen proteins of S100 family take part in regulation of apoptosis, and maturation of primordial nervous system (fetal) [Poletaev, 2008]. Therefore antibody-dependent disturbances of according processes may be related to some forms of malignancy, embryo death cases as well as to malformation of the nervous tube. Consequently the investigation for serum content of autoantibodies against S100 and preventive treatment in necessity should be recommended before pregnancy to each woman with external marker signs of HPV infection (warts, condylomas with any location).

7. Non-infection causes of immune deviations in women of fertile ages

Bacterial and/or viral infection (acute as well as activation of opportunistic infection) probably is the most often reason of deviations in activity of the immune system of investigated person, monitored by changes in serum content of natural autoantibodies. However other reasons conditioned the long-term immune deviations negatively influencing upon general fertility state, conception, pregnancy course and fetal development may be also important. Tight functional interrelation and prominent mutual influences the immune and neuro-endocrine systems [Poletaev et al., 2002] provides effect of falling dominoes. Any changes in the nervous system or endocrine system will obligatory lead to functional changes in the immune system. For example stroke, or thyroidal pathology, or hypothalamic dysfunction, etc. will be accompanied by changes in production and serum content plurality of autoantibodies, sometimes prominent and long-lasting [Poletaev, 2010]. In this connection even chronic psychogenic stresses may become the reason for immune deviations, negatively influencing upon fertility state [Poletaev, 2010]. Corresponding cases may be effectively treated by specialist in psychotherapy with or without using of antidepressants or similar medicine. Different ecological pollutants also can influence upon the immune state and, mediately, the fertility of investigated patient. The same situation may be provoked by incompetent medication in a course of non-professional "self-treatment". All above mentioned factors indicate for necessity of careful analysis of patient anamnesis: clarification of the main reason(s) leading to immune deviations in observed woman may become the first step in correction of reproductive dysfunction in each individual case.

8. Maternal immune imprinting

The biological meaning of a maternal organism in the development of a fetus is exclusive and maternal influences upon child's phenotype, have a priority compared to the paternal ones. It is illustrated clearly by the phenomenon of the epigenetic maternal immune imprinting of a system: Mother-Fetus-Child. The essence of this phenomenon is the "inheritance" by the child's organism many of the individual traits of the immune state of the mother, but not the father [Poletaev, 2008]. As a result, specific features of a child's immunity/autoimmunity become more or less an accurate copy (imprint) of the maternal immune state.

The adaptive meaning of maternal immune imprinting is evident. This phenomenon is responsible for the resistance acquisition against infection diseases by any newborn before the first real contact with the widespread viruses and bacteria. A more pronounced anti-infection immunity in the mother provides more potent inborn resistance against the same infection in her child [Lemke & Landor, 1999]. Observations of such kind provide the

ground for possible induction of the inborn resistance to infectious diseases in a child after an active immunization of the mother before her pregnancy. If such approaches will be introduced in medical practice, it should help to reject certain vaccinations or at least decrease their number and frequency for the babies [Poletaev, 2010].

Unfortunately, the Nature is lack of perfectness, and there is another (negative) side of the coin. If mother has been suffered from any kind of immune deviations, the undesirable effects can be produced upon her child directly, as well as indirectly by mechanism of maternal immune imprinting. For example systemic lupus erythematosus in the mother may lead to the development of newborn's lupus in babies at 4-8 months of the postnatal life [Poletaev, 2008]. Woman with abnormally elevated production of autoantibodies against insulin and/or insulin receptors can "imprint" these features in the immune state of her child. As a result, an abnormally elevated production of the same Autoantibodies may be revealed in a 4-6 years old child, and may become a risk factor for the early development of the diabetes mellitus [Budykina, 1998]. The elevated production of anti-thyroid autoantibodies may be revealed for years in children, whose mothers had thyroid problems, and may become the risk factor for the thyroid gland diseases in child [Poletaev, 2008]. Elevated rates of the same forms of pathology in children (endocrine, cordial, nephrological, etc.) which was presented in mothers during pregnancy course [Khlystova, 1987] may be directly related to the phenomenon of maternal immune imprinting.

The main mechanisms of the maternal immune imprinting remain obscure although, we can propose that the fact of antigenic specificity of the phenomenon implies the participation of specialized autoantibodies (probably anti-idiotypic autoantibodies) and/or AG-specific lymphocytes. Transferred trans-placentally maternal anti-idiotypic autoantibodies and/or memory lymphocytes can be the basic elements, which provide a specific activation and tuning of certain clones of the fetal T- and B-lymphocytes, and become main triggers of the inborn pre-formation of the Immunculus of the fetus-newborn-child (similar to maternal ones).

Future investigations of the maternal immune imprinting may provide the new approaches in prediction and treatment of a large group of inborn abnormalities. Besides, the comprehension of the phenomenon may serve as an impetus for the promotion of the fundamental research in the fields of maternal-fetal interactions.

9. ELI-P-complex method

Immune abnormalities reflecting changes in blood serum content of autoantibodies may be found in 85-95% of women suffering from habitual miscarriages or other complications of pregnancy. Long-lasting immune deviations do not necessarily lead to unsatisfactory pregnancy outcomes, but obligatory accompanied by sharp raise of probability of miscarriages, fetal deaths, or developmental malformations [Poletaev, 2008]. Another important issue is the influence of maternal immune deviations upon the health state of her future child. Abnormal maternal changes in serum autoantibodies content during pregnancy if not lead to fetal loss, practically always influence on the newborn health state by means of direct transplacental transfer and by means of maternal immune imprinting [Poletaev, 2008]. Accordingly, evaluation of embryotropic autoantibodies before planned pregnancy (especially in women with obstetrical complications in anamnesis) may become an important preventive measure aimed to decrease of unsatisfactory results of pregnancy.

Especially if predictive diagnosis was combined with treatment, run over under control of immune parameters. It should be noted - in opposite to genetic aberrations, the immune deviations may be effectively treated in the most cases.

Soon after Chernobyl disaster the specialized immunochemical methods for mass-scale investigation of the general health state as well as reproductive health state inhabitants of polluted areas were worked out in the former Soviet Union. These methods were generally named as ELI-Tests (from: **Enzyme-Linked-Immune-Tests**). One of these methods, just method ELI-P-Complex (abbreviation "P" - from Pathology in Pregnancy) was intended for preventive investigations of a fertile age women. Since 1994 the method ELI-P-Complex has been used successfully for prognosis of the development of planned pregnancy in general obstetrician practice in Russia. Method is intended for analysis of individual "profiles" (patterns) of twelve autoantibodies of IgG class in the sample of blood serum. It is based upon evaluation of partial changes in the contents of autoantibodies against choriogonadotropin, ds-DNA, β 2-Glycoprotein I, collagen II type, Fc-fragment of IgG, insulin, thyroglobulin, S100, Spr-06, ANCA, TrM-03, and KiM-05 [Poletaev, 2010]. In spite of diagnostic and prognostic effectiveness of the method proved in thousands investigations, the detailed mechanisms mediating influence of immune deviations measured by ELI-P-Complex upon the gestation process should be elucidated. Nevertheless, there is basis for some propositions. For example, any long-lasting active infection process (viral or bacterial) may be etiologically related to antiphospholipid syndrome induction and accompanied, in particular, by abnormally elevated serum levels of autoantibodies against β 2-Glycoprotein I and DNA [Poletaev, 2008]. The mentioned autoantibodies could be pathogenically related to changes in blood coagulation [Sherer & Shoenfeld, 2004] which, in turn, may cause vascular problems in placenta and affect the gestation process. Relative surplus of anti-collagen II autoantibodies may indicate inborn or acquired defects of the connective tissue and active adhesion process. Changes in serum autoantibodies against S100 are typical for some women with still-births and fetal/newborns neural malformations in anamnesis, and are related in most cases with active replicated papilloma viruses. A surplus of autoantibodies against choriogonadotropin may be the reason for deficiency in this hormone, which is important for placenta development and maturation, as well as for cases of premature ovarian failure [Tuohy & Altuntas, 2007]. Excess of autoantibodies against Fc-fragments of IgG (Rheumatoid factor) is indicator of inflammatory processes of any localization. Elevated peak of autoantibodies against Spr-0.6 may be indication of declining fertility and in most cases is sensitive marker sign of endometritis and/or inflammatory processes in other pelvic organs. Abnormal rise of autoantibodies against insulin, thyroglobulin, ANCA, TrM-03, and KiM-05 in detected profiles may be markers of diabetic fetopathy, thyroidal abnormalities, vasculopathy and kidney-related disorders in pregnant women [Poletaev, 2010]. An early detection (especially before planned pregnancy) of relative deviations in serum content some of measured autoantibodies is especially important for revealing of individuals with elevated risk of abnormalities expected at pregnancy and implementation of necessary prophylactic measures.

10. Clinical illustrations

The main field for using of ELI-P-Complex method is screening of women planning their pregnancy, IVF including. Immune deviations revealed by this method are related to or reflect some individual health problems, and characteristic changes of autoantibodies profiles, that

should be considered as prompting message for obstetrician about peculiar changes in woman's organism, which may be additionally investigated and effectively treated before pregnancy.

10.1 Some examples

In accordance to observations by Zhegulina [2002] 94% of women suffering from thyroid pathology were characterized by changes in serum content of embryotropic autoantibodies. Adequate preventive treatment under control of ELI-P-Complex method leads to 2,5-fold decreasing of unsatisfactory result frequency of the following pregnancy compared to pregnancy of women without immune control.

In accordance to observations by Nukhnin [2007] normal serum content of embryotropic autoantibodies has been found only in 7,4% of pregnant women with obstetrician complications in anamnesis, and deviations were typical in 93,6% of such women. Abnormal decreasing of numerous embryotropic autoantibodies was directly associated with miscarriages, placental insufficiency, and preeclampsia. Abnormal serum rise of them was typical for miscarriages, stillbirth, preeclampsia, and inborn anomalies.

In accordance to observations by Cherepanova [2008] there are direct relations between changes in serum content of some of embryotropic autoantibodies in early pregnancy and cases of pre-term abruption of placenta, preeclampsia at late pregnancy, and abnormal uterine bleedings at delivery. Special algorithm for evaluation of risk level of the noted complications was proposed. Abnormal decreasing of some of embryotropic autoantibodies as well as abnormal elevation was associated with deviations in the blood coagulation.

In accordance to observations by Makarov [2009] decreasing in serum content of some of embryotropic autoantibodies in early pregnancy gives possibility to screen women of the high risk for the future preeclampsia developing. Some changes in embryotropic autoantibodies serum levels provide possibility to differentiate between group of women with preeclampsia and chronic hypertension.

In accordance to Serova [2000] very different factors (infection agents, endocrine disfunction, environmental pollutions, drugs, chronic stresses, etc.) can be ground for steady changes in production and blood serum content of embryotropic autoantibodies. Characteristic of individual serum profiles of embryotropic autoantibodies may indicate to the main cause of revealing changes, and effective individualized correction (etiologic treatment) of women under control of embryotropic autoantibodies provides 5 to 8-fold rise of satisfactory result of pregnancy following.

In accordance to observations by Kluchnikov et al., [2001]., if children were born by women with the normal parameters of ELI-P-Complex method, at least 70% of them was evaluated as practically healthy persons at ages 4-6 years old. In opposite, no more then 15% children were evaluated as practically healthy if were born from women with steady deviated parameters of serum' autoantibodies.

Described examples represent only a small part of the general massive data obtained during the last twenty years and indicate clear necessity of wide using of preliminary evaluation of different embryotropic autoantibodies in women serum before planned pregnancy, especially in women belonging to a group of obstetrician risk.

Antigen	Possible clinical consequences of abnormal changes in relative serum content of according natural autoantibodies
Chorionic Gonadotropin	Excess of autoantibodies against this AG usually is indication of endocrine dysfunction and may be the cause of the functional insufficiency of choriogonadotropin. The last may lead to infertility, placental malformation, and placental insufficiency. Most cases of prolonged (months and years) abnormally elevated production of such autoantibodies is related to recent treatment by Pregnyl or Choragon during preparation for IVF. Besides excess of autoantibodies against this AG can be a marker sign of premature ovarian insufficiency. Rarely it may be indication for malignancy (tumor of pituary gland mostly).
DNA	Rise of autoantibodies against this AG may indicate for activation of apoptosis (virus-induced mainly). Rarely it may be indication for systemic autoimmune disease or malignancy. Excess of such autoantibodies may reveal embryotoxic effects.
B2-Glycoprotein I	Excess of autoantibodies against this AG is marker sign of anti-phospholipid syndrome which may be the cause of a small vessels thrombosis in placenta and other organs and leads to placental insufficiency. Rarely it may be indication for systemic autoimmune disease or malignancy. Excess of such autoantibodies may reveal embryotoxic effects.
Collagen II	Excess of such autoantibodies usually is indication for adhesions and scars formation. Besides excess of autoantibodies against this AG may be sign of pathological changes in a connective tissue. Excess of such autoantibodies may reveal embryotoxic effect.
Fc-fragment of IgG	Excess of autoantibodies against this AG (Rheumatoid factor) is indicator of inflammatory processes of any localization as well as of elevated production of proinflammatory cytokines. Excess of such autoantibodies may reveal embryotoxic effects.
Insulin	Excess of autoantibodies against this AG may be pathogenic factor for diabetic fetopathy. Besides elevated autoantibodies against insulin can be sign of the endothelial dysfunction and vasculopathy, and may indicate initiated or forming gestational diabetes or insulin-dependent diabetes type I
Thyroglobulin	Excess of autoantibodies against this AG may be marker sign of the existing or forming disturbances in the thyroid gland. Excess of such autoantibodies may reveal embryotoxic effects.
S100	The most often reason for long-term elevated production of such autoantibodies is human papilloma virus infection (by mechanism of molecular mimicry). Excess of autoantibodies against S100 proteins may lead to deviations of general morphogenesis and cellular differentiation in embryo, and be cause for stillbirth at the beginning, in the middle, or at the end of pregnancy. Besides it may be reason of malformation of the nervous system because S100 is involved in differentiation and migration of neuroblasts of primordial nervous system.
Spr-06	Excess of such autoantibodies usually is marker sign of endometritis (in the most cases) and/or inflammatory processes in other pelvic organs (rarely). Excess of autoantibodies against Spr-06 may be cause of declining fertility in women and men.
ANCA	Excess of ANCA-specific autoantibodies is typical sign of different forms of small vessel vasculitis and vasculopathy. The last may be reason for deterioration of placental blood flow, as well as other organ malfunction related to the problems with blood circulation.
TrM-03	Excess of autoantibodies against TrM-03 is sign of trombocytopathy and may lead to the following deviations: 1) Elevated lysis of platelets which leads to pathological bleeding; 2) excessive aggregation of platelets (without their lysis) and trombotic events
KiM-05	Excess of autoantibodies against KiM-05 should be considered as marker sign of active inflammatory process in the renal tissue

Table 1. List of antigens used for detection and analysis of changes in relative serum contents of according autoantibodies by ELI-P-Complex method.

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12. References

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