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USE OF IMMUNOGLOBULIN DRUG IN INTRAUTERINE INFECTIONS DURING PREGNANCY

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✓ ***Resume***

The article discusses the fetal problems of intrauterine infections. One of the important reasons for this is related to the damage caused by acute and inflammatory viral infections in the early stages of pregnancy. The presented material describes the types of intrauterine infections, instructions for intravenous administration of immunoglobulins based on treatment methods. The effectiveness of their use in intrauterine infections of pregnant women was evaluated.

Keywords: intrauterine infections, intravenous immunoglobulin, fetus, placenta, IFA.

ПРИМЕНЕНИЕ ИММУНОГЛОБУЛИНА ПРИ ВНУТРИУТРОБНЫХ ИНФЕКЦИЯХ ВО ВРЕМЯ БЕРЕМЕННОСТИ

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✓ ***Резюме***

В статье обсуждаются фетальные проблемы внутриутробных инфекций. Одна из причин этого заключается в том, что острые или воспалительные вирусные инфекции поражают ранние сроки беременности. В представленном материале описаны различные внутриутробные инфекции, инструкции по внутривенному введению иммуноглобулинов с методами их лечения. Оценена эффективность их применения при внутриутробных инфекциях беременных.

Ключевые слова: внутриутробные инфекции, внутривенное введение иммуноглобулинов, плод, плацента, ИФА.

HOMILADORLIK DAVRIDA BACHADON ICHI INFEKSIYALARIDA IMMUNOGLOBULIN PREPARATINI QO‘LLASH

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✓ ***Rezyume***

Maqolada bachadon ichi infeksiyalarining homila muammolari muhokama qilingan. Buning muhim sabablaridan biri homiladorlikning dastlabki davrlarida o‘tkir va yallig’lantiruvchi virusli infeksiyalar tomonidan yetkaziladigan zarar bilan bog‘liq. Taqdim etilgan materialda bachadon ichi infeksiya turlari tavsifi, immunoglobulinlarni davolash usullariga tayanib vena ichiga kiritish bo‘yicha yo‘riqnoma aks ettirilgan. Ulardan homilador ayollarning bachadon ichi infeksiyalarida foydalanish samaradorligiga baho berilgan.

Kalit so‘zlar: bachadon ichi infeksiyalari, tomir ichiga immunoglobulin yuborish, homila, yo‘ldosh, IFA.

Relevance

The infectious pathology of pregnancy and newborns is one of the leading medical problems of modern obstetrics and Perinatology.

Intrauterine infections-this is a group of infectious and inflammatory diseases that produce various pathogens, but have the same clinical manifestations as the fetus and newborn, expressed in similar epidemiological indicators.

The negative impact of infections transmitted by a woman during pregnancy on the condition of the fetus and newborn baby has been proven in many research studies.

Further, according to the data presented in various literature, at least 10% of pregnant women have certain infectious clinical symptoms, which allow them to be detected and treated in a timely manner.

In most women, however, this continues in a latent, subcutaneous manner, and if we take into account the physiological immunosuppression at the time of pregnancy, it becomes clear that the causes of such an unexplained course of infection can lead to serious complications for the mother and fetus.

The development of complications in the fetus and the sequence of a newborn with a chronic infection in the mother:

1. Chronic infection in the mother
2. Immunity status changes
3. Violation of immunity in the fetus and newborn
4. Violation of the early adaptation period
5. Neurological, somatic development or endocrine disorders in a child

The presence of infection in the mother increases the risk that pregnancy and childbirth will end with negative consequences, but this does not always mean that the fetus is infected. Pathogens of infection penetrate into the fetus in the following ways:

- transplacental (goes to the fetus through the placental barrier in a hematogenous way);
- outgoing (through the cervical canal and fetal shell);
- descending (through the fallopian tubes);
- transmural (through the myometrium and decidual shell);
- the path of sexual intercourse (when the fetus passes through the infected birth canal).

The risk of infectious agents passing from the mother to the future child through the uterus increases even more in cases where a woman has severe somatic, obstetric and gynecological, infectious anamnesis and immunological tolerance.

Intrauterine infection causes the following common pathologies:

- placental insufficiency;
- chronic hypoxia;
- fetal growth retardation syndrome;
- fetal malformation;
- infectious diseases;
- stillbirth.

Gestasis (80.2%), the presence of chronic diseases in the mother (74.3%), chronic intrauterine hypoxia of the fetus (71.8%), anemia (63.4%), involuntary abortions and stillbirths (62 .2%), exacerbation of chronic pyelonephritis (53.6%), surgical correction of isthmic-cervical insufficiency, long-term dehydration during childbirth affects the occurrence of intrauterine infections (II) are the factors that show.

The above cases are also leading among the causes of negative perinatal consequences (N Ye. Ken. N. V. Arzhanikidze, 2004, V. I. Kulakov and others, 2005).

At the same time, 1.76% of babies born to 8 healthy mothers, 8.6% of children born to mothers with chronic infection, 21.8% of children born to mothers with late gestosis have an infectious process caused by II. The occurrence of intrauterine infection depends on whether the infection process in a pregnant woman is primary or secondary, as well as on the extent and speed of the spread of inflammation. The effect of intrauterine infection on the embryo and fetus is caused by a complex of the following factors:

- pathological effects of microorganisms and their specific toxins (infectious disease, fetal hypoxia, delay in fetal development);

• implantation and placentation process disorders (low placentation, placenta previa);
• reduction of metabolic processes and immunological protection in the fetus.

In the pathogenesis of II, it is possible to distinguish "maternal", " placenta-specific ", "fetus-specific" stages of development:

1. "Maternal" stage refers to the beginning of the infectious process within the lower parts of the urogenital area. Developing vulvovaginitis or cervicitis can lead to infection of the fetal membranes or infection of the fetus from postpartum contact. Urogenital infections are characterized by latent transmission, which is explained by the abundance of bacteriostatic substances in the mucous membrane of the cervix.

2. The "placenta-specific" stage is observed in the spread of the inflammatory process through the hematogenous path and occurs in bacteremia, viremia. Placental insufficiency and subsequent intrauterine hypoxia of the fetus pose an additional risk to the fetus.

3. In the "fetus-specific" stage, the infection process spreads to the organs and tissues of the fetus. This condition is caused by the failure of the microbial barrier of the uterus-placenta and placenta-fetus, and its border 9 is formed from the chorionic epithelial layer. Any manifestation of the "fetus-specific" stage of infection begins with the placenta and passes with morphological signs in the amniotic membrane, chorionic villi, or umbilical cord.

The urgency of the problem of intrauterine infection is not only limited to serious consequences before and after childbirth, manifested in the mother-child, but it is also associated with the development of complex diseases that often lead to disability in children suffering from severe forms of congenital infection and a decrease in the quality of life as a whole.

The frequency of intrauterine infections ranges from 6 to 53%, among premature babies it reaches 70% (N.Ye. Kan, N.V. Orzhonikidze, 2003; A.Ya.Senchuk, Z.M.Dubossarskaya, 2005).

The infectious effect can be manifested by the disruption of the organogenesis and functional formation of systems, the subsequent generalization of the inflammatory process, and the continuation of the effect of the infectious agent with clinical manifestations (I.S. Sidorova et al., 2000; V.K. Orekhov, 2002).

The lack of specific clinical manifestations, the possibility of viral-bacterial and non-bacterial associations outside the world creates the problem of accurately identifying the pathogen that causes adequate grounds for the treatment of the middle way, and this perinatal infection is especially relevant (A.P. Pomogayeva, 2000).

Taking into account the wide spread and seriousness of the prognosis, early diagnosis of intrauterine infections in pregnant women, development of high-precision methods of effective treatment is one of the priority directions of medicine.

As mentioned above, according to the essence of pregnancy, the state of immunosuppression is considered.

The immune system, like the whole body, is aimed at the implantation and development of the placenta during pregnancy. In this case, the state of local immunity is especially important, that is, the immune mechanisms in the endometrium, where the processes of implantation, invasion and development of the unborn fetus take place. The endometrium is represented by epithelial tissue and a large number of blood vessels. Therefore, this area is very susceptible to bacterial agents and viruses. According to A.D. Makatsaria and N.V. Dolgushina (2004), viruses mainly damage cells of epithelial origin and vascular endothelium. Viruses affect the vascular endothelium both directly and indirectly. Also, the presence of infection can create unfavorable conditions for the adequate development of the trophoblast and cause complications in the form of the risk of miscarriage, geostasis, and placental insufficiency. These pathogens can cause the development of proautoimmune processes in pregnant women due to the common antigenic structures.

Treatment of infected pregnant women is always associated with certain limitations due to the adverse effects of antibiotics on the fetus. Viral infections are more difficult to treat because they have the ability to remain in the body for life with periodic activation of the immune system (A. M. Savicheva, 2005).

The most important part of protecting the body against viral infection is humoral immunity represented by immunoglobulins. Currently, immunotherapy is used in the fight against severe viral infections.

Immunoglobulin therapy is defined as the use of a combination of antibodies obtained from healthy human donors to treat different conditions. The principal components of intravenous immunoglobulin (IVIG) are IgG antibodies, which compromise about 90% of the IVIG. Antibodies are glycoproteins synthesized and secreted by plasma cells (activated B cells) to respond to antigenicstimulation with the primary purpose of a specific immune response to result in different physiological and/or pathological processes.

The basic structural unit is primarily formed by two heavy and two light chains. The difference between the heavy chains results in different kinds of antibodies: IgG, IgA, IgM, IgE, and IgD. After synthesis, formed antibodies functions by binding with a specific antigen epitope. This binding subsequently results in specific actions that ultimately help neutralize and inactivate the pathogenic organisms or trigger a specific immune response.

The use of human serum in the scientific field has been reported as early as the 19th century. Before the mid-20th century, most IVIG uses revolved around the management of infectious diseases. The use of immunoglobulin isolated from the human serum in non-infectious conditions was first reported in 1952. International collaborations were organized to investigate the use of immunoglobulins further. These collaborations' main goals were to standardize the treatment dose, efficacy, indications, and route of administration.

Expanded efforts suggested using the intravenous formulation in the management of specific conditions in the non-adult population. The first use of IVIG in neonates was reported in 1987by Hara et al., who used IVIG to treat an infant with hemolytic anemia due to Rh incompatibility. Since that time, clinical use and application in neonates and fetuses have increased significantly, and investigators have attempted to search for the best evidence for use, safety, and adverse effects. Recently, tremendous effort has been placed on the role of IVIG therapy to treat complications related to Coronavirus-19 viral infection in adults as well as the pediatric and neonatal population. A snapshot of important events in immunoglobulin therapy history is shown in Figure 1.

Figure 1. Timeline showing the important historical events in the process of immunoglobulin discovery,synthesis, and clinical applications. IVIG: Intravenous immunoglobulin.

1890 year	First reported use of serum containing antibodies in an animal experiment
1900-1950 years	Multiple reports of human serum use to treat infectious diseases
1952 year	First reported use of immunoglobulin therapy in immunodeficiency
1979 year	Consensus agreement on the use of IV route to administer immunoglobulin
1987 year	First reported use of IVIG to treat hemolytic anemia in neonates
1988-2020 years	Expanded off-label use of IVIG in pediatrics and neonates
2020 year	Use of IVIG for treatment of COVID-19 related conditions.

Immunotherapy with intravenous immunoglobulins (III) primarily involves the use of their biological immunoregulatory properties. In addition to the direct anti-infective effect, they are able to control the immunological balance.

Despite the strong evidence and the clear indications for using IVIG in adults and its clinical applications in the pediatric population, the evidence is less clear regarding neonates. A summarized list of suggested clinical indications for IVIG use in the neonatal population is shown in Table 1. As this research area has been active for the past 40 years, this review highlights the practical aspects and the most recent evidence about IVIG use in the fetal and neonatal population.

Suggested Clinical Indications of IVIG Use in Fetuses and Neonates.

1. Alloimmune hemolytic disease of the newborn
2. Fetal and Neonatal immune-mediated thrombocytopenia (FNAIT and ITP)
3. Neonatal infections:
4. Sepsis treatment and prophylaxis
5. Enterovurus infection

6. Parvovirus infection
7. COVID-19 related neonatal disease
8. Congenital CMV
9. Neonatal hemochromatosis (GALD)
10. Primary immunodeficiency
11. Neonatal Kawasaki disease
12. Neonatal lupus

Note: Suggested uses of IVIG in fetuses and neonates. FNAIT: fetal and neonatal alloimmune thrombocytopenia, ITP: idiopathic thrombocytopenic purpura, COVID-19: coronavirus disease 19, CMV: cytomegalovirus, GALD: gestational autoimmune liver disease.

The purpose of clinical research.

Treatment of pregnancies complicated by viral intrauterine infections by intravenous injection of human immunoglobulin, prevention of negative consequences of infectious pathologies of the fetus.

Materials and research methods.

The study was conducted under prospective control at RSPGSPMC (Republican specialized obstetrics and gynecology scientific-practical medical center), Department of Fetal Medicine. Human normal immunoglobulin was used for treatment. Normal human immunoglobulin is a natural component of blood plasma. These immunoglobulins actively cross the placenta. On the surface of the trophoblast there are class G immunoglobulin receptors. Together, these receptors capture immunoglobulins from the mother's blood and transfer them directly to the blood of the fetus.

30 pregnant women with a gestation period of 26-35 weeks were admitted to inpatient treatment with polyhydramnios, patients with confirmed and suspected intrauterine infection, autoimmune disease and fetal cyst.

Indications for treatment are severe obstetric and gynecological history (spontaneous abortion, undeveloped pregnancy, antenatal fetal death, intrauterine infection of the fetus in the previous pregnancy), clinical signs of viral infection activation during this pregnancy, conditions and all patients underwent intrauterine procedures such as amniosynthesis, cordotsynthesis, and information about the presence and activity of infection was obtained through IFA, PCR check-ups, signs of viral infection on ultrasound examination, 11-19 mm expansion of the lateral ventricles, thin and dense amniotic fluid exon markers, fetal embryo, tocoplasm were determined.

The material therapeutic cordocentesis for the diagnosis of viral infections in IFA was - intrauterine blood transfusion, ascetic amniocentesis, and pleural fluid. Procalcitonin, D-dimer, IL - 4,6,8 were added.

Results and discussion

When analyzing data on the progress of previous pregnancies, it was found that 33.3% of women had spontaneous abortions in the 7-14 week period; 45% had an undeveloped pregnancy confirmed by histological examination, and 5.5% of the pregnancies ended in antenatal fetal death.

In the study of gynecological history, 100 percent of women diagnosed inflammatory diseases of the pelvic organs (endometritis, cervicitis) before pregnancy, as well as primary or secondary infertility, autoimmune ooforitis. Cervicitis and colpitis during pregnancy are detected in 100% of cases.

When analyzing the complications of this pregnancy, the influence of unfavorable factors was noted - in 63% of cases, acute respiratory viral infection in the period of 6-8 weeks (the period of the 1st wave of trophoblast invasion). The effect of the same factors was in 47% of women in the period of 16-18 weeks (the period of the 2nd wave of trophoblast invasion).

In addition, all women underwent pelvic ultrasound at 18 to 22 weeks and 26 to 35 weeks of pregnancy. Indications for the appointment of IVIG at 18-22 weeks were signs of threatened abortion, manifested in the form of chorionic detachment in 78% of cases. These periods are especially important in pregnancy, because at this time the first and second wave of trophoblast invasion occurs. Perhaps, taking into account the women's gynecological history, the reason for the separation of the chorion during this period is the presence of chronic infection centers in the uterine cavity. In addition, laboratory-confirmed signs of activation or acute viral infection served as guidelines.

Later (26-35 weeks), there were indications for the use of IVIG, as well as activation with ultrasound signs of intrauterine infection or laboratory-confirmed signs of acute viral infection (anechoic inclusions in the liver 33.3%, the presence of pelriffic) thickening of the heart or endocardial walls) in 22.2% of cases,

oligohydramnios in 45% and polyhydramnios in 22.2%, placental prematurity and thickening in 78%. Taking into account the influence of negative factors during the waves of trophoblast invasion, the frequency of development of gestosis was evaluated. Among all checked-up women, 8 had mild gestosis.

In our study, the number of premature births was 16.7%. The causes of premature termination of pregnancy were pre-placental bleeding, gestosis against the background of autoimmune disease and secondary antiphospholipid syndrome. 8 women gave birth through circumcision, 22 women gave birth through natural childbirth. The condition of newborns after birth was 7-8-9 points according to the Apgar scale in 83.3% of cases. 5 of the newborns were transferred to the department of premature babies, and the rest were discharged home in satisfactory condition. No perinatal mortality or morbidity was observed.

Conclusion

Thus, if intrauterine infections are confirmed during pregnancy, the use of immunotherapy helps to preserve pregnancy and reduce the frequency of its complications.

Based on this, we will consider the following basic methods:

1. Patients at risk should undergo the following studies: ultrasound, fetal doppler, infection testing.

2. For any genital infections and purulent-inflammatory diseases during pregnancy, it is advisable to supplement antibiotic therapy with immunomodulatory therapy aimed at restoring the immune status.

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