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Cytokine gene polymorphism and miscarriage.

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AbstractThe problem of recurrent miscarriage is an actual problem of modern medicine. According to world statistics, about 15-20% of pregnancies end in miscarriage. There are many mechanisms involved in normal pregnancy. One of them is an immune mechanism. Since the fetus is a "stranger" in relation to the maternal body, the formation of high-grade protective mechanisms for the full implantation of the embryo is necessary. In the case of destruction of the immune regulatory mechanisms there is an infringement of implantation and placentation, leading to miscarriage. According to some researchers, about half of the cases of miscarriage are caused by an imbalance of pro- and anti-inflammatory cytokines. At the same time, the ratio of these cytokines not only in mother organism, but also in the embryonic tissue is important. Polymorphisms of corresponding cytokines influence on the level of cytokine production. This review is devoted to the analysis of materials for the study of the role of cytokine gene polymorphism in the development of miscarriage.

Miscarriage is now becoming one of the priority health problems in many countries. Statistical data for the whole world show that about 15-20% of pregnancies end in miscarriage [1]. Miscarriage is a multifactorial disease with multi-component pathogenesis, forming on the background of adverse exogenous and endogenous factors. There are a number of regulatory the mechanisms participating in the successful development of pregnancy. The main ones are immune, endocrine and metabolic mechanisms. Normal implantation, placentation and a full blood flow promote occurrence and the successful development of pregnancy. Violation of one or more of these processes leads to disruption of the various stages of embryonic development.

One of the main causes of early embryonic loss is genetic factors. However, if earlier it was believed that the basic hereditary causes of miscarriage are chromosomal aberrations, but recently the effect of gene mutations and gene polymorphisms on the violation of pregnancy are being studied increasingly [2, 3, 4, 5]. For example, it is proved that the gene polymorphism folate cycle contributes to increasing the risk of miscarriage. This is due to the participation of the products of folic acid in many cellular processes, including the synthesis of purines and pyrimidines, DNA methylation and others [6, 7]. It is also shown that thrombophilia associated with genetic factors contribute to impaired fetal growth [8], as they may cause thrombosis during pregnancy [9, 10]

At the same time, the statistics show that about half of the cases of spontaneous abortion are associated with impaired functioning of the immune system. This is due to the reaction of the maternal organism on the fetus which is perceived as allograft due to paternal antigens. Immune disorders can be associated with genotype features, including cytokines genes and their gene polymorphism. The early stages of embryogenesis depend on the ratio of production and activity of pro- and anti-inflammatory cytokines involved in the immune response of mother to the fetus [11, 12, 13].

The purpose of this review is to analyze the impact of various cytokines and their gene polymorphism on the miscarriage.

The role of cytokine imbalance in miscarriage.

Cytokines are proteins which are synthesized predominantly by cells of the immune system and regulate a variety of processes, including cell differentiation, inflammation, hematopoiesis and others. To date, more than two hundred cytokines, that are able to regulate the duration and strength of the immune response and inflammation, are known. Feature cytokines are the following: One cytokine can act on several cell types, a cytokine can be produced by several types of cells, one cell can produce several cytokines, and several cytokines can activate the same function in several cells. It should be noted that in addition to cells of the immune system cells oviduct cells, endometrium, and the embryo also produce cytokines [14]. Cytokines act on receptors on the surface of target cells. The ability of cytokines to amplify or attenuate the production of other cytokines causes as positive as negative regulatory processes. Thus, cytokines, cytokine-producing cells and cytokine-specific receptors on their target cells are combined into a single receptor-cytokine regulatory network of the immune system. Thus, the cytokines are mediators between cell activating growth processes of cells, their differentiation, migration and apoptosis. Thus, to classify these peptides is extremely difficult. According to the structure cytokines are divided into interleukins, chemokines, interferons, growth factors, tumor necrosis factor family of hematopoietic cytokines et al.

Classification of cytokines in the structure.

Group	Features of the structure	Cytokines
1	α- spiral strands, short chain	IL-2, IL-3, IL-4, IL-5, IL-7, IL-9, IL-13, IL-15, IFN-γ, M-CSF, GM-CSF
	α- spiral strands, long chain	IL-6, IL-10, IL-11, oncostatin M
2	β- folded structures, long chain	family TNF, IL-1, TGF-β
3	α/β short chain	chemokines
4	Mixed mosaic structure	IL-12

Functionally, cytokines are divided into pro-inflammatory and anti-inflammatory [15].

The role of cytokines in embryonic development.

According to modern concepts, the stages of oocyte maturation, its adhesion, implantation, formation and growth of the placenta are cytokine-dependent processes and controlled by the immune system. Immune cells producing cytokines are located in all organs of the genital tract of women (ovaries, endometrium, uterus, and vagina).

Fig. 1

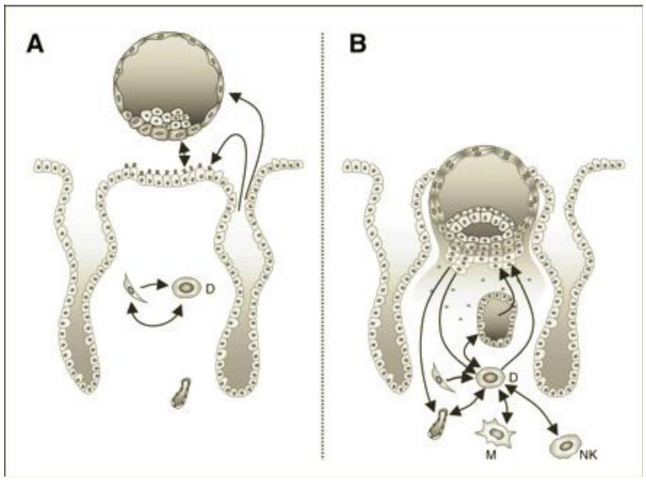
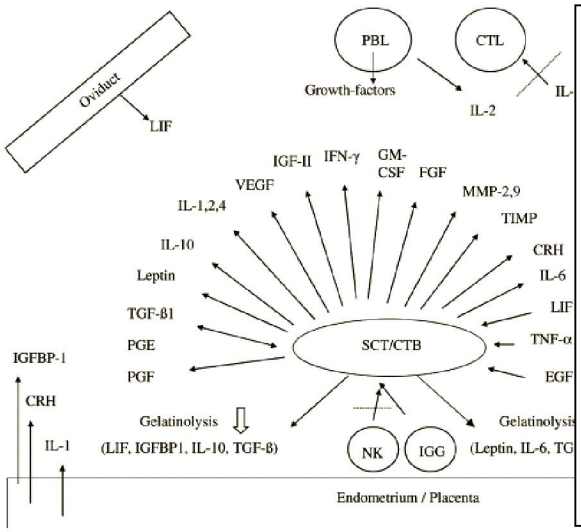


Fig. 1 Participation of cytokines in the processes of interaction between trophoblast and endometrium (A – pre-implantation; B – implantation; effects of cytokines are shown as arrows) [16].

Blastocyst stage is the most important stage of implantation. Further formation of the placenta provides nourishment, protection, development of the fetus and the successful child bearing. All of these processes include active intercellular interactions involving several families of cytokines. The most important ones are a family of cytokines IL-6, TGF-β, IL-1, and chemokines, a number of CSF and IL-15 [16]. Cytokines of IL-6 family are involved in the formation of the placenta. In particular it is shown that IL-11 and its receptor are produced by stromal cells and trophoblast [17, 18]. Leukemia inhibitory factor LIF, which stimulates the expression of tissue inhibitor of metalloproteinases (TIMP) in fibroblasts, plays an important role. Expression of LIF by endometrial glands and stromal cells is regulated by IL-1, TNF-α, TGF-β and estradiol [19, 20]. Important role in trophoblast invasion and implantation belongs to IL-1, IL-4, IL-6, IL-10, TNF, epidermal growth factor (EGF), hepatocyte growth factor (HGF), TGF-β, IGFBP-1 and IGF -II. Formation and growth of trophoblast differentiation and invasion happen with the participation of cytokines. nvasive capacity decreases with increasing levels of IL-6 and IL-10, TGF-β, TNF, IFNγ [21, 22].

Fig.2



The spectrum of cytokines involved in the process of implantation and invasion (SCT – syncytiotrophoblast, CTB – cytotrophoblast, NK – natural killers, IGG – immunoglobulin G, PBL – peripheral blood lymphocyte, CTL – cytotoxic T lymphocyte, B-L – B lymphocyte) [23].

Participation of a number of molecules which belong to the family of IL-6, including LIF and IL-11 is required for the implementation of embryo implantation [24]. L-11 regulates gene expression and cell cycle control and components of the extracellular matrix during decidualization [25]. It is assumed that LIF and IL-11 increase adhesion of endometrial epithelial cells to fibronectin and collagen on the surface of the blastocyst [26]; increase the expression of the epithelial cells of endometrial integrin A2. It is shown that the level of IL-11 and its receptor in the epithelium of the endometrium in women with miscarriage is decreased [27]. IL-11 causes dose-dependent decrease in the synthesis of pro-inflammatory cytokines (TNF-α) in the cells of the endometrium [28]. Without the normal LIF gene expression in the uterus implantation is impossible [29]. The maximum level of LIF gene expression observed in endometrial cells at a stage of implantation. At the same time, LIF receptor gene is expressed in the blastocyst [30]. During the adhesion of the blastocyst begins produce LIF by itself. At the same time, the mother cells increase production of gp130 and LIF-receptor. Adhesion induces differentiation of trophoblast cells in the cytotrophoblast and syncytiotrophoblast. Blastocyst starts to secrete IL-1, which activates the expression of LIF in the endometrium, which contributes to the completion of implantation. IL-1 activates synthesis of LIF in the endometrium [29], furthermore, IL-1 increases expression of integrin subunits β3, which plays an important role in adhesion [31]. According to the literature it is known that fetal cells produce IL-1R1, IL-1β and IL-1ra [31, 32]. Other families of cytokines IL-6 are also involved in the regulation of early embryonic development, and in the regulation of the nervous and muscular systems. Therefore, gene defects of common subunit gp130 of their receptors lead to serious violations and mortality in the embryonic period [15]. Role of certain cytokines in the regulation embryonic development is traced most closely by the data obtained in knockout mice deficient in the

corresponding genes (Table. 2).

Table 1 - The role of cytokines, cytokine receptors and signaling molecules in the regulation of embryonic development by the data obtained in knockout mice [16, 33].

defective genes	Developmental disorders
LIF	Disorders of implantation
IL-6	Reduced fertility
IL-11R	Disorders of embryonic development after implantation
Gp130	Embryonic lethality
STAT3	Embryonic lethality
SCF	Reproductive disorders
M-CSF	Reproductive disorders
GM-CSF	Dysfunction of the placenta
TGF	Embryonic and early postnatal lethality

For successful embryo implantation timing of readiness of endometrium implantation and embryo development is needed [34]. Peripheral blood lymphocytes have progesterone receptors on their surfaces in physiological pregnancy. Thus, the dependence of the growth of cells which contain these receptors on the duration of pregnancy occurs. Progesterone receptor by interacting with T CD8 + cells stimulates the synthesis of progesterone-induced blocking factor. This factor stimulates the immune response of the maternal organism towards the fetus on NK-cells (CD56 + CD16-). If these cells are present, the maternal immune response is carried by Th2, which is accompanied by synthesis of IL-3, IL-4, IL-10, and IL-13. In this case, certain immune homeostasis and normal development of the fetus is provided and maintained. Increasing production of cytokines by Th2 leads to increased production of asymmetric antibodies that compete with precipitating antibodies. Thus, these antibodies act as "blocking" antibodies. They protect the embryo antigens from the maternal exposure and prevent its destruction by maternal immune system. If amount of progesterone is low or its receptors are damaged, progesterone-induced blocking factor is small. In this case, the mother's immune response to trophoblast is carried by lymphokine-activated killer (LAK), bearing the markers CD56 + CD16 +. It induces the synthesis of pro-inflammatory cytokines by Th-1, providing an abortifacient effect by influencing the trophoblast apoptosis and inhibiting its development [35]. Uterine NK cells secrete several angiogenic factors including angioprotein 2 and VEGF [36, 37]. This activity of NK cells is dependent on the level of IFNγ. High doses of interferon-γ can inhibit implantation processes and angiogenesis [38]. The effects of NK-cells are performed by using NCRs, which regulate NK cell cytotoxicity and cytokine production. It is shown that in the peripheral blood of non-pregnant women with high risk for recurrent pregnancy loss level of NK-1is changed [39]. Furthermore, it is shown that in abortive decidual cells and endometrium tissue of women with pregnancy loss expression NCRs profile is changed.

Cytokines of TGF family are also important in the regulation of implantation and fetal development. TGF-β and activins are synthesized and secreted by cells of the epithelial lining of the fallopian tube and uterus and stimulate the synthesis of LIF. Cytokine receptors of TGF family are expressed on cells at various stages of embryo development. At the same time, TGF-β1 is secreted by cells of the embryo at the blastocyst stage. Perhaps these factors are involved in the pre-implantation development of the fetus and the interaction of maternal and fetal cells during implantation to maintain normal gestation. A number of cytokines TGF family are synthesized in the placenta by trophoblast cells and regulate the production of estrogen, progesterone, placental lactogen. Some TGF are synthesized by maternal decidua cells and stimulate their differentiation and regulating cytotrophoblast invasion [40].

The role of cytokine gene polymorphism in miscarriage.

The study of cytokine gene polymorphism in miscarriage is an actual problem of modern medicine. Identification of SNP, affecting the level of certain cytokines, promotes the formation of a database on predictor of miscarriage. Furthermore, it should be understood that both genes maternal organism and embryonic genes involved in the development of tissue pathology.

A) Investigation of cytokine gene polymorphism in the tissues of maternal origin in early embryonic losses.

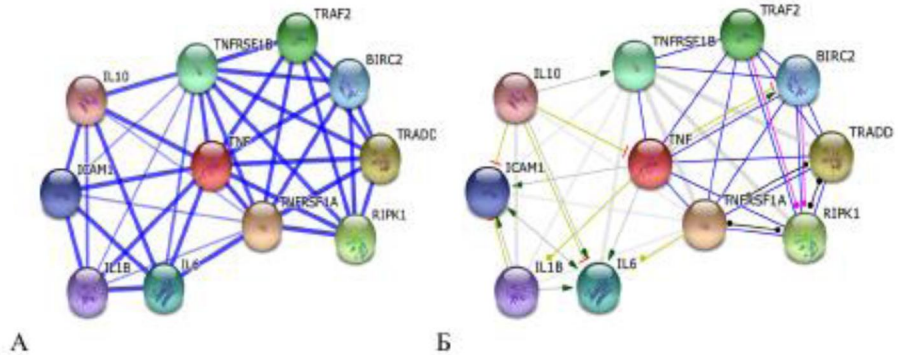
Literature data about the possible association between polymorphisms of the gene promoter region of IL-1β and the risk of disease in the I trimester of pregnancy are controversial. Some authors [41, 42, 43] believe that the presence of a polymorphism of the gene promoter region of IL-1β is not associated with an increased risk of miscarriage. Wang Z. et al [44, 45], Bombell S. [12] found an increased frequency of polymorphic variant of IL-1β (-511, -31) in women with pregnancy loss. At the same time it is shown that gene polymorphism receptor antagonist of IL-1β (IL-1Ra) is frequently seen in spontaneous abortion and idiopathic recurrent pregnancy loss [46, 47].

The literature sources about a possible link between the presence of polymorphism of the gene promoter region of IL-10 and the risk of disease in the I trimester of pregnancy are controversial. Some authors [12, 13, 48, 49, 50] believe that the presence of polymorphisms -592A, -819T, -1082A promoter region of IL-10 gene is not associated with an increased risk of miscarriage. At the same time Costeas and his colleagues [51] revealed that the presence of these three allelic variants is associated with the risk of miscarriage. At the same time Kamali-Sarvestani E. colleagues [52] have demonstrated the lack of correlation of polymorphism -592A promoter region of IL-10 gene c risk of miscarriage in the population of Iranian women. Cochery-Nouvellon E. and his colleagues established that among women with non-developing pregnancy rate registration polymorphic variant of the gene of IL-10 was significantly lower compared with women with spontaneous abortion in the first trimester. It is known that IL-10 has been actively involved in ensuring maternal immune tolerance of the organism to the developing fetus. In addition, IL-10 reduces the expression of molecules - coagulation activators by decidual cells [53]. Thus, changes in the level of gene expression of IL-10 associated with the presence of a polymorphic variant of a gene can lead to a breach of the early stages of human embryogenesis.

There is no consensus about the possible link between the presence of polymorphism in the promoter region of the gene and the risk of disease TNFα in the 1 trimester of pregnancy. Some authors [13, 48] believe that the presence of the polymorphism -308A TNFα gene promoter region is not associated with an increased risk of miscarriage. Kamali-Sarvestani E. colleagues [52] demonstrated the presence of the polymorphism -308A relationship promoter region of the gene TNFα with the risk of miscarriage in the population of Iranian women. Palmirotta and colleagues revealed that the haplotype -376G / -308A / -238G TNFα gene is a protective factor that contributes to the reduction of tumor necrosis factor.

B) Investigation of cytokine gene polymorphism in the tissues of maternal origin in early embryonic losses.

24500 gene expression analysis in decidual tissue of women with recurrent miscarriage using Illumina Ref-8 chip 155 identified genes whose expression level is more than two times different from control. At the same time 23% of them are genes of the immune response. Proportion of functional groups of other genes does not exceed 18%.



А Б

Fig. 3. In silico model of interaction of the proteins encoded by the genes of cytokines [56] (A - thickness of the lines between the molecules reflects the degree of correlation between protein, B - type arrow indicates the nature of the relationship between proteins).

Data of references about a possible link between the presence of polymorphism of the gene promoter region of IL-6 and the risk of disease in the 1 trimester of pregnancy are controversial. Some authors [12, 49, 50] believe that the presence of a polymorphism -174S gene promoter region of IL-6 is not associated

with an increased risk of miscarriage. Saijo Y. colleagues [57] revealed an association with recurrent pregnancy loss by the presence of the allele polymorphism -634S -634S-G gene of IL-6 in a population of Japanese women. Among the residents of China with recurrent spontaneous abortions genotype frequency 634GG gene IL-6 is also reduced compared to the control [43]. Costeas and his colleagues [51] revealed that the presence of polymorphism 634S-G gene of IL-6 associated with the risk of miscarriage.

Thus, the functioning of cells as maternal as embryonic origin changes when developing pregnancy. However, the scope of changes in the pattern of cytokines gene expression in embryonic tissue more as compared to the maternal organism. Directivity of these changes is related to the increase in the total level of pro-inflammatory cytokines. The increase in pro-inflammatory level with simultaneous suppression of the immune regulatory level may be an important mechanism involved in the destruction of the early stages of human embryogenesis [58]. The combination of a normal genotype of the cells with the presence of maternally derived polymorphic variant of the gene IL-1β in cells found in the pathology of chorionic the first trimester of pregnancy. In such a situation the appearance of imbalances in the synthesis of pro-inflammatory cytokine cells of embryonic and maternal origin is possible. The presence of a polymorphic variant of the gene IL-1β in the cells of the chorion causes higher production of the cytokine in cells of embryonic origin.

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Тарабаева А.С., Бижигитова Б.Б., Битанова Э.Ж. Калиева Л.Г.. Нурмуханбетова А.А. Мухтарханова Д. Полиморфизм генов цитоктнов и невынашивание беременности

Ключевые слова: цитокины, полиморфизм генов, невынашивание беременности

Аннотация Проблема привычного невынашивания беременности является актуальной во многих странах мира. По данным мировой статистики около 15-20% беременностей заканчиваются самопроизвольными абортами. Течение нормальной беременности обусловлено множественными механизмами. Одним их них является иммунный механизм, так как плод является «чужим» по отношению к материнскому организму. Поэтому, необходимо формирование полноценных защитных механизмом для нормальной имплантации и плацентации. В случае нарушения иммунорегуляторых механизмов эти процессы нарушаются, что приводит к невынашиванию беременности. Согласно исследованиям ряда авторов, около половины случаев невынашивания беременности вызваны дисбалансом про- и противовоспалительных цитокинов. При этом имеет значение не только сотношение цитокинов материнского организма, но и цитокинов зародышевой ткани. Полиморфизм генов соответствующих цитокинов оказывает влияние на их продукцию. В данном обзоре представлен анализ материалов, посвященных изучению роли полиморфизма генов цитокинов на невынашивание беременности.

Тарабаева А.С., Бижигитова Б.Б., Битанова Э.Ж. Калиева Л.Г.. Нурмуханбетова А.А. Мухтарханова Д. Питокиндердің тектік полиморфизмы және жүктілікті көтереалмаушылық

Кілттік сөздер: цитокиндер, тектік полиморфизм, жүктілікті көтереалмаушылық

Аннотация Жүктіліктің әдетті көтереалмаушылығы әлемнің көптеген елдерінің өзекті мәселесі болып келеді. Дүниежүзілік статистика бойынша жүктіліктердің 15-20% өздігінен дамыған түсікпен аяқталады. Жүктілікті көптеген механизмдер қалыпты қылып сақтайды. Ана организміне ұрық организмі «бөтен» болғандықтан жүктілікті сақтауда иммунды механизм де бар. Сондықтан, қалыпты имплантация мен плацентацияның толық жарамды қорғаныс механизмдері қалыптасуы өте маңызды. Егер иммунды реттеуші үрдістер ақауланса, жүктілік сәтті аяқталмайды. Бірқатар зерттеушілер мәлеметтері бойынша жүктіліктің сәтсіздіктерінің жартысына жуық саны қабыну алды және қабынуға қарсы цитокиндерінің дисбалансымен шақырылады. Бұл жағдайларда тек қана ана организмінің ғана емес, ұрықтық тіндерінің де цитокиндерінің арақатысының маңызы бар. Цитокиндердің тектерінің полиморфизмы сәйкес цитокиндердің өніміне әсер ететіні белгілі. Осы шолуда цитокиндердің тектерінің полиморфизмының жүктілікті көтереалмаушылығына деген әсерін зерттеу бағытында бар мәлеметтердің сараптамасы келтірілген.

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