The immunological role of the placenta in the adaptive relationship between mother and fetus in the dynamics of pregnancy

El papel inmunológico de la placenta en la relación adaptativa entre la madre y el feto en la dinámica del embarazo

Shubin D.Yu. Russia, Republic of Mordovia, Saransk, 430005, Bolshevitskaya street 68, National Research Ogarev Mordovia State University, mr.danilka2012@mail.ru;
Labzina M.V. Russia, Republic of Mordovia, Saransk, 430005, Bolshevitskaya street 68, National Research Ogarev Mordovia State University, LudmilaMedin@yandex.ru;
Abramova S.V. Russia, Republic of Mordovia, Saransk, 430005, Bolshevitskaya street 68, National Research Ogarev Mordovia State University, elasv@yandex.ru;
Nechaykin A.S. Russia, Republic of Mordovia, Saransk, 430005, Bolshevitskaya street 68, National Research Ogarev Mordovia State University, nechaykinas@rambler.ru;
Markina A.E. Russia, Republic of Mordovia, Saransk, 430005, Bolshevitskaya street 68, National Research Ogarev Mordovia State University. Kireevalinka@yandex.ru;
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Abstract

The concept of a mother-fetus immunological system is a bidirectional relationship in which, on the one hand, fetal antigens are represented. On the other hand, they are recognized by maternal antibodies. The placenta is the barrier through which information is exchanged between two interconnected organisms. The authors consider the role of this organ in adaptation relationships at different stages of pregnancy. The descriptive-analytical method is conducted to meet the aim of the study. Based on the results, the need to monitor the main placental proteins of a woman was noted, which allows controlling the placenta's malfunction, which, in turn, is the leading cause of perinatal morbidity and mortality.

Keywords: Pregnancy, fetus, placenta, immunological system, adaptation mechanism, trophoblast.

Resumen

El concepto de sistema inmunológico madre-feto es una relación bidireccional en la que, por un lado, están representados los antígenos fetales. Por otro lado, son reconocidos por anticuerpos maternos. La placenta es la barrera a través de la cual se intercambia información entre dos organismos interconectados. Los autores consideran el papel de este órgano en las relaciones de adaptación en las diferentes etapas del embarazo. Se lleva a cabo el método descriptivo-analítico para cumplir con el objetivo del estudio. Con base en los resultados, se observó la necesidad de monitorear las principales proteínas placentarias de la mujer, lo que permite controlar el mal funcionamiento de la placenta, que, a su vez, es la primera causa de morbimortalidad perinatal.

Palabras clave: Embarazo, feto, placenta, sistema inmunológico, mecanismo de adaptación, trofoblasto.

Introduction

The causes and adaptive mechanisms of the tolerance of the mother's body to a half-foreign embryo are one of the difficult but fascinating mysteries of nature, over the solution of which more than one generation of physiologists, histologists, immunologists, geneticists, obstetricians are fighting[1-4].

As experimental and clinical data accumulated, various hypotheses and theories were put forward, but the truth remains vague[5-7].

The most reasoned and logical slender for the study were three hypotheses proposed years ago[8-11]:

1) anatomical separation (tissue barrier) between the pregnant and embryo (fetus), where the placenta plays the dominant role. But current knowledge allows us to exclude this hypothesis since the previously existing opinions about total protection of the fetal placenta from various external agents, including the mother's tissue antigens, have not been confirmed.

2) Antigenic immaturity of the fetus.

Research and discussion on the topic could continue, but the following should be noted[12-14]:

1) immune conflicts between the mother and the embryo are possible already at the beginning of pregnancy when it is not correct to talk about antigenic claims of the embryo;

2) How to explain the causes of fetal tolerance in the third trimester of pregnancy, when ready-made antibodies to mother's tissues are already in his body?

3) immunological inertia (tolerance) of the mother. For the past 20 years, they have been trying to confirm this hypothesis. However, so far, separate fragments of this mechanism are being studied: humoral, tissue tolerance to the antigens of the mother (and the fetus), the existing adaptation mechanisms of the organisms of the mother and embryo (fetus) at different stages of pregnancy, but there is no specific, objectively proven theory yet.

The main reason for this situation, it seems to us - the concept of authors every newly discovered factor is considered the main link in the complex, formed over millions of years of human evolution, the hierarchy of the relationship of an adult organism with its perfected homeostasis and a newly emerging organism, which, despite obvious immaturity, plays a leading, dominant role in this biological tandem[15,16].

Methods

The study's chief purpose was to analyze the role of this organ in adaptation relationships at different stages of pregnancy. To that end, the descriptive-analytical method is conducted, and several related sources are taken into account.

It is known that the trophoblast antigen occurs at approximately 5-8 weeks of intrauterine development and the fetal antigens at the 12th week. So what initiates the antagonistic relationship with the mother's body, the fetus, or the trophoblast?

The issue of the degree of involvement and influence on the immune relationship between mother and fetus of cell-mediated (Th1) and humoral (Th2) immune links has not been elucidated to date[17].

The theory of T. Wegmann, which existed in the past decade, argued the modulation of immunity in pregnant women towards the humoral link, arguing this by a shift in the differentiation of T-helpers during physiological pregnancy towards Th -2 cells, i.e., along the humoral direction[2,3]. The fact is that the preferential development of the immune response according to the humoral type is considered less dangerous for the fetus because the Th -1 type (cell-mediated) of the immune response significantly increases the risk of rejection of the fetus as a foreign antigen. However, the experimental and clinical data accumulated to date contradict the basic provisions of the dominant theory[1,18].

It turned out that the increased blood content of the pregnant Th -1 complex of cytokines does not always indicate a dysfunctional course and prognosis of pregnancy and, conversely, with a complicated course of pregnancy, a high titer of Th -2 cytokines can be observed.

It was also found that in the early days of physiological pregnancy, both in the blood and in the tissues of the emerging placenta, an increase in the intracellular synthesis of cytokines of both type Th - 1, in particular cells encoded as CD4 + IL-2 +, CD4 + IFN-Y +, and Th -2 - type (CD4 + IL-4 +, CD4 + IL)

In addition, the preferential activation of the humoral link of immunity in physiological pregnancy is not confirmed when determining blood immunoglobulins since the content of IgA and IgM in the dynamics of pregnancy does not change significantly. The exception is IgG, the concentration of which in the blood is slightly reduced due to its penetration into the blood of the fetus. It is believed that in this way, the fetus at the end of pregnancy, forms the passive immunity necessary for him in the initial period (3-4 months) of extra-uterine life[6,19].

IgG penetration through the placenta (trophoblast) is associated with their ability to settle on Fc receptors on the outer membrane of the trophoblast, which protects IgG molecules from damage by lysosomal enzymes during pinocytosis[13].

Note, as is known, class G immunoglobulins belong to the main class of immunoglobulins responsible for antibacterial humoral immunity. During pregnancy, a feature of the mother's humoral immune defense is the switching with cytotoxic immunoglobulins of subclass G 2 to the production of non-cytotoxic immunoglobulins of subclass G1. Such an adaptation mechanism prevents the development of antibody-dependent toxicity reactions aimed at fetal rejection.

It has also been proved that the complement system does not change significantly during pregnancy, and the observed relative increase in leukocytosis indicators does not affect the course of pregnancy[2].

At the same time, there is evidence that in pregnancy, fetoplacental tissues spontaneously secrete cytokines inhibiting the cellular immune response and promoting the activation of the humoral immune response by increasing the concentration of interleukins 4,5,10 and transforming growth factor (βF). This activation is especially noticeable in the second and third trimesters of pregnancy when the number of lymphocytes that respond by secreting interleukin 4 to contact paternal leukocytes that contain foreign antigens inherited by the fetus increases significantly the mother's blood. In the third trimester, the ability of blood mononuclears to produce interleukins two is generally reduced, which indicates the development of a specific immune response to foreign fetal antigens in the pregnant body, moreover, with a predominance of the humoral form of the response over the cellular one[12,15,20].

Here it is also appropriate to pay attention to the increased production of anti-inflammatory cytokines by monocytes during pregnancy compared to the production of non-pregnant women, which indicates another adaptation mechanism for the immune protection of pregnant women[3].

They tried to somehow bring to a common denominator the available information on this problem, the concept of regulating the mother's immune system during pregnancy was proposed: the cellular and soluble placenta products have a multi-directional modulating effect on the innate and acquired links of the mother's immune system, so the specific immune response is suppressed, and the non-specific, on the contrary, is intensified[4].

Critically considering this point of view, in general, it can be recognized as correct, but it, unfortunately, lacks specifics does not answer the main question: what personal mechanisms ensure the formation of the immune tolerance of the pregnant body and prevent immune conflicts of the mother's fetus at different stages of its such long intrauterine development[17,19].

Therefore, based on the available reliable facts, we will try to analyze the information and answer key questions of this important problem for obstetricians.

1. Why are trophoblast antigens (5-6 weeks after fertilization of the egg), and not the fetus (only at the 12th week of embryogenesis), the first to appear in the initial pregnancy?

To answer this question, you need to recall the sequence of stages of zygote formation.

After ejaculation in the vagina, a small number of sperm as a result of their own mobility and under the influence of the "pumping" function of the abdomen enter the lumen of the fallopian tube. Since sperm are a foreign body for the mother's body, their entry into the uterus and into the pipe causes stress and, as a result, spasm of the eastmus (for 3 days). Thus, the path to the rest of the sperm in the uterine cavity is closed, and optimal conditions are created for the advancement of sperm entering the pipe and fertilization of the egg. We have already considered these conditions with you.

At the same time, sperm in the uterine cavity begins to penetrate (destroy) the endometrium due to their own proteolytic enzymes, preparing the site for the upcoming nidation of blastocysts. Their time is limited to 2 days since on day three, the spasm of the isthmic part of the pipe is removed (probably due to the increasing concentration of progesterone produced by the yellow ovarian body)[11]. At the same time, the products of metabolism of spermatozoa getting into the endometrium (you already know that the term of life of spermatozoa after ejaculation doesn't exceed three days), are antigens in relation to the woman's organism and therefore cause in her the nonspecific protective reaction programmed in a genome: congestion of macrophages on the border with the taken root blastocyst and also the beginning of the formation of antibodies in relation to the functioning trofoblast[5].

The intensity of the immune response, as is known, depends on two main conditions - the strength of the antigenic properties of the "aggressor" and the balance of the protective mechanisms of the body subjected to aggression. Since the antigenic properties of trophoblast due to its small size are poorly expressed, the immune response responses of the pregnant woman are also weakly expressed at first but constantly increase by 5-6 weeks of embryogenesis detected stably.

1. What adaptation mechanisms protect the embryo from maternal protective immune responses of "rejection"?

From fertilization, the egg is reliably protected from any external effects by a shiny shell (zona pellucida). Read more: When the sperm reaches the shiny shell of the egg, the front of the sperm membrane specifically binds to the shiny shell receptors. After that, the acrosome is instantly resorbed, releasing all acrosomal enzymes. Enzymes also quickly create a hole in the shiny shell into which the "suc-

cessful" sperm enters. Within the next 30 minutes, the cell membrane of the sperm head and the oocyte merge to form a single cell. It is also known that a few minutes after the first sperm enters the shiny shell, Ca2 + ions begin to diffuse into the egg and cause the release into the surrounding space by exocytosis of many near-membrane vesicles. Bubble granules contain substances that prevent other sperm and antigens from penetrating through the shiny shell[14,18].

Surprisingly, the protective properties of the shiny shell are so effective that even spermatozoa fixed on it - "competitors" begin to fall off. An active role in this process is played by trophoblasts - cells located on the outer surface of the membranes of the shiny shell surrounding the blastocyst. In addition to the protective function of the trophoblast, they perform a trophic function, capturing the cells of the decidual membrane, destroying and assimilating them, helping in this way to use metabolic products to feed the developing embryo during 8-10 weeks of pregnancy.

At this stage of pregnancy, the trophoblast itself is reliably protected from immune aggression of the mother's body since it is surrounded by a layer of amorphous fibrinoid substance from mucopolysaccharides[4,5].

But for the sake of objectivity, it should be said that the functional activity of the trophoblast - the structures of the maternal part of the placenta most fully begin to manifest only after connection with the chorion - the fruiting structure of the placenta.

On the 6-7 days of development, the trophoblast is differentiated into cell layers - cytotrophoblast and syncytiotrophoblast. Around the same time (on the 8-9 day of pregnancy), a protrusion (primary villi) is formed from the trophoblast towards the decidual uterine membrane. As we know, the decidual sheath is a transformed tissue of the functional layer of the endometrium, containing all the necessary nutrients: glycogen, lipids, vitamins, etc., necessary for feeding the embryo in the first weeks of its life[8,9].

Literally 3-4 days later (12-13 days after fertilization), connective tissue begins to grow from the side of the chorion into the primary villi - secondary villi are formed, and from the beginning of week 3, blood vessels develop in the villi. Tertiary villi are formed. This completes the placentation step[10-14].

By the way, we recall that in the process of evolution of humans and animals with the placental method of fetal trophy, the chorion began to form from trophectoderm and extracranial mesenchyma and currently has approximately the same structure. In other words, in phylogenesis, an interspecific universal adaptation mechanism for life support and protection of the embryo was formed[9,10].

Results and Discussion

Chorial plate currently represents the chorion in humans. The villi (conditionally divided into stem, anchor, intermediate, terminal) consists of a connective tissue stroma, covered with highly active multifunctional layers cytotrophoblast and syncyotrophoblast cells (simplastotrophoblast) [6]. The structure of the connective tissue stroma of the chorion is made up of a small amount of collagen fibers, a basic intercellular substance containing a large amount of glycoproteins and acidic compounds: hyaluronic acid, chondroitin sulfates. Of the cellular elements, the stroma contains fibroblasts at the initial stages of differentiation, myofibroblasts with an increased content of cintoskeleton contractile proteins: actin, myosin, desmin, etc., and macrophages (in the form of round Kashchenko-Gofbauer cells). The latter, we believe, form the "first line" of the nonspecific immune defense of the mother's body against fetal antigens[18].

This is confirmed by the high content of macrophages at the mother-fetus border of the emerging trophoblast at different terms of pregnancy and the gradual decrease in their number as it continues to develop[15].

In addition, the trophoblast is a kind of immunosorbent that inactivates the immunoaggression of maternal antigens in various ways. So, from the moment of formation, the trophoblast begins to produce specific proteins: trophoblastic β1-globulin (TBG) and glycodelin.

Currently, the immunosuppressive function of TBG has been proved, which the trophoblast begins to produce in small quantities, gradually increasing its concentration by the end of pregnancy, or, more precisely, up to 35-36 weeks, that is, until the physiological "aging" of the placenta[4].

Table 1. The nature of changes in the trophoblastic β globulin (TBG) content in the mother's blood in the dynamics of physiological pregnancy (M ± m)

Protein name	Pregnancy periods in weeks		
	(1) 8-12	(2) 13-16	(3) 17-20
TBG (mg/L)	29,80 ±2,77	66,00 ±6,21	162,75 ±16,81

As can be seen from the data presented in table 1, the concentration of the studied protein in the mother's blood every four weeks of the first half of pregnancy increases many times: from 12 to 16 weeks by 2.2 times, and at the end of the first half of pregnancy by 5.5 times compared with the initial (1) indicator ($p < 0.01$), which indicates the active participation of TBG in the protein exchange of the pregnant woman[7,11].

The content of glycodelin in the pregnant blood serum, on the contrary, begins to increase in the early stages of pregnancy, reaching a maximum by 12 weeks, and then its level is lyrically reduced and by the end of pregnancy reaches a minimum. Given these dynamics, there is high reason to consider glycodelin one of the most active defenders against immune aggression in the first trimester of pregnancy when other mechanisms are not yet sufficiently developed[5].

The researchers paid close attention to placental lactogen (PL), alpha-fetoprotein (AFP), and prolactin of the other specific proteins.

It is believed that PL and other placental hormones are synthesized by syncytiotrophoblast, cytotrophoblast and decidual tissue.

It has been established that SM is multifunctional - it has prolactin somatotropin activity and has luteotropic and lactogenic effects, maintaining the secretory function of the yellow ovarian body in the first trimester of pregnancy. Since the SM is close in structure to growth hormone, it is believed that its main biological function is to regulate protein, carbohydrate, and lipid metabolism in the organisms of the mother and fetus[3,12].

AFP can only conditionally be called the "placenta protein" since it initially begins to be synthesized in the embryo's yolk sac and from 13 weeks of pregnancy - in the liver of the fetus[16,17].

According to the structure of a glycoprotein weighing 69,000, AFP consists of one polypeptide chain containing 600 amino acids and about 4% carbohydrates. Already at 5-6 weeks in the embryo's tissues, AFP accounts for about 30% of all proteins. AFP enters amniotic fluid from the body of the fetus.

In the blood of pregnant women, an increase in the concentration of AFP occurs from 10 weeks (up to 10-20 mg/ml) and gradually increases, by 32-34 weeks it reaches 300 mg/ml, and then by the end of pregnancy, its concentration decreases to 80-90 mg/ml[9].

The maximum AFP concentration (23 mg/l) in near-sea waters is observed at 14-15 weeks, followed by a gradual decrease to 1 mg/l.

The intensity of AFP entry into the blood of pregnant and perinatal waters depends mainly on the degree of permeability of the placental barrier and the functional fullness of the kidneys and the gastrointestinal tract of the fetus.

The physicochemical properties of AFP are very close to adult albumin - serum albumin. The main function of serum albumin is transport, so AFP is thought to be a fetal transport protein. It has a very high affinity for polyunsaturated fatty acids (PUFA), which are necessary for the formation of cell membranes. Therefore, it is believed that the main function of AFP is the selective binding of PUZHK in the placenta and their transfer from the mother's blood to the blood and fetal cells since PUZHK are not synthesized either by the embryo or by the adult body, but only with plant food[14].

Other important functions of AFP include immunosuppressive since during the development of the embryo, new proteins (antigens) appear, and in the absence of immunosuppression, it would produce antibodies against these new proteins, which would entail serious consequences. In addition, AFP protects the fetus from immune rejection by the mother's body[20].

In pregnancy, changes in the blood AFP level in the mother can be observed in the following cases[21-22]:

a) increases

1. with a large fruit, multiplicity;
2. viral liver necrosis in the fetus;
3. neural tube malformation (anencephaly, spina bifida);
4. umbilical hernia in the fetus;
5. kidney and urinary tract abnormalities in the fetus;
6. non-rotation of the anterior abdominal wall in the fetus;
7. oesophageal and duodenal atresia in the fetus;
8. Shereshevsky-Turner syndrome;

b) downgrading

1. Down syndrome in the fetus (after 10 weeks of pregnancy);
2. trisomy 18;
3. fetal retardation (fetal fetal retardation);
4. antenatal fetal death;
5. threatening abortion;
6. bubble drift;

To diagnose these disorders, AFP is used - a test of the Tatarinov-Abelev reaction. Such triple screening combines a certain level of AFP, unbound estriol, and CG.

Prolactin is a polypeptide consisting of a single chain comprising 199 amino acids and has a weight of about 24 kilodaltons. It is similar in structure to growth hormone and SM. A feature of the prolactin molecule is the presence of three disulfide bridges in it[13,22].

Due to the heterogeneity of the prolactin molecule, it is divided into glycolic, phosphorylated, sulfated, and destroyed forms.

In the blood, circulation of 4 isoforms of prolactin is possible, the origin of which is apparently associated with different post-translational modifications of the polypeptide chain[23].

Prolactin receptors are found in virtually all human body tissues, including some parts of the central nervous sys-

tem. Its lactotrophic cells of the pituitary gland are secreted, as well as: the mammary gland, placenta, central nervous system, immune system (white blood cells, including lymphocytes)[7,24].

Why does lactation not occur during pregnancy with a high prolactin concentration in the mother's blood? Inhibits lactation with a high blood content of pregnant progesterone secreted by the placenta, after which lactation occurs in childbirth.

During pregnancy, high levels of prolactin support estrogens. At the same time, prolactin contributes to the inhibition of the function of the yellow ovarian body, reduces the secretion of estrogens by follicles and progesterone in the yellow body after childbirth, i.e. prevents the onset of the next pregnancy during breastfeeding (but not always!)[23,25].

Prolactin provides immune tolerance of the embryo during pregnancy. The involvement of prolactin in immune responses is confirmed by the fact of an increase in its secretion by lymphocytes and other leukocytes when activating immunity arising in cases of inflammatory processes, infections and, conversely, a decrease in secretion when using glucocorticoids and other immunosuppressants[22].

Prolactin takes part in angiogenesis. Its mechanism of action in such processes can be both direct (stimulation of proliferative vascular wall endothelial cells) and influencing the production of various proangiogenic factors, particularly vascular endothelial growth factor[1,21].

Placental α1-microglobulin (PAMG)

PAMG belongs to the class of low molecular weight proteins that bind insulin-like growth factors and thus modulate the action of somatotropin. During pregnancy, PAMG is synthesized mainly by decidual tissue, which allows us to consider an indicator of the function of the maternal part of the placenta. PAMG is mainly found in near-sea waters. In the first trimester of pregnancy, its concentration in perinatal waters is 100-1000 times higher than in pregnant blood serum. The maximum concentration of this protein in amniotic fluid is observed in 20-24 weeks of pregnancy, and by 35 weeks it decreases by 15 times[7,25].

α2-microglobulin fertility (AMGF)

Protein synthesis is carried out in the decidual tissue, that is, it also reflects functional activity in the tissue of the maternal part of the placenta. Its content in placental tissues is 6.9% of all placental proteins. The concentration of protein in the placenta is observed mainly in the first and second trimesters, when the content of AMHF in it is 100 times higher than in the third trimester[8].

In the first half of pregnancy, AMGF is released mainly into amniotic fluid, where its concentration is almost 200 times higher than the level determined in the blood serum of the pregnant woman. The maximum level of AMGF in the paranatal fluid reaches 10-20 weeks of pregnancy and then gradually decreases.

PAPP-A (pregnancy-associated plasma protein-A pregnancy-associated plasma A protein.) The structure refers to high-molecular tetramers - enzymes of the metallopeptidase class. It is not strictly specific to pregnancy. The protein is synthesized by endometrial cells, found in the large intestine, follicles, mucous membranes, and kidneys.

During pregnancy, PAPP-A is formed in syncytiotrophoblast cells. The protein concentration begins to increase from 7-8 weeks of pregnancy, increases by two times every 4-5 days and by 10 weeks increases by about 100 times! By the end of pregnancy, the PAPP-A content in the mother's blood reaches 100 mng/ml

Normal serum PAPP-A is a 93% indicator of normal pregnancy development.

PAPP-A has immunosuppressive property, provides suppression of immune reactivity of mother's body to fetus[9,10].

Conclusions

According to the facts presented, in the dynamics of physiological pregnancy, proteins produced by the placenta, mainly its maternal part, have an immunosuppressive effect, protecting the fetus from antigens circulating in the mother's blood and vice versa, blocking their own antigens, reducing the likelihood of "immuno-rejection" by the mother's body.

This probability is most real in women with Rh - a negative blood factor. In addition to the "ordinary" immune conflict, both the pregnant body and the fetus must include protective and compensatory mechanisms to form additional immunotolerance.

In the normal course of pregnancy, the immunological response of the mother ensures tolerance to the fetus. However, defects in the placenta-fetus connection can lead to various complications: bleeding, hypertension, preeclampsia, spontaneous abortion, and others. Thus, knowledge about the immunological role of the placenta during pregnancy will allow us to understand the etiological pathogenesis of disorders better and build tactics for the treatment and prevention of pregnancy pathologies.

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